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Tuberculin reactivity in adults after 50 years of universal bacille Calmette—Guérin vaccination in Taiwan

Y.P. Yeh[a], D.L. Luh[b], S.H. Chang[c], J. Suo[d], H.J. Chang[e], T.H.H. Chen[f,*]

[a] *Taichung County Health Bureau, Taichung, Taiwan*
[b] *Department of Public Health, Chung Shan Medical University, Taichung, Taiwan*
[c] *Graduate Institute of Epidemiology, College of Public Health, National Taiwan University, Taipei, Taiwan*
[d] *Departments of Internal Medicine and Health, TaoYuan General Hospital, TaoYuan, Taiwan*
[e] *Bureau of National Health Insurance, Taipei, Taiwan*
[f] *Institute of Preventive Medicine, College of Public Health, National Taiwan University, Room 207, No. 19 HsuChow Road, Taipei, Taiwan*

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Summary We aimed to assess whether tuberculin reactivity in adults is affected by bacille Calmette—Guérin (BCG) vaccination after 50 years of universal BCG vaccination with 80—95% coverage. A community-based study on tuberculin reactivity in 619 participants was conducted in February 2000 in Keelung city, Taiwan. Information on BCG vaccination policies and annual risk of infection (ARI) in the underlying population was extracted from consecutive national prevalence surveys relating to the period 1952—1997. Compared with the expected ARI estimate, the standardized morbidity ratio of positive tuberculin response for vaccination in infancy was 2.2 (95% CI 0.3—15.5) for those aged <10 years. The corresponding figures for older age groups ranged from 3.6 (95% CI 2.2—5.9) for those aged 10—12 years to 0.7 (95% CI 0.5—0.9) for those aged 57—67 years. This suggests that the effect of BCG vaccination on positive tuberculin response in adults aged >30 years is probably negligible irrespective of age at vaccination or revaccination and that the tuberculin skin test can be used to diagnose TB in control programmes in countries with moderate or high incidence of TB.

1. Introduction

Routine bacille Calmette—Guérin (BCG) vaccination against tuberculosis (TB) infection has been public

* Corresponding author. Tel.: +886 2 2358 7620; fax: +886 2 2358 7707.
E-mail address: stony@episerv.cph.ntu.edu.tw (T.H.H. Chen).

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policy in Taiwan for the past 50 years, with a high coverage rate of 80—95% (Suo and Hwang, 1998; Taiwan Provincial Tuberculosis Control Bureau, 1981). Despite this, TB incidence in Taiwan, particularly in adults, is still at least six times higher than in developed countries (Centers for Disease Control and Prevention, 2001; Taiwan Provincial Chronic Disease Control Bureau, 2001).

This finding has two implications. First, the high incidence in adults aged 25—44 years suggests that reactivation of subclinical TB infection is unlikely to be the sole explanation (Alland et al., 1994; Barnes et al., 1997; Borgdorff et al., 2001; Braden et al., 1997; Small et al., 1994; Vynnycky and Fine, 1997). Second, TB infection as measured by the tuberculin skin test (TST) is not only confounded by BCG vaccination, but is also largely dependent on age and other risk factors associated with the local prevalence of TB (American Thoracic Society/Centers for Disease Control and Prevention, 2000; Centers for Disease Control and Prevention, 1998; Comstock et al., 1971; Ildirim et al., 1995; Menzies and Vissandjee, 1992; Menzies et al., 1992; Moreno et al., 2001; Sepulveda et al., 1990, 1995). For those with a higher degree of exposure to TB in areas with high prevalence rates, the risk of infection may outweigh the false positivity caused by BCG vaccination (American Thoracic Society/Centers for Disease Control and Prevention, 2000). Tuberculin reactivity after BCG vaccination for adults in western countries with a low prevalence of TB could therefore differ from that experienced in countries with moderate or high prevalence rates, such as Taiwan (American Thoracic Society/Centers for Disease Control and Prevention, 2000; Centers for Disease Control and Prevention, 1998).

The evaluation of tuberculin reactivity after BCG vaccination is complex and affected by factors such as vaccine dose and manufacturer (Menzies, 2000), age at vaccination (Chee et al., 2001; Menzies and Vissandjee, 1992), time between vaccination and tuberculin skin testing (Chee et al., 2001; Comstock et al., 1971; Menzies and Vissandjee, 1992; Menzies et al., 1992), booster vaccination of BCG (Ildirim et al., 1995; Sepulveda et al., 1990, 1995) and type of tuberculin (Rieder, 1999). Of these, age when vaccinated and time elapsed since vaccination have been investigated (Chee et al., 2001; Menzies and Vissandjee, 1992; Menzies, 2000). Most of the evidence from earlier studies relates to children and adolescents but rarely to adults older than 25—30 years, in particular those vaccinated after infancy (Chee et al., 2001; Comstock et al., 1971; Ildirim et al., 1995; Menzies, 2000; Menzies and Vissandjee, 1992; Menzies et al., 1992; Moreno et al., 2001; Sepulveda et al., 1990, 1995). The effect of BCG vaccination on TST reactions in adults remains unclear. The aim of this study was to determine the extent to which tuberculin reactivity is inflated by past BCG vaccination in adults in Taiwan.

2. Materials and methods

2.1. Study population and design

We conducted a community-based TST study in Malin and Yuri (two districts of Keelung city, located in the northernmost part of Taiwan) during February 2000. The annual TB incidence rate in both areas was 68.2 per 100 000 people in 1999, close to the national figures (Taiwan Provincial Chronic Disease Control Bureau, 2001).

A total of 734 subjects were selected randomly from the population registry and invited (by telephone and pamphlets) to undergo a TST. Written informed consent was obtained from all subjects before testing began. Ethical approval was obtained from the Health Bureau of Keelung city.

Two public health nurses were responsible for administering the TST which contained 1 tuberculin unit of purified protein derivative (PPD) of the RT23 strain (1 TU PPD RT23) and was given intradermally on the volar surface of the left forearm using the Mantoux method. BCG scars on the deltoid area of the left arm of each TST recipient were also inspected. Tuberculin indurations were measured 48—72 h after injection by the same nurses using the palpation method. All TST procedures followed the national guidelines issued by the Taiwan Provincial Chronic Disease Control Bureau (1999).

A close-structured questionnaire was also used to collect information on age, gender, residence, work place, BCG vaccination history and details of past exposure to TB.

2.2. BCG vaccination and cut-off point for positive tuberculin skin tests

Table 1 shows the BCG vaccination policies for children (including BCG vaccination in infancy and after infancy, repeated BCG vaccination [boosters] and modality of tuberculin screening) followed in Taiwan since the 1950s (Suo and Hwang, 1998; Taiwan Provincial Tuberculosis Control Bureau, 1981). Five vaccination groups were identified: non-vaccinated (age >67 years), school vaccination (37—67 years), old mixed vaccination (26—36 years), young mixed vaccination (10—25 years) and infancy vaccination (<10 years). The young and old mixed vaccination groups were vaccinated during

Table 1 Universal bacille Calmette–Guérin (BCG) vaccination policies in Taiwan according to birth cohorts

Vaccination history	Birth cohort (Age at entry to study [years])	BCG vaccination in infancy	Booster[a]	Screening for schoolchildren[b]		Percentage with BCG scar[c]
				Grade 1	Grade 6	
None	Pre-1933 (>67)	–	–	–	–	6.4
School vaccination	1933–1943 (57–67)	–	–	Universal[d]		17.8
	1944–1963 (37–56)	–	–	Universal	Universal	77.5
Old mixed vaccination	1964–1969 (31–36)	+	+	–	Selective[e]	95.6
	1970–1974 (26–30)	+	+	–	Selective[f]	100.0
Young mixed vaccination	1975–1987 (13–25)	+	–	Selective[e]	Selective[f]	100.0
	1988–1990 (10–12)	+	–	Selective[e]	–	100.0
Infancy vaccination	Post-1990 (<10)	+	–	–	–	96.3

[a] Repeated BCG vaccination for first-grade schoolchildren with no BCG scar.
[b] Tuberculin skin tests were used for screening tuberculosis infection in first and/or sixth grade schoolchildren and BCG vaccination given to those with negative reactions.
[c] Data from the study population.
[d] Aimed at all schoolchildren aged 4–17 years old.
[e] Aimed at children with no BCG scar.
[f] Aimed at children with no or one BCG scar.

infancy and given boosters when in grade 1 (approximately 6 years after infancy) or grade 6 (approximately 12 years after infancy).

Distributions of induration size were examined following the guidelines from the International Union Against Tuberculosis and Lung Disease (Bleiker et al., 1989). A positive TST response was defined as induration size >10 mm according to national guidelines (Taiwan Provincial Chronic Disease Control Bureau, 1999).

2.3. Historic data on annual risk of tuberculosis infection

The effect of BCG vaccination on tuberculin conversion is generally assessed by comparing tuberculin conversion rates in vaccinated and unvaccinated groups (Chee et al., 2001; Comstock et al., 1971; Ildirim et al., 1995; Menzies and Vissandjee, 1992; Menzies et al., 1992; Moreno et al., 2001; Sepulveda et al., 1990, 1995). Unfortunately, in countries with high BCG vaccination coverage and catch-up programmes, data on non-vaccinated adults are not often available. In order to represent the non-vaccinated group in our study, we used data from consecutive national tuberculin surveys (Suo and Hwang, 1998; Taiwan Provincial Chronic Disease Control Bureau, 2001; Taiwan Provincial Tuberculosis Control Bureau, 1981) to estimate the expected tuberculin conversion rate in the study population, i.e. the prevalence of natural TB infection. Each survey covered an approximately 10-year interval between the years 1952 to 1997, and included schoolchildren aged around 6 years who did not have a BCG scar.

The annual risk of infection (ARI) was first estimated from each of the consecutive national tuberculin surveys by assuming a constant infection rate from birth to age at survey (Cauthen et al., 1988). The ARIs in 1952, 1962, 1972, 1981, 1991 and 1997 were estimated to be 2.5% (95% CI 2.4–2.6%), 1.7% (95% CI 1.4–2.0%), 1.2% (95% CI 1.1–1.3%), 1.0% (95% CI 0.9–1.2%), 0.4% (95% CI 0.4–0.5%) and 0.4% (95% CI 0.3–0.5%) respectively (Du, 1952; Suo and Hwang, 1998; Taiwan Provincial Tuberculosis Control Bureau, 1981; Taiwan Provincial Chronic Disease Control Bureau, 2001). Since the ARI declined slowly, at a rate of 1–3% per year, we assumed the ARI estimate to be constant during each 10-year interval.

2.4. Statistical analysis

Using the above ARI estimates, the expected tuberculin conversion rates for individuals in the study

population were extrapolated using the following equation, with the age of 30 years used as an example: Expected $\text{rate}_{(\text{age } 0-30)} = 1-(1-\text{ARI}_{(\text{age } 0-1)}) \times (1-\text{ARI}_{(\text{age } 1-2)}) \times (1-\text{ARI}_{(\text{age } 2-3)}) \ldots \times (1-\text{ARI}_{(\text{age } 29-30)})$. The same equation was used for other age groups studied. The formula was developed by Styblo et al. (Cauthen et al., 1988) and is similar to the traditional Kaplan–Meier survival method (Collett, 1994).

Taking the expected tuberculin conversion rate as the reference for the non-vaccinated group, BCG effects were estimated as described above. An epidemiological measure, the standardized morbidity ratio (SMR), calculated as the ratio of observed tuberculin conversion rate (O) from the study subjects to the expected tuberculin conversion rate (E), was also calculated. This was to remove confounding with age and/or cohort effects, which reflect not only changing infection risks over time but also years of exposure to TB in the community. The time elapsed since BCG vaccination was taken into consideration for the different BCG vaccination groups, as it also correlated with age.

The time-dependent Cox proportional hazards regression model (Collett, 1994), which makes allowance for the interaction between age and time elapsed since BCG vaccination and their effect on positive TST response, was used to estimate the adjusted odds ratios (AOR): $h(t, Z(t)) = h_0(t) \times \exp(\gamma \times V \times g(t) + \beta Z)$ where $h(t, Z(t))$ is the tuberculin conversion rate at age t; $h_0(t)$ is the baseline hazard function; V is the BCG vaccination group classified according to vaccination policy (Table 1) and also represents time elapsed since BCG vaccination; $g(t)$ is the time function, represented by age t of the subject (age is also the proxy indicator for cumulative risk of TB infection of the subject which approximates to the unconfounded tuberculin reactivity of the BCG-vaccinated subjects); γ indicates risk of acquiring tuberculin reactivity among each BCG vaccination group after taking time elapsed since vaccination into account; and Z represents covariates like gender, residence, work place and possible exposure to TB.

All analyses were conducted using SAS release 8.01 (SAS Institute Inc., Cary, NC, USA).

3. Results

Of the 734 subjects involved, 619 (84.33%) completed the TST. The reasons for non-response included failure to return to have the skin test reading ($n = 105$), unknown BCG scar status ($n = 2$) and refusal to participate ($n = 8$). The distribution of all baseline characteristics except age was the same in non-responders ($n = 115$) and responders ($n = 619$). All P values were greater than 0.05. Around 44% and 24% of non-responders were in the infancy vaccination (<10 years) and school vaccination (37–67 years) groups respectively, compared with around 3% and 50% of the responders. The proportion with a BCG scar was more than 90% in all age groups since the 1964–1969 cohorts (Table 1). The gender and age distribution of the study population is shown in Table 2.

3.1. Distribution of induration size and positive tuberculin skin test response

Figure 1 shows the distribution of induration size by BCG vaccination history, with an anti-mode at 1–4 mm and mode at 10 mm or so, for all but the infancy vaccination group. The frequency of atypical mycobacterial cross-reactivity may be low. Figure 2 shows the positive TST response rates by age group using induration sizes of 5 mm, 10 mm, and 15 mm as cut-off points. The expected risk of natural TB infection was also plotted. The curve for the induration size larger than 15 mm is close to the ARI curve. This finding was in agreement with previous findings using TST size >15 mm as a practical cut-off point for a BCG-vaccinated population (Chee

Table 2 Age and gender distribution of Taiwanese study population by BCG vaccination history

Vaccination history	Age (years)	Males *n* (%)	Females *n* (%)	Total *n* (%)
None	>67	73 (11.8)	67 (10.8)	140 (22.6)
School	57–67	64 (10.3)	88 (14.2)	152 (24.6)
	37–56	76 (12.3)	93 (15.0)	169 (27.3)
Old mixed	31–36	19 (3.1)	26 (4.2)	45 (7.3)
	26–30	12 (1.9)	14 (2.3)	26 (4.2)
Young mixed	13–25	27 (4.4)	33 (5.3)	60 (9.7)
	10–12	2 (0.3)	9 (1.5)	11 (1.8)
Infant	<10	8 (1.3)	8 (1.3)	16 (2.6)
Total		281 (45.4)	338 (54.6)	619 (100)

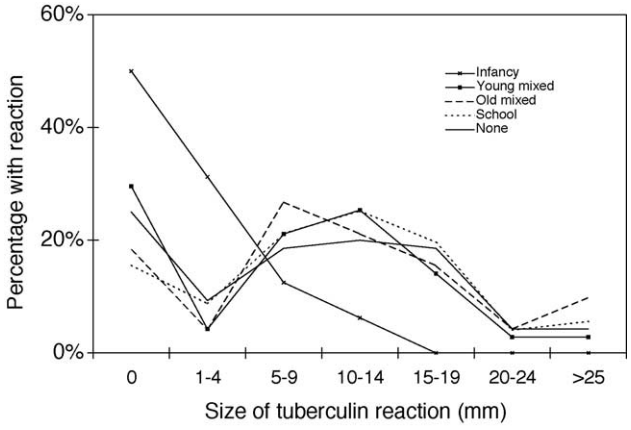

Figure 1 Distribution of tuberculin skin test reaction by BCG vaccination history. Age at entry to study: infancy vaccination group: <10 years; young mixed vaccination group: 10—25 years; old mixed vaccination group: 26—36 years; school vaccination group: 37—67 years; none (non-vaccinated group): >67 years.

et al., 2001); its curve is close to the ARI curve before the age of 40 years. The area between the 10 mm cut-off point and ARI curves represents positive TST responses possibly caused by BCG vaccination interference.

3.2. Positive tuberculin skin test response by vaccination group

The univariate analysis found that only gender and history of contact with non-familial TB cases were significant predictors of a positive TST response.

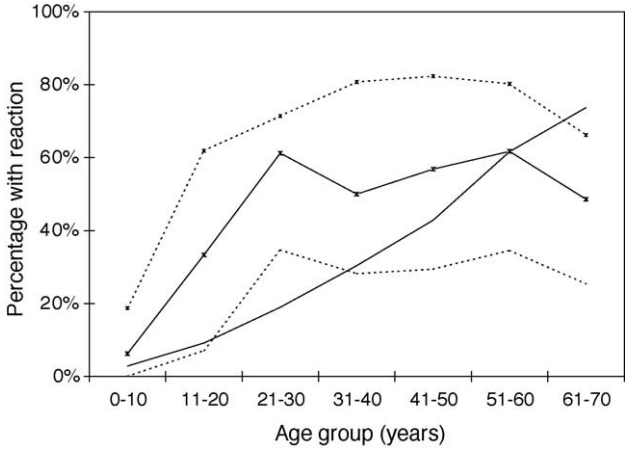

Figure 2 Tuberculin skin test reaction by age group using induration sizes of 5 mm (dashed line with stars), 10 mm (solid line with stars) and 15 mm (dashed line) as cut-off points vs. the expected risk of natural tuberculosis infection estimated from historic data on the annual risk of TB infection (solid line).

Table 3 Effect of bacille Calmette—Guérin (BCG) vaccination history on positive tuberculin response by standardized morbidity ratio and Cox proportional hazards regression model

Vaccination history	Age (years)	Positive TST[a] (%)	Standardized morbidity ratio (95% CI)[b]			Proportional hazards regression model	
			Without BCG scar	With BCG scar	Total	Adjusted odds ratio[c] (95% CI)[b]	*P*
School	57—67	48.0	0.6 (0.4—0.8)	0.9 (0.5—1.5)	0.7 (0.5—0.9)	1.0 (1.0—1.0)	<0.001
	37—56	60.4	1.4 (0.9—2.0)	1.3 (1.1—1.7)	1.4 (1.1—1.6)	1.1 (1.1—1.1)	<0.001
Old mixed	31—36	44.4	1.9 (0.3—13.5)	1.5 (1.0—2.4)	1.5 (1.0—2.4)	1.3 (1.2—1.3)	<0.001
	26—30	61.5		2.8 (1.7—4.5)	2.8 (1.7—4.5)	1.7 (1.0—2.7)	0.0351
Young mixed	13—25	50.0		3.7 (2.2—6.0)	3.7 (2.2—6.0)	2.4 (1.1—5.3)	0.0282
	10—12	18.2		3.6 (2.2—5.9)	3.6 (2.2—5.9)	4.7 (0.9—25.1)	0.0722
Infant	<10	6.3		2.3 (0.3—16.4)	2.2 (0.3—15.5)		
Male		63.0				1.4 (1.1—1.8)	0.0031
TB contact[d]		69.0				1.8 (1.1—2.8)	0.0168

[a] Positive tuberculin skin test (TST) defined as induration size ≥10 mm. Data from historic national TST surveys were used to derive expected risk of tuberculosis infection for each cohort.
[b] 95% confidence intervals of standardized morbidity ratios were derived by Taylor method (Sahai and Khurshid, 1996).
[c] Odds ratios were adjusted for age, gender, time since BCG vaccination and risk of tuberculosis infection.
[d] Contact with non-family members who were infected with tuberculosis.

Further analysis, by multiple logistic regression, identified both age and gender as major determinants for tuberculin reactivity. After adjusting for age and gender, other variables were not statistically significant (data not shown).

Table 3 shows the estimated SMRs of positive TST response by BCG vaccination history. The estimates of SMR decrease with age, particularly from the age of 30 years onwards. Similar findings were observed when the time-dependent Cox proportional hazards regression model was used. The AORs for the young mixed, old mixed and school vaccination groups decreased with age from 4.7 (95% CI 0.9—25.1) to 1.0 (95% CI 1.0—1.0) (Table 3). In addition, the model also found that being male and having contact with non-family members who were infected with TB had independent effects on tuberculin reactivity, with AORs up to 1.4 (95% CI 1.1—1.8) and 1.8 (95% CI 1.1—2.8) respectively.

4. Discussion

Tuberculin reactivity after BCG vaccination is always a difficult issue for health professionals involved in TB treatment and control in that BCG vaccination may confound the response of tuberculin reactivity. The present study is distinct from previous studies that focused on children, adolescents or young adults (Chee et al., 2001; Comstock et al., 1971; Ildirim et al., 1995; Menzies, 2000; Menzies and Vissandjee, 1992; Menzies et al., 1992; Moreno et al., 2001; Sepulveda et al., 1990, 1995) in that it includes all age groups.

Earlier studies found age at vaccination to be a major determinant of the waning of BCG interference (Chee et al., 2001; Menzies, 2000; Menzies and Vissandjee, 1992). For adults aged <20 years who received BCG vaccination in infancy, the confounding effect waned rapidly, becoming negligible within 10—15 years (Chee et al., 2001; Menzies, 2000; Menzies and Vissandjee, 1992). On the other hand, for those who received vaccination after infancy, the effect might wane more slowly and persist for longer (Menzies, 2000; Menzies and Vissandjee, 1992).

Our findings for younger subjects agree with this viewpoint. The highest SMRs and AORs were found in the young mixed groups aged 10—25 years (Table 3) who received BCG vaccination in infancy and were revaccinated 6 or 12 years later (Table 1). The higher AOR of 4.7 in the group aged 10—12 years who were revaccinated 6 years after infancy suggests that the positive TST response was strongly affected by the confounding effect of revaccination. The lower AOR of 2.4 in the group aged 13—25 years who were revaccinated 6 or 12 years after infancy suggests that the effect of BCG revaccination remained but had waned due to the longer time elapsed since vaccination.

For the old mixed and school vaccination groups who were aged 26—30 years or older and received vaccination at least 20 years ago, the positive TST response declined rapidly in the following years indicating that the effect of BCG vaccination on these groups, regardless of age at vaccination, may be minimal. This finding was consistent with the previous finding of Sepulveda et al. (1995) that there is a lack of correlation between BCG revaccination after infancy and tuberculin reactivity in subjects over 30 years of age.

These observations complement those of Menzies et al. (1992) and indicate that the potential role of the TST in TB control in countries with high prevalence rates for adults aged >30 years cannot be dismissed because of the potential interference of BCG vaccination. This point has been also addressed in a recent study in east Taiwan where the underlying population was at high risk for TB infection and also had high BCG vaccination coverage. The tuberculin reactivity was mainly due to either active or latent TB infection rather than past BCG vaccination. The study further suggested that high BCG vaccination coverage in this region does not seem to limit the usefulness of the tuberculin test (Bowerman, 2004). Our results coupled with this finding strongly support the policy that adults in Taiwan who are at risk of acquiring TB infection may need to receive routine tuberculin tests in appropriate clinical settings and community contact investigations in order to ascertain secondary cases of active or latent TB infection (American Thoracic Society/Centers for Disease Control and Prevention, 2000; Centers for Disease Control and Prevention, 1998).

To distinguish the effect of BCG vaccination from TB infection among subjects with a positive TST response, particularly for adolescents and adults in countries with a high TB prevalence rate, we assessed the effect of BCG by comparing the observed TST curve with the expected ARI. This approach not only takes age at vaccination into account but also time elapsed since BCG vaccination. In addition, both effects and their interaction were also considered by the use of the time-dependent Cox proportional hazards regression model.

A TST reaction size of >15 mm as a cut-off point for TST positivity has been suggested for older children who received BCG vaccination after infancy (Chee et al., 2001). Figure 2 shows that the 15 mm reaction curve is close to the ARI curve up to the

age of 40 years and that the disparity between the two curves increases after this age. This means that the >15 mm cut-off point would induce more false negative results and underestimate the tuberculin reactivity for those aged >40 years.

Our study has two limitations. Our results regarding the type of TST should be interpreted cautiously because our TST study was based on 1 TU PPD RT23 rather than 2 TU PPD RT23 or 5 TU PPD-S, both of which give similar positive TST responses. However, we believe the use of 1 TU PPD RT23 is unlikely to have much influence on the results because we compared the observed BCG-vaccinated TST in subjects with the expected tuberculin reactivity, which was estimated from historic national tuberculin surveys based on 1 TU PPD RT23 TST. In addition, Wang et al. (2002) found in a recent meta-analysis of the effect of BCG vaccination on TST that the relative risks for vaccinated and unvaccinated groups were identical: 2.65 (95% CI 1.83—3.85) for 2TU RT23 and 2.85 (95% CI 2.05—3.95) for 1TU RT23. Our findings in Table 3 were very similar.

In Figure 1, the differences between the TST results for those vaccinated in infancy and those vaccinated at an older age might be due to strong BCG interference in the infancy vaccination group. We did not use skin test antigen of atypical mycobacterium to distinguish between TB infection and atypical mycobacterium infection. However, as the distribution of tuberculin induration size in our study showed a clear anti-mode and mode, misclassification due to atypical mycobacterium infection is thought to be negligible.

In conclusion, we found that the effect of BCG vaccination on positive TST response for those who were vaccinated in infancy and revaccinated 6 or 12 years later was compatible with earlier findings with a higher number of positive TSTs in those aged up to 30 years. However, the effect of BCG vaccination on TST response in adults older than 30 years was negligible regardless of age at vaccination. This suggests that the TST can be used to diagnose TB in adults receiving remote BCG vaccination in areas or targeted groups with a high prevalence rate or risk of TB.

Conflicts of interest statement
The authors have no conflicts of interest concerning the work reported in this paper.

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