Influence of Bacille Calmette-Guérin Vaccination on Size of Tuberculin Skin Test Reaction: To What Size?

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Background. Previous bacillus Calmette-Guérin (BCG) vaccination can confound the results of a tuberculin skin test (TST). We sought to determine a cutoff diameter of TST induration beyond which the influence of BCG vaccination was negligible in evaluating potential *Mycobacterium tuberculosis* infection in a population of health care workers with a high vaccination rate and low incidence of tuberculosis.

Methods. From 1991 through 1998, all new employees at the University Hospital of Lausanne, Switzerland, underwent a 2-step TST at entry visit. We also gathered information on demographic characteristics, along with factors commonly associated with tuberculin positivity, including previous BCG vaccination, history of latent *M. tuberculosis* infection, and predictors for *M. tuberculosis* infection.

Results. Among the 5117 investigated subjects, we found that influence of BCG vaccination on TST results varied across categories of age (likelihood ratio test, 0.0001). Prior BCG vaccination had a strong influence on skin test results of ≤18 mm in diameter among persons <40 years old, compared with the influence of factors predictive of *M. tuberculosis* infection. Prior latent *M. tuberculosis* infection and travel or employment in a country in which tuberculosis is endemic also had significant influences.

Conclusions. Interpretation of TST reactions of ≤18 mm among BCG-vaccinated persons <40 years of age must be done with caution in areas with a low incidence of tuberculosis. In such a population, except for persons who have never been vaccinated, TST reactions of ≤18 mm are more likely to be the result of prior vaccination than infection and should not systematically lead to preventive treatment.

The tuberculin skin test (TST), introduced in 1910 by Mantoux, is one of the oldest diagnostic tests used in clinical medicine. It remains the only technique to identify latent *Mycobacterium tuberculosis* infection. However, the TST has various shortcomings, mainly because several factors others than latent *M. tuberculosis* infection can influence its positivity. Intersubject variability in biological response to tuberculin [1], interreader variability [1], the booster effect [2–4], immune response to nontuberculous mycobacterial antigens [3, 5, 6], and previous vaccination with bacillus Calmette-Guérin (BCG) can all be responsible for a positive TST result [5, 7–12]. BCG vaccination is the main problem in interpreting TST results, in particular in countries where the rate of vaccination is high and the prevalence of tuberculosis is low. One must be cautious in interpreting TST reactions because of the potential implications associated with a positive result, such as the need for chest radiography and 6- to 9-month preventive chemotherapy, the risk of treatment hepatotoxicity, and the anxiety generated in the patient. Whereas it is generally assumed that a TST reaction of ≥15 mm in diameter is due to *M. tuberculosis* infection [13–15], positive TST reactions of <15 mm are more difficult to interpret in countries in which the prevalence of tuberculosis is low and the rate of prior vaccination remains high despite discontinuation of mass immunization (as in Switzerland, for example). This problem is an everyday challenge in hospitals in which the TST is routinely performed when new health care workers are hired. It is therefore important to assess the influence of previous BCG vaccination on TST positivity. In our study, we tried to determine, according to the age of subjects, a cutoff for TST reaction size beyond which this influence was negligible.

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PATIENTS AND METHODS

Data collection. This was a prospective cohort study involving all new health care workers hired by the University Hospital of Lausanne, Switzerland, from January 1991 through March 1998. At the entry visit, information on new employees was obtained, including demographic data and data pertaining to the following characteristics (possibly related to tuberculin reactivity): country of origin, occupation, history of travel to a country with a high incidence of tuberculosis, history of employment in a hospital in a country with a high incidence of tuberculosis, history of occupational or household exposure to active tuberculosis, history of latent *M. tuberculosis* infection, receipt of prior TSTs, and previous BCG vaccination.

Countries of origin were categorized into those with low (<24 cases per 100,000 population per year), moderate (24–99 cases per 100,000 population per year), or high (≥100 cases per 100,000 population per year) incidence of tuberculosis, as reported by the 1997 report of the World Health Organization. Occupation status was determined according to whether the employee was in contact with patients. Latent *M. tuberculosis* infection was considered only for employees who demonstrated tuberculin conversion, underwent thorough evaluation of risk factors and chest radiography, and received preventive chemotherapy. Vaccination records were checked for vaccination status and number of previous TSTs received. If the record was unavailable, information regarding immunizations was extracted from the interview. Subjects were not screened for the presence of a BCG vaccination scar because of possible confusion with smallpox vaccination scars and because BCG vaccination does not elicit scars in up to 25% of people [16].

Employees for whom former BCG vaccination, treatment for latent *M. tuberculosis* infection, or tuberculosis exposure could not be determined were excluded from the analysis. History of treatment for active tuberculosis was also a criterion for exclusion.

TSTs. Also at the entry visit, a 2-step TST by the Mantoux method was done. Subjects were injected intradermally with 0.1 mL of tuberculin (2 U of RT 23; Berna) on the forearm. In the absence of a white papule confirming the intradermal injection, the test was repeated immediately on the opposite forearm. Trained nurses of the Unit of Occupational Health measured the transverse diameter of induration at 48–72 h after administration and sought medical advice in cases in which the results were doubtful. Reactions were determined by measuring transverse diameter of induration. Induration of ≥10 mm in diameter was considered a positive result.

Subjects with a negative reaction were administered a second TST on the contralateral forearm 8–15 days after the first test. Induration was again measured 48–72 h after administration.

Some health care workers were not retested for the following reasons: if they had already gone through a 2-step testing with no evidence of a booster effect, if they had never been vaccinated with BCG, or if they had been tested <1 year before the current test.

Statistical analysis. We compared employees who had a positive TST result with those who had a negative TST result at the following induration diameter cutoff values: 10 mm, 15 mm, 18 mm, and 20 mm . We used the 2-sided Wilcoxon rank sum test for continuous variables and the χ^2 test for proportions. The significance level was .05 for all tests. Significant univariate predictors of a positive test result were then candidates for inclusion in a logistic regression model that was built through a forward selection process. BCG vaccination status was always forced in the model. Each of the excluded covariates was then tested for possible confounding. The Wald test was used to report the significance level of the predictors in the final model.

To investigate whether BCG vaccination had different effects on the result of TST across different age categories, we created an interaction term with age (categorized as <30, 30–39, and ≥40 years old) and BCG vaccination. The likelihood ratio test was used to assess the significance of this interaction term. In case of significant interaction, a separate regression model of predictors of TST result was built for each category of age. These models were made homogenous by including every covariate that was found significant in ≥1 of the categories of age. Statistical analyses were done with Stata 6.0 statistical software (Stata).

RESULTS

Study population. Of 6721 eligible new health care workers, 433 were not included because they refused the test or did not show up for evaluation, and 1171 were excluded because of insufficient data. Thus, the study population comprised 5117 subjects. The only meaningful difference between excluded and included employees was in terms of origin from a country with a low to moderate incidence of tuberculosis (75% in the excluded population vs. 91% in the included population). Among the 5117 health care workers included in the study, 2764 (54%) received a second TST. The characteristics of the population are listed in table 1. Ages ranged from 14 to 63 years.

BCG vaccination status was extracted from medical records for 4758 persons (93%) and from interview for 359 (7%), the latter representing 9.7% of the unvaccinated group and 6.7% of the vaccinated group.

TST results. Of 5117 health care workers, 2037 (40%) had a TST reaction of ≥10 mm in diameter on the first test. In addition, among the 2764 subjects given a second test, 400 had positive results on retesting. These employees were representative of all age groups. Thus, 2437 health care workers overall

Table 1. Characteristics of study population of health care workers and univariate predictors for a positive tuberculin skin test (TST) result.

Variable	No. (%) of subjects (n = 5117)	Percentage of subjects with TST reaction of ⩾10 mm (n = 2437)	P
Sex			
Male	1631 (32)	52	<.001
Female	3486 (68)	45	
Incidence of tuberculosis in country of origin[a]			
Low	4617 (90)	44	
Moderate to high	495 (10)	53	.004
Occupation[b]			
Contact with patients	3650 (71)	47	.606
No contact	1463 (29)	49	
History of travel to country with high incidence of tuberculosis			
Yes	493 (10)	57	<.001
No	4624 (90)	46	
History of work in country with high incidence of tuberculosis			
Yes	114 (2)	66	<.001
No	5003 (98)	47	
History of tuberculosis contact[c]			<.001
Occupational contact only	1050 (20)	55	
Household contact only	167 (3)	56	
Occupational and household contact	56 (1)	54	
None	3844 (76)	45	
History of latent *Mycobacterium tuberculosis* infection			
Yes	65 (1)	71	<.001
No	5052 (99)	47	
History or record of BCG vaccination			
Yes	4664 (91)	51	<.001
No	453 (9)	12	
Prior documented TSTs			.027
0	1224 (24)	43	
1–4	2705 (53)	46	
⩾5	1188 (23)	54	
Age, years[c]			<.001
<30	2833 (55)	41	
30–39	1486 (29)	55	
⩾40	798 (16)	54	

NOTE. BCG, bacille Calmette-Guérin; low incidence of tuberculosis, <24 cases per 100,000 population per year; moderate incidence, 24–99 cases per 100,000 population per year; high incidence, ⩾100 cases per 100,000 population per year.

[a] n = 5112.
[b] n = 5113.
[c] n = 5117.

(48%) had a positive TST result. Univariate predictors of a positive TST result were male sex, origin from a country with moderate to high incidence of tuberculosis, travel to a country with a moderate or high incidence of tuberculosis, work in a hospital in a country with a moderate or high incidence of tuberculosis, history of tuberculosis contact, history of latent *M. tuberculosis* infection, prior BCG vaccination, prior TSTs, and older age (table 1).

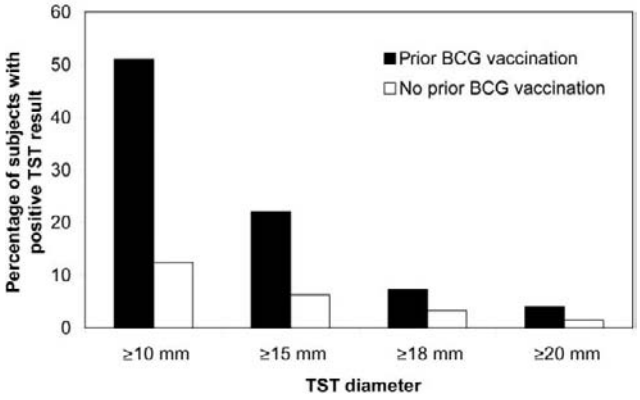

Figure 1. Comparison of tuberculin skin test (TST) reactivity among bacille Calmette-Guérin (BCG)–vaccinated ($n = 1146$) and nonvaccinated ($n = 228$) health care workers, by diameter of TST reaction.

There was a very clear effect of prior BCG vaccination on TST results: 51% of vaccinated subjects had positive TST results, compared with only 12% of unvaccinated employees (table 1). The influence of vaccination status on TST diameter was also statistically significant at the 3 larger cutoff diameters (⩾15 mm, ⩾18 mm, and ⩾20 mm) in univariate analysis (figure 1).

In multivariate analysis, we found that the influence of prior BCG vaccination on TST result varied significantly across age categories ($P = .0001$) (table 2 and figure 2). Up to 40 years of age, vaccination was the strongest predictor of a positive TST result at cutoffs of 10 mm (adjusted OR, 15.0 for employees <30 years old and 12.4 for employees 30–39 years old) and 15 mm (adjusted OR, 9.2 and 12.2, respectively), and was still an independent predictor at a diameter of 18 mm (adjusted OR, 4.5 for employees <30 years old and 9.7 for employees 30–39 years old). Other significant factors were origin from a country with a moderate to high incidence of tuberculosis, a history of tuberculosis contact, a history of latent *M. tuberculosis* infection, and a high number (⩾5) of prior TSTs.

Among subjects ⩾40 years old, prior vaccination was no longer associated with a positive TST result except at a cutoff of 10 mm in diameter (adjusted OR, 2.4). For that age category, only a history of *M. tuberculosis* infection and origin from a country with moderate to high incidence of tuberculosis were statistically associated with a positive TST result at greater cutoff values (figure 2).

Only 193 subjects (4%) had a TST reaction of ⩾20 mm in diameter. The influence of prior BCG vaccination was no longer significant at this cutoff point, but adjusted ORs for age groups <30 years old (adjusted OR, 3.4) and 30–39 years old (adjusted OR, 4.9) were still high (table 2). For TST reactions of this diameter, only latent *M. tuberculosis* infection, tuberculosis contact, and origin from a country with a moderate to high incidence of tuberculosis were statistically significant predictors of tuberculin reactivity.

DISCUSSION

The effect of prior BCG vaccination on tuberculin reactivity has been known for a long time [5–11]. However, some recent studies tend to minimize this effect [15, 17–19]. In a study involving schoolchildren in Singapore, Chee et al. [18] found that, among those who had been vaccinated once at birth, induration of 10 mm in diameter was the most sensitive and specific cutoff value for predicting the development of tuberculosis. Induration of 16 mm in diameter was more predictive for teenagers who had been revaccinated than for those who had been vaccinated only once. Among contacts of patients with tuberculosis in The Gambia, the size of the TST reaction was related to the duration and proximity of contact but was not influenced by the presence of a BCG scar [19]. A meta-analysis by Wang et al. [15], including 26 studies published from 1966 through 1999 (but only 4 studies with discrete data for measurement of TST reactions), concluded that a positive reaction of ⩾15 mm in diameter was more likely to be caused by *M. tuberculosis* infection than by previous BCG vaccination.

According to Centers for Disease Control and Prevention (CDC) guidelines, BCG immunization status should not be taken into account in the decision to treat latent *M. tuberculosis* infection [14]. The guidelines also recommend that a TST re-

Table 2. Adjusted ORs for a positive tuberculin skin test (TST) result at different cutoff points according to bacille Calmette-Guérin (BCG) vaccination.

	Age, years		
TST reaction diameter	<30 ($n = 2833$)	30–39 ($n = 1486$)	⩾40 ($n = 798$)
⩾10 mm[a]	15.0[b] (8.5–26.3)	12.4[b] (6.3–24.5)	2.4[b] (1.4–3.9)
⩾15 mm[c]	9.2[b] (4.1–20.9)	12.2[b] (3.8–39.3)	1.2 (0.7–2.2)
⩾18 mm[d]	4.5[b] (1.4–14.3)	9.7[b] (1.3–71.1)	0.8 (0.4–1.6)
⩾20 mm[e]	3.4 (0.8–14.1)	4.9 (0.7–36.4)	1.2 (0.4–3.6)

NOTE. Data are OR (95% CI).

[a] Adjusted OR for tuberculosis contact, work in a country in which tuberculosis is endemic, age, latent *Mycobacterium tuberculosis* infection, and occupation involving contact with patients ($n = 2437$).

[b] $P < .05$.

[c] Adjusted OR for occupation involving contact with patients, tuberculosis contact, and age ($n = 1060$).

[d] Adjusted OR for occupation involving contact with patients, tuberculosis contact, age, latent *M. tuberculosis* infection, and sex ($n = 350$). Among subjects <30 years old, no unvaccinated subject had a positive test result of ⩾18 mm in diameter. Therefore, BCG vaccination is a perfect predictor and a multivariate model including it is not possible.

[e] Adjusted OR for travel to country in which tuberculosis is endemic, sex, age, and latent *M. tuberculosis* infection ($n = 193$). Among subjects <30 years old, no unvaccinated subject had a positive test result of ⩾20 mm in diameter. Therefore, BCG vaccination is a perfect predictor and a multivariate model including it is not possible.

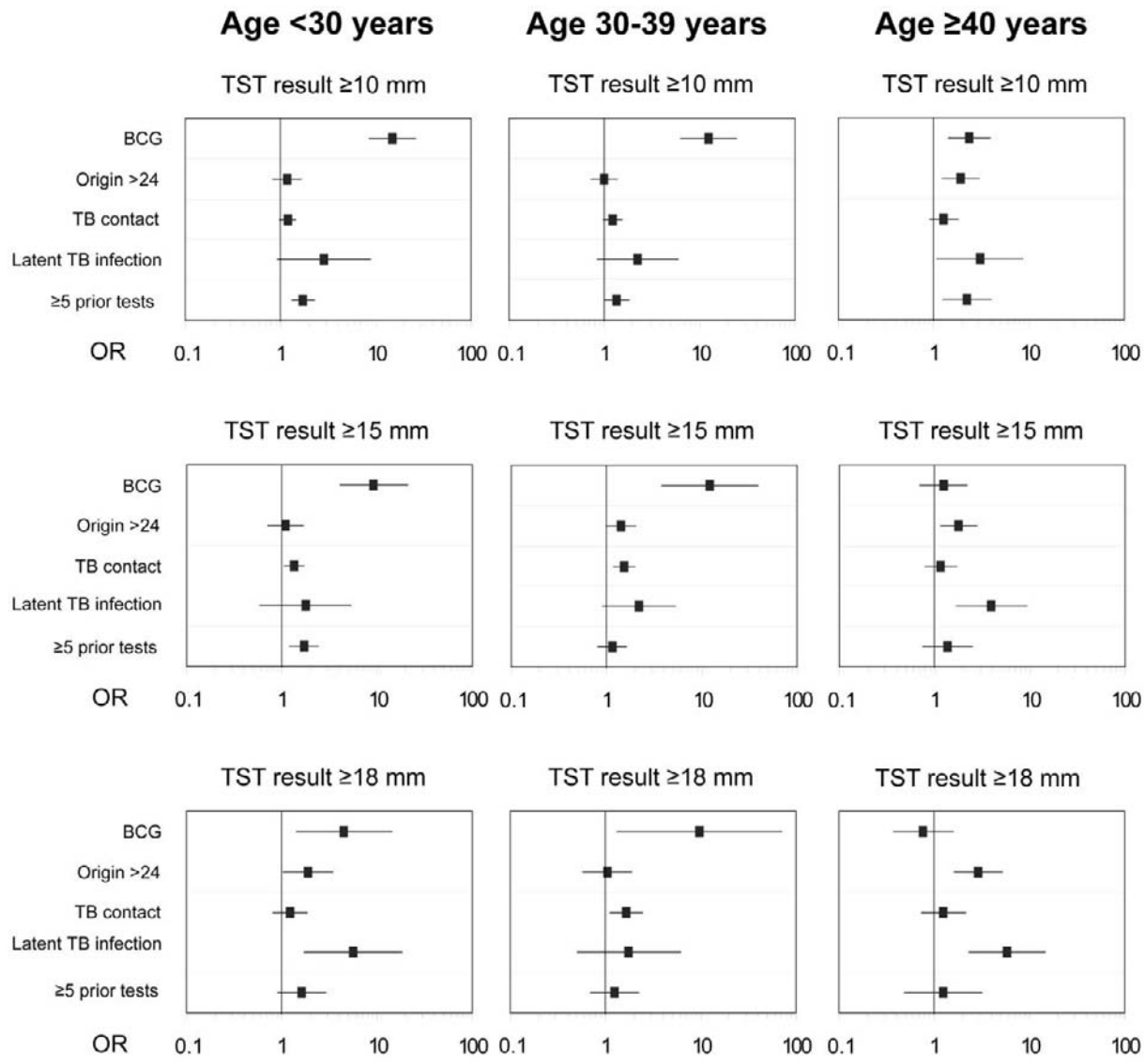

Figure 2. Multivariate predictors for a positive tuberculin skin test (TST) result at different cutoff diameters according to age (only significant predictors are shown). BCG, bacille Calmette-Guérin; origin >24, origin from a country with moderate to high incidence of tuberculosis (i.e., >24 cases per 100,000 population per year); TB, tuberculosis or *Mycobacterium tuberculosis*. *Bars,* 95% CIs.

action of ⩾15 mm in diameter should be considered diagnostic of latent *M. tuberculosis* infection among persons at low risk for tuberculosis.

In our study population, we found that 2437 (48%) of the subjects had a TST reaction of ⩾10 mm in diameter, and 1060 (21%) had a TST reaction of ⩾15 mm in diameter. All of the individuals in the latter group should have received preventive therapy according to the CDC guidelines. The usual predictors for *M. tuberculosis* infection, such as origin from a country with a moderate to high incidence of tuberculosis, a history of tuberculosis contact, and a history of latent *M. tuberculosis* infection, were all significant at some point, although inconsistently across categories of age and TST reaction size (figure 2). Some of the positive reactions may indeed have been caused by actual *M. tuberculosis* infection. However, considering the rarity of documented prior *M. tuberculosis* infection in our study population (found in 65 of 5117 subjects), it seems very unlikely that such a proportion of health care workers had all been infected. These findings raise doubts concerning latent infection with *M. tuberculosis* being the cause of tuberculin positivity in our study population. Therefore, we assume that these results are likely to be due to factors other than *M. tuberculosis* infection—the primary factor being BCG vaccination.

As is the case for all studies of this subject, an important limitation in our study was the frequent lack of official documents regarding BCG immunization status for employees

coming from countries where there is a high prevalence of tuberculosis. For those persons, we had to rely exclusively on employees' recall of having been vaccinated, thereby raising the problem of misclassification of vaccination status. Because only 7% of employees did not have medical records, we think that this was not a significant source of error. However, we must assume that a certain number of persons who claimed never to have been vaccinated did unknowingly receive BCG immunization in their childhood, thus minimizing the effect of vaccination on TST results in our study.

Another limitation was the lack of 2-step testing for employees who had never been vaccinated. This may have accentuated the difference between the vaccinated and unvaccinated groups, because only the BCG-vaccinated group gained additional positive TST results on retesting. However, we think that this bias minimized, rather than increased, the influence of BCG on TST results, because misclassified BCG recipients would have been most likely to have positive results on repeat testing, as we suggested above.

Our study showed a significant difference in the rate of positive reactions among BCG recipients and nonrecipients, even for reactions of ⩾15 mm and ⩾18 mm in diameter (figure 1). We found that this influence of BCG vaccination varied with age. Vaccination was a very important predictive factor for TST reactions of ⩾10 mm, ⩾15 mm, and ⩾18 mm in diameter among employees who were <40 years old (table 2 and figure 2). Of note, although BCG vaccination was not significantly associated with TST reactions of ⩾20 mm in diameter, respective ORs adjusted for age groups <30 years old (OR, 3.4) and 30–39 years old (OR, 4.9) strongly suggested an influence of vaccination on those reactions. Among subjects ⩾40 years old, prior vaccination seemed to have an effect on tuberculin reactivity only when a 10-mm cutoff was used, but the small number of subjects in this age group ($n = 775$) must be kept in mind.

The fact that, among the 65 employees who reported having received preventive therapy, as many as 29% had a negative TST result (table 1) also raises doubts about the actual diagnosis of *M. tuberculosis* infection, even though tuberculin reversion following antituberculous prophylaxis has been reported [20]. It is more likely that some of the employees simply showed evidence of postvaccinal tuberculin reactivity, which faded with time.

Although a tuberculin reaction of ⩾15 mm in diameter is generally considered to be a good criterion for identifying latent *M. tuberculosis* infection in vaccinated persons at low risk for tuberculosis [13–15], our findings show that indurations of up to 18 mm in diameter (and probably up to 20 mm in diameter in persons <40 years old) are more likely attributable to previous BCG vaccination in areas of low tuberculosis prevalence. Our observations are consistent with those already published by De March-Ayuela [21] in 1990. Unlike the findings of Chee et al. [18] and the conclusions of the meta-analysis by Wang et al. [15], our results suggest that TST induration diameter is not a reliable criterion for distinguishing tuberculin reactivity caused by infection with *M. tuberculosis* from that caused by remote BCG vaccination. This point is of great importance for tuberculosis control policies among health care workers in industrialized countries where prevalence of tuberculosis is low and the rate of prior vaccination is still high (despite discontinuation of mass BCG immunization at birth). At their entry visit, health care workers often undergo a routine TST, and the finding of a large-sized induration is not infrequent, as evidenced in our study. These employees sometimes receive antituberculous preventive treatment on the basis of a single positive TST result, although they show no risk factors for *M. tuberculosis* infection. How many of them are treated each year for postvaccinal tuberculin reactivity instead of *M. tuberculosis* infection? Our study clearly demonstrates that positive TST results should not systematically lead to the prescription of antituberculous prophylaxis to vaccinated employees, whatever the size of induration, but must result in strict individual evaluation of risk. Indeed, these recommendations obviously do not apply to persons with known risk factors for *M. tuberculosis* infection, such as contact with an infectious patient, for whom a TST would not be done as a routine test but as part of a postexposure investigation. The incidence of tuberculosis is also an important factor in the interpretation of TST results, and the influence of BCG vaccination on tuberculin positivity has less importance than does *M. tuberculosis* infection in areas of endemicity, which could explain the difference between the results of the studies by Chee et al. [18] (conducted in Singapore, where the 1987–1997 tuberculosis incidence was 48–56 cases/100,000 population per year) and Lienhardt et al. [19] (conducted in The Gambia, where 1999 tuberculosis incidence was 118 cases/100,000 population per year) and the results of our study (conducted in Switzerland, where 2000 tuberculosis incidence was 8.7 cases/100,000 population per year) [22].

The results of our study also point out the need for a better diagnostic tool to accurately identify latent *M. tuberculosis* infection. Although its many drawbacks are well known, the TST has never been replaced, simply because, to date, it is the only test approved for diagnosis of latent *M. tuberculosis* infection. However, recent studies of a T cell–based enzyme-linked immunospot assay [23–25] showed that this ex vivo test appears to be more accurate than the TST in identifying persons with latent *M. tuberculosis* infection, and most interestingly, it is not associated with former BCG vaccination. In the future, this sensitive and specific test might put an end to the troublesome interpretation of the century-old TST.

Determination of tuberculin reactivity and a booster phenomenon for health care workers at their hire may be of par-

ticular help in assessing the presence of latent *M. tuberculosis* infection in the event of later contact with a documented case of tuberculosis. This is considered one of the indications for routine use of TST.

The present study shows that interpretation of routine TSTs remains difficult in BCG-vaccinated persons and must be done with caution, particularly when there is no available information on prior tests or investigation of a booster effect. In areas with low incidence of tuberculosis, except for persons who have never been vaccinated, TST reactions of up to 18 mm in diameter in persons <40 years old are more likely to be the result of prior vaccination than of infection and should not systematically lead to preventive chemotherapy.

Of note, the influence of BCG immunization on tuberculin reactivity varies with age and tends to be more pronounced for young adults. This population is likely to be most at risk for a positive TST result not related to *M. tuberculosis* infection but to BCG vaccination. Thus, caution should be applied when drawing conclusions in the absence of significant risk factors or evidence for *M. tuberculosis* infection. Moreover, the lack of specificity of TST results shows the current uncertainties surrounding the diagnosis of latent *M. tuberculosis* infection in such situations and underlines once again the need for a more accurate test.

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