ARTICLE

Risk of Active Tuberculosis Among Schoolchildren in Hong Kong

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Objective: To estimate the risk of active tuberculosis (TB) and its implication on preventive treatment among BCG-vaccinated schoolchildren.

Design: Cohort and case-control designs.

Setting: Community settings in a high-prevalence area.

Participants: Children in primary school. The main exposure was their tuberculin response.

Main Outcome Measures: Of 94 928 primary schoolchildren tuberculin tested during a routine school revaccination program in 1999, 656 with a tuberculin response at 20 mm or more were followed up prospectively through the territory-wide TB registry up to December 31, 2003, for the development of TB. In a separate case-control analysis, the tuberculin responses of children who subsequently had active TB (at the age of 10-15 years) were compared with those of their sex- and age-matched classmates to ascertain the relative risks of TB for different tuberculin reaction categories. The absolute and relative risks were applied to the 1999 cohort for estimating the incidence of TB among different tuberculin reactors.

Results: The annual incidence (95% confidence interval) of active TB was estimated to be 13.4 (5.6-40.6) per 100 000 for the entire cohort and 7.5 (2.4-24.5), 7.5 (1.7-32.0), 16.0 (4.4-57.2), 92.6 (26.6-320.2), and 340.6 (163.3-626.4) per 100 000 for children with a tuberculin reaction at 0 to 4, 5 to 9, 10 to 14, 15 to 19, and 20 mm or more, respectively. By using 10 mm as the cutoff, 482 (95% confidence interval, 163-1391) children have to be treated to prevent a single case of active TB within 5 years. Treatment will cover 17.5% of the cohort, but prevent only 54.1% of all active TB cases.

Conclusion: It is desirable to reexamine the existing screening method for BCG-vaccinated children from high-prevalence countries.

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TUBERCULIN SKIN TESTING has been used for a long time as a diagnostic test for latent tuberculosis (TB) infection. Tuberculin-positive children from high-prevalence countries are regularly given treatment for latent TB infection in the United States,[1] while such treatment is seldom recommended in the absence of other risk factors like recent contact or human immunodeficiency virus infection in their home countries. It would be desirable to quantify the actual risk of TB among these children, so that the appropriateness of the recommendation can be examined in light of better scientific evidence. While a prospective cohort might be the ideal approach to tackle this issue, the relatively low incidence of disease[2] among children poses a significant problem in relation to sample size and follow-up.

In many countries with a high prevalence of TB, neonatal BCG vaccination is regularly performed.[3] For the past 30 years, BCG (Glaxo strain) has been given to all newborns in Hong Kong, with a coverage rate of about 99%.[4] BCG revaccination was also practiced among primary schoolchildren (aged mainly from 6-12 years) until its cessation in 2000. All primary schools in Hong Kong were covered. The BCG team (a group of well-experienced inoculators) of the Tuberculosis and Chest Service used to visit each primary school once every 4 years in rotation to conduct tuberculin skin testing with 1 U of purified protein derivative (PPD) RT-23. Schoolchildren with a tuberculin reaction of 9 mm or less were of-

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fered revaccination. In general, treatment for latent TB infection was not offered. The revaccination program was stopped in 2000 on the advice of the local Advisory Committee on Immunization. A postcessation surveillance program was launched from January 1, 2001, to June 30, 2003, to record the BCG revaccination history of all TB patients aged 10 to 15 years on notification. With data available from these regular services, we engaged in a 2-part study, combining the benefits of cohort and case-control design, to quantify the risk of active TB among schoolchildren in Hong Kong.

METHODS

PART 1: COHORT STUDY

From the paper records of the School Revaccination Program, all schoolchildren with a tuberculin response at 20 mm or more in 1999 were retrieved, and cross matched with the computerized statutory TB notification registry in Hong Kong every 6 months until December 31, 2003, using name (in English), sex, and date of birth as identifiers. The medical and public health records of all identified TB cases were retrieved from relevant chest clinics or hospitals for verification of identity and confirmation of the diagnosis. An active case of TB was defined as disease proved by isolation of *Mycobacterium tuberculosis* or, in the absence of bacteriological confirmation, disease diagnosed on clinical, radiological, and/or histological grounds together with an appropriate response to treatment. The incidence of active TB was quantified, with the 95% confidence interval estimated by assuming a Poisson distribution in the occurrence of the cases.

PART 2: MATCHED CASE-CONTROL STUDY

The school BCG records of active TB patients aged 10 to 15 years, from January 1, 2001, to June 30, 2003, were retrieved together with those of their classmates. Each case was matched to 8 controls by class, sex, and age to control for the potential confounding effects of these variables, and to maximize the statistical power to detect any significant differences among multiple tuberculin reaction categories. All students who had not been tested with a tuberculin skin test during the school BCG revaccination were excluded. Univariate conditional logistic regression analysis was used because of the matched design to estimate the odds ratios for active TB among different tuberculin reaction categories.[5] A commercially available software program (SPSS version 10; SPSS Inc, Chicago, Ill) was used for analysis. $P<.05$ was considered statistically significant.

The odds ratios obtained in part 2 were multiplied to the absolute incidence derived for the strongest reactors in part 1 to obtain the annual risks of active TB for other tuberculin reaction categories. These were then applied to the 1999 cohort to estimate the numbers needed to treat to prevent a single case of active TB. For simplicity, only those active TB cases occurring within the first 5 years were considered, and the protective efficacy of treatment was assumed to be 100%.

The study has been approved by the Ethics Committee of the Department of Health of Hong Kong.

RESULTS

In 1999, a total of 94 928 primary school students were successfully tested for tuberculin response in the School Revaccination Program. The distribution of tuberculin skin test results is summarized in the **Figure**. Of those with a tuberculin test reaction of less than 10 mm, 99.7% were given a BCG revaccination. Of 662 students (0.7%) with a tuberculin reaction at 20 mm or more, 6 with missing data on date of birth were excluded, leaving 656 students for analysis. All except 6 (0.9%) were Chinese. Approximately 54% were females. The mean (SD) age was 9.80 (2.13) years. The mean (SD) duration of follow-up was 4.48 (0.26) years.

Up to December 31, 2003, 10 active TB patients (7 pulmonary, 1 extrapulmonary, and 2 combined) were identified. Four cases were confirmed by culture, including one with a positive sputum smear result. The diagnosis of the rest was verified by their clinicoradiological picture and subsequent response to treatment. There were 7 female and 3 male patients (Fisher exact test, 2-tailed; $P=.36$). The median age at disease onset was 12.5 (range, 9.5-13.6) years. The median interval from tuberculin skin testing to the development of disease was 286.5 (range, 20-1649) days. All of them had received a BCG vaccination at birth. Three reported a history of TB contact (2 household and 1 nonhousehold) within 5 years. All enjoyed good health in the past, except for one with Down syndrome. The incidence rate of active TB was 340.6 (95% confidence interval, 163.3-626.4) per 100 000 person-years among schoolchildren with a tuberculin reaction at 20 mm or more.

From January 1, 2001, to June 30, 2003, a total of 103 active TB patients aged 10 to 15 years were reported to the Department of Health. Fourteen had not met the school BCG team because of recent immigration or cessation of the School Revaccination Program. Five students missed the tuberculin skin testing because of parental refusal or absence from school, and the school BCG records of 1 student could not be retrieved, leaving 83 patients with complete tuberculin skin testing records (from December 8, 1992, to March 27, 2000) for analysis. The mean (SD) age of these 83 patients at notification of disease was 14.18 (1.54) years, and the mean (SD) interval from tuberculin skin testing to disease was 5.21 (2.00) years. All 83 patients (59 pulmonary, 20 extrapulmonary, and 4 both) were new cases. Only 16 (19.3%) were positive for TB by sputum smear result, and 30 (36.1%) were confirmed to have TB by culture result. The rest met the definition for active TB by their clinicoradiological picture and subsequent response to treatment. The neonatal BCG vaccination history was available for only 75 patients. Seventy-four reported BCG vaccination and 1 did not. BCG scars were checked in 76 patients, with 16 showing 0 scars, 45 showing 1 scar, and 15 showing 2 scars. Matching the 83 patients by class identified 2505 classmates in 79 different schools. Eighty-four students did not participate in the regular revaccination program, leaving 2421 with tuberculin skin testing results.

The proportions of males were 39.8% and 49.1% among patients and their classmates, respectively ($P=.10$). The mean (SD) age at tuberculin skin testing was 8.97 (1.88) years for patients and 8.90 (1.79) years for their classmates (unpaired t test, $P=.72$). The mean (SD) tuberculin test response was 9.64 (7.95) mm for patients and 4.09 (5.13) mm for their classmates (unpaired t test, $P<.001$). All students with a tuberculin response at 9 mm or less had been revaccinated.

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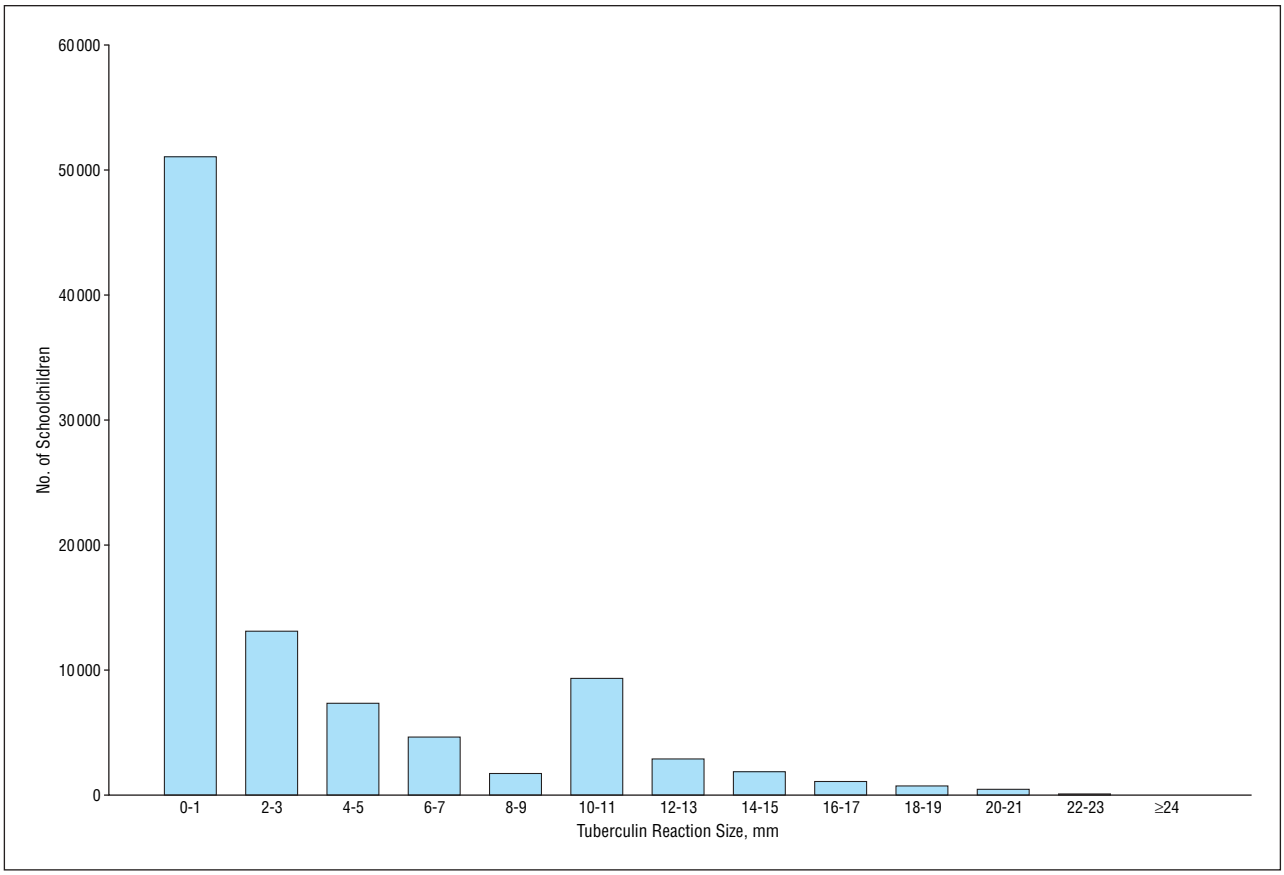

Figure. Distribution of tuberculin response among 94 928 children in primary schoolchildren in Hong Kong.

A total of 649 sex-, age-, and class-matched controls were successfully matched to the 83 patients in a ratio of 8:1, except for 4 patients in special classes (for whom 2, 4, 5, and 6 controls were matched, respectively). The selected controls differed significantly from those disease-free classmates not chosen as controls by sex (39.4% vs 52.6% males; χ^2 test, $P<.001$) and age (mean±SD, 9.05±1.95 vs 8.85±1.74 years; unpaired t test, $P=.02$), but there was no significant difference in their distribution of tuberculin response (χ^2 test, $P=.17$).

The cases and matched controls were comparable by sex (39.8% vs 39.4% males; χ^2 test, $P=.96$) and age (mean±SD, 8.97±1.88 vs 9.05±1.95 years; paired t test, $P=.75$). The distribution of tuberculin responses between cases and controls is summarized in **Table 1**. **Table 2** shows the results of univariate conditional logistic regression analysis of the tuberculin responses for all identified active TB cases and their controls. Similar results were obtained when analysis was restricted to the 30 culture-confirmed cases and their matched controls.

On applying the incidence rate derived in part 1 and the odds ratios of Table 2 to the 94 928 primary schoolchildren tuberculin tested in 1999, the respective incidences of active TB among different tuberculin reactors are summarized in **Table 3**. **Table 4** lists the proportions of the student population to be covered and the number of active TB cases preventable within 5 years by using different cutoffs, based on the estimations shown in Table 3.

Table 1. Comparison of Tuberculin Responses Between Active TB Patients and Their Sex-, Age-, and Class-Matched Controls During the School BCG Revaccination Program*

Tuberculin Reaction, mm	Patients (n = 83)	Classmates (n = 649)
0-4	33 (39.8)	454 (70.0)
5-9	5 (6.0)	64 (9.9)
10-14	13 (15.7)	94 (14.5)
15-19	18 (21.7)	30 (4.6)
≥20	14 (16.9)	7 (1.1)

Abbreviation: TB, tuberculosis.
*Data are given as number (percentage) of each group. $P<.001$ (χ^2 test) for the difference between groups.

COMMENT

In this study, tuberculin reaction size was a strong predictor of active TB. The overall pattern was similar to the J-shaped pattern reported in northern Malawi, apart from the absence of a definite trough among those with low-grade sensitivity.[6] The risk started to increase for the 10- to 14-mm group, and increased sharply for a reaction size of 15 mm or more, supporting previous studies[7] that the latter is more indicative of infection among subjects with a previous BCG vaccination. By using 10 mm as the cutoff, 482 children have to be treated to prevent a single case of active TB within 5 years (Table 4). Treatment will

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Table 2. Effect of Tuberculin Responses on Relative Odds of Active TB in Univariate Conditional Logistic Regression Analysis*

Tuberculin Reaction Category, mm	Odds Ratio (95% Confidence Interval)
0-4	0.022 (0.007-0.072)
5-9	0.022 (0.005-0.094)
10-14	0.047 (0.013-0.168)
15-19	0.272 (0.078-0.940)
≥20	1.000

Abbreviation: TB, tuberculosis.
*The case-control ratio was 1:8; cases and controls were matched for sex, age, and class (83 classes in total). The model coefficients were as follows: –2 log likelihood = 280.49 and χ^2 = 117.24 (P<.001).

Table 3. Estimated Incidence of Active TB Among Children in Primary School Tested With Tuberculin Skin Test in 1999

Tuberculin Reaction, mm	No. (%) of Schoolchildren	Active TB Rate per 100 000 Person-Years*	No. (%) of Cases per Year†
0-4	68 099 (71.7)	7.5 (2.4-24.5)	5.1 (39.8)
5-9	10 195 (10.7)	7.5 (1.7-32.0)	0.8 (6.2)
10-14	13 250 (14.0)	16.0 (4.4-57.2)	2.1 (16.4)
15-19	2722 (2.9)	92.6 (26.6-320.2)	2.5 (19.5)
≥20	662 (0.7)	340.6 (163.3-626.4)	2.3 (18.0)
Overall	94 928 (100.0)	13.4 (5.6-40.6)	12.8 (100.0)

Abbreviation: TB, tuberculosis.
*The 95% confidence intervals are given in parentheses, and those for tuberculin reaction categories other than 20 mm or more were estimated by keeping the TB incidence for the latter at the mean level.
†Individual percentages may not total 100 because of rounding.

Table 4. Effect of Using Different Cutoffs in Tuberculin Skin Testing on Proportions of Schoolchildren Eligible for Treatment of Latent TB Infection and Potential TB Cases Preventable Within 5 Years

Cutoff, mm	No. (%) of Schoolchildren Eligible	No. (%) of TB Cases Prevented in 5 y*	No. of Children Needed to Treat to Prevent 1 Case†
≥0	94 928 (100.0)	63.8 (100.0)	1487 (469-4533)
≥5	26 829 (28.3)	38.3 (60.0)	700 (226-2092)
≥10	16 634 (17.5)	34.5 (54.1)	482 (163-1391)
≥15	3384 (3.6)	23.9 (37.5)	141 (53-375)
≥20	662 (0.7)	11.3 (17.7)	59 (32-122)

Abbreviation: TB, tuberculosis.
*Assuming 100% efficacy of treatment of latent TB infection.
†Data in parentheses are 95% confidence intervals.

cover 17.5% of the cohort, but prevent only 54.1% of all active TB cases. If the cutoff is increased to 15 mm, only 141 children need treatment to prevent a case of active TB. Only 3.6% of children will be subjected to treatment, but an additional 16.6% of cases will be missed.

Among schoolchildren incidentally found to have a tuberculin reaction at 20 mm or more, the annual incidence of active TB was as high as 341 per 100 000. However, their risk of disease falls far short of the figure of 12.9% within the first year,[8] and 1.6% per year from the second year to the seventh year[1] for unvaccinated tuberculin-positive TB contacts. Among those children with a tuberculin reaction between 15 and 19 mm, the risk was 92.6 per 100 000, which was comparable with the figure of 90.4 per 100 000 reported among similar vaccinated children in Singapore.[9] Such risk is just a quarter of those with a tuberculin reaction at 20 mm or more. Because most of both groups were likely to have been infected, more recent infection might have contributed to the greater risk among those with the strongest tuberculin reaction.

Children from birth to the age of 14 years have a lower risk of active TB compared with those at other ages.[2] In 2001, the TB notification rates were 5.4, 3.5, 13.5, and 52.5 per 100 000 for those aged 0 to 4, 5 to 9, 10 to 14, and 15 to 19 years, respectively. A question naturally arises whether tuberculin-positive children at the mean age of 9 years may have a higher risk of developing active TB in the late teens. However, the risk of developing disease has been reported to decrease substantially with the passage of time after infection.[8] In high-prevalence areas, substantial ongoing transmission is expected, and the protective effect of isoniazid treatment has been well reported to decrease with time, at least among human immunodeficiency virus–infected subjects.[10,11] Among a cohort of tuberculin reactors (aged 1-18 years) detected during a BCG trial from 1949 to 1951, the annual risk of developing active TB (averaged over 20 years) was also lowest among those aged 7 to 12 years at recruitment.[12] Even in low-prevalence areas, 55% of immigrants with TB had the condition diagnosed within the first 5 years of arrival.[13] Considering the less than 100% protective efficacy of the recommended treatment, compounded by often poor adherence and sometimes isoniazid resistance, in field conditions,[14,15] the numbers needed to treat to prevent an active TB case are unlikely to deviate excessively from those previously estimated.

One unit of PPD RT23 was used in this study, not the 5 U of PPD standard commonly used in the United States. Stronger reactions might be expected if 2 U of PPD RT23 (the equivalent of 5 U of PPD standard[16,17]) were used. This would increase the percentage of children to be covered with each cutoff, and the number of children to be treated to prevent a single case of active TB. Because children with a tuberculin reaction at 10 mm or more were not revaccinated, BCG revaccination would not confound the results for any cutoffs more than 9 mm, even if there was any protective effect.

Undernotification is always a point of concern for all notifiable diseases.[18] In a local audit of TB notifications by reviewing discharge codes, microbiological reports, or hospital reports in 1995, the undernotification rates were 3.0%, 27.6%, and 31.4% for chest clinics, chest hospitals, and general hospitals, respectively.[19] After a series of improvement measures, notifications from sources other than chest clinics increased drastically,[20] in line with what was previously observed in 2 London, England, hospitals.[21,22] With incomplete notification, some degree of underestimation is likely, but it would be expected to affect all tuberculin reactor categories. Because tuberculin test-

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ing was done during primary school age, the bulk of the 1999 cohort should be in the age range of 10 to 14 years from the time of tuberculin testing to the end of 2003. The estimated incidence of active TB for the study cohort was 13.4 per 100 000 person-years (Table 3), while the reported incidences from the territory-wide TB notification registry were 13.5, 8.5, and 10.3 per 100 000 person-years for children aged 10 to 14 years in 2001,[2] 2002,[23] and 2003,[24] respectively. Even if we apply the relative risks derived from part 2 directly to the notification figures for the same years, there will not be any substantial changes in the various estimates in Table 3 and 4.

Considering the sharp contrast in disease risk between those with a tuberculin reaction of less than 15 mm and those with a reaction of 15 mm or more (Table 2), it might be worthwhile to reexamine the existing tuberculin test screening criterion in children with clear documentation of BCG vaccination, at least outside the contact settings. A tuberculin reaction is known to wane rapidly after neonatal BCG vaccination.[25,26] However, in a study[27] on 2588 randomly selected Saudi children, while the tuberculin-positive rate was not significantly different between vaccinated and unvaccinated children at the age of 5 years, the tuberculin sensitivity increased more steeply with age in the BCG-vaccinated than in the unvaccinated children, so that the difference between the 2 groups became statistically significant in those aged 12 and 13 years. Because booster phenomenon is also well reported in BCG-vaccinated children,[28] the possibility of interaction with ongoing environmental antigenic stimulation cannot be completely excluded. An interferon γ assay measuring the production of interferon γ in T lymphocytes on stimulation with PPD is not expected to differentiate false-positive cross-reactors from those with genuine infection.[29] However, a modified version of that test using ESAT-6 and CFP-10, antigens not present in BCG, has recently been reported to show a high degree of sensitivity and specificity for culture-confirmed TB, which is unaffected by previous BCG vaccination.[30,31] The modified test also showed a better correlation with the degree of exposure than the tuberculin test in a mass contact screening exercise.[32] It is conceivable that an adapted version of the test may help to sort out the truly infected children among BCG-vaccinated immigrants from high-prevalence areas. More systematic studies are, therefore, warranted in this direction.

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