The Effect of BCG Vaccination on Tuberculin Reactivity and the Booster Effect Among Hospital Employees

Santiago Moreno, MD; Rosa Blázquez, MD; Abel Novoa, MD; Isabel Carpena, MD; Ana Menasalvas, MD; Cristobal Ramirez, PharmD; Carmen Guerrero, MD

Background: We estimated the effect of remote BCG vaccination on tuberculin reactivity and the booster effect among hospital employees.

Methods: Cross-sectional survey at a university hospital. All personnel employed during a 24-month period were included in the study. Employees were administered 2-step tuberculin testing, and BCG vaccination scars were verified.

Results: Of 665 hospital employees studied, 239 (36%) had been vaccinated with BCG in childhood. Significant tuberculin reactions ($\geq 5$ mm) were more frequent among BCG-vaccinated (60%) than among nonvaccinated (29%) employees (odds ratio [OR], 3.6; 95% confidence interval [CI], 2.6-5.2). The predictive value of tuberculosis infection increased with increasing reaction size and greater age (from 37% in subjects 30 years or younger with indurations $\geq 5$ mm to 100% in subjects 50 years or older with indurations $\geq 15$ mm). Among 374 employees with a negative tuberculin test reaction who underwent a second test, 39 (43%) of 91 vaccinated subjects had a positive booster reaction in contrast to 51 (22%) of 232 nonvaccinated subjects (OR, 3.4; 95% CI, 2-5.7). Neither different size criteria nor different definitions of the booster effect had an impact on the predictive value of tuberculosis infection.

Conclusions: Remote BCG vaccination largely influences the tuberculin reaction and the boosting phenomenon among hospital employees. The interpretation of the results of 2-step tuberculin testing in a BCG-vaccinated subject must take into account age, size of the reaction, and local prevalence of tuberculosis infection. No single criterion, however, can accurately separate reactions caused by true infection from those caused by BCG vaccination.

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Although tuberculosis has long been recognized as an occupational hazard for health care workers,1,2 concern about the risk of acquisition of the infection has increased recently after reports of occupationally acquired tuberculous infection and disease among hospital employees.3-6 This concern led the Centers for Disease Control and Prevention to revise previous recommendations and to publish more stringent and comprehensive guidelines for reducing the risk of transmitting Mycobacterium tuberculosis in the hospital environment.7 Central in the Centers for Disease Control and Prevention recommendations is the monitoring of tuberculous infection of hospital personnel who are likely to be exposed to tuberculous patients, through periodic tuberculin testing. Two-step testing (ie, administration of a second tuberculin test after 1 to 3 weeks when there has not been a significant reaction to a first test) is the procedure recommended in the initial examination of hospital employees, so that a boosted response can be elicited in those with remote tuberculosis infection. The reaction to the boosted (second) test is considered to indicate the infection status of the person tested.

Vaccination with BCG has been used, and is still being used, for its potential to prevent the development of tuberculosis in persons who are at risk of acquiring the infection. The capability to protect against drug-sensitive and drug-resistant M tuberculosis has led to the proposal of administering the vaccine to health care workers who are at high risk of contracting the infection, especially when they are immunosuppressed and multidrug-resistant tuberculosis is a possibility.8,9 The potential for complications of the use of BCG vaccine in immunocompromised persons has not been determined. The effect that BCG vaccination may have on tuber-
SUBJECTS AND METHODS

STUDY POPULATION AND DATA COLLECTION

The study population was recruited from the employees at Hospital Morales Meseguer, a 400-bed institution in Murcia, Spain, in a 24-month period. In Murcia, BCG immunization was routinely given to newborns from October 1965 to May 1980, and to schoolchildren aged 6 to 14 years from 1965 to 1976. Vaccination was done by intradermal administration in the shoulder area of 0.1 mL of a lyophilized Göteborg strain from the Seruminstitut, Copenhagen, Denmark.

Hospital employees were excluded from this study if they had a documented history of a positive tuberculin skin test, a previous diagnosis of tuberculosis, or an identifiable cause of immunosuppression, including the administration of corticosteroids or other immunosuppressive therapy. No person was undergoing treatment for suspected or confirmed tuberculosis. Before skin testing and reading, all participants had the following data collected: sex, age, departmental group (physicians, nursing, other, clinical, and administrative), degree of direct contact with patients (categorized as frequent, infrequent, or rare or no contact), previous tuberculin skin tests, and BCG vaccination status. The BCG vaccination status of each person was determined by recording the presence of the vaccine scar. The BCG vaccination scars were identified on the upper third of the upper arm, usually no more than 4 cm below the shoulder vertex. No data could be collected regarding the age of the subjects when vaccinated (whether in infancy or later) or the number of subjects with repeated vaccinations.

TUBERCULIN TESTING

To evaluate the response to tuberculin, intradermal injection of 2 U of the RT-23 strain, equivalent to 5 TU of purified protein derivative (PPD), was administered into the volar surface of the forearm with disposable syringes and 27-gauge needles. Responses were read by the ballot method at 48 to 72 hours after administration, and the maximum induration in millimeters was recorded. The PPD test was administered and the results were interpreted by a single trained nurse. At the time of reading, the nurse was unaware of the person’s BCG vaccination status. A positive response to the PPD test was defined as an induration of 5 mm or more in diameter at 48 to 72 hours after administration of the antigen.

Employees with a reaction to the first test of less than 5 mm had a second PPD test applied 1 to 3 weeks later on the other forearm. The techniques for testing and reading were the same as for the initial tuberculin test. A positive booster effect was defined as a reaction to the second PPD test of 5 mm or more. All employees with a positive initial or second tuberculin test were referred for further medical evaluation and appropriate therapy.

ANALYSIS

For purposes of analysis, hospital employees were divided into 2 groups according to whether they had received BCG vaccination. The groups were compared by means of the test or Mann-Whitney test for continuous data, and Fisher exact test for categorical data. To evaluate the effect of BCG vaccination on tuberculin reactivity, odds ratios with 95% confidence intervals were calculated. Multiple logistic regression analysis was used to determine the risk factor associated with a positive initial or second tuberculin test.

To determine the value of different tuberculin reactions in predicting tuberculosis infection in BCG-vaccinated hospital employees, the sensitivity, specificity, and positive predictive values of different reaction sizes (≥3, ≥10, and ≥15 mm) were calculated. In these calculations, according to a national consensus in Spain, we assumed that a tuberculin reaction of 3 mm or more had a sensitivity of 100% and a negative predictive value of 100% in our area, ie, all those with tuberculous infection would manifest at least this reaction, and that those with a tuberculin reaction of 5 mm or more, and not BCG vaccinated, were actually infected with tuberculosis (ie, nontuberculous mycobacterial infections as a cause of false-positive reaction are extremely rare). These assumptions are based on studies that evaluated the prevalence of nontuberculous mycobacterial infection in Spain. Given the strong association observed between tuberculin reactivity and age, all calculations were made for different age groups (<30, 30-49, and ≥50 years).

To make the calculations, the disease status for BCG-vaccinated persons was considered to be the same as that for persons not BCG vaccinated. All statistical associations were assessed with 2-tailed tests. A P value of less than .05 was considered to indicate statistical significance.

RESULTS

STUDY POPULATION

The rate of tuberculosis in our area is approximately 35 cases per 100,000 population. From 1995 to 1997, 32 to 35 new cases of culture-proved tuberculosis were diagnosed annually at Hospital Morales Meseguer, and case...
rates ranged from 244.4 to 281.5 per 100,000 hospital discharges. Between January 1, 1995, and December 31, 1996, 813 persons were employed at the hospital. Of them, 665 (82%) were eligible to participate in the study. The 199 employees who did not participate in the study did not differ in their characteristics of the employees and those who did not participate in the study did not differ in their reasons for nonparticipation (44 patients). Eighteen employees refused to participate. Employees who participated and those who did not participate in the study did not differ in their baseline characteristics.

Overall, 239 participants (36%) had received BCG vaccination. The characteristics of the employees and the univariate statistics for the BCG-vaccinated and non-BCG-vaccinated groups are shown in Table 1. When compared with the nonvaccinated group, BCG-vaccinated subjects were significantly older ($P = .007$). There were no significant differences in the departmental group to which employees belonged, the degree of contact with patients, or the proportion of subjects who had previously been tuberculin tested.

In total, 356 (56%) of 640 hospital employees who underwent 2-step tuberculin testing had a positive reaction, including those who reacted to the first and to the second tuberculin tests. The rate of tuberculin reactivity was significantly influenced by BCG vaccination. Of 234 BCG-vaccinated employees, 182 (78%) had significant reactions, compared with 174 (43%) of 406 nonvaccinated subjects ($P < .001$).

### INITIAL TUBERCULIN TESTING

Of the 665 participants, 266 (40%) had significant reactions ($\geq 5$ mm) to the first tuberculin skin test. The antecedent of BCG vaccination was highly predictive of a positive result. Of the 239 employees who had received BCG vaccination, 143 (60%) had significant tuberculin reactions, compared with 123 (29%) of the 426 nonvaccinated subjects (odds ratio, 3.6; 95% confidence interval, 2.6-5.2). These differences were also present for tuberculin reactions measuring 10 mm or more or 15 mm or more, but disappeared for reactions measuring 20 mm or more (Table 2). Overall, the distribution of the size of reactions among employees who were vaccinated with BCG was not different from that of nonvaccinated employees. No size criterion ($\geq 5$, $\geq 10$, $\geq 15$, or $\geq 20$ mm) could accurately separate reactions caused by true infection from those caused by BCG vaccination.

Multivariate analysis of characteristics presented in Table 1 showed that, in addition to BCG vaccination, only age was associated with a significant tuberculin reaction ($P < .001$). The association between greater age and tuberculin reactivity was seen in both vaccinated and nonvaccinated subjects. Among employees who were not BCG vaccinated, a positive reaction was found in 18% of those younger than 30 years and in 64% of those older than 50 years. Similarly, among BCG-vaccinated employees, a positive reaction was found in 52% and 71% of subjects younger than 30 years and older than 50 years, respectively. The differences in tuberculin reactivity among vaccinated and nonvaccinated employees were present in all age categories considered, except in those older than 50 years. Other factors, such as the sex of patients, the departmental group, the degree of contact with patients, or previous administration of the tuberculin test, were not found to be predictive of a positive tuberculin reaction.

### THE BOOSTER EFFECT

Of the 399 employees who had a negative tuberculin test, 374 (94%) underwent a second test 1 to 3 weeks later. For different reasons, 5 BCG-vaccinated and 20 non-BCG-vaccinated employees did not receive a second test. A positive booster reaction (a difference of $\geq 5$ mm between the first and the second tests) was observed in 90 subjects (23%); a difference of 10 mm or more was observed in 78 subjects (20%) ($P = .3$). As for the first tuberculin test, BCG vaccination had a significant effect on the boosting phenomenon (Table 3). Of the 91 hospital employees vaccinated with BCG who had a second tuberculin test, 39 (43%) had a positive booster reaction, compared with 51 (18%) of 283 employees who were not vaccinated.

#### Table 1. Characteristics of Hospital Employees According to BCG Vaccination Status*

<table>
<thead>
<tr>
<th></th>
<th>BCG-V</th>
<th>Non–BCG-V</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eligible population</td>
<td>NA</td>
<td>NA</td>
<td>813</td>
</tr>
<tr>
<td>Participants, No. (%)</td>
<td>239 (36)</td>
<td>426 (64)</td>
<td>665 (100)</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)†</td>
<td>36.1 (22-62)</td>
<td>30.6 (21-63)</td>
<td>33.1 (21-63)</td>
</tr>
<tr>
<td>$\leq 35$, No. (%)</td>
<td>118 (49)</td>
<td>315 (74)</td>
<td>433 (65)</td>
</tr>
<tr>
<td>$&gt; 35$, No. (%)</td>
<td>121 (51)</td>
<td>111 (26)</td>
<td>232 (35)</td>
</tr>
<tr>
<td>Departmental group, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physician</td>
<td>71 (30)</td>
<td>58 (14)</td>
<td>129 (19)</td>
</tr>
<tr>
<td>Nursing</td>
<td>112 (47)</td>
<td>237 (56)</td>
<td>349 (52)</td>
</tr>
<tr>
<td>Other clinical</td>
<td>23 (10)</td>
<td>80 (20)</td>
<td>103 (16)</td>
</tr>
<tr>
<td>Administrative</td>
<td>33 (14)</td>
<td>45 (11)</td>
<td>78 (12)</td>
</tr>
<tr>
<td>Contact with patients, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None/rare</td>
<td>65 (27)</td>
<td>99 (23)</td>
<td>164 (25)</td>
</tr>
<tr>
<td>Infrequent</td>
<td>90 (38)</td>
<td>146 (34)</td>
<td>236 (35)</td>
</tr>
<tr>
<td>Frequent</td>
<td>84 (35)</td>
<td>181 (42)</td>
<td>265 (40)</td>
</tr>
<tr>
<td>Previously tested, No. (%)</td>
<td>71 (30)</td>
<td>108 (25)</td>
<td>179 (27)</td>
</tr>
</tbody>
</table>

*BCG-V indicates vaccinated with BCG vaccine; non–BCG-V, not vaccinated; and NA, not applicable. Because of rounding, percentages may not all total 100.

†$P < .01$.

#### Table 2. Size of Initial Tuberculin Skin Test Reaction by BCG Vaccination Status**

<table>
<thead>
<tr>
<th>Reaction Size, mm (n = 239)</th>
<th>BCG-V</th>
<th>Non–BCG-V</th>
<th>Difference (95% CI)</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\geq 5$</td>
<td>143 (60)</td>
<td>123 (29)</td>
<td>31 (23-39)</td>
<td>3.6 (2.6-5.2)</td>
</tr>
<tr>
<td>$\geq 10$</td>
<td>124 (52)</td>
<td>109 (26)</td>
<td>26 (18-34)</td>
<td>3.1 (2.2-4.4)</td>
</tr>
<tr>
<td>$\geq 15$</td>
<td>57 (24)</td>
<td>68 (16)</td>
<td>8 (1-15)</td>
<td>1.6 (1.1-2.5)</td>
</tr>
<tr>
<td>$\geq 20$</td>
<td>7 (3)</td>
<td>8 (2)</td>
<td>1 (0-4)</td>
<td>1.6 (0.5-4.8)</td>
</tr>
</tbody>
</table>

**BCG-V indicates vaccinated with BCG vaccine; non–BCG-V, not vaccinated; and CI, confidence interval.
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caused by BCG vaccination. The boosting phenomenon
rately separate reaction caused by true infection from that
loss infection. No single criterion, however, can accu-
size of the reaction, and the local prevalence of tubercu-
vaccinated subject must take into account the age, the
nting, the interpretation of a tuberculin reaction in a BCG-
major determinants of the tuberculin reaction. In this set-
given between approximately 15 and 30 years earlier, are
uberculosis, we found that age and BCG vaccination,
hospital employees in an area with a high prevalence of
In this prospective survey of tuberculin reactivity among
Table 3 shows the overall sensitivity, specificity, and
predictive value of different tuberculin reactions to
establish tuberculosis infection in an employee of
our hospital with remote BCG vaccination. The size of
the reaction affects the positive predictive value of a
positive test, which ranges from 48% for reactions of 5
mm or more to 67% for reactions of 15 mm or more. As
previously stated, we have assumed, to make these cal-
culations, that a tuberculin reaction of 5 mm or more has
a sensitivity of 100% and a specificity of 100% in per-
sons not vaccinated with BCG in our area.
Since age was found to be independently associated
with a positive tuberculin test, calculations were made
that took into account the age of the employee
(Table 5). As expected, the predictive value of a posi-
tive test increases with the size of the reaction and with
the age of the employee, ranging from 37% in subjects
younger than 30 years with reactions of 5 mm or more
to 100% in subjects older than 50 years with reactions of
15 mm or more.
With regard to the interpretation of a booster effect
in a BCG-vaccinated hospital employee, the predictive
value of a positive test was low whatever definition was
considered (Table 4). The use of more stringent criteria,
 ie, greater difference between the second and the first tests,
results in diminished sensitivity with no improvement
in the positive predictive value. Reactions of 15 mm or
more appear to be highly specific and, thus, not attrib-
utable to vaccination with BCG.

### PREDICTIVE VALUE OF A TUBERCULIN
### REACTION IN BCG-VACCINATED EMPLOYEES

Table 4 shows the overall sensitivity, specificity, and
positive predictive value of different tuberculin reactions
to establish tuberculosis infection in an employee of
our hospital with remote BCG vaccination. The size of
the reaction affects the positive predictive value of a
positive test, which ranges from 48% for reactions of 5
mm or more to 67% for reactions of 15 mm or more. As
previously stated, we have assumed, to make these cal-
culations, that a tuberculin reaction of 5 mm or more has
a sensitivity of 100% and a specificity of 100% in per-
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utable to vaccination with BCG.

### COMMENT

In this prospective survey of tuberculin reactivity among
hospital employees in an area with a high prevalence of
tuberculosis, we found that age and BCG vaccination,
given between approximately 15 and 30 years earlier, are
major determinants of the tuberculin reaction. In this set-
ting, the interpretation of a tuberculin reaction in a BCG-
vaccinated subject must take into account the age, the
size of the reaction, and the local prevalence of tubercu-
losis infection. No single criterion, however, can accu-
rately separate reaction caused by true infection from that
called BCG vaccination. The boosting phenomenon is
also largely affected by previous BCG vaccination. In
2-step tuberculin testing, large reactions with the sec-
ond tuberculin test have a high specificity, but the pre-
dictive value of tuberculosis infection is low.
Previous reports have evaluated the effect of BCG
vaccination on tuberculin reactivity in different popula-
tion groups, with results ranging from 0% to 90% of sig-
nificant reactions in vaccinated subjects.19-21 This vari-
ability seems to be influenced by multiple factors,
including the type and infecting dose of the BCG vac-
cine used, the number of vaccinations, the age at vacci-
nation, the time interval from vaccination to tuberculin
testing, and the effect of repeated tuberculin testing.21-24
In a community-based survey in Quebec, the authors
found that the most important determinant of effect of
BCG vaccination on tuberculin reactivity was the age at
which the subject was vaccinated (7.9% of the subjects

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**Table 3. Booster Effect Among Hospital Employees According to BCG Vaccination Status**

<table>
<thead>
<tr>
<th>Reaction Size or Difference, mm</th>
<th>BCG-V (n = 91)</th>
<th>Non-BCG-V (n = 283)</th>
<th>Difference in Reaction Size, mm</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>39 (43)</td>
<td>51 (18)</td>
<td>12 (7 to 20)</td>
<td>3.4 (1.7 to 6.1)</td>
</tr>
<tr>
<td>10</td>
<td>35 (38)</td>
<td>43 (15)</td>
<td>8 (5 to 11)</td>
<td>3.5 (2.3 to 5.3)</td>
</tr>
<tr>
<td>15</td>
<td>11 (12)</td>
<td>18 (6)</td>
<td>7 (3 to 16)</td>
<td>2.0 (0.9 to 4.4)</td>
</tr>
</tbody>
</table>

*BCC-V indicates vaccinated with BCG vaccine; non–BCG-V, not
vaccinated; and CI, confidence interval.

**Table 4. Sensitivity, Specificity, and Positive Predictive Value of Different Tuberculin Reactions and Different Definitions of Booster Reactions in Hospital Employees With Remote BCG Vaccination**

<table>
<thead>
<tr>
<th>Reaction Size or Difference, mm</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>Positive Predictive Value (95% CI), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuberculin Test Reaction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥5</td>
<td>100</td>
<td>56</td>
<td>48 (39.6-56.4)</td>
</tr>
<tr>
<td>≥10</td>
<td>89</td>
<td>63</td>
<td>50 (40.9-59.1)</td>
</tr>
<tr>
<td>≥15</td>
<td>55</td>
<td>89</td>
<td>67 (52.8-72.2)</td>
</tr>
<tr>
<td>Booster Reaction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥5</td>
<td>100</td>
<td>69</td>
<td>41 (26-57.8)</td>
</tr>
<tr>
<td>≥10</td>
<td>87</td>
<td>72</td>
<td>40 (24.4-57.8)</td>
</tr>
<tr>
<td>≥15</td>
<td>31</td>
<td>92</td>
<td>45 (18.1-75.4)</td>
</tr>
</tbody>
</table>

*CI indicates confidence interval.
†Sensitivity of 100% is assumed for a reaction size of 5 mm or more and
for a difference between reactions to the second and the first tests of 5 mm
or more.

**Table 5. Positive Predictive Value of Different Tuberculin Reactions According to Age in Hospital Employees With Remote BCG Vaccination**

<table>
<thead>
<tr>
<th>Reaction Size, mm</th>
<th>Age, y</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤30</td>
<td></td>
</tr>
<tr>
<td>30-39</td>
<td></td>
</tr>
<tr>
<td>40-49</td>
<td></td>
</tr>
<tr>
<td>≥50</td>
<td></td>
</tr>
<tr>
<td>≥5</td>
<td>37</td>
</tr>
<tr>
<td>≥10</td>
<td>42</td>
</tr>
<tr>
<td>≥15</td>
<td>60</td>
</tr>
</tbody>
</table>
who had been BCG vaccinated in the first year of life had significant reactions compared with 18.3% and 25% of those who had been vaccinated at 2-5 years and at 6 years or older, respectively.\textsuperscript{24} Unfortunately, we have not been able to confirm these findings in our study, since the age of BCG vaccination was lacking in the vast majority of cases. However, we have found that the age of the hospital employee was highly predictive of a positive reaction. In an area where tuberculosis is highly prevalent, an increasing chance of older employees being exposed to tuberculosis sources in the hospital setting, as well as in the community, is the most likely explanation for this finding. This is supported by the fact that the influence of age on the tuberculin reaction affects persons who have been vaccinated with BCG and, even more significantly, persons who have not been vaccinated.

Despite the findings of different studies, it is unclear at present how to interpret a significant tuberculin reaction in hospital employees who received BCG vaccination long ago, and what recommendations are to be given. From previous reports, it seems clear that positive tuberculin reactions in persons vaccinated in the first year of life should be regarded as indicative of tuberculosis infection.\textsuperscript{24} In the case of persons who have been BCG vaccinated later in life, more than 1 factor should be considered before a recommendation can be made. The size of the reaction has been shown to have some predictive value in several studies, with a trend to larger inductions in persons with true infection. Since the predictive value of a positive test is highly affected by the expected prevalence of the disease in the population, the local prevalence of tuberculosis infection is of great importance in decision making. From the findings of this study, we have calculated the positive predictive value of different tuberculin reactions in BCG-vaccinated persons according to the expected prevalence of tuberculosis infection in a given area (Table 6). These data highly agree with those calculated by Menzies and Vissandjee,\textsuperscript{24} based on their survey in Quebec. Both the expected prevalence and the size of the reaction determine the probability that a person is infected with \textit{M tuberculosis}. Since the prevalence of tuberculosis infection is expected to be higher in older people, age is an additional factor to be considered, especially when prevalence rates are unknown. It should be noted that the interpretation of the test results may be different for areas with different conditions, such as a higher prevalence of atypical mycobacteria.

Of special importance in health care personnel and other hospital employees is the interpretation of the booster effect after 2-step tuberculin testing.\textsuperscript{7} Booster reactions have been associated with previous BCG vaccination or sensitization with atypical mycobacteria.\textsuperscript{22,25-27} and a recent study from Canada found that tuberculous infection was rarely the cause of a booster effect in young adults.\textsuperscript{27} Only 2.5% of the students who were not BCG vaccinated had a positive booster reaction, in contrast to 10.1% of those who were BCG vaccinated. In our population of hospital employees, with a prevalence of tuberculous infection higher than that among young students in Quebec, tuberculous infection seems not to be uncommon as a cause of a positive booster effect. Up to 22% of persons not vaccinated with BCG had a significant reaction with the second tuberculin test, with a much higher rate in persons who were BCG vaccinated (43%). It is unlikely that factors other than tuberculous infection, such as greater age or atypical mycobacteria, might explain this observation. Multivariate analysis failed to show an association between a positive booster effect and age in our study, and atypical mycobacterioses are extremely rare in our area.\textsuperscript{12,18} Thus, it seems that a high prevalence of tuberculous infection may result in frequent positive booster reactions, even in young people. In these groups, routine 2-step tuberculin testing should be considered in settings other than periodic testing of hospital personnel. The interpretation of the test results, both initial tuberculin and the booster reaction, may be different for areas with different conditions, such as a higher prevalence of atypical mycobacteria. However, even in areas or countries with a high prevalence of atypical mycobacterioses, the local prevalence of tuberculosis continues to be the major factor to be considered for an adequate interpretation of the tests.

The predictive value of a positive booster effect in BCG-vaccinated persons is low, regardless of the definition considered. Large reactions (a difference of ≥15 mm between the second and the first tests) have high specificity but do not significantly increase the predictive value. Practical decisions, such as recommendation of chemoprophylaxis to hospital employees, must take into account other factors because of the high rate of false-positive results. As with the initial tuberculin test, the prevalence of tuberculosis infection is possibly the major determinant.

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\section*{REFERENCES}


3. Centers for Disease Control and Prevention. Nosocomial transmission of mul-

\begin{table}
\centering
\begin{tabular}{|c|c|c|c|}
\hline
\textbf{Expected Prevalence, %} & React. Size, mm & \textbf{$\geq5$} & \textbf{$\geq10$} & \textbf{$\geq15$} \\
\hline
5 & 14 & 16 & 38 \\
10 & 24 & 28 & 62 \\
15 & 33 & 40 & 85 \\
20 & 35 & 44 & 85 \\
25 & 45 & 49 & 76 \\
30 & 49 & 53 & 79 \\
50 & 62 & 66 & 86 \\
\hline
\end{tabular}
\caption{Table 6. Positive Predictive Value of Different Tuberculin Reactions in Persons With Remote BCG Vaccination According to Expected Prevalence of Tuberculosis Infection}
\end{table}


