



Published in final edited form as:

*Am J Perinatol.* 2019 October ; 36(12): 1264–1270. doi:10.1055/s-0038-1676614.

## Evolution of the Bacillus Calmette–Guerin Scar and Its Association with Birth and Pregnancy Characteristics in a Prospective Cohort of Infants in Iquitos, Peru

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### Abstract

**Background**—Bacillus Calmette–Guerin (BCG) scar formation is considered a visual marker of vaccination and cell-mediated immune response. This study characterized the association between pregnancy and birth characteristics with BCG scar formation.

**Methods**—Pregnant women were enrolled prospectively. Infants were followed up for the first 6 months of life, and the diameter of the BCG scar was recorded. Marginal models were fitted to assess the association of BCG scar diameter with pregnancy and birth characteristics using linear regressions with generalized estimating equations.

**Results**—A total of 307 infants were enrolled, of whom 19.2% (59/307) were of low birth weight. Among those with known gestational age, 7.1% were preterm births (2/295). Overall, 98.7% (303/307) of infants developed a BCG scar. BCG scar trends in a tropical environment, such as the Amazon, differ from the trends evidenced in the capital of Peru. For every additional week of gestational age, the mean scar diameter increased by 0.1 mm (95% confidence interval [CI]: 0.02, 0.24;  $p = 0.017$ ). Maternal illness during pregnancy impacted BCG scar size, as the infants of mothers who self-report fever had a smaller scar diameter (1 mm, 95% CI: 0.5, 1.8 mm;  $p = 0.001$ ).

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#### Authors' Contributions

F. S. and G. O. L. contributed to data analysis and manuscript elaboration, M. P. O. and L. C. contributed to study design and data collection, and P. P. Y., R. H. G., and M. N. K. contributed to study design, data analysis, and manuscript elaboration.

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Conflict of Interest  
None declared.

**Conclusion**—The immune reaction to the BCG vaccination is affected by gestational age at birth and systemic inflammatory episodes during pregnancy.

## Keywords

Bacillus Calmette–Guerin; preterm births; tuberculosis; Peru

Tuberculosis is currently the leading cause of infectious disease deaths in the world, surpassing HIV for the first time since the start of the epidemic.<sup>1</sup> The *Mycobacterium bovis* Bacillus Calmette–Guerin (BCG) vaccine is currently the only approved vaccine for tuberculosis, is the only vaccine administered to prevent severe disease by *Mycobacterium tuberculosis* in children, and constitutes an important strategy for disease control in low- and middle-income nations (LMICs). In Latin America, BCG coverage exceeds the global average, and Peru specifically reports 94% coverage rates.<sup>2,3</sup>

The BCG vaccine is administered intradermally in the upper forearm of the newborn. The live attenuated vaccine induces CD8 and CD4 T-cell response 4 to 8 weeks after its administration.<sup>4</sup> Scar formation at the inoculation site is considered a visual marker of vaccination and immunity against *M. tuberculosis*.<sup>5–7</sup> In LMICs, BCG scar formation is associated with an increase in child survival<sup>5,8–10</sup>—an observation that is hypothesized to be a result of overall immune development in the vaccinated infant.<sup>10</sup> However, no association has been found between scar size and vaccine-specific immunity.<sup>11</sup>

Scar formation is delayed among low birth weight infants, although the majority do develop a scar.<sup>12–14</sup> As a result, the World Health Organization recommends that among the low birth weight infants (<2,500 g), the BCG vaccine should only be administered after the infant has achieved adequate weight. However, the relationships between preterm delivery and scar formation and size are inconclusive.<sup>14</sup> Similarly, little is known about the association of maternal characteristics and pregnancy complications with the size of the BCG scar.

A prospective cohort study conducted in Lima, Peru, between 1998 and 1999 characterized BCG scar formation in a periurban setting of Lima. In this study, 98% of children developed a scar.<sup>15</sup> However, the association of low birth weight, preterm births with the size and evolution of the BCG scar was not evaluated. Here, we describe the evolution of BCG scar diameter in infants born in a low-resource setting in the Peruvian Amazon during the same period and explore the relationship of scar size with birth and pregnancy characteristics. Additionally, we compare the evolution of scarring between this population and the previous Lima cohort.<sup>15</sup>

## Methods

### Study Site and Population

The study was conducted in Iquitos, the capital city of the Loreto region, located in the northeastern Peruvian Amazon. The overall population of Loreto is of 931,218 individuals, of whom 60.4% live in urban areas. Over a third (38.6%) of the population is 0 to 14 years old.<sup>3</sup> BCG coverage is estimated at 90.6%, whereas the incidence of tuberculosis is 101.9

per 100,000 individuals per year.<sup>3,16</sup> Although the reported prevalence of low birth weight is 6.6%, this statistic is based on only 55.9% of newborns weighed at birth. In comparison, 6.4% of infants are born with a low birth weight in Lima, where 93.4% of newborns are weighted.<sup>3</sup>

### Data Collection

Pregnant women attending antenatal controls at the Regional Hospital of Loreto, Iquitos Peru, were enrolled in a prospective cohort study between April 2005 and September 2006. Informed written consent was obtained during the antenatal care visit. Demographic information, and pregnancy and birth characteristics were obtained from medical records and from a survey administered by a nurse at birth. Normal birth weight infants received the BCG vaccine at birth, whereas low birth weight infants received the vaccine once they achieved a weight of 2,500 g. BCG administration was witnessed by a trained field worker.

Once BCG was administered, infants were followed biweekly for 6 months. At each visit, the diameter of the scar formed by BCG vaccine was measured at both transversal and vertical planes using a standardized measuring tape.<sup>15</sup> An average of both measures was calculated and recorded in millimeters. Gestational age was measured by the date of the last menstruation and by the Ballard Maturational Scores (range of 5–55 within 24 hours of birth).

As a method of comparison, we reanalyzed the data from 68 children enrolled in a previous cohort study in Lima, details of which have been previously published.<sup>15</sup> This study does not contain data on the mother's pregnancy history or continuous health information of newborns.

The study was approved by the Institutional Review Board of Johns Hopkins Bloomberg School of Public Health (Baltimore, MD) and of Asociación Benéfica Prima (Lima, Peru).

### Statistical Analysis

Scar diameter was modeled as a continuous outcome. Scar diameters above 20 mm were considered outliers based on the assessment of the measurement distribution and on clinical considerations. Days since BCG administration were used to model the change in scar diameter over the 6-month follow-up (12 visits or 168 days of follow-up). Covariates included birth weight (kg), Ballard Maturational Scores to estimate gestational age (range: 5–50), maternal body mass index (weight (kg)/height<sup>2</sup>), and the time interval (days) between birth and the administration of BCG vaccine.<sup>17</sup> Other covariates included the sex of the infant, the presence or absence of labor complications, the occurrence of fever during pregnancy (maternal self-report), and antibiotic consumption during pregnancy. Given that smoking and alcohol use during pregnancy are associated with lower birth weight, we also examined these characteristics among our study participants. Finally, maternal self-report of dengue and malaria infections during pregnancy were also included.

To assess baseline associations between the main exposure, birth weight, and other predictors related to the infant in relation to pregnancy characteristics, we performed two-sided *t*-tests for continuous covariates, and chi-square and Fisher exact tests for bivariate

covariates. The marginal model was assessed using simple and multiple linear regressions with generalized estimating equations. The models were fitted with robust variance estimation and an autoregressive variance–covariance structure to account for the within-child correlation between the repeated measures of the scar diameter over multiple visits. Collinearity of covariates was assessed by the variance inflation factor. Variables included in the final multivariate model were selected after examining QIC (Quasi-likelihood under the Independence model Criterion) values and considering their relevance as predictors of infant immunological status at birth and during the first 6 months of life. Time since BCG vaccination was modeled with the inclusion of both linear and squared predictors. Finally, the interaction between time and covariates related to pregnancy was also assessed. Type I error was set at 0.05 for all analysis, and all statistical analysis was performed in STATA 14.0 (Stata Corp, College Station, TX).

## Results

A total of 324 mothers were enrolled, and at least one follow-up visit was completed for 307 infants. Of those 307 children, 203 (62.7%) were followed for 6 months (12 visits), 267 (82.4%) for at least 5 months, and 306 (94.4%) for at least 2 months. Among the children with at least one complete visit, 59 (19.2%) weighed less than 2,500 g at birth and 248 (80.8%) had a normal birth weight. Gestational age according to the Ballard Maturational Scores was known for 295 infants. Eleven low birth weight infants were also preterm (18.6%), and 10 normal birth weight infants were preterm (4%). All but four children never developed a scar. Of those who did not develop a scar, only one was low birth weight and two were preterm. Birth and maternal characteristics are presented in ►Table 1. Among low birth weight children, an average of 26.4 (21.3–31.4) days elapsed from birth to BCG immunization, whereas only 3.2 (2.3–4.2) days elapsed for normal birth weight children ( $p < 0.001$ ). A similar pattern was found for preterm infants (►Table 1). Thirty-nine (15%) mothers reported fever during pregnancy overall, whereas eight (14.3%) mothers of low birth weight infants and 3 (10.5%) mothers of preterm infants reported fever. Similarly, 51 of 307 (20.5%) mothers reported malaria during pregnancy, of whom 10 delivered a low birth weight infant and 1 delivered a preterm infant. Among all children who developed a scar, the mean scar diameter was 3.6 mm (interquartile range: 3–4 mm). Overall, the mean scar diameter was 3.1 mm at 1 month, 4.2 at 2 months, 4.5 mm at 3 months, 3.7 mm at 4 months, 3.2 mm at 5 months, and 2.6 mm at 6 months. No difference was found between the final scar diameter of low birth weight, preterm infants and that of normal birth weight, full-term infants.

The evolution of the BCG scar diameter following vaccination increased nonlinearly over time; this was characterized in the marginal model through the inclusion of a quadratic time term (►Table 2). Additionally, unadjusted models showed that for each one-point increase in the Ballard Maturational Score, related to gestational age, the mean scar diameter increased by 0.13 mm (95% confidence interval [CI]: 0.03, 0.2 mm;  $p = 0.010$ ). Overall, the mean scar diameter of preterm infants was 1.4 mm (95% CI: 0.4, 2.4 mm;  $p = 0.006$ ) smaller than that of full-term infants. After adjusting for time since vaccination, preterm infants had a scar diameter that was 1.3 mm (95% CI: 0.4, 2.2 mm;  $p < 0.001$ ) smaller than that of full-term infants. Preterm delivery did not modify the evolution of the scar diameter over time.

Among children whose mother reported fever during pregnancy, the mean scar diameter was 1 mm (95% CI: 0.4, 1.6 mm,  $p < 0.001$ ) smaller compared with that of children whose mothers did not report fever. This relationship remained significant after adjusting for time since vaccination. Among children whose mother reported malaria during pregnancy, scar diameter was 0.4 mm (95% CI: 0.1, 0.6 mm;  $p = 0.006$ ) larger than that of children whose mothers who did not report malaria during pregnancy. However, after adjusting for reported maternal fever and time since vaccination, this relationship was no longer statistically significant. All other covariates were not statistically significantly associated with a change in scar diameter.

The final marginal model was adjusted for gestational age (according to the Ballard Maturational Score), birth weight, fever, and malaria during pregnancy. The evolution of the mean scar diameters (mm) throughout study visits by low birth weight, preterm status, and the presence or absence of fever during pregnancy is presented in ► Fig. 1.

The largest diameter among children in Iquitos (4.3 mm) was reached approximately 3 months after BCG administration in comparison to 2 months after BCG administration among the children of the Lima cohort (largest diameter: 3.6 mm). In Iquitos, the scar diameter decreased consistently until the end of follow-up. However, the scar diameter of children in Lima remained relatively constant and slightly increased at 6 months. The final scar diameter at visit 12 was 2.3 mm among the children of the Iquitos cohort and 3.4 mm among the children of the Lima cohort ( $p < 0.001$ ) (► Fig. 2).

## Discussion

This study provides new insights into the evolution of the BCG vaccine scar in infants living in tropical, low-resource settings. Prior studies have documented a “formation” phase following BCG administration, shifting to a “stabilization” phase at 2 months after BCG administration.<sup>15</sup> Our data show a maximum inflection point at a similar point in time. However, after plateauing for approximately 4 weeks, scar diameters in Iquitos decreased sharply, in a manner inconsistent with a “stabilization” phase. The final scar diameter at 6 months (2.3 mm) is low in comparison to prior studies in Mexico and Brazil, where final diameters were between 4.5 and 6 mm.<sup>12,14</sup> In this cohort, 98.7% of full-term children and 95.2% of preterm children developed scars, a proportion considered to be high if compared with reports from other LMICs.<sup>9,18–20</sup> We found no association between low birth weight and scar diameter, which is similar to what has been reported previously.<sup>12</sup> Previous studies have also shown that low birth weight infants have a similar immune response to the BCG vaccine compared with normal weight infants.<sup>12,14</sup> However, our findings do suggest that gestational age is associated with a smaller scar diameter. Additionally, children whose mothers reported an episode of fever during pregnancy had a reduced scar diameter. These results suggest that a systemic inflammatory reaction during pregnancy may alter the immune response to the BCG vaccine. However, they should be interpreted with caution since the number of mothers with fever was low ( $N = 39$ ) and because fever is a nonspecific symptom. Women in Iquitos are exposed to fever during pregnancy given the large burden of vector-borne diseases in the region, including dengue and malaria.<sup>21,22</sup> The association between scar diameter and malaria was significant in unadjusted but not in

adjusted models. Nevertheless, these results suggest that maternal illness may affect the immune reaction of the infant to BCG. Prior studies evaluating maternal infections during pregnancy and its effect of BCG vaccine efficacy produced inconclusive results.<sup>23,24</sup> Further research is needed to evaluate the effect of maternal and infectious and chronic diseases on the impact of BCG vaccine efficacy.

Socioeconomic and sanitation indicators also improved rapidly in Peru from 1999, (when the Lima study was conducted) to 2006, the time of this study. During the same period, child health indicators differed widely between Iquitos and Lima. Future studies should take into consideration sanitation indicators at the household level and association between immunity and BCG vaccination. Additionally, it would be of interest to compare current BCG scar diameters with those recorded more than one decade ago.

We did not examine the association of the scar diameter with concurrent and future health outcomes in children. Scar diameter is associated with child survival,<sup>5,9,10,25</sup> and Barreto et al reported a lower incidence of hookworm infections in children with a BCG scar.<sup>26</sup> Additionally, undernourished children have been shown to have a lower probability of scarring.<sup>27</sup> A further limitation of this study is that infants were not followed up until the BCG scars had reached a “stabilization” phase, which would have allowed a direct comparison with the size of the scar found during Lima’s stabilization phase. Finally, future studies should measure immunological correlates of protection to better understand the relationship between scar size and maternal health.

## Conclusion

In a birth cohort in a low-resource, tropical area of Peru, preterm children developed smaller BCG scars, compared with children born to term. Birth weight was not associated with scar development. These observations point to the BCG scar as a monitorable sentinel of vaccination when assessing programmatic coverage, as well as an indicator of cell-mediated immunity.

## Acknowledgments

### Funding

This work was supported by the National Institutes of Health (NIH) 5D43TW009349–03 “Inter-American Training for Innovations in Emerging Infectious Diseases” (to GOL). F. S. was supported by FONDECYT-CONCYTEC (grant contract number 246–2015-FONDECYT), and the UJMT Fogarty Global Health Fellows Consortium comprising Johns Hopkins University, the University of North Carolina, Morehouse University, and Tulane University (NIH Research Training Grant # D43 TW009340 funded by the NIH Fogarty International Center, NINDS, NIMH, NHBLI and NIEHS). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

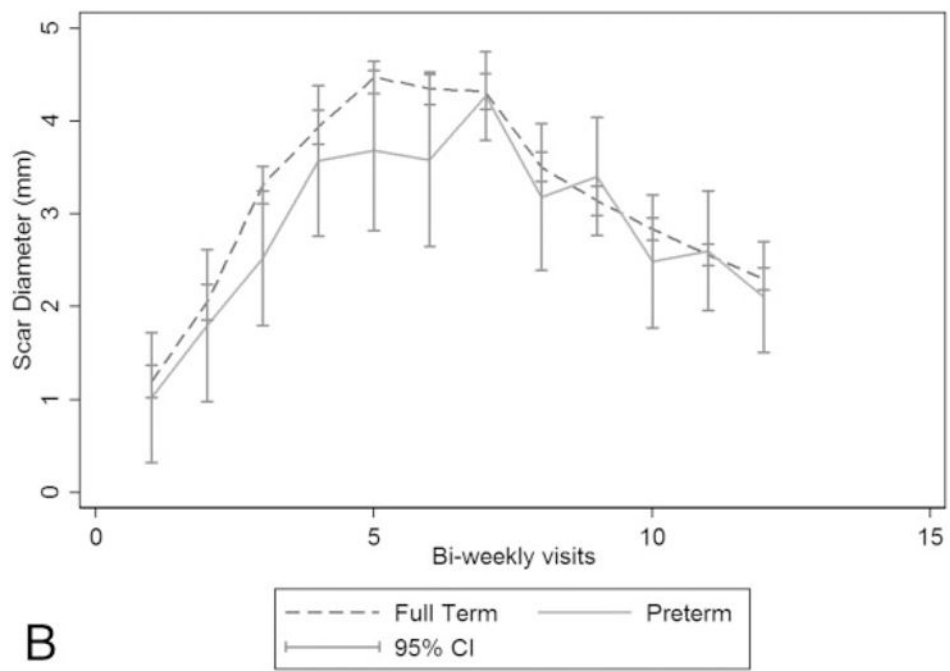
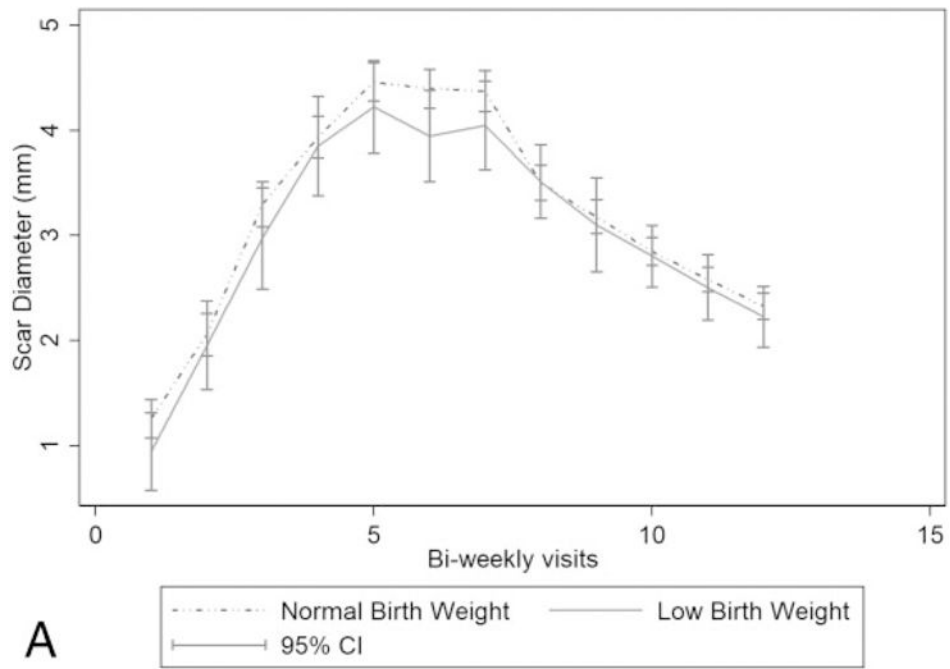
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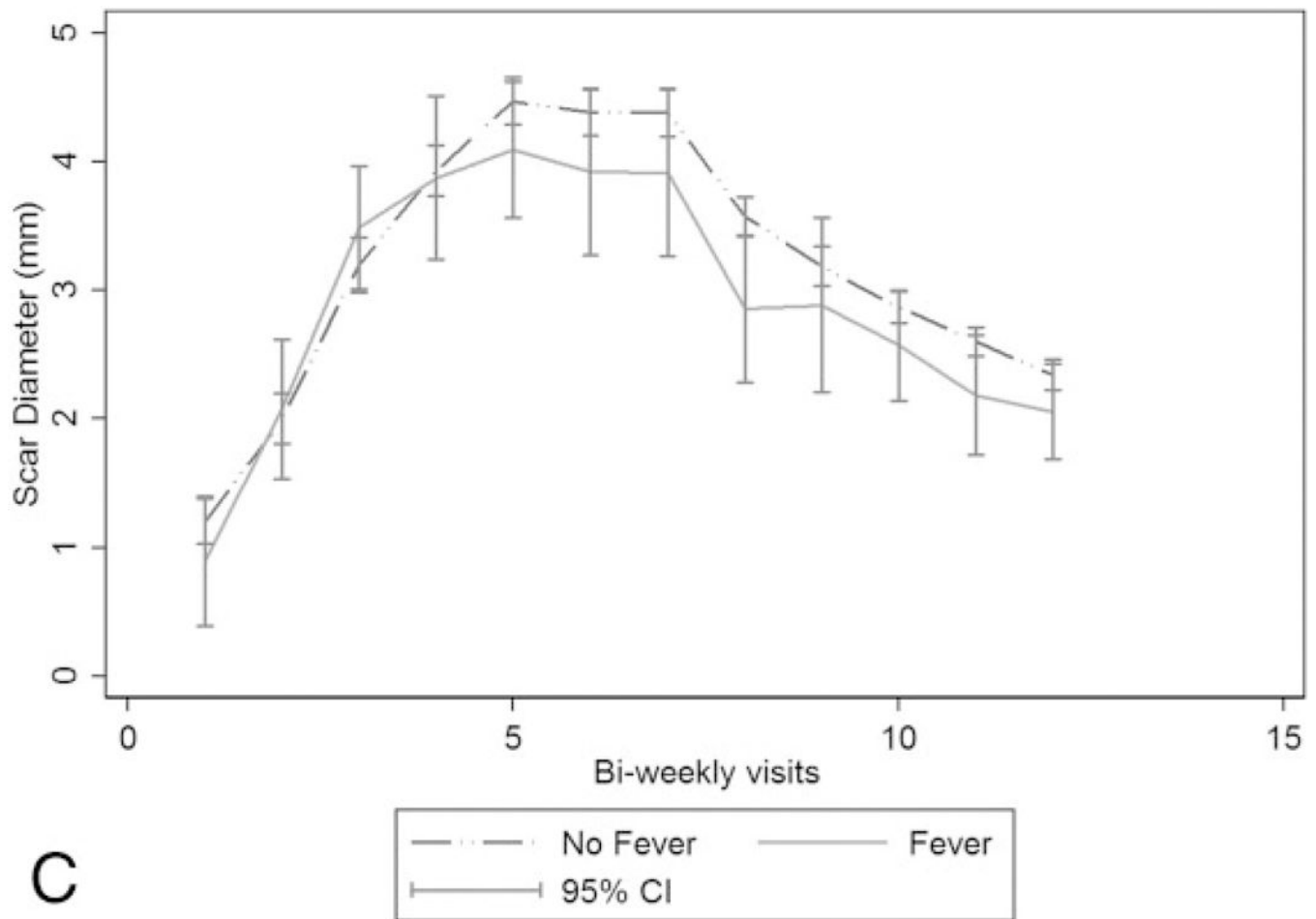


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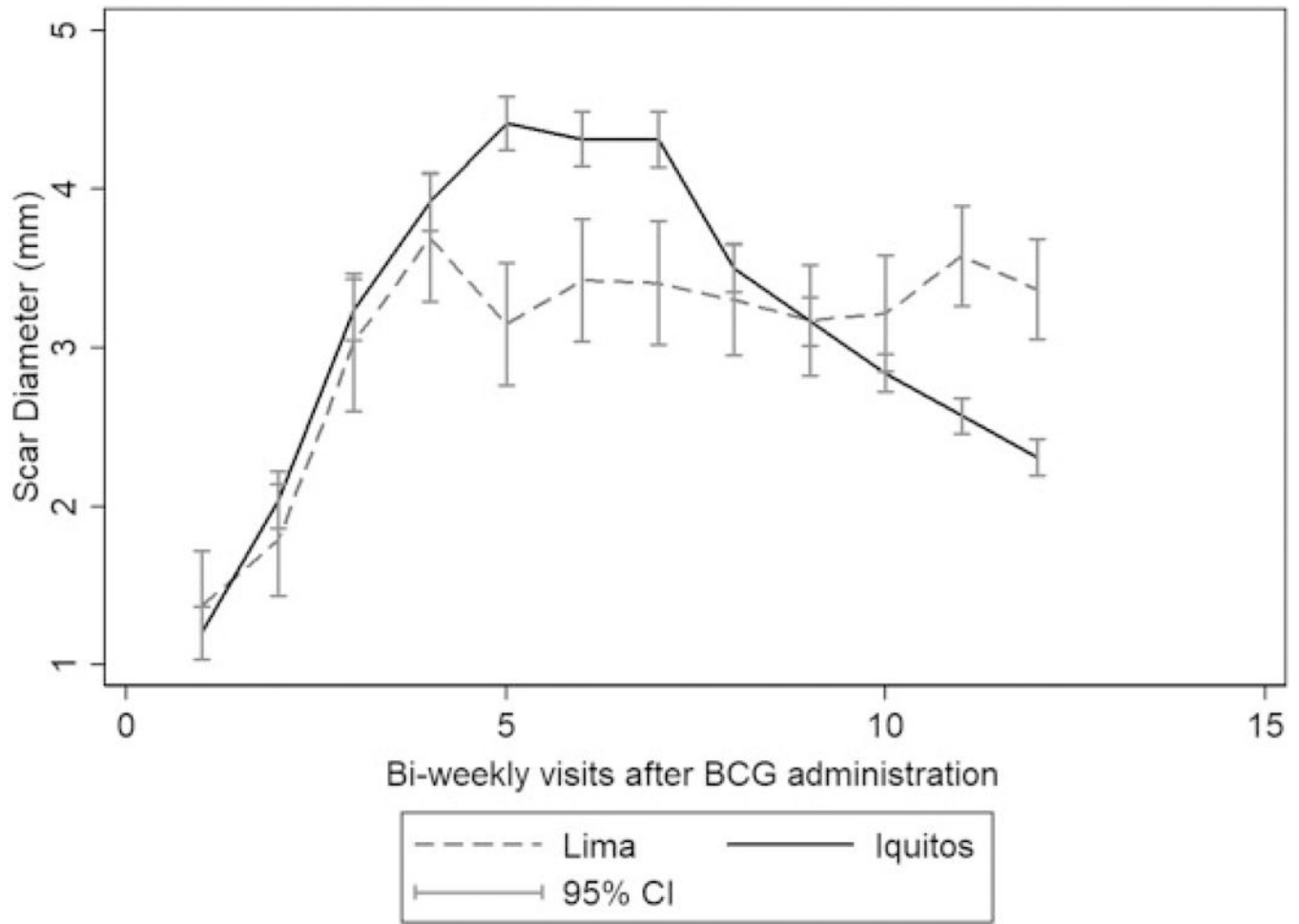
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**Fig. 1.** Evolution of the Bacillus Calmette–Guerin (BCG) scar diameter according to birth weight, gestational age, and maternal self-report of fever. (A) Evolution of the diameter of the BCG scar (mm) according to birth weight from birth to 6 months of age. *Dashed line* indicates normal birth weight. *Solid line* indicates low birth weight. (B) Evolution of the diameter of the BCG scar (in millimeters) according to gestational age (by Ballard Maturational Scores) from birth to 6 months of age. *Dashed line* indicates term births. *Solid line* indicates preterm births. (C) Evolution of the diameter of the BCG scar (in millimeters) according to maternal self-report of fever during pregnancy from birth to 6 months of age. *Dashed line* indicates no fever. *Solid line* indicates fever.



**Fig. 2.** Evolution of the Bacillus Calmette–Guerin scar diameter (in millimeters) in two distinct prospective birth cohorts: Iquitos (*solid line*) and Lima (*dashed line*), from birth to 6 months of age.

**Table 1**

Children's baseline characteristics by birth weight and gestational age

	Low birth weight (<2,500 g) (N = 59)	Normal birth weight (>2,500 g) (N = 248)	p-Value	Preterm births (N = 21)	Term births (N = 274)	p-Value
<b>Children characteristics</b>						
<b>Sex</b>						
Female	25 (42.4%)	131 (53.3%)	0.254	12 (57.1%)	140 (51.3%)	0.605
Male	34 (57.6%)	115 (46.8%)		9 (42.9%)	133 (48.72%)	
Birth complications	27 (45.8%)	10 (4.1%)	<0.001	7 (33.3%)		<0.001
Birth to BCG interval (mean days [95% CI])	26.4 (21.3–31.4)	3.2 (2.3–4.2)	<0.001	22.7 (10.7–34.8)	5.5 (4.3–6.7)	<0.001
<b>Pregnancy characteristics</b>						
Maternal BMI	22.1 (21.3–22.3)	22.5 (22.1–22.9)	0.323	22 (20.5–23.4)	22.5 (22.2–22.9)	0.459
Fever	8 (13.6%)	31 (12.5%)	0.395	2 (9.5%)	36 (13.1%)	0.357
Alcohol Consumption	31 (56.4%)	118 (49.6%)	0.364	6 (31.6%)	136 (51.9%)	0.100
Smoking	1 (1.8%)	0 (0%)	0.340	0 (0%)	1 (0.37%)	1
Antibiotic use	27 (47.4%)	113 (46.4%)	0.927	10 (50%)	124 (46.4%)	0.758
Malaria infection	10 (17.5%)	41 (16.9%)	0.903	1 (5%)	47 (17.5%)	0.215
Dengue infection	5 (8.8%)	19 (7.8%)	0.788	1 (5%)	22 (8.2%)	1

Abbreviations: BCG, Bacillus Calmette–Guerin; BMI, body mass index; CI, confidence interval.

**Table 2**

Association between BCG scar diameter and infant and pregnancy characteristics

	Crude		p-Value		Adjusted		p-Value	
	Change in scar diameter (mm)	95% CI			Change in scar diameter (mm)	95% CI		
<b>Children characteristics</b>								
Time (days between birth and BCG administration)	0.08	0.07–0.092	< <b>0.001</b>		0.08	0.07–0.09	< <b>0.001</b>	
Time ^ 2	-0.0004	-0.0005 to -0.0004	< <b>0.001</b>		0	-0.0005 to -0.0004	< <b>0.001</b>	
Sex	0.12	-0.19 to 0.44	0.440					
Birth weight (grams)	0	-0.0002 to -0.0006	0.346		$2.97 \times 10^{-5}$	$-3.49 \times 10^{-4}$ to $-4.09 \times 10^{-4}$	0.878	
Gestational age (weeks)	0.13	0.03–0.23	<b>0.010</b>		0.13	0.02–0.24	<b>0.017</b>	
Preterm birth	-1.41	-2.42 to -0.40	<b>0.006</b>					
Birth complications	-0.79	-1.72 to 0.14	0.095					
<b>Pregnancy characteristics</b>								
Maternal BMI	-0.01	-0.06 to 0.05	0.817					
Alcohol consumption	-0.04	-0.34 to 0.26	0.795					
Fever	-0.1	-1.64 to -0.35	<b>0.002</b>		-1.14	-1.82 to -0.46	<b>0.001</b>	
Malaria infection	0.37	0.10–0.64	<b>0.006</b>		0.26	-0.09 to 0.61	0.143	
Dengue infection	0.15	-0.70 to 1	0.731					
Antibiotic consumption	-0.17	-0.47 to 0.13	0.268					

Abbreviations: BCG, Bacillus Calmette–Guerin; BMI, body mass index; CI, confidence interval.

Note: Bold values signify  $p < 0.05$ .