



Impact of intensified case-finding strategies on childhood TB case registration in Nepal

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Setting: Seven intervention districts with intensified childhood tuberculosis (TB) case-finding strategies implemented by a non-governmental organisation and seven control districts under the National Tuberculosis Programme, Nepal.

Objectives: To assess the differences in childhood TB case registrations and case registration rates per 100 000 population between two time periods (Year 1 = March 2012–March 2013 and Year 2 = March 2013–March 2014) in intervention and control districts.

Design: Retrospective record review using routinely collected data.

Results: Childhood TB cases increased from 271 to 360 between Years 1 and 2 in the intervention districts (case registration rate from 18.2 to 24.2/100 000) and from 97 to 113 in the control districts (13.4 to 15.6/100 000): the increases were significantly higher in the intervention districts compared with the control districts. The increases were also significantly higher in children aged 0–4 years and in those with smear-negative pulmonary TB and extra-pulmonary TB. Of the various case-finding strategies, household contact screening, private-public mix services and mobile health chest camps produced the highest yield of TB.

Conclusion: A package of intensified case-finding strategies in children was associated with an increase in childhood TB case registrations in Nepal. Additional diagnostic approaches to increase case registrations also need to be considered.

Tuberculosis (TB) remains a global public health problem, with an estimated 9 million cases and 1.5 million deaths in 2013.¹ Of these, there were an estimated 550 000 new childhood cases, constituting 6.1% of the global total, with 80 000 deaths due to TB amongst human immunodeficiency virus (HIV) negative children and an unknown number of deaths amongst HIV-infected children. This high mortality makes TB an important disease in the context of over-all child survival.²

Of the estimated childhood TB cases, only 275 000 children aged ≤ 14 years (50% of the estimated burden) were notified to national TB programmes in 2013. Thus at the global level there is a large case detection gap for this particular age group, which is also suggested by modelling studies.^{1,3} Several factors make the detection and diagnosis of TB in children difficult: non-specific symptoms, which make it easy to mistake childhood TB for malnutrition and/or HIV/AIDS (ac-

quired immune-deficiency syndrome);^{4,5} paucibacillary disease; non-specific chest radiographic findings;⁶ and the fact that children with TB often come from families that are poor, lack knowledge about TB and live in communities with limited access to health services.

To improve the case detection, diagnosis and treatment of TB in children, the World Health Organization (WHO) launched the 'Roadmap for Childhood Tuberculosis', which advocates for better engagement and accountability at all levels of the health system and community.⁷ Improved integration, coordination and communication among different care providers and a more decentralised and comprehensive approach should help to improve childhood TB case detection.

In Nepal, the National Tuberculosis Programme (NTP) adopted the WHO recommended DOTS strategy in 1996. In 2011–2012, the estimated incidence rate of TB in Nepal was 163 per 100 000 population and all forms of TB among children aged 0–8 years constituted 4.4% of all TB cases.⁸ In the 2014 WHO global tuberculosis report, the proportion of TB cases in 2013 in children aged < 15 years was estimated to be even lower, at 2.7%.¹ However, it is recognised that a large number of childhood cases are not diagnosed or registered by the NTP, and the actual burden of TB among children aged < 15 years is unknown. As a result, the NTP has been advocating for and adopting intensified case-finding strategies.

Since 2013, the Stop TB Partnership TB REACH Wave 3 programme has been engaged in intensified early TB case detection amongst children aged 0–14 years in low case-finding districts through the involvement of volunteers and community members. The project is implemented by a non-governmental organisation (NGO) working in partnership with the NTP in 10 districts with various intensified case-finding strategies. We aimed to assess whether these intensified case-finding strategies have led to an increase in childhood case detection. The specific objectives in seven districts in Nepal that implemented intensified case-finding strategies for childhood TB between March 2013 and March 2014 were 1) to describe the case-finding strategies and the yield of TB; and 2) to determine childhood TB case registrations, rates and patterns of disease in comparison with i) the previous year (March 2012–March 2013) in the same districts when no intensified case finding was implemented; and ii) seven control districts where no intensified case finding was implemented during the same two time periods (March 2012 and March 2014).

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TABLE 1 Intensified childhood case-finding activities and their description in Nepal, 2013–2014

Childhood case-finding activity	Description
Household contact screening	Childhood contacts of smear-positive PTB index cases were screened using a standard screening form by volunteers at household level; children with at least two symptoms suggestive of TB, those aged <8 years with no symptoms or those who had not received BCG were referred to designated sites for diagnosis; volunteers collected two samples of sputum from those who could submit the specimens and these were sent to the nearest microscopy centre; children with presumptive TB who could not produce sputum were referred for chest radiography, tuberculin skin testing and for physician assessment at a designated hospital; asymptomatic children aged 8–14 years were not referred for diagnostic evaluation; no isoniazid preventive therapy was given to asymptomatic children under the TB REACH programme
Private-public mix services	Children diagnosed with TB by private practitioners were identified and referred to the NTP for treatment; the costs of diagnosis in the private facilities were reimbursed under the WHO TB REACH programme
Mobile health chest camps	Mobile camps were set up in hard-to-reach areas; a 1 day orientation was given to volunteers and FCHV, followed by two days of camp; FCHV were sent to the community prior to the camp to screen children and priority for screening was given to contacts of TB- and HIV-positive index cases; volunteers referred all suspected cases from the community to the mobile camps, which were staffed by a medical doctor and paramedical officers with laboratory facilities on site for smear microscopy and tuberculin skin testing
Community home-based care visits	Children with HIV/AIDS or children whose parents were living with HIV were screened by selected volunteers in each district through door-to-door visits using a standard screening form; the same criteria for referring children for diagnosis were used as for household contact screening
Screening of children at school	Trained volunteers were sent to schools for childhood screening and the same criteria for referring children for diagnosis were used as for household contact screening
Safe motherhood health services	Safe motherhood service providers in maternal and child clinics were sensitised about childhood TB and asked to refer children with presumptive TB to the nearest TB centre for diagnosis

PTB = pulmonary tuberculosis; TB = tuberculosis; BCG = bacille Calmette-Guérin; NTP = National Tuberculosis Programme; WHO = World Health Organization; FCHV = female community health volunteers; HIV = human immunodeficiency virus; AIDS = acquired immune-deficiency syndrome.

METHODS

Study design

This was a retrospective record review comparing the changes in childhood TB case detection in intervention and control districts.

Study setting

Nepal and tuberculosis control

Nepal is a landlocked country in South Asia, with an area of 147 181 km² and a population of 26 494 405.⁹ According to the 2014 WHO global tuberculosis report, in 2013 there were an estimated 43 000 TB cases in Nepal; 34 000 TB cases were notified, 17 000 were bacteriologically confirmed and there were about 5000 TB-related deaths.¹ The National Tuberculosis Centre (NTC), established in 1989 to oversee TB management in Nepal, has one Regional Tuberculosis Centre (RTC), five regional points and 75 district level points throughout the country. Within each district, the basic management units for diagnosis and treatment are the district hospitals and primary health care centres (PHCs).

Childhood tuberculosis

The Nepal NTP guidelines recommend that the diagnosis of TB in children be based on history and examination (which includes symptoms, a history of TB contact, weight and height and an assessment of growth), tuberculin skin testing, smear microscopy of sputum and other specimens for acid-fast bacilli, chest radiography and appropriate investigations of extra-pulmonary sites.^{10,11} The diagnosis of smear-negative pulmonary TB (PTB) and extra-pulmonary TB

(EPTB) tends to be made at the district level or higher level hospitals where paediatric expertise is available.

Intensified childhood tuberculosis case finding

From March 2013, an NGO called 'Friends Affected and Infected Together in Hand' (FAITH), with the support of the TB REACH project, started implementing intensified early TB case detection amongst children aged 0–14 years in 10 districts of Nepal. In consultation with the NTP, these districts were selected on the basis of poverty, higher population density and lower notification rates of childhood TB case finding. The intensified case-finding strategies are shown in Table 1. Children diagnosed with TB through these screening activities were registered for treatment under the DOTS-based NTP.

Study sites (intervention and control districts)

Seven of the 10 districts (intervention districts) that started intensified case finding in March 2013 (Chitawan, Makawanpur, Bara, Parsa, Rautahat, Mahottari and Dhanusha) were included in the study. Three districts were not included because of delays in or incomplete implementation of activities. Seven control districts were chosen based on the population proportion and the size of the district (the control group population needed to cover at least 30% of the evaluation population) and because they had no intensified case-finding strategies being implemented (Baglung, Dolakha, Gulmi, Nawalparasi, Nuwakot, Ramechhap, and Sindhuli). Although most of the intervention districts are based in flat geographic areas and the control districts in hilly areas, there is some mixture between

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TABLE 2 Childhood case-finding activities in seven districts in Nepal between March 2013 and March 2014 showing number of children screened and number diagnosed with TB

Childhood case finding activity	Children screened <i>n</i>	Children diagnosed with all forms of TB <i>n</i> (%)	Number needed to screen to identify one TB case <i>n</i>
Household contact screening*	11 421	106 (0.9)	108
Private-public mix services	1 099	25 (2.3)	44
Mobile health chest camps†	2 107	51 (2.4)	41
Community home-based care visits	602	3 (0.5)	200
Screening of children at school‡	811	0	–
Safe motherhood health services	700	0	–

*Number of index TB cases for which household contact screening was carried out = 4 668.

†Number of mobile health chest camps conducted = 14.

‡Number of schools visited for screening = 7.

TB = tuberculosis.

the two. They also share similar characteristics: where there is a district hospital in either the intervention or control district, there is always a paediatric specialist situated in this facility; government health facilities are similarly distributed between the intervention and control districts, and all of these facilities have good transportation and comparatively easy access to care.

Study population

Children aged 0–14 years who were diagnosed and registered with TB in the intervention and control districts were included in the study. In the intervention districts, this included children diagnosed in the year before intensified case-finding activities started (Year 1: 16 March 2012–15 March 2013) and the year during which case-finding activities were implemented (Year 2: 16 March 2013–15 March 2014). In the control districts, this included children in the same two time periods during which there was no intensified case finding. All children diagnosed with TB were treated according to national TB guidelines.

Variables, data collection and data sources

Data variables included intensified case-finding strategies with numbers of children screened and yield of TB; the aggregate number of all TB cases registered in each of the districts for Year 1 and Year 2; and, for childhood TB, the district, registration number, age, sex, type and category of TB. The estimated childhood population was obtained from the national census in 2011.¹² Data sources were quarterly reports of the FAITH, TB treatment cards, TB treatment registers and NTP annual reports, and data were captured in paper-based structured data collection questionnaires.

Data entry and data analysis

Data were double-entered, validated and analysed using EpiData software, version 3.1 for entry and version 2.2.2.182 for analysis (EpiData Association, Odense, Denmark). Frequencies and proportions were calculated. The χ^2 test was used to compare the differences in changes between Year 1 and Year 2 between the intervention and control districts. Differences at the 5% level ($P < 0.05$) were regarded as significant.

Ethics

Permission to conduct the study was obtained from the Nepal NTP. Ethics approval was obtained from the Nepal Health Research Council (NHRC), Kathmandu, Nepal, and the Ethics Advisory Group (EAG) of the International Union Against Tuberculosis and Lung Disease, Paris, France. As this was a record review, the need for informed patient consent was waived by the ethics committees.

RESULTS

The numbers of children screened and diagnosed with all forms of TB by the different case-finding strategies are shown in Table 2. Household contact screening, private-public mix services and mobile health chest camps produced the highest yield of TB.

Childhood TB case registrations in the intervention and control districts are shown in Table 3. As a proportion of all TB cases, the intervention districts showed a significant increase in childhood TB between Years 1 and 2 (from 3.9% to 5.0%, $P < 0.001$), while the control districts showed no significant difference (from 4.2% to 4.9%, $P = 0.15$). There was an increase in the number of childhood TB cases in both the intervention and control districts between Years 1 and 2, but the percentage increase was significantly higher in the intervention districts. By age group, the percentage increase was significant in those aged 0–4 years but was not significant in those aged 5–14 years. Significant percentage increases were seen in children with smear-negative PTB and EPTB, but not in those with smear-positive PTB. Similar findings were observed when childhood TB case registration rates were compared between the intervention and control districts (Table 4).

DISCUSSION

This is the first study in Nepal to assess the impact of intensified case-finding strategies in improving the case detection and diagnosis of childhood TB. The findings are encouraging: there was a significant increase in absolute numbers of TB case registrations and case registration rates during the implementation of strategies in the intervention districts compared with the period before case-finding strategies started and compared with results in the control districts. The increase was particularly apparent in young children aged 0–4 years and in children with smear-negative PTB and EPTB.

The strengths of this study were the district-based nature of the intensified case-finding strategies, the large numbers of children screened, the use of uniform TB algorithms for childhood TB diagnosis in all districts and standardised programme data to assess whether there was any change in case registrations. While we used a 'before and during' approach in the seven intervention districts to assess changes in case registrations, we also used seven control districts assessed for case registrations during the same two time periods. We used the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines and sound ethics principles for the conduct and reporting of this ob-

TABLE 3 Childhood TB case registrations in Nepal in seven districts undertaking active childhood TB screening strategies and in seven districts with no active TB screening

Characteristics	Districts with active childhood TB screening			Districts with no active childhood TB screening			P value of difference between two proportions (A and B)
	No active screening (Mar 2012–Mar 2013) <i>n</i>	Active screening (Mar 2013–Mar 2014) <i>n</i>	Difference between the two periods A <i>n</i> (%)	No active screening (Mar 2012–Mar 2013) <i>n</i>	No active screening (Mar 2013–Mar 2014) <i>n</i>	Difference between the two periods B <i>n</i> (%)	
All TB cases (adult and child)	7003	7181		2290	2319		
Childhood TB cases, <i>n</i> (%)	271 (3.9)	360 (5.0)	+89 (33)	97 (4.2)	113 (4.9)	+16 (16)	0.001
By age group							
0–4 years	62	100	+38 (61)	15	17	+2 (13)	0.001
5–14 years	209	259*	+50 (24)	82	96	+14 (17)	0.2
Unrecorded	0	1	–	0	0	–	
By type of TB							
Smear-positive PTB	43	52	+9 (21)	12	17	+5 (42)	0.1
Smear-negative PTB	136	147	+11 (8)	28	21	–7 (25)	<0.001
Extra-pulmonary TB	90	161	+71 (79)	57	75	+18 (32)	<0.001
Unrecorded	2	0	–	0	0	–	–

*Age missing for one observation.

TB = tuberculosis; PTB = pulmonary tuberculosis.

TABLE 4 Childhood TB case registration rates in Nepal in seven districts undertaking active childhood TB screening strategies and in seven districts with no active TB screening

Characteristics	Districts with active childhood TB screening			Districts with no active childhood TB screening			P value of difference between rates (A and B)
	No active screening (Mar 2012–Mar 2013) <i>n</i>	Active screening (Mar 2013–Mar 2014) <i>n</i>	Difference between the two periods A <i>n</i> (%)	No active screening (Mar 2012–Mar 2013) <i>n</i>	No active screening (Mar 2013–Mar 2014) <i>n</i>	Difference between the two periods B <i>n</i> (%)	
Estimated childhood population	1 489 785	1 489 785		722 597	722 597		
All childhood TB cases, /100 000	18.2	24.2	+6.0 (33)	13.4	15.6	+2.2 (16)	<0.001
By age group, TB cases /100 000:							
0–4 years	4.2	6.7	+2.5 (60)	2.1	2.4	+0.3 (14)	0.002
5–14 years	14.0	17.4	+3.4 (24)	11.3	13.2	+1.9 (17)	0.07
By type of TB, /100 000:							
Smear-positive PTB	2.9	3.5	+0.6 (21)	1.7	2.4	+0.7 (41)	0.9
Smear-negative PTB	9.1	9.9	+0.8 (9)	3.9	2.9	–1.0 (26)	0.002
Extra-pulmonary TB	6.0	10.8	+4.8 (80)	7.9	10.4	+2.5 (32)	0.01

TB = tuberculosis; PTB = pulmonary tuberculosis.

servational study.^{13,14} The study had some limitations. The duration of the intervention was only one year, and a longer duration might have been more helpful in assessing the value of this approach. The data were secondary and there may have been errors in data recording in the TB registers. The diagnosis of TB in children is also notoriously difficult,^{4–6} and mistakes may have been made.

Community-based approaches are becoming increasingly accepted as a way of improving health care services, with community volunteers and doorstep delivery of interventions used to improve maternal and child health.¹⁵ Household contact screening is a recognised way of increasing childhood TB case detection,¹⁶ and our findings confirm the value of this approach. The increased detection of children aged 0–4 years in this context may be due to the closer exposure of young children to affected index patients,

particularly mothers with infectious PTB,¹⁶ and the fact that screening in such children takes place even if they do not have TB symptoms. Engaging the private sector in Pakistan was successful in increasing PTB case notifications in both adults and children,¹⁷ and we found similar success in our study, which focused only on children. We were unable to find published reports documenting the value of screening children in mobile health camps, but in our study this approach appeared to yield satisfactory results. While screening for TB in the school environment has been used previously,¹⁸ we did not find this approach or the integration with safe motherhood services to be useful. More targeted screening, for example, focused on mothers with presumptive or diagnosed TB, might have a better yield, and this should be further evaluated. Similarly, while community home-based care is an established activity for providing support and care for people living with HIV/

AIDS and is associated with reduced morbidity and mortality,¹⁹ we did not find it helpful in identifying significant numbers of children with TB, perhaps because health facility-based services where intensified case detection takes place already exist.

There are three programmatic implications from our study. First, it would seem that household contact screening, engaging with the private sector and setting up regular mobile health camps are the most productive in terms of identifying children with TB. Screening at schools and engaging more fully with safe motherhood services yielded no cases of TB. With a total package that cost about US\$225 000 for the year for 10 districts, a decision needs to be made as to whether it is cost-effective to continue with some of these low-yield approaches.

Second, within the context of the intensified case-finding package it may be worth assessing and including other approaches. For example, health care workers need to be better trained to recognise the symptoms and signs of TB, as better awareness of health workers at microscopy centres has led to an increase in the case detection of TB in children in Bangladesh.²⁰ Sputum smear microscopy has low sensitivity for diagnosing TB, and other diagnostic modalities should be considered. An important diagnostic development is a sensitive, specific, fully automated and commercially available nucleic acid amplification test, the Xpert® MTB/RIF assay (Cepheid Inc, Sunnyvale, CA, USA) for use with sputum and other body specimens.²¹ The cartridge-based system, which requires minimal laboratory expertise, produces results in less than 2 hours. Current work suggests that Xpert is useful in the diagnosis of PTB in children,^{22,23} and this new technology needs to be evaluated within the context of intensified case finding in children. Xpert was found to be highly sensitive in this regard in a pilot study in Tanzania,²⁴ but it will only really be useful if specimen collection in children is improved and if the technology is brought as close to the patient as possible.

Third, a recent modelling exercise estimated that about 32 000 children globally had multidrug-resistant TB (MDR-TB, defined as resistance to isoniazid and rifampicin) in 2010, yet the total number of cases of childhood MDR-TB that had ever been reported in 40 years of scanned literature was only 2% of the number of cases estimated to have occurred in 2010.²⁵ There were nearly 500 confirmed cases of MDR-TB in Nepal in 2013 out of an estimated 1100 cases (43% case detection).¹ These cases were mainly in adults, and the true burden in children remains largely unknown. The use of Xpert, which has the capacity to accurately diagnose rifampicin resistance,²¹ would be a step in the right direction to close this large case detection gap.

In conclusion, this study has shown that a package of community-based intensified case-finding strategies in children can be implemented at the district level and is associated with an increase in TB case registrations and case registration rates, particularly in children aged 0–4 years and in those with smear-negative PTB and EPTB.

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Contexte : Sept districts d'intervention avec des stratégies intensifiées de recherche active des cas de tuberculose (TB) mis en œuvre par une organisation non gouvernementale et sept districts témoins gérés par le Programme National Tuberculose au Népal.

Objectifs : Evaluer les différences en termes d'enregistrement des cas de TB de l'enfant et de taux d'enregistrement pour 100 000 population entre deux périodes (année 1 = mars 2012 à mars 2013 et année 2 = mars 2013 à mars 2014) dans les districts d'intervention et les districts témoins.

Schéma : Revue de dossiers rétrospective grâce aux données recueillies en routine.

Résultats : Les cas de TB de l'enfant ont augmenté de 271 à 360 entre l'année 1 et l'année 2 dans les districts d'intervention (le taux d'enregistrement est passé de 18,2 à 24,2/100 000) et de 97 à 113

dans les districts témoins (13,4 à 15,6/100 000) : les augmentations ont été significativement plus importantes dans les districts d'intervention par rapport aux districts témoins. Les augmentations ont également été plus importantes chez les enfants de 0 à 4 ans et chez ceux qui ont eu une TB pulmonaire à frottis négatif et extra-pulmonaire. Parmi diverses stratégies de recherche des cas, le dépistage des contacts familiaux, les services conjoints privés-publics et les camps de santé mobiles pour la TB ont été les plus performants.

Conclusion : Un paquet de stratégies intensifiées de recherche des cas a été associé à une augmentation des enregistrements de cas de TB de l'enfant au Népal. Il faut également envisager des approches diagnostiques supplémentaires pour augmenter encore l'enregistrement des cas.

Marco de referencia: Siete distritos de intervención en los cuales una organización no gubernamental aplica estrategias de búsqueda intensificada de casos de tuberculosis (TB) en los niños y siete distritos testigos del Programa Nacional contra la Tuberculosis de Nepal.

Objetivos: Evaluar las diferencias en el registro de los casos de TB en la niñez y la tasa de registro de TB por 100 000 habitantes, en dos períodos (el primer año, de marzo del 2012 a marzo del 2013 y el segundo, de marzo del 2013 a marzo del 2014) en los distritos de intervención y los distritos testigos.

Método: Fue este un estudio retrospectivo en el cual se analizaron los datos recogidos de manera sistemática.

Resultados: Los casos de TB en la niñez aumentaron de 271 a 360 durante los períodos del estudio en los distritos de intervención (tasa de registro de casos de 18,2 a 24,2/100 000) y de 97 a 113 en los

distritos testigos (de 13,4 a 15,6/100 000) y el incremento de los casos fue significativamente mayor en los distritos de intervención. Se observó un aumento con significación estadística en los niños del grupo de 0 a 4 años de edad, en los niños con TB pulmonar y baciloscopia negativa y con TB extrapulmonar. De las diferentes estrategias de búsqueda de casos, la detección sistemática de los contactos domiciliarios, los servicios mixtos público y privado y los puestos móviles de campaña de salud respiratoria alcanzaron el mayor rendimiento diagnóstico de TB.

Conclusión: La introducción de un conjunto de estrategias de búsqueda intensificada de casos en los niños se asoció con un aumento en el registro de los casos de TB en Nepal. Se precisa también examinar la posibilidad de aplicar nuevos enfoques diagnósticos con el propósito de mejorar el registro de casos.