A Prospective Study of Bacillus Calmette-Guérin Scar Formation and Tuberculin Skin Test Reactivity in Infants in Lima, Peru

Eunice M. Santiago, BSc*; Elise Lawson, BSc*; Kari Gillenwater, BSc*; Sheela Kalangi, BSc*; Andrés G. Lescano, MHS†‡; Gregory Du Quella, BSc*; Kristin Cummings, MD*; Lilia Cabrera, RN*; Cecilia Torres*; and Robert H. Gilman, MD§

ABSTRACT. Objectives. To determine the sensitivity of the bacillus Calmette-Guérin (BCG) scar as an indicator of previous vaccination and to ascertain the tuberculin skin test (TST) response in infancy after vaccination in a community from an area hyperendemic for tuberculosis (TB).

Methods. In a birth cohort of healthy term infants from Lima, Peru, a single dose of BCG vaccine was administered within the first month of life. Scar formation was assessed biweekly during the first 6 months and again at 3 years after vaccination. TST response was evaluated 6 months after vaccination.

Results. Six months after vaccination, 99% (68) of the newborns exhibited a BCG scar (>2 mm). Scar size did not differ by sex, birth weight, age at vaccination, or nutritional status in the first 2 months. Eighty percent of the participants were found 3 years after vaccination, and all of them had a BCG scar. Mean TST reaction size 6 months after vaccination was 2.9 ± 0.3 mm. No association was found between sex or age at BCG vaccination and TST size. Only 3 children had a TST >10 mm, and the 3 had a TB contact at home.

Conclusions. The BCG scar was a sensitive indicator of vaccination status up to 3 years after the administration of the vaccine in the first month of life. Although nearly a quarter of the children had a TST response >5 mm 6 months after vaccination, TST reactions >10 mm did not occur in the absence of exposure to a person with tuberculosis. A cutoff of 10 mm should be used for disease control purposes in people who are born in countries where TB is endemic. Pediatrics 2003;112:e298–e302.

URL: http://www.pediatrics.org/cgi/content/full/112/4/e298; tuberculosis, children, Peru, BCG scar, tuberculin skin test.

ABBREVIATIONS. TB, tuberculosis; WHO, World Health Organization; BCG, bacillus Calmette-Guérin; TST, tuberculin skin test; CI, confidence interval.

Tuberculosis (TB) has been declared a global emergency by the World Health Organization (WHO) and is expected to cause 30 million deaths in the coming decade.1–3 Although investigations pertaining to TB vaccines are resurging,4,5 immunization against TB is limited to the bacillus Calmette-Guérin (BCG) vaccine. The WHO recommends a single BCG vaccine at birth in countries with a high prevalence of active TB disease.3,6

The presence or absence of a BCG scar is often used as an indicator of previous vaccination in clinical settings as well as surveys performed by health institutions such as the Expanded Program on Immunization to assess vaccine uptake.7 However, the sensitivity of the BCG scar as an index of vaccination status is still the subject of controversy.6 Failure to form a scar may be related to factors such as lack of maturation of the immune system,8 faulty technique, or use of a nonpotent vaccine.9

In Peru, intradermal administration of BCG is given at birth at any health facility, such as a hospital or health post. This is part of the regular immunization program following WHO guidelines.10 Since 1991, the same strain of BCG has been used across the country. In 2000, the estimated incidence of active pulmonary TB in Peru was 111 cases per 100 000,11 but in one area, it has been reported to be 364 per 100 00012 despite 95% coverage of BCG vaccination at birth and a human immunodeficiency virus prevalence of <0.5%.11 In countries with such a high TB incidence, diagnostic algorithms include the tuberculin skin test (TST) as a screening tool, particularly in children.13,14

It has been shown that the BCG may affect the TST by factors such as strain and dose,15 number of vaccines administered,16,17 time since vaccination,18 age and nutritional status,19 and method of vaccine administration.20 However, the scope of these effects is unclear. Therefore, for the TST to be interpreted in the context of potential previous BCG vaccination, there is a need for a reliable indicator of vaccine status, as well as an understanding of the effect of BCG on TST size.

Reports on the percentage of children who scar after BCG vaccination vary widely.21–26 This study was conducted to determine the sensitivity of scarring after BCG vaccination in a developing country hyperendemic for tuberculosis. We describe the BCG scar formation process for 6 months after vaccine
administration in a birth cohort from a shantytown in Lima, Peru. To ascertain the effect of BCG vaccine given at birth on the TST response, we also administered a TST 6 months after vaccination. For verifying whether the scar persisted throughout time, 1 additional assessment was performed 3 years after vaccination.

METHODS

Study Site and Population

This study was conducted in Las Pampas de San Juan de Miraflores, a periurban shantytown 25 km south of the center of Lima. It is composed of 50 communities with an estimated population of 40,000 consisting mainly of migrants of low socioeconomic status. In the past, emigration rates have decreased and families in these communities are similar in socioeconomic status, housing quality, and access to public utilities. This population has been described in the past.

Between September 1998 and February 1999, 122 women who were in their last trimester of pregnancy and attending local health posts in this shantytown were invited to participate in this study. Informed consent was obtained from the mother at this time. Six neonates who were premature and presented serious neonatal problems requiring prolonged medical treatment or hospitalization were excluded from the study. An additional 16 newborns were not included because their mothers declined participation.

Of the 100 term neonates recruited, 18 were not located for follow-up. An additional 5 did not complete the initial 6-month follow-up, and 4 were lost to follow-up before receiving the TST. Another 4 participants were excluded because they were vaccinated after the first month of life. A total of 69 children were included in the final analyses.

Vaccination and Follow-up

Nurses from the Peruvian Ministry of Health injected 0.1 mL of the BCG vaccine (Pasteur-Mérieux-Connaught, Lyon, France) intradermally into the deltoid region of the right arm of the neonates. During 6 months after vaccination, study nurses performed biweekly in-home assessments to reassess scar presence. Scar size was measured 48 to 72 hours later using the pen method.

RESULTS

Participant Population

Of the 69 newborns analyzed in the study, 56% (38) were male. Mean birth weight was 3.3 ± 0.4 kg. Three children (4.5%) were classified as low birth weight (<2.50 kg). Median age at BCG vaccination was 5 days, with values ranging from 0 to 29 days.

Scar Formation and Scar Size

Sixty-eight children exhibited a visible BCG scar (>2 mm) within the first 6 months after vaccination, representing a scar failure rate of 1.4%. The child who did not form a scar during this period was a girl of normal birth weight (3.0 kg) who was vaccinated at 20 days of age. Thirty-one children (45%) were vaccinated within the first 48 hours after birth. There was no significant difference in scar size between these infants and the rest of the group (P = .248).

After analyzing scar size by weekly periods, we identified 2 stages in the scar formation process: the formation phase and the stabilization phase (Fig 1). The formation phase, during which the scar size increased steadily, lasted on average 7.5 weeks after vaccination (Fig 2). The subsequent stabilization phase continued throughout the first 6 months of life.

Fifty-five (80%) of the participants were found 3 years after vaccination for scar presence assessment. All had a scar at this time, including the girl who initially did not form a scar. This infant showed scar presence at weeks 19 and 21 with a final scar size of 2 mm at 3 years after vaccination. Scars 3 years after vaccination were approximately 1.7 mm larger than at 6 months after vaccination (95% CI: 1.4–2.1 mm; Fig 3).

Statistical Analysis

For determining the average scar size over time, measurements were classified on the basis of the time of BCG vaccination in 1-week periods. We defined 2 phases in the scar development, formation and stabilization (Fig 1). For predicting mean scar size, the formation phase was fitted using a cubic polynomial regression with days after BCG vaccination as the independent variable. The stabilization phase was fitted using a linear regression model. The random effects component was used to take into account that there were repeated measurements of the same individual.

Nutritional status indicators during the first 6 months, height-for-age and weight-for-height, were calculated according to the WHO reference population using EPIINFO 6.04. Degrees of stunting were classified according to height-for-age z score as mild (z score < -1) or moderate to severe (z score < -2). Wasting was defined as a weight-for-height z score of < -2.

The effect of age at vaccination, sex, and birth weight on BCG scar size and TST reaction size was examined using χ², t tests, and Pearson correlation coefficient. All tests were calculated in a 2-tailed manner, and confidence intervals (CIs) were set at 95%.

SPSS (SPSS, Inc, Chicago, IL) and STATA 7.0 (Stata Corp, College Station, TX) were used for data analyses.

Ethical Approval

This study was approved by the Ethical Review Boards of Johns Hopkins University Bloomberg School of Public Health and Asociación Benéfica PRISMA (Peruvian NGO), both of which have US Federal Wide Assurance approval.
Mean TST reaction size 6 months after vaccination was 2.9 mm; 3 (4%) children had a positive reaction (>10 mm), and 20% had reaction sizes between 5 and 9 mm (Fig 4). There was no association between sex and TST size ($P = .475$; $t$ test). No significant correlation was found between the infants who were vaccinated within 48 hours after birth and those who were vaccinated afterward and TST size. The 3 positive reactors had a history of contact with
compared with the TST-negative group (P < .001, t test). They also had significantly larger BCG scars when applied after BCG vaccination usually produces a reaction of <10 mm. This is consistent with studies that show an association between TST reactions 5 to 9 mm and the presence of a BCG scar.13,39,40 We also found an association between TSTs >10 mm and contact with a person with active TB. This suggests that TST positivity of >10 mm among these infants was associated with TB exposure rather than with other factors (eg, age, nutritional status, time since vaccination). These 3 infants also had significantly larger scars than the rest of the group. This finding may suggest that other than having had previous exposure to Mycobacterium tuberculosis, these children might have been hyperresponders to mycobacterial antigen.

In the United States, TB cases among the foreign-born accounted for the majority of the cases (51%) in 2002.41 Considering that TB disease and latent infection rates differ among countries,41,42 we recommend that in foreign-born individuals with evidence of BCG at birth, only a TST reaction >10 mm should be considered evidence of previous M tuberculosis exposure.

Another aspect that underscores the importance of assessing BCG scar presence is its relation to TST reactivity. Our results demonstrate that a TST applied after BCG vaccination usually produces a reaction of <10 mm. This is consistent with studies that show an association between TST reactions 5 to 9 mm and the presence of a BCG scar.13,39,40 We also found an association between TSTs >10 mm and contact with a person with active TB. This suggests that TST positivity of >10 mm among these infants was associated with TB exposure rather than with other factors (eg, age, nutritional status, time since vaccination). These 3 infants also had significantly larger scars than the rest of the group. This finding may suggest that other than having had previous exposure to Mycobacterium tuberculosis, these children might have been hyperresponders to mycobacterial antigen.

In our study, the BCG scar in healthy term infants was a sensitive indicator of vaccination status when administered within the first month of life. Scar presence persisted 3 years after vaccination.21,26 Adolescents from this same community with vaccination records were examined for BCG scar presence, a sensitive indicator of vaccination status when administered soon after at birth.21,26

Similar to our findings, another study observed that the BCG scar is formed within the first 6 months after vaccination.38 This study did not, however, document the progression of scar formation. We observed that the defining stages in the scar formation process took place particularly during the first 8 weeks, after which the scar stabilized. High repeatability of BCG scar measurements with increasing time after vaccination has also been reported before, signifying that the character of the scar stabilizes over time.21,38

### DISCUSSION

In our study, the BCG scar in healthy term infants was a sensitive indicator of vaccination status when administered within the first month of life. Scar presence persisted 3 years after vaccination.21,26 Adolescents from this same community with vaccination records were examined for BCG scar presence, a sensitive indicator of vaccination status when administered soon after at birth.21,26

Similar to our findings, another study observed that the BCG scar is formed within the first 6 months after vaccination.38 This study did not, however, document the progression of scar formation. We observed that the defining stages in the scar formation process took place particularly during the first 8 weeks, after which the scar stabilized. High repeatability of BCG scar measurements with increasing time after vaccination has also been reported before, signifying that the character of the scar stabilizes over time.21,38

A person with active TB at home (P < .001, t test). They also had significantly larger BCG scars when compared with the TST-negative group (P < .001, t test). These 3 children had chest radiographs taken as part of their subsequent medical evaluation, all of which were normal.

#### TABLE 1. Effects of Birth Weight, Sex, Known TB Contact, TST Positivity (10 mm and 5 mm cutoff), and Nutritional Status on BCG Scar Size During the First 6 Months After Vaccination, TST Reaction, and BCG Scar Size 3 Years After Vaccination

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N = 69</th>
<th>Mean Scar Size at 6 Months PV (P Value)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Mean TST Size at 6 Months PV (P Value)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>N = 55</th>
<th>Mean Scar Size at 3 Years PV (P Value)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>64</td>
<td>3.4 ± 0.1</td>
<td>3.0 ± 0.3</td>
<td>3</td>
<td>5.2 ± 1.6</td>
</tr>
<tr>
<td>Low</td>
<td>3</td>
<td>3.3 ± 0.1</td>
<td>3.0 ± 0.2</td>
<td>50</td>
<td>3.8 ± 1.5</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>38</td>
<td>3.6 ± 0.1</td>
<td>3.2 ± 0.3</td>
<td>31</td>
<td>5.1 ± 1.9</td>
</tr>
<tr>
<td>Female</td>
<td>30</td>
<td>3.2 ± 0.1</td>
<td>2.6 ± 0.3</td>
<td>24</td>
<td>5.0 ± 1.3</td>
</tr>
<tr>
<td>Age at vaccination</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥48 h</td>
<td>31</td>
<td>3.7 ± 0.1</td>
<td>3.0 ± 0.3</td>
<td>26</td>
<td>5.5 ± 1.6</td>
</tr>
<tr>
<td>3–29 d</td>
<td>38</td>
<td>3.2 ± 0.1</td>
<td>2.9 ± 0.3</td>
<td>29</td>
<td>4.8 ± 1.6</td>
</tr>
<tr>
<td>TB contact*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>21</td>
<td>4.0 ± 0.1</td>
<td>3.6 ± 0.4</td>
<td>16</td>
<td>5.5 ± 1.8</td>
</tr>
<tr>
<td>No</td>
<td>48</td>
<td>3.2 ± 0.09</td>
<td>2.6 ± 0.3</td>
<td>39</td>
<td>5.0 ± 1.6</td>
</tr>
<tr>
<td>TST reaction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥10 mm</td>
<td>3</td>
<td>5.7 ± 0.2</td>
<td>10.3 ± 0.05</td>
<td>2</td>
<td>6.0 ± 0.1</td>
</tr>
<tr>
<td>0–9 mm</td>
<td>66</td>
<td>3.3 ± 0.1</td>
<td>2.6 ± 0.3</td>
<td>53</td>
<td>5.1 ± 1.6</td>
</tr>
</tbody>
</table>

PV indicates postvaccination.

**Fig 4.** TST reaction size 6 months after vaccination among infants who were vaccinated with BCG at birth.

This table shows the effects of birth weight, sex, known TB contact, TST positivity (10 mm and 5 mm cutoff), and nutritional status on BCG scar size during the first 6 months after vaccination, TST reaction, and BCG scar size 3 years after vaccination.
ences could account for numerous variations in re-
actogenicity and immunogenicity.

Finally, we found no association between nutri-
tional status and scar formation. Although children
with serious neonatal problems, including severe
malnutrition, were excluded from our study, many
of the participants were stunted at some point during
the observation period. However, this did not impair
scar formation.

CONCLUSIONS

Our results show that infants who were vaccinated
within the first month of life nearly always formed a
scar. Thus, a BCG scar was a sensitive marker of
vaccination status. Because nearly a quarter of the
children had a TST response of >5 mm 6 months
after vaccination, a cutoff of 10 mm should be used
for disease control purposes.

ACKNOWLEDGMENTS

Funding for this project was provided by the National Insti-
tutes of Health TREAT Training Grant TW00910, the USAID TB
Research Grant NIH N-A-0096-9008-00, the Training Grant T35
AI07646-01, and the anonymous RG-ER Fund for the advance-
ment of research in tropical medicine.

We thank Dr Carlton Evans and Dr Daniel E. Roth for com-
ments and support.

REFERENCES

to antituberculosis drugs. World Health Organization-International
Organization against Tuberculosis and Lung Disease Working Group on Anti-
1294–1303

statement: Global burden of tuberculosis: estimated incidence, preva-
lence, and mortality by country. WHO Global Surveillance and Moni-
toring Project. JAMA. 1999;282:677–686

Switzerland: WHO; 2001

4. Ginsberg AM. What’s new in tuberculosis vaccines? Bull World Health
Organ. 2002;80:483–488

5. Horwitz M, Harth G. A new vaccine against tuberculosis affords greater
survival after challenge than the current vaccine in the guinea pig

ton, DC: American Society for Microbiology; 1994

7. Expanded Programme on Immunization. Programme review. Wkly Epi-
demiol Rec. 1994;69:687–690

response two years after BCG vaccination at birth. Arch Dis Child.
1984;59:614–619

9. Hasfield JW, Allan J. Windebank W. Sensitivity of neonates to tuber-

10. World Health Organization. WHO Global Tuberculosis Programme and
Programme on vaccines. Statement on BCG revaccination for the

11. Programa Nacional de control de la tuberculosis. Tuberculosis en el Perú:
Salud del Peru; 2001

LZ, Cardenas V. Hyperendemic pulmonary tuberculosis in a Peruvian

Tuberculosis reactivity in a pediatric population with high BCG vaccina-


15. Bunch-Christensen K. Evaluation of BCG in children, the effect of strain


17. Elidrin I, Hacimustafaoğlu M, Edir B. Correlation of tuberculin indu-
rubation with the number of Bacillus Calmette-Guerin vaccines. Pediatr
 Infect Dis. 1995;14:1060–1063

18. Young T, Mirdad S. Determinants of tuberculin sensitivity in a child
population covered by mass BCG vaccination. Tuberc Lung Dis. 1992;73:
100–108

Respirology. 1999;4:311–317

20. D’Arcy H, Sutherland I, Thomas J. The immunity conferred by effective
BCG and vole bacillus vaccines, in relation to individual variations in
induced tuberculin sensitivity and to technical variations in the vac-
cines. Tubercle. 1967;48:201–210

21. Fine PEM, Ponnighaus JM, Maune N. The distribution and implications
of BCG scars, with particular reference to a population in Northern

22. Bollag U, Bollag-Albrecht E. Tuberculin reaction and the extent of the
vaccination scar following BCG vaccination in newborn infants. Schweiz

23. Rani SH, Vijayalakshmi V, Sunil K, Laksheki KA, Suman LG, Murthy
RJ. Cell mediated immunity in children with scar-failure following BCG


reaction in healthy infants vaccinated with BCG at birth. Rev Chil

26. Sedaghatian MR, Kardouzi K. Tuberculin response in preterm infants

27. Berkman DS, Lescano AG, Gilman RH, Lopez SL, Black MM. Effects of
stunting, diarrhoeal disease and parasitic infection during infancy on

Effects of Cryptosporidium parvum infection in Peruvian children:
1998;148:497–506

indicator for tuberculin control. Lancet. 1995;345:416–419

RH. Basic epidemiology of tuberculosis in Peru: a prevalence study of
 tuberculin sensitivity in a Pueblo joven. Am J Trop Med Hig. 1992;47:
721–729

pen method for the measurement of skin tuberculin reactions (Mantoux

Station, TX: Sta a Press; 1999

33. Centers for Disease Control and Prevention. EPINUT from EPInfo.
Atlanta, GA: Centers for Disease Control and Prevention. Available at:
http://www.cdc.gov/epiinfo/index.htm

34. Jeena PM, Chhagan MK, Topley J, Coovadham MI. Safety of the intra-
dermal Copenhagen 1331 BCG vaccine in neonates in Durban, South

35. Karalliede S, Katugaha LP, Uragoda CG. Tuberculin response of Sri

36. Agarwal RK, Kapur D, Kumar S. Development of BCG scar in relation to
the age and nutritional status. Indian Pediatr. 1998;25:293–299

1995;32:1323 (letter)

38. Floyd S, Ponnighaus JM, Bliss L, et al. BCG scars in northern Malawi:
sensitivity and repeatability of scar reading, and factors affecting scar


Etiop Med J. 1993;31:265–270

41. Centers for Disease Control and Prevention. Trends in tuberculous
2003;52:217–220, 222

42. Salinas Solano C, Altuhe Urregeetoea L, Espana Yandiola P, Capelas-
stegui Satiz A, Quintana Lopez J. Tuberculosis among immigrants in

43. Behr M, Small P. A historical and molecular phylogeny of BCG strains.
Vaccine. 1999;17:915–922

44. Fine PEM, Carneiro IAM, Milstien JB, Clements CJ. Issues relating to the
Department of Vaccines and Biologicals. In: WHO Vaccines and Biologicals
[Publ]. No. 99-23; Geneva, Switzerland, World Health Organization;
1999;1–45. Available at: http://www.who.int/vaccines-
A Prospective Study of Bacillus Calmette-Guérin Scar Formation and Tuberculin Skin Test Reactivity in Infants in Lima, Peru
Eunice M. Santiago, Elise Lawson, Kari Gillenwater, Sheela Kalingi, Andrés G. Lescano, Gregory Du Quella, Kristin Cummings, Lilia Cabrera, Cecilia Torres and Robert H. Gilman
Pediatrics 2003;112:e298
DOI: 10.1542/peds.112.4.e298

Updated Information & Services
including high resolution figures, can be found at:
http://pediatrics.aappublications.org/content/112/4/e298

References
This article cites 37 articles, 4 of which you can access for free at:
http://pediatrics.aappublications.org/content/112/4/e298#BIBL

Subspecialty Collections
This article, along with others on similar topics, appears in the following collection(s):
Infectious Disease
http://www.aappublications.org/cgi/collection/infectious_diseases_sub

Permissions & Licensing
Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
http://www.aappublications.org/site/misc/Permissions.xhtml

Reprints
Information about ordering reprints can be found online:
http://www.aappublications.org/site/misc/reprints.xhtml

American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN®
A Prospective Study of Bacillus Calmette-Guérin Scar Formation and Tuberculin Skin Test Reactivity in Infants in Lima, Peru

Eunice M. Santiago, Elise Lawson, Kari Gillenwater, Sheela Kalangi, Andrés G. Lescano, Gregory Du Quella, Kristin Cummings, Lilia Cabrera, Cecilia Torres and Robert H. Gilman

*Pediatrics* 2003;112;e298
DOI: 10.1542/peds.112.4.e298

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://pediatrics.aappublications.org/content/112/4/e298