

# High Prevalence of Active and Latent Tuberculosis in Children and Adolescents in Tibetan Schools in India: The Zero TB Kids Initiative in Tibetan Refugee Children

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**Background.** Tuberculosis (TB) prevalence is high among Tibetan refugees in India, with almost half of cases occurring in congregate facilities, including schools. A comprehensive program of TB case finding and treatment of TB infection (TBI) was undertaken in schools for Tibetan refugee children.

**Methods.** Schoolchildren and staff in Tibetan schools in Himachal Pradesh, India, were screened for TB with an algorithm using symptoms, chest radiography, molecular diagnostics, and tuberculin skin testing. Individuals with active TB were treated and those with TBI were offered isoniazid-rifampicin preventive therapy for 3 months.

**Results.** From April 2017 to March 2018, we screened 5391 schoolchildren (median age, 13 years) and 786 staff in 11 Tibetan schools. Forty-six TB cases, including 1 with multidrug resistance, were found in schoolchildren, for a prevalence of 853 per 100 000. Extensively drug-resistant TB was diagnosed in 1 staff member. The majority of cases (66%) were subclinical. TBI was detected in 930 of 5234 (18%) schoolchildren and 334 of 634 (53%) staff who completed testing. Children in boarding schools had a higher prevalence of TBI than children in day schools (915/5020 [18%] vs 15/371 [4%];  $P < .01$ ). Preventive therapy was provided to 799 of 888 (90%) schoolchildren and 101 of 332 (30%) staff with TBI; 857 (95%) people successfully completed therapy.

**Conclusions.** TB prevalence is extremely high among Tibetan schoolchildren. Effective active case finding and a high uptake and completion of preventive therapy for children were achieved. With leadership and community mobilization, TB control is implementable on a population level.

**Keywords.** tuberculosis; pediatrics; Tibet; case finding; preventive therapy.

Approximately 1 million children develop tuberculosis (TB) and 250 000 die of the disease annually [1–3]. Tibetan refugees in India, mostly settled in the northern and southern states of Himachal Pradesh, Uttarakhand, and Karnataka, have very high TB rates, with a large proportion occurring in children [4–7]. Residence in congregate living facilities and a combination of socioeconomic, biomedical, and political challenges over several decades contribute to the high TB burden in the Tibetan refugee population. TB infection rates of 65%–98% have been reported for Tibetan immigrants in the United States and Canada [8–10].

A population-wide active TB case finding campaign between 2011 and 2013 identified a case prevalence of 394 per 100 000 among Tibetan schoolchildren in India [5]. Because of the high burden of TB in Tibetan refugee children, we undertook a TB case finding and preventive therapy program in Tibetan schools in northern India. We present here the findings from the first year of the initiative in which schoolchildren and staff residing in Tibetan schools in India were screened and treated for TB disease and infection on a population level using a community-based approach.

## METHODS

### Study Setting and Population

The Zero TB Kids project is a collaboration between the Delek Hospital, Dharamsala; the Johns Hopkins University School of Medicine; the University of Wisconsin–Madison; and the Central Tibetan Administration Department of Health (CTA-DoH) and Department of Education (CTA-DoE). Spiritual and political leaders of the Tibetan exile community endorsed the project prior to its launch [11]. Between April 2017 and March

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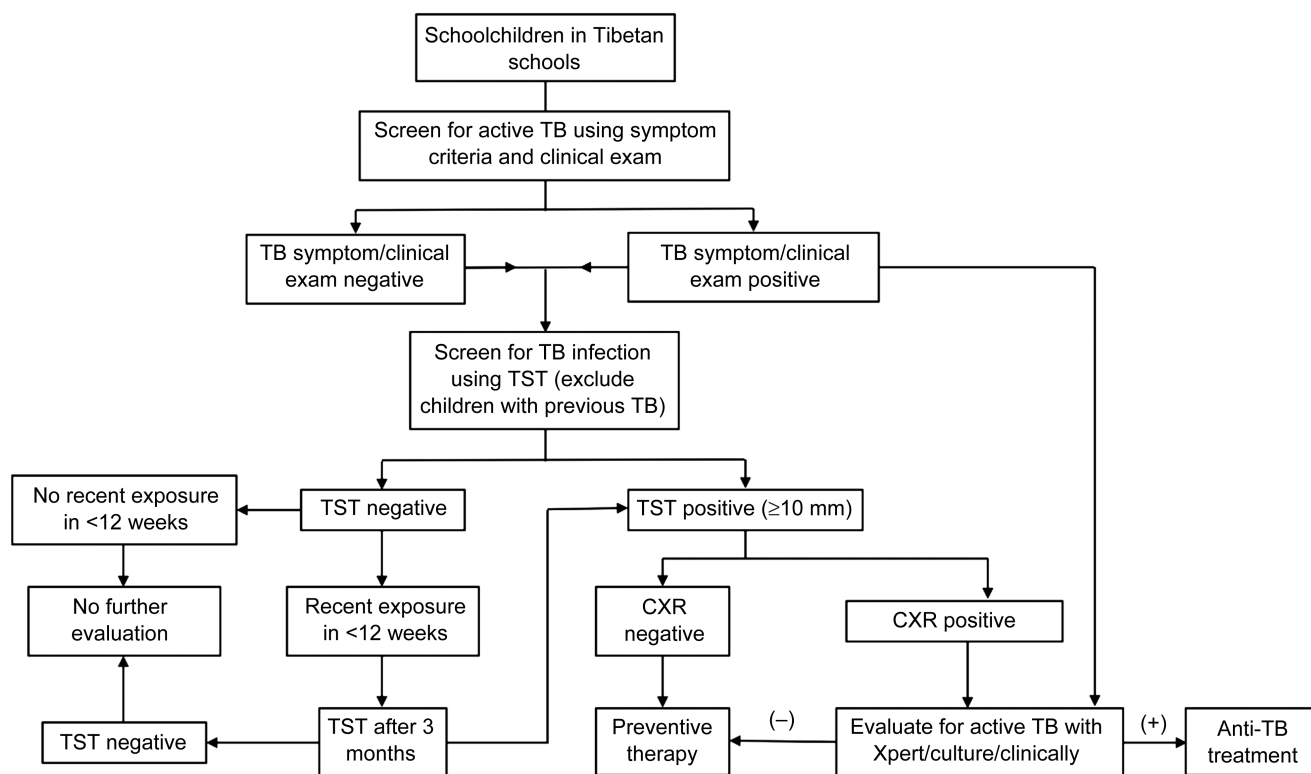
2018, Zero TB Kids conducted on-site screening for active and latent TB among children and staff residing in 7 boarding and 4 Tibetan day schools in the state of Himachal Pradesh, India. The boarding schools are home to the children, many of whom are from poor families living in Tibetan settlements across India and Nepal. Children from prekindergarten to grade 12 are cared for by housemothers in the school dormitories and hostels. All students and staff at each school were eligible for TB symptom screening and testing for latent TB infection (TBI), which were performed at the school. Anti-TB treatment was provided at a CTA-DoH treatment facility. The study was ruled exempt by the Johns Hopkins Medicine Institutional Review Board as a public health initiative and approved by the CTA-DoH, CTA-DoE, and each school administration. Identifying information of participants was maintained by the Department of Health and anonymized data were provided to Johns Hopkins University personnel. Consent was obtained from parents by the Department of Health and the school before treatment was provided to children.

### Project Design and Procedures

#### Screening for Active TB

The algorithm followed for screening for active and latent TB and for providing preventive therapy is shown in [Figure 1](#). Basic demographic information was provided by the school administration. TB exposure history in the current and previous school years at school was obtained through review of school health records.

Additional information on index or source TB cases in the schools was obtained from the DoH treatment facility. Children and staff members were considered contacts of a TB case if they shared living space or a classroom at the time of the latter's diagnosis. Each schoolchild and staff member was interviewed by project staff using a standardized questionnaire. Information was collected on TB-related symptoms including cough, fever, night sweats, weight loss, and fatigue as well as past TB history or exposure, other health conditions, and receipt of concomitant medications. Each participant was examined by a project medical officer. Individuals with cough  $\geq 2$  weeks or other symptoms underwent further evaluation with a chest radiograph (CXR) and/or testing of respiratory secretions with the Xpert MTB/RIF IV assay (Cepheid, Sunnyvale, California). Children with TB symptoms who were not able to produce sputum had a gastric aspiration performed at the school infirmary for Xpert testing. Sputum or lavage fluid from all Xpert-positive individuals underwent culture using the Mycobacterial Growth Indicator Tube system (Becton Dickinson, Sparks, Maryland) and drug susceptibility testing at the P. D. Hinduja National Laboratory in Mumbai. Second-line drug susceptibility testing was performed for isolates with rifampicin resistance by Xpert. Because this was a school-wide TB screening program, contacts of recent cases were automatically evaluated for active TB under the study algorithm. For cases presenting passively afterward, contact evaluation was carried out, but results are not yet available.



**Figure 1.** Study flowchart. Abbreviations: CXR, chest radiograph; TB, tuberculosis; TST, tuberculin skin test.

### Screening for Latent TB and Preventive Therapy

TBI was diagnosed by tuberculin skin testing (TST) using 5 TU of purified protein derivative RT23 (Span Diagnostics, Surat, India). Induration measuring  $\geq 10$  mm after 2–3 days was considered positive.

Preventive therapy with 3 months of daily isoniazid and rifampicin (3HR) was provided to TST-positive individuals

after ruling out active TB with CXR and, if warranted, an Xpert test. Children and staff with exposure only to drug-resistant TB cases were not provided preventive therapy but underwent routine monitoring according to World Health Organization (WHO) guidelines. People with mixed exposure to both drug-susceptible and drug-resistant TB cases were provided preventive therapy with 3HR. Individuals with a diagnosis of

**Table 1. Characteristics of Students and Staff Screened for Latent and Active Tuberculosis Under the Zero TB Kids Project at Tibetan Schools in Himachal Pradesh State, India, 2017–2018**

Characteristics	All Participants (N = 6177)	Students (n = 5391)	Staff (n = 786)
Age, y, median (IQR)	14 (10–17)	13 (10–16)	40 (33–48)
Sex			
Female	3172 (51.4)	2700 (50.1)	472 (60.0)
Male	3005 (48.7)	2691 (49.9)	314 (40.0)
Occupation			
Student	5391 (87.3)	5391 (100)	...
Teacher	393 (6.4)	...	393 (6.4)
Housemother	107 (1.7)	...	107 (1.7)
Office staff	81 (1.3)	...	81 (1.3)
Cook	41 (0.7)	...	41 (0.7)
Other staff	164 (2.7)	...	164 (2.7)
Place of birth			
India	4946 (80.1)	4414 (81.9)	532 (67.7)
Tibet	776 (12.6)	531 (9.9)	245 (31.2)
Nepal	422 (6.8)	414 (7.7)	8 (1.0)
Bhutan	25 (0.4)	24 (0.5)	1 (0.1)
Other	8 (0.1)	8 (0.2)	0 (0.0)
Ethnicity			
Tibetan	5790 (93.8)	5020 (93.1)	770 (98.0)
Indian	94 (1.5)	80 (1.5)	14 (1.8)
Himalayan origin <sup>a</sup>	292 (4.7)	290 (5.4)	2 (0.3)
Weight, kg, median (IQR)	45.5 (32–56)	42.6 (31–53)	65 (57–74)
History of previous TB treatment			
Previously treated for TB	274 (4.4)	135 (2.5)	139 (17.7)
Previously treated for MDR-TB	6/275 (2.2)	3/135 (2.2)	3/139 (2.2)
Exposure to TB case in past 2 y	1685 (27.3)	1601 (29.7)	84 (10.7)
Exposure to drug-susceptible TB	1286 (20.8)	1229 (22.8)	57 (7.3)
Exposure to MDR-TB <sup>b</sup>	108 (1.8)	105 (2.0)	3 (0.4)
Drug susceptibility status unknown	291 (4.7)	267 (5.0)	24 (3.1)
Received BCG vaccine <sup>c</sup>			
Yes	5855 (94.8)	5159 (95.7)	696 (88.6)
No	309 (5)	224 (4.2)	85 (10.8)
Unknown	13 (0.2)	8 (0.2)	5 (0.6)
Coexisting medical conditions			
Asthma	24 (0.4)	15 (0.3)	9 (1.2)
Seizure disorder	23 (0.4)	22 (0.4)	1 (1.1)
Chronic hepatitis B	128 (2.1)	88 (1.6)	40 (5.1)
Hypertension	40 (0.7)	0 (0)	40 (5.1)
Diabetes mellitus	8 (0.1)	1 (0.0)	7 (0.9)
Acid peptic disease	36 (0.6)	20 (0.4)	16 (2.0)
Other conditions	17 (0.3)	13 (0.2)	4 (0.5)

Data are presented as no. (%) unless otherwise indicated.

Abbreviations: BCG, Bacille Calmette-Guérin; IQR, interquartile range; MDR-TB, multidrug-resistant tuberculosis; TB, tuberculosis.

<sup>a</sup>Includes non-Tibetan students from the Ladakh, Kinnaur, and Lahaul areas of India and Nepal.

<sup>b</sup>History of MDR-TB in last 5 years. School nurse/parent contacted for confirmation when a child responded positive to contact with drug-resistant TB. Pleural TB successfully treated with first-line antituberculosis therapy with no drug susceptibility test result was considered drug susceptible.

<sup>c</sup>BCG vaccine status (left arm scar) checked only for people born in Tibet. Persons born outside Tibet were assumed to have received BCG at birth under their national immunization program.

chronic hepatitis B virus (HBV) infection had liver enzyme tests and abdominal ultrasonography performed before being provided preventive therapy. Those with elevated bilirubin levels or liver enzymes (alanine aminotransferase or aspartate aminotransferase) greater than twice the upper limit of normal or with ultrasound findings of liver parenchymal disease were not provided preventive therapy. Preventive therapy medications packed and labeled with recipients' name in separate boxes were distributed to housemothers who supervised therapy every morning for children. Parents provided supervision for children who were day scholars. Staff members self-administered preventive therapy. Adherence was further ensured through a treatment card that housemothers and staff checked after each dose. The project staff conducted monthly follow-up for preventive therapy recipients at each school.

Side effects experienced by participants were recorded on treatment cards developed for the initiative. Hepatotoxicity from isoniazid or rifampicin was determined by the clinician based on development of (1) clinical symptoms of nausea, vomiting, loss of appetite, tiredness, upper abdominal pain, or jaundice; (2) elevated serum aminotransferases ( $\geq 5$  times upper limit of normal); and (3) subsidence of symptoms/laboratory values following discontinuation of drug [12]. Preventive therapy was temporarily withheld in the event of hepatotoxicity or other adverse drug reactions as determined by the clinician and restarted after subsidence of symptoms and laboratory values. Preventive therapy regimen was modified to 4 months of rifampicin where isoniazid was implicated, or to 6 months of isoniazid where rifampicin was implicated. Therapy modification or premature termination was carried out by the clinician in consultation with the school nurse, housemothers, individuals, and parents. Project staff communicated via phone with school nurse and housemothers once every 2 weeks to discuss outstanding issues related to preventive therapy implementation.

#### Data Collection and Statistical Analysis

Data were processed and analyzed using Stata version 13.1 software (StataCorp, College Station, Texas). Descriptive, univariate, and multivariable logistic regression analyses adjusting for age and sex were carried out to assess the risk of TB infection and disease for schoolchildren.

## RESULTS

#### Study Population and TB Exposure History

Between April and October 2017, 5391 schoolchildren and 786 staff in 11 Tibetan schools (7 boarding schools [ $n = 5726$ ] and 4 day schools [ $n = 451$ ]) were screened for TBI and disease. The median age of students was 13 years (interquartile range [IQR], 10–16 years) and 50% were female (Table 1). The majority of the population (95%) had received Bacille Calmette-Guérin (BCG) vaccination. Previous TB treatment was reported by 135 (3%)

students and 139 (18%) staff members; 6 individuals with previous therapy (2%) had been treated for multidrug-resistant TB (MDR-TB). Thirty percent ( $n = 1601$ ) of schoolchildren reported close contact with a TB case in the past 2 years, including 108 (2%) who were exposed to MDR-TB. Twenty-six percent of schoolchildren had exposure to a TB case in school and 3% had exposure to a TB case at home. Eighty-eight (2%) schoolchildren and 40 (5%) staff reported having chronic HBV infection.

#### Active TB

There were 47 TB cases in total, of which 46 were detected in 5391 schoolchildren for a prevalence of 853 per 100 000 (Table 2). One child had MDR-TB. The median age of the children with TB was 16 years (IQR, 14–17 years; Table 3). Among staff members ( $n = 786$ ), 1 case was detected (prevalence, 127/100 000), which was extensively drug resistant (XDR) with resistance to isoniazid, rifampicin, ofloxacin, and kanamycin. Another staff member had disease with nontuberculous mycobacteria. All cases were detected in the 7 boarding schools. The TB prevalence in schoolchildren at the 7 boarding schools was 916 per 100 000 (range 371–3205 per 100 000). The prevalence in children aged  $< 15$  years was 307 per 100 000. Of the 47 TB cases (46 schoolchildren and 1 staff member), 43 were pulmonary and 4 were extrapulmonary (1 lymph node, 1 hip joint, and 2 pleural TB). Of the 43 pulmonary cases, 41 (95%) were Xpert positive, of which 6 (15%) were acid-fast bacilli smear positive and 14 (34%) were culture positive (Supplementary Table 1). Gastric aspirates constituted 63% ( $n = 26$ ) of Xpert-positive specimens. Cough in the previous 2 weeks was commonly reported (15%

**Table 2. Prevalence of Active Tuberculosis (TB) Disease Among Students and Staff Screened for Active TB in Various Tibetans Schools in Himachal Pradesh, India, 2017–2018**

School	No. of Students Screened	No. of Staff Screened <sup>c</sup>	No. of TB Cases in Students	TB Disease Prevalence in Students (per 100 000)
School A <sup>a</sup>	523	58	10	1952
School B <sup>a</sup>	809	116	7	865
School C <sup>a</sup>	1311	253	6	458
School D <sup>a</sup>	1149	128	9	783
School E <sup>a</sup>	812	85	3	369
School F <sup>a</sup>	161	26	5	3106
School G <sup>a</sup>	255	40	6	2353
School H <sup>b</sup>	28	9	0	0
School I <sup>b</sup>	47	10	0	0
School J <sup>b</sup>	111	9	0	0
School K <sup>b</sup>	185	52	0	0
Overall	5391	786	46	853

Abbreviation: TB, tuberculosis.

<sup>a</sup>Boarding schools, where all TB cases were detected for a prevalence of 916 per 100 000 (46/5020) students.

<sup>b</sup>Day schools.

<sup>c</sup>Only 2 staff members were diagnosed with active disease: 1 with extensively drug-resistant TB and 1 with nontuberculous mycobacterial disease.

**Table 3. Relationship Between Baseline/Clinical Characteristics and Risk of Tuberculosis Disease Among Schoolchildren in Various Tibetan Schools in Himachal Pradesh, India, 2017**

Characteristic	Schoolchildren Detected With TB Disease (n = 46)	Schoolchildren Without TB Disease (n = 5345)	TB Risk (Univariate Analysis) OR (95% CI)	PValue	TB Risk (Multivariable Analysis) OR <sup>a</sup> (95% CI)	PValue
Age, y, median (IQR)	16 (14–17)	13 (10–15)	1.2 (1.1–1.4)	< .001	1.2 (1.1–1.4)	< .001
Sex						
Female	24 (52.2)	2676 (50.1)	Referent	.776	Referent	.795
Male	22 (47.8)	2669 (49.9)	0.92 (.5–1.6)	...	0.93 (.5–1.7)	...
Previous TB history	1 (2.2)	134 (2.5)	0.88 (.1–6.3)	.886	0.45 (.06–3.4)	.438
No previous TB history	45 (97.8)	5211 (97.5)	Referent	...	Referent	...
Recent exposure (<2 y) to a TB case <sup>b</sup>						
Yes	30 (65.2)	1571 (29.4)	4.5 (2.4–8.3)	.002	2.8 (1.5–5.5)	.002
No	16 (34.8)	3771 (70.6)	Referent	...	Referent	...
TST <sup>+</sup> , recently exposed	28 (65.1)	426 (40.8)	2.9 (1.5–5.6)	.001	2.6 (1.3–5.2)	.006
TST <sup>+</sup> , not recently exposed	15 (34.9)	618 (59.2)	Referent	...	Referent	...
Multiple TB exposure						
Exposed to 1 case	9 (30.0)	988 (62.9)	Referent	.001	Referent	.003
Exposed to ≥2 cases	21 (70.0)	583 (37.1)	4.0 (1.8–8.7)	...	3.5 (1.5–8.0)	...
Exposure setting in school						
Classroom	10 (35.7)	605 (43.8)	Referent	.888	Referent	.993
Dormitory/hostel	9 (34.2)	510 (36.9)	1.1 (.4–2.6)	.030	1.0 (.4–2.5)	.063
Classroom and dormitory/hostel	9 (32.1)	198 (14.3)	2.8 (1.1–6.9)	...	2.4 (.95–6.2)	...
Cough in last 2 wk						
Yes	17 (37.0)	808 (15.1)	3.3 (1.8–6.0)	< .001	2.8 (1.5–5.1)	.001
No	29 (63.0)	4537 (84.9)	Referent	...	Referent	...
Fever in last 2 wk						
Yes	5 (10.9)	171 (3.2)	3.7 (1.4–9.5)	.007	3.4 (1.3–8.7)	.012
No	41 (89.1)	5175 (96.8)	Referent	...	Referent	...
Night-sweats in last 2 wk						
Yes	5 (10.9)	201 (3.8)	3.1 (1.2–8.0)	.018	2.0 (.8–5.3)	.142
No	41 (89.1)	5144 (96.2)	Referent	...	Referent	...
Weight loss in last 1 mo						
Yes	12 (26.1)	847 (15.9)	1.9 (.96–3.6)	.063	1.3 (.6–2.5)	.503
No	34 (73.9)	4498 (84.2)	Referent	...	Referent	...
Increased tiredness in last 2 wk						
Yes	13 (28.3)	586 (11.0)	3.2 (1.7–6.1)	< .001	1.9 (.97–3.8)	.063
No	33 (71.7)	4759 (89.0)	Referent	...	Referent	...

Data are presented as no. (%) unless otherwise indicated.

Abbreviations: CI, confidence interval; IQR, interquartile range; OR, odds ratio; TB, tuberculosis; TST, tuberculin skin test.

<sup>a</sup>Adjusted for age and sex.

<sup>b</sup>Schoolchildren were considered exposed to *Mycobacterium tuberculosis* if they were sharing classroom or residential quarters with another student at the time of the latter's TB diagnosis. Students diagnosed with lung or pleural TB were considered index TB cases.

[n = 825]), but 29 of 44 children (66%) with active lung or pleural TB did not have cough. The positive predictive value for cough was 2% in this setting. On multivariable analyses, increasing age, exposure history, multiple exposures, exposure in both classroom and dormitory, cough >2 weeks, and fever in the last 2 weeks had statistically significant associations with TB disease among schoolchildren (Table 3). Among TST positives, those with a recent TB exposure had higher risk of disease (odds ratio [OR], 2.6; P = .002). The majority of TB cases (n = 42/47 [90%]) were detected after CXR examination following TST positivity.

### TB Infection

A total of 5234 schoolchildren and 634 staff members were screened for TBI. The prevalence of TBI was 18% (930/5234) for schoolchildren and 53% (334/634) for staff members (Table 4). TST was not performed for 135 schoolchildren and 139 staff members who had active TB previously and for 22 schoolchildren and 13 staff for other reasons including refusals. The median induration of reactive TSTs was 16 mm (IQR, 13–19 mm) for schoolchildren, 18 mm (IQR, 13–20 mm) for staff, and 18 mm (IQR, 14–20 mm) for persons diagnosed with active TB. TST conversion was assessed after 12 weeks for 250



**Table 4. Prevalence of Tuberculosis Infection Among Students and Staff in Various Tibetan Schools in Himachal Pradesh, India, 2017**

School	No. of Students Screened for TB Infection	No. of Staff Screened for TB Infection	TB Infection Prevalence in Students, No. (%)	TB Infection Prevalence in Staff, No. (%)
School A <sup>a</sup>	513	50	140 (27)	11 (22)
School B <sup>a</sup>	779	198	188 (24)	64/198 (65)
School C <sup>a</sup>	1281	208	183 (14)	109/208 (52)
School D <sup>a</sup>	1106	82	208 (19)	49/82 (60)
School E <sup>a</sup>	795	77	97 (12)	42/77 (55)
School F <sup>a</sup>	157	22	47 (30)	15/22 (68)
School G <sup>a</sup>	234	31	52 (22)	16/31 (52)
School H <sup>b</sup>	28	8	1 (4)	1/8 (13)
School I <sup>b</sup>	47	9	4 (9)	5/9 (56)
School J <sup>b</sup>	111	8	3 (2.7)	2/8 (25)
School K <sup>b</sup>	183	41	7 (4)	20/41 (49)
Overall	5234	734	930/5234 (18)	334/634 (53)

Abbreviation: TB, tuberculosis.

<sup>a</sup>Boarding school.

<sup>b</sup>Day school.

schoolchildren in 2 schools who were newly exposed and TST negative at the time of screening. Thirty-two (13%) schoolchildren converted to TST positive and 1 TB case was diagnosed among converters. TBI was higher in the boarding schools than the day schools: 19% vs 4% ( $P < 0.001$ ) for schoolchildren and 54% vs 42% ( $P = .078$ ) for staff. Increasing age, male sex, TB exposure history, exposure to  $\geq 2$  cases, and exposure in dormitory were significantly associated with an increased risk of TBI (Table 5). Risk of TBI for staff members was described in Supplementary Table 2. Distribution of TBI and disease by age categories and sex is presented in Supplementary Figure 1.

#### TB Preventive Therapy and Outcomes

Of 930 schoolchildren and 334 staff with TBI, 888 and 332, respectively, were eligible to receive preventive therapy after excluding active disease (42 TST-positive active TB disease in schoolchildren and 2 TST-positive active disease in staff). Preventive therapy was provided to 90% (799/888) of schoolchildren and 30% (101/332) of staff with latent TBI. Thirty-three children and 45 staff members had contraindications to preventive therapy, including 24 with chronic HBV infection. Of those eligible, preventive therapy was declined by 56 (6%) schoolchildren and 186 (56%) staff. Nine people with exclusive MDR-TB contact were not provided preventive therapy. Two hundred twenty-seven (25%) people developed at least 1 treatment side effect, almost all of which were attributed to isoniazid. Toxicity was more common in adolescents aged 10–18 years (36%) and less common for children aged 5–9 years (14%). Fatigue, drowsiness, and gastrointestinal complaints were reported by 8%–10% of schoolchildren and 5%–13% of staff receiving preventive therapy. Eleven schoolchildren (1.4%) and 1 staff member (1.0%) experienced hepatotoxicity that was attributed to isoniazid, and

elevated liver enzymes and symptoms regressed after the drug was discontinued. Preventive therapy was permanently stopped for 2 people with hepatotoxicity; 10 others went on to successfully complete treatment. Twenty of 45 (44%) individuals with latent TB and HBV coinfection received preventive therapy with isoniazid and rifampicin, and 1 developed hepatotoxicity requiring discontinuation of treatment. Preventive therapy was modified to 4 months of rifampicin alone for 7 (0.8%) people, isoniazid preventive therapy for 6 months for 1 person (0.1%), and prematurely terminated for 5 (0.6%) people due to drug toxicity. Of the 900 people who were provided preventive therapy, 857 (95%) successfully completed therapy, 5 (0.6%) prematurely stopped preventive therapy, 7 (0.8%) were lost to follow-up, and therapy was ongoing for 30 (3.4%) people (Supplementary Table 3).

#### DISCUSSION

We detected a high prevalence of TB disease (853/100 000) and infection (18%) among Tibetan schoolchildren in India and a high prevalence of TBI in adult staff (53%). The majority of the cases were subclinical (66%), including 1 MDR-TB case and 1 XDR-TB case detected in a child and a staff member, respectively. One-fifth of the schoolchildren investigated for TB were Xpert positive, nearly twice of what was reported (11%) for children in a recent systematic review [13]. The infection prevalence observed for Tibetan adults (53%) was comparable to the rate observed for Tibetan refugees in New York City (65%) in 1995–1999 but lower than the prevalence of 96%–98% observed for Tibetan refugees in Minnesota and Toronto in 1992–1994 and 1998–2000, respectively [8–10].

The proportion of new TB disease detected among schoolchildren in Tibetan boarding schools during the 1-year study period (916/100 000) is  $>4$  times that of India's incidence (211/100 000 in 2016) [2], and higher than the incidence observed in high-HIV-prevalence settings such as South Africa (781/100 000 in 2016) [2]. HIV infection is uncommon in the Tibetan community [5, 7]. The proportion of new TB cases detected in Tibetan children aged  $<15$  years (307/100 000) was 5–8 times higher than the incidence calculated for children aged  $<15$  years for India (63/100 000), China (41/100 000), and globally (54/100 000) based on data from the WHO [2]. The heterogeneity of TB prevalence across various Tibetan boarding schools (371–3201 per 100 000) could be due to many factors, including recent TB cases in the school, overcrowding and ventilation in the dormitories, and healthcare facilities and healthcare access for the school. The low smear positivity is likely due to the disease being paucibacillary in the majority of the cases and Xpert's higher sensitivity than smears. Culture sensitivity was probably compromised by the need to transport specimens from schools to a referral laboratory.

Nearly one-third (26%) of students reported exposure to someone with active TB in the previous 2 years at school, suggesting that over several years the majority of the school population would be contacts, especially as children enroll in the

**Table 5. Relationship Between Various Baseline/Clinical Characteristics and Risk of *Mycobacterium tuberculosis* Infection Among Schoolchildren in Various Tibetan Schools in Himachal Pradesh, India, 2017**

Characteristics of Schoolchildren	Schoolchildren With TB Infection, n/N (%)	Risk of TB Infection (Univariate Analysis), OR (95% CI)	PValue	Risk of TB Infection (Multivariable Analysis), OR (95% CI)	PValue
<b>Age range, y</b>					
≥5–9	77/1121 (6.9)	Referent	...	Referent	...
10–14	365/2398 (15.2)	2.4 (1.9–3.2)	< .001	2.4 (1.9–3.1)	< .001
15–19	458/1621 (28.3)	5.3 (4.1–6.9)	< .001	5.4 (4.2–7.0)	< .001
20–24	30/92 (32.6)	6.6 (4.0–10.8)	< .001	6.5 (4.0–10.7)	< .001
<b>Sex</b>					
Female	414/2625 (15.8)	Referent	...	Referent	...
Male	516/2609 (19.8)	1.3 (1.1–1.5)	< .001	1.4	< .001
<b>Body weight, kg</b>					
≤24	44/595 (7.4)	Referent	...	Referent	...
25–39	201/1751 (11.5)	1.6 (1.2–2.3)	.005	1.1 (.8–1.6)	.540
40–54	386/1874 (20.6)	3.2 (2.3–4.5)	< .001	1.5 (.97–2.2)	.071
55–69	261/877 (29.8)	5.3 (3.8–7.5)	< .001	1.9 (1.2–2.9)	.006
≥70	38/136 (27.9)	4.9 (3.0–7.9)	< .001	1.6 (.9–2.8)	.113
<b>Recent exposure (&lt;2 y) to a TB case<sup>a</sup></b>					
Yes	433/1430 (30.3)	2.9 (2.5–3.4)	< .001	2.0 (1.7–2.4)	< .001
No	497/3802 (13.1)	Referent	...	Referent	...
<b>Exposure setting in school</b>					
Classroom	146/578 (25.3)	Referent	...	Referent	...
Dormitory/hostel	168/497 (33.8)	1.5 (1.2–2.0)	.002	1.4 (1.1–1.9)	.010
Both dormitory/hostel & classroom	76/197 (38.6)	1.9 (1.3–2.6)	< .001	1.7 (1.2–2.4)	.005
Other unspecified setting	17/68 (25)	1.0 (.6–1.8)	.963	0.9 (.5–1.7)	.831
<b>Exposure to TB case at home<sup>b</sup></b>					
No	873/5078 (17.2)	Referent	< .001	Referent	< .001
Yes	57/156 (36.5)	2.8 (2.0–3.9)	...	2.3 (1.6–3.2)	...
<b>Multiple exposures</b>					
No history of exposure	498/3807 (13.1)	Referent	...	Referent	...
Contact with 1 case	216/871 (24.8)	2.2 (1.8–2.6)	< .001	1.7 (1.4–2.1)	< .001
Contact with ≥2 cases	216/556 (38.9)	4.2 (3.5–5.1)	< .001	2.7 (2.2–3.4)	< .001
<b>BCG vaccine status</b>					
No	46/214 (21.5)	Referent	...	Referent	...
Yes	880/5012 (17.6)	0.8 (.6–1.1)	.141	1.4 (.96–1.9)	.078

Abbreviations: BCG, Bacille Calmette-Guérin; CI, confidence interval; OR, odds ratio; TB, tuberculosis.

<sup>a</sup>Schoolchildren were considered to be exposed to *Mycobacterium tuberculosis* if they were sharing a classroom or residential quarters with another student at the time of the latter's TB diagnosis. Students diagnosed with lung or pleural TB were considered index TB cases.

<sup>b</sup>Exposure at home was identified in the schoolchildren by asking them during the screening process whether anyone in their family had TB while they were at home in the last 2 years. Exposure at home was assessed for children in sixth grade or higher.

boarding schools at an early age. We observed a higher risk (OR, 3.0;  $P = .002$ ) of TB disease among recently exposed schoolchildren. While 26% contacts were reported to have occurred within the school, the contact history in household (3%) in the previous 2 years for schoolchildren was also substantial and higher than the estimated global rate; a modeling study estimated that 15 million children had household TB exposure in 2010—that is, approximately 0.8% of the global child population [14]. Our findings of higher risk of infection in boarding schools (19%) than day schools (5%) and dormitories than classrooms (OR, 1.4;  $P = .01$ ) suggest that the living facilities, including their ventilation and time spent in them, play important roles in TB transmission and acquisition. The TB infection rate we

observed for schoolchildren aged 5–20 years (18%) was higher than the rate (11%) observed for children aged 5–20 years in rural China [15] and the estimated rate of 3.5% (67 million of 1.9 billion children) for children aged <15 years globally [14]. Among TST-positive schoolchildren, we were able to confirm established knowledge that those who are recently exposed have higher risk of disease progression compared with those not recently exposed (OR, 2.6;  $P = .006$ ) [16–18]. We observed high TST conversion (13%) for children recently exposed to TB, underscoring the need for regular screening. Although 95% of schoolchildren received BCG vaccine, the majority (~90%) received it at birth and are now older than 5 years; as such, false-positive TST reactions are less of a concern [19].

We ensured the community's acceptance of large-scale case finding and implementation of preventive therapy [20, 21] by sensitizing and mobilizing the community about the Zero TB Kids program months in advance through (1) news channels and newspapers regularly accessed by the community; (2) Zero TB Kids social media campaign; (3) advocacy and support by community leaders and care providers; and (4) engagement of community members in planning and making decisions. We ensured active involvement of school nurses, housemothers, and parents, the key care providers, by organizing a special meeting at each school between them, the school administrator, and the project staff to facilitate open discussions on ensuring adherence and improving care of children detected with active TB. The lower uptake of preventive therapy among staff (31%) compared to schoolchildren (86%) may have been due to the program's emphasis on children, as well as the older age and a lower perception of risk of staff and the absence of standard guidelines for treating older contacts of cases in global TB guidelines.

Despite a high prevalence of HBV infection, the rate of hepatotoxicity in our study population (1%) was similar to rates reported for other populations. Because 98% of the side effects were attributed to isoniazid, a preventive therapy regimen of 4 months of rifampicin or once-weekly isoniazid-rifapentine could improve acceptance and tolerance [22–27]. The majority of children with seizure disorder (88%) could not receive preventive therapy due to unclear guidelines and physician hesitancy in the context of drug–drug interactions with anti-epileptic agents. Our community-based approach ensured excellent adherence to preventive therapy (>98%), which has been low in most preventive therapy initiatives [20–22, 28].

TB preventive therapy is grossly underimplemented in high-burden countries. Globally, only 13% of children aged <5 years eligible for preventive therapy in 2016 received it, while in India, a mere 1.9% of eligible children aged <5 years received preventive therapy [2]. Global guidelines for TB preventive therapy did not exist for older children (aged >5 years), adolescents, and adults in high-burden countries until early 2018, despite a proven benefit across age groups [29–32]. TB control efforts and policies targeting children and adolescents will be essential to the achievement of the 90-90-90 targets of the Global Plan to End TB, as well as the WHO's End TB Strategy to end the global TB epidemic by 2035 [33]. New guidelines from the WHO issued in 2018 now clarify that household contacts of people with pulmonary TB should be offered preventive therapy [31]. Our initiative is the first of its kind to include population-level implementation of preventive therapy in a multipronged strategy to control and eliminate TB in an at-risk population in India. With this effort, we have demonstrated that TBI screening and preventive therapy can be successfully implemented on a large scale in high-TB-burden

settings and have identified important challenges in the process. This initiative also highlights the importance and feasibility of community mobilization in efforts to control TB in vulnerable populations, including children and refugees.

### Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyrighted and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

### Notes

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