Acute Lower Respiratory Infection Among Bacille Calmette-Guerin (BCG)–Vaccinated Children

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**KEY WORDS**

childhood immunization, Bacille Calmette-Guerin (BCG) vaccine, diphtheria-tetanus-pertussis (DTP) vaccine, respiratory tract infection, developing countries

**ABBREVIATIONS**

apRR—adjusted/propensity score-weighted relative risk
ALRI—acute lower respiratory infection
BCG—Bacille Calmette-Guerin
CI—confidence interval
DHS—Demographic and Health Survey
DTP—diphtheria, tetanus, pertussis
IQR—interquartile range
MICS—Multiple Indicator Cluster Survey
PS—Propensity Score
RR—Relative risk

Dr Hollm-Delgado contributed to the study concept, design, and analysis, to interpretation of results, and drafted the manuscript; Dr Stuart contributed to the study analysis design, interpretation of results, and review and revision of the manuscript; Dr Black contributed to the study concept and design, interpretation of results, and review and revision of the manuscript; and all authors approved the final version of the manuscript as submitted.

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**WHAT’S KNOWN ON THIS SUBJECT:** Bacille Calmette-Guerin (BCG) vaccination may provide benefits beyond protecting against pediatric tuberculosis. Evidence suggests links between cell-mediated immunity from tuberculosis and bacterial/viral-related pneumonia but the impact of BCG on acute lower respiratory infection is not fully known.

**WHAT THIS STUDY ADDS:** BCG-vaccinated children had a lower risk of suspected acute lower respiratory infection. Protection was amplified when children were vaccinated against diphtheria-tetanus-pertussis (DTP). Number of DTP doses did not modify this effect, but order in which vaccines were received did.

**OBJECTIVE:** To determine whether Bacille Calmette-Guerin (BCG) vaccination is linked to the risk of acute lower respiratory infection (ALRI) among children <5 years of age.

**METHODS:** Data from Macro International Demographic and Health Surveys and United Nations Children’s Fund Multiple Indicator Cluster Surveys were used to identify a primary cohort of 58,021 children in 19 countries (2005–2010) and a secondary cohort of 93,301 children in 18 countries (2000–2007). Information was collected by trained interviewers during home visits using standardized questionnaires, review of vaccination health cards, and measurement of health indicators.

**RESULTS:** BCG vaccination was associated with a 17% to 37% risk reduction for suspected ALRI in both cohorts. The only vaccine or vitamin supplement to modify the effect of BCG was diphtheria-tetanus-pertussis (DTP; P < .001). The order in which the vaccines were first received was central to this phenomena (BCG before DTP, adjusted/propensity score–weighted relative risk [apRR]: 0.79, 95% confidence interval [CI]: 0.70–0.89; BCG with DTP, apRR: 0.82, 95% CI: 0.71–0.94; and BCG after DTP, apRR: 1.00, 95% CI: 0.87–1.13) but not number of DTP doses received. Other modifiers included vaccine strain used in immunization programs, chlorinating drinking water, using wood-burning fuel cook stoves, and owning livestock.

**CONCLUSIONS:** Children vaccinated with BCG had a significantly lower risk of suspected ALRI. Clarification is needed as to whether this is due to reductions in the underlying risk of tuberculosis or ALRI per se. *Pediatrics* 2014;133:e73–e81
Bacille Calmette-Guerin (BCG) vaccines represent one of the most widely used forms of childhood immunization in the world. Most effective at preventing miliary and meningeal forms of pediatric tuberculosis, the vaccine has gained much attention in recent years for its unintended health benefits, including risk reductions in cancer, asthma and overall child mortality. Some evidence suggests BCG vaccination may also be associated with lower risks of acute lower respiratory infections (ALRI) and respiratory syncytial virus in children from Guinea-Bissau. Presence of scarring at inoculation sites has also been linked to risk reductions in pneumonia-related childhood mortality in Brazil. However, determining whether these results are generalizable to children living outside indicated study regions is difficult given established variations in adaptive immune responses to BCG between and within local populations over time.

A link between cell-mediated immunity from tuberculosis and pathogens causing bacterial/viral-related ALRI has previously been raised. Tuberculosis is thought to increase the risk of superinfection with major causes of community-acquired childhood pneumonia—namely, Streptococcus pneumoniae and Haemophilus influenzae type B. Tuberculin skin test reactivity can also act as a risk marker for Mycoplasma pneumonia among the elderly and is correlated with clinical severity and radiographic presentation of pulmonary lesions caused by M pneumonia. Beyond this evidence, the literature on BCG-ALRI associations remain limited, likely due to several factors including historical difficulties in ascertaining vaccination status from health records or vaccination cards, high BCG vaccination rates in the general population (85% worldwide coverage rate with national coverage ranging from 43% to 99%), and ethical constraints in conducting randomized clinical trials to evaluate routinely used childhood vaccines. Further complicating this line of research has been the established ineffectiveness of BCG for inducing protective immunity against tuberculosis among adults and its contraindicated use among HIV-infected individuals.

Considering the importance of clarifying the role of BCG in the development of ALRI, we undertook an exploratory analysis of national health survey data from 33 low- and middle-income countries (1) to examine globally whether BCG vaccination is associated with the risk of suspected ALRI from birth to 60 months of age and (2) to identify possible modifiers of this effect.

METHODS
Source of Data
Data regarding suspected ALRI and BCG status were extracted from the United Nations Children's Fund Multiple Indicator Cluster Survey (MICS) and Macro International Demographic and Health Survey (DHS). These nationally representative household surveys were conducted in low- and middle-income countries once every 5 years with the primary goal of collecting demographic and population health data on women of reproductive age (15–49 years) and children <5 years of age. Both surveys used a multistage sampling process in which sampling units (eg, census enumeration blocks) were first selected with a probability proportional to cluster size. Households within each sampling cluster were then randomly chosen in which eligible women and children were finally identified. Trained interviewers used standardized questionnaires to collect information from participants during home interviews on a range of issues related to population, health, and nutrition. This included asking mothers questions related to maternal-child health such as access to antenatal care during previous pregnancy, receipt of tetanus vaccine before last birth, breastfeeding status of child, and mother’s highest educational level. In a subset of surveys, trained personnel also measured children’s weight (grams), recumbent length (meters) if <2 years of age, and standing height (meters) if ≥2 years.

Selection Criteria
Our primary study cohort consisted of subjects identified from DHS-V surveys conducted between 2005 and 2010 in countries using single or multiple BCG vaccine strains in their national immunization program. Types of vaccine strains used in national immunization programs were identified from previously published literature. Given the known variability in the effectiveness of BCG across populations, we then validated our primary cohort results by assembling a secondary cohort of children from DHS and MICS surveys conducted between 1986 and 2010 in countries using only single BCG vaccine strains in their immunization program. This cohort was also used to characterize strain and temporal changes in BCG effects. Children in the primary cohort were excluded from the secondary cohort to ensure mutually exclusive study groups. Data were thus extracted for the primary cohort from 19 DHS surveys in 19 countries and, for the secondary cohort, from 56 DHS and 26 MICS surveys in 30 countries. None of these countries used H influenzae type B or S pneumoniae vaccines in their immunization programs at the time that health surveys were conducted.
and whose mother and/or caregiver presented interviews with a health card documenting the child's vaccination schedule. Children whose health card indicated that they were not vaccinated but whose mother/guardian recalled them as having been vaccinated (eg, immunization campaign) were excluded from our analysis. We also excluded children with incomplete BCG and disease outcome data, yielding a data set of 58,021 children from 38,678 households in 19 countries for the primary cohort, and 153,169 children from 96,454 households in 26 countries for the secondary cohort. Removing 11,400 overlapping subjects from the primary cohort, our secondary cohort consisted of 141,769 children. Complete confounder information was available for 58,021 children in the primary cohort and 93,301 in the secondary cohort.

**Classification of Disease Outcomes and BCG Vaccination Status**

Our primary outcome was suspected ALRI, which occurred if parents/guardians reported a child as having a cough accompanied by rapid or difficult breathing during the 2 weeks before home-based interviews. It should be noted that children with pulmonary tuberculosis typically present chronic cough in the absence of respiratory distress and thus would be classified as having chronic cough in the absence of respiratory distress and thus would be noted that children with chronic cough accompanied by rapid or difficult breathing during the 2 weeks before home-based interviews. Our primary outcome was suspected ALRI using complete subject analysis and adjusting models for clustering within households and communities. The following a priori confounders were included in our model: children's age, gender, breastfeeding status, low birth weight (ie, <2500 g), number of household members, mother's highest education level (none, primary, secondary, or postsecondary), household use of clean-burning fuel stove, household use of tobacco, wealth index score (poorest, poorer, middle, richer, richest), and residing in rural versus urban settings. Our reference group was BCG unvaccinated children. Additional analysis was performed evaluating the risk of suspected ALRI by age at time of BCG vaccination, period of time since vaccination, calendar year of vaccination (only secondary cohort), vaccine strain or genotype (only secondary cohort), sequential ordering of BCG in relation to other childhood vaccines, and population burden of childhood HIV (<10% prevalence [low burden] vs ≥10% [high burden]).

Vaccine strain/genotype analysis was based only on secondary cohort members vaccinated between 2003 and 2007, because strain type could not be verified beyond this time period. To visually and statistically assess nonlinear dependency structures for continuous variables, we conducted nonparametric regression using generalized additive models fitted with smoothing splines. For linear effects, statistically significant trends were assessed by including factors as continuous terms in the marginal regression model. For nonlinear effects, factors were categorized at critical points where effects would change. Host and environmental modifiers of vaccine effectiveness were identified by individually testing cross-product terms between BCG and each of the following factors: gender, age, low birth weight, weight-for-age or height-for-age z score, breastfeeding status, rural versus urban setting, household use of tobacco, type of fuel used in cook stove, ownership of different types of livestock, and manner in which household drinking water was decontaminated.

Because receipt of vaccination could itself be acting as a surrogate for other health-related factors, we weighted models by the inverse probability of the conditional likelihood of being vaccinated (ie, propensity score model). Factors in the model included published determinants of vaccine use namely, children's age, gender, low birth weight, breastfeeding status, weight-for-age z score, height-for-age z score, residing in rural versus urban setting, presence of radio or television at home, number of persons residing in household, and wealth index score, as well as mother/caregiver's age, highest educational level, mother's vaccination...
status against tetanus, and access to antenatal care during last pregnancy). With <10% of the propensity score model database missing values, multiple multivariate imputation \((m = 5)\) by chained equations\(^{31,32}\) was used to impute data. Numerical balance in covariate distributions between vaccination groups were assessed by calculating the standardized bias for each covariate before and after weighting. The measure was estimated as the group difference in means or proportions divided by the SD for the overall population. Factors were considered balanced between vaccinated and nonvaccinated groups if the absolute value of the weighted standardized difference in mean values were <0.25.

Statistical analyses were performed by using SAS version 9.3 (SAS, Cary, NC) and IVEware version 0.2 (Ann Arbor, MI). Johns Hopkins Bloomberg School of Public Health Institutional Review Board office determined this research project to be nonhuman subject research (DDHS regulation 45 CFR 46.102).

RESULTS

Among 58,021 survey participants in the primary cohort, 8682 (15%) children were reported as having suspected ALRI during the 2 weeks preceding study interviews, from which 2844 (33%), 7733 (89%), and 7819 (90%) were also reported as having diarrhea or acute and chronic malnutrition, respectively. Of the participants, 55,928 (98%) children were BCG vaccinated. Median age at vaccination was 1 month (interquartile range [IQR]: 0–1 month), with more than half of children being inoculated with BCG before DTP (35,657/46,467 or 77%) and measles vaccines (36,021/36,792 or 98%), within the same month (26,563/28,464 or 93%) as a polio vaccine, and after a vitamin A supplement (19,432/20,240 or 96%). Median time since vaccination was 22 months (IQR: 9–37). Children were BCG vaccinated between 2000 and 2010 in the primary cohort and between 1995 and 2009 in the secondary cohort. Secondary cohort children were comparable to those in the primary cohort in terms of BCG vaccination rates (90.529/93.301 or 97%), median age at vaccination (1 month, IQR: 0–2 months), and time since vaccination (22 months, IQR: 10–38 months). Strongest determinants of BCG vaccine uptake included mother's highest level of education, access to antenatal care, and wealth index score.

Association Between BCG and Suspected ALRI in Both Cohorts

BCG vaccination was associated with a 17% to 37% risk reduction in suspected childhood ALRI among both study cohorts. Table 1 shows protective effects were stronger in regions with a low HIV burden and remained protective if ALRI was accompanied by acute or chronic malnutrition. The pattern of this effect depended on a child's age at time of vaccination (Fig 1), particularly if inoculated from birth to 9 months of age. An increasingly protective trend was also identified by calendar year of vaccination when including the factor as a continuous term in the model (primary cohort, adjusted/propensity score–weighted relative risk [apRR]: 0.94, 95% confidence interval [CI]: 0.92–0.96; secondary cohort, apRR: 0.93, 95% CI: 0.90–0.96, but no trend was identified by time since vaccination (primary cohort, apRR: 0.99, 95% CI: 0.99–1.00; secondary cohort, apRR: 0.99, 95% CI: 0.98–0.99) for children 9 to 60 months of age. In the secondary cohort, BCG was more protective if children were vaccinated with BCG Pasteur strains (apRR: 0.45, 95% CI: 0.36–0.55) compared with those vaccinated using BCG Russia/Bulgaria (apRR: 0.67, 95% CI: 0.54–0.83), BCG Japan (apRR: 0.75, 95% CI: 0.56–1.00) and BCG Denmark (apRR: 0.77, 95% CI: 0.63–0.95) strains. This strain difference remained even after stratifying models by vaccine genotype (BCG Genotype II, apRR: 0.69, 95% CI: 0.55–0.88; BCG Genotype III, apRR: 0.77, 95% CI: 0.63–0.95; BCG Genotype IV, apRR: 0.45, 95% CI: 0.36–0.55).

Modifiers of BCG Vaccine Effectiveness in the Primary Cohort

Figure 2 shows that the only vaccine or vitamin supplement to modify the BCG-ALRI association was DTP (DTP-vaccinated children, apRR: 0.70, 95% CI: 0.61–0.82; DTP unvaccinated children, apRR: 1.21, 95% CI: 0.99–1.48). This effect remained when accounting for use of 3 DTP doses, a standard global marker for overall vaccine uptake. Among children vaccinated with DTP, modification was strongest if BCG was given before or within the same month as the first dose of DPT but not after (BCG before DTP, apRR: 0.79, 95% CI: 0.70–0.89; BCG with DTP, apRR: 0.82, 95% CI: 0.71–0.94; or BCG after DTP, apRR: 1.00, 95% CI: 0.87–1.13). However, this effect was not influenced by number of DTP vaccinations received (1 dose, apRR: 0.55, 95% CI: 0.43–0.69; 2 doses, apRR: 0.95, 95% CI: 0.68–1.34; or 3 doses, apRR: 0.79, 95% CI: 0.63–1.00). Figure 3 shows that BCG-ALRI associations were also modified if families owned horses, goats, or sheep; used chlorinated drinking water; or used wood-burning fuel cook stoves.

DISCUSSION

Our population-based analysis in 33 countries over a 25-year time period revealed that children vaccinated with BCG had a 17% to 37% lower risk of presenting suspected ALRI compared with those left unvaccinated. Protection was amplified if children were co-vaccinated against DTP, with order of vaccine administration playing a central role in the magnitude of this effect. Although number of DTP doses did not
modify the effectiveness of BCG against suspected ALRI, increased reactivity to both tuberculin and DTP antigens after BCG vaccination has been shown in other studies.\(^{33,34}\) In particular, endotoxins within whole-cell pertussis vaccines are thought to act as adjuvants during the primary immune response to other vaccines, possibly by increasing carrier-specific helper T cells.\(^{35}\) Our study also revealed a small but increasingly protective trend in the effect of BCG over successive calendar years. Although this finding is inconsistent with a previously proposed theory suggesting that the ineffectiveness of BCG against adult tuberculosis may be due to attenuated immunogenicity after successive in vitro passages of the vaccine,\(^{36}\) it is interesting to note that the strongest protective effects observed in our study occurred in regions using BCG Pasteur strains (ie, a genealogically younger vaccine strain).\(^{37}\) Additional research is needed to clarify whether these findings represent a true strengthening of vaccine effectiveness against suspected ALRI or temporal changes in residual confounding.

In terms of vaccine effect modifiers, participants exposed to wood smoke were more likely to present with suspected ALRI if they were BCG vaccinated. Reasons for this effect are not clear. However, indoor wood smoke, a known risk factor for lower respiratory infections,\(^{38,39}\) may enhance the risk of infection by increasing exposure to environmental sources of mycobacteria. This finding is consistent with previous studies that showed a positive association between indoor wood smoke and childhood tuberculosis.\(^{40,41}\) In contrast, the protective effect of BCG against other respiratory pathogens, such as influenza, was not observed in our study. This may be due to the lower incidence of influenza in the study population or the limited power of the study to detect a significant effect.

### Table 1: Impact of BCG Vaccination on the Risk of Suspected Acute Lower Respiratory Infection among Children in Both Study Cohorts

<table>
<thead>
<tr>
<th>Disease Outcome</th>
<th>Primary Cohort(^a)</th>
<th>Secondary Cohort(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Pneumonia Cases/Total No. Subjects (%)</td>
<td>No. of Pneumonia Cases/Total No. Subjects (%)</td>
</tr>
</tbody>
</table>
| Pneumonia                                      | Not BCG Vaccinated (18) | 829/5928 (13) | Unweighted By PS | 0.83 (0.74–0.94) | 882/2772 (32) | 19
|                                                | BCG Vaccinated (13)   | 829/5928 (13) | Weighted by PS  | 0.83 (0.74–0.94) | 882/2772 (32) | 19
| Low country burden of pediatric HIV            | Not BCG Vaccinated (19) | 461/2390 (16) | Unweighted By PS | 0.75 (0.66–0.86) | 581/2390 (31) | 16
|                                                | BCG Vaccinated (14)   | 461/2390 (16) | Weighted by PS  | 0.75 (0.66–0.86) | 581/2390 (31) | 16
| High country burden in pediatric HIV           | Not BCG Vaccinated (15) | 368/2278 (16) | Unweighted By PS | 1.09 (0.85–1.40) | 321/2404 (34) | 36
|                                                | BCG Vaccinated (10)   | 368/2278 (16) | Weighted by PS  | 1.09 (0.85–1.40) | 321/2404 (34) | 36
| Pneumonia plus diarrhea\(^c\)                  | Not BCG Vaccinated (7)  | 272/5051 (5)   | Unweighted By PS | 0.92 (0.78–1.12) | 329/2219 (15) | 55
|                                                | BCG Vaccinated (5)    | 272/5051 (5)   | Weighted by PS  | 0.92 (0.78–1.12) | 329/2219 (15) | 55
| Pneumonia plus acute malnutrition\(^c\)        | Not BCG Vaccinated (14) | 616/53775 (11) | Unweighted By PS | 0.85 (0.74–0.97) | 800/2650 (30) | 28
|                                                | BCG Vaccinated (11)   | 616/53775 (11) | Weighted by PS  | 0.85 (0.74–0.97) | 800/2650 (30) | 28
| Pneumonia plus chronic malnutrition\(^c\)      | Not BCG Vaccinated (17) | 747/25101 (14) | Unweighted By PS | 0.84 (0.74–0.93) | 819/2709 (30) | 10
|                                                | BCG Vaccinated (14)   | 747/25101 (14) | Weighted by PS  | 0.84 (0.74–0.93) | 819/2709 (30) | 10

**Notes:**

- PS, propensity score; RR, relative risk.
- Models using the primary cohort were adjusted for the following covariates: child’s age, gender, breastfeeding status, family size, low birth weight, mother’s highest level of education, household use of clean-burning fuel stove, household use of tobacco, wealth index score, and rural versus urban setting.
- Models using the secondary cohort were adjusted for the following covariates: child’s age, gender, breastfeeding status, family size, mother’s highest level of education, household use of clean-burning fuel stove, and rural versus urban setting. Birth weight, tobacco use, and wealth index score were not adjusted for in the model because of incomplete information and differences in survey data collection for these variables between DHS and MICS surveys.
- Estimates based on a generalized estimating equation regression model weighted by a child’s inverse likelihood of being vaccinated.

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**References:**

if owning sheep or goats (ie, zoonotic sources of mycobacteria)40 and enhanced protection if owning horses (ie, animal more resistant to mycobacteria). Chlorinating drinking water was also protective, possibly by removing residual mycobacteria commonly found in drinking water distribution systems.41,42 Taken together, these observations support

FIGURE 1
A. Nonparametric relationship between time since BCG vaccination and risk of suspected ALRI from birth to 60 months of age in the primary cohort. B. Relative risk of suspected ALRI among children 9 to 60 months old, by age at BCG vaccination in the primary cohort. *Age categories based on developmental milestones in infant immunity maturation: overall antibody concentrations lowest at 3 months; maternal serum antibodies disappear by 9 months. #See table 1 footnote for adjusted variables. PS, propensity score.

FIGURE 2
Interactions between BCG and other standard childhood vaccinations or vitamin supplements on the risk of suspected ALRI in the primary cohort. Symbols: Bars (I), 95% CI; dots (○), point estimate. Models were stratified by whether children did (●) or did not receive (○) the other vaccine/supplement. Reference group was BCG unvaccinated children for all plots. See Table 1 footnote for adjusted variables.
<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Not BCG Vaccinated</th>
<th>BCG Vaccinated</th>
<th>Adjusted Relative Risk (95% CI)</th>
<th>P Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>383/2093</td>
<td>8299/55 928</td>
<td>0.83 (0.7–0.9)</td>
<td>—</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boys</td>
<td>194/1044</td>
<td>4261/28 250</td>
<td>0.83 (0.7–1.0)</td>
<td>0.87</td>
</tr>
<tr>
<td>Girls</td>
<td>189/1049</td>
<td>4038/21 678</td>
<td>0.83 (0.7–1.0)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 11 months</td>
<td>101/604</td>
<td>2147/13 590</td>
<td>0.96 (0.8–1.2)</td>
<td>Ref</td>
</tr>
<tr>
<td>11 – 23.9 months</td>
<td>103/439</td>
<td>2370/14 420</td>
<td>0.72 (0.6–0.9)</td>
<td>0.04</td>
</tr>
<tr>
<td>24 – 39.9 months</td>
<td>101/528</td>
<td>2160/14 481</td>
<td>0.73 (0.6–0.9)</td>
<td>0.07</td>
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<tr>
<td>≥40 months</td>
<td>78/522</td>
<td>1622/14 637</td>
<td>0.78 (0.6–1.0)</td>
<td>0.13</td>
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<tr>
<td>Low birth weight</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>No</td>
<td>373/2034</td>
<td>7788/52 827</td>
<td>0.82 (0.7–0.9)</td>
<td>0.43</td>
</tr>
<tr>
<td>Yes</td>
<td>10/59</td>
<td>511/3101</td>
<td>1.10 (0.5–2.2)</td>
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<tr>
<td>Weight-for-age z score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; −3 SD</td>
<td>46/306</td>
<td>876/67 885</td>
<td>0.93 (0.7–1.3)</td>
<td>0.95</td>
</tr>
<tr>
<td>−3 to 2.9 SD</td>
<td>307/1632</td>
<td>663/64 435</td>
<td>0.80 (0.7–0.9)</td>
<td>0.69</td>
</tr>
<tr>
<td>≥3 SD</td>
<td>30/155</td>
<td>787/47 10</td>
<td>0.90 (0.6–1.4)</td>
<td>Ref</td>
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<tr>
<td>Height-for-age z score</td>
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<td></td>
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<tr>
<td>&lt; −3 SD</td>
<td>185/977</td>
<td>4119/25 650</td>
<td>0.84 (0.7–1.0)</td>
<td>0.52</td>
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<tr>
<td>−3 to 2.9 SD</td>
<td>196/7104</td>
<td>4143/29 841</td>
<td>0.81 (0.7–1.0)</td>
<td>0.56</td>
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<tr>
<td>≥3 SD</td>
<td>2/12</td>
<td>37/437</td>
<td>0.45 (0.1–3.4)</td>
<td>Ref</td>
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<td>Breastfeeding status</td>
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<td>No</td>
<td>339/699</td>
<td>3049/21 356</td>
<td>0.72 (0.6–0.9)</td>
<td>0.07</td>
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<td>Yes</td>
<td>244/400</td>
<td>526/54 672</td>
<td>0.89 (0.8–1.0)</td>
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<td>Type of community</td>
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<td></td>
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<td></td>
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<tr>
<td>Urban</td>
<td>68/343</td>
<td>1597/13 570</td>
<td>0.65 (0.5–0.9)</td>
<td>0.07</td>
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<td>Rural</td>
<td>320/1750</td>
<td>679/52 358</td>
<td>0.87 (0.8–1.0)</td>
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<td>Household uses tobacco</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>No</td>
<td>11/68</td>
<td>265/1682</td>
<td>0.82 (0.7–0.9)</td>
<td>0.66</td>
</tr>
<tr>
<td>Yes</td>
<td>37/2025</td>
<td>803/54 228</td>
<td>1.01 (0.5–2.1)</td>
<td></td>
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<tr>
<td>Type of fuel stove</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Electricty</td>
<td>3/23</td>
<td>155/2102</td>
<td>0.56 (0.2–1.8)</td>
<td>0.82</td>
</tr>
<tr>
<td>Paraffin/kerosene</td>
<td>5/42</td>
<td>141/1869</td>
<td>0.60 (0.2–1.5)</td>
<td>1.00</td>
</tr>
<tr>
<td>Liquid propane/natural gas/biogas</td>
<td>5/50</td>
<td>322/2914</td>
<td>0.67 (0.3–1.8)</td>
<td>0.88</td>
</tr>
<tr>
<td>Coal/ignite/charcoal</td>
<td>188/612</td>
<td>1584/2334</td>
<td>0.76 (0.6–0.9)</td>
<td>Ref</td>
</tr>
<tr>
<td>Dung</td>
<td>2/7</td>
<td>71/202</td>
<td>0.88 (0.1–5.5)</td>
<td>0.81</td>
</tr>
<tr>
<td>Wood</td>
<td>174/2350</td>
<td>590/39 795</td>
<td>1.19 (1.0–1.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ownership of livestock</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Avian</td>
<td>173/974</td>
<td>3965/25 745</td>
<td>0.85 (0.7–1.0)</td>
<td>0.91</td>
</tr>
<tr>
<td>Bovine</td>
<td>220/1159</td>
<td>4534/28 183</td>
<td>0.80 (0.7–0.9)</td>
<td></td>
</tr>
<tr>
<td>Pigs</td>
<td>292/1543</td>
<td>648/43 271</td>
<td>0.83 (0.7–1.0)</td>
<td>0.82</td>
</tr>
<tr>
<td>Yes</td>
<td>91/550</td>
<td>1811/12 657</td>
<td>0.82 (0.7–1.1)</td>
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<tr>
<td>Horse</td>
<td>303/1804</td>
<td>7358/51 274</td>
<td>0.89 (0.8–1.0)</td>
<td>0.08</td>
</tr>
<tr>
<td>No</td>
<td>80/289</td>
<td>941/4654</td>
<td>0.68 (0.3–0.9)</td>
<td></td>
</tr>
<tr>
<td>Sheep</td>
<td>342/1542</td>
<td>778/52 858</td>
<td>0.87 (0.8–1.0)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>No</td>
<td>43/151</td>
<td>519/3070</td>
<td>0.48 (0.3–0.7)</td>
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</tr>
<tr>
<td>Yes</td>
<td>279/1487</td>
<td>612/64 3114</td>
<td>0.77 (0.7–0.9)</td>
<td>0.02</td>
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<tr>
<td>Goat</td>
<td>304/606</td>
<td>2173/12814</td>
<td>1.00 (0.8–1.3)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>359/1883</td>
<td>781/52 2958</td>
<td>0.78 (0.7–0.9)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Yes</td>
<td>24/110</td>
<td>487/2970</td>
<td>1.59 (1.0–2.6)</td>
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</tr>
<tr>
<td>Type of water treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boiled</td>
<td>342/1847</td>
<td>6837/43 671</td>
<td>0.87 (0.8–1.0)</td>
<td>0.29</td>
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<tr>
<td>Yes</td>
<td>41/237</td>
<td>1454/12 144</td>
<td>0.67 (0.5–0.9)</td>
<td></td>
</tr>
<tr>
<td>Chlorinated</td>
<td>301/1833</td>
<td>7093/49 284</td>
<td>0.91 (0.8–1.0)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>No</td>
<td>82/551</td>
<td>1282/6531</td>
<td>0.53 (0.4–0.7)</td>
<td></td>
</tr>
<tr>
<td>Strained</td>
<td>371/2017</td>
<td>8054/32 028</td>
<td>0.85 (0.8–1.0)</td>
<td>0.07</td>
</tr>
<tr>
<td>No</td>
<td>12/67</td>
<td>237/2607</td>
<td>0.40 (0.2–0.8)</td>
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</tr>
<tr>
<td>Filtered</td>
<td>381/2068</td>
<td>8194/55 047</td>
<td>0.82 (0.7–0.9)</td>
<td>0.73</td>
</tr>
<tr>
<td>No</td>
<td>2/16</td>
<td>97/768</td>
<td>0.89 (0.2–4.1)</td>
<td></td>
</tr>
<tr>
<td>Distilled</td>
<td>382/2065</td>
<td>8164/54 573</td>
<td>0.82 (0.7–0.9)</td>
<td>0.35</td>
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<tr>
<td>Yes</td>
<td>1/19</td>
<td>127/1242</td>
<td>2.02 (0.3–15)</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 3**

Host and environmental modifiers of the association between BCG vaccination and suspected ALRI in the primary cohort. Symbols: Bars (---), 95% CI; dots (●), point estimate. Pneum, pneumonia; Ref, reference category. Bold text indicates significant P value. See Table 1 footnote for adjusted variables.
previous suggestions that environmental mycobacteria may interfere with adaptive immunity conferred by BCG.43,44

**Study Strengths and Limitations**

Our study represents the first, to our knowledge, to evaluate a link between BCG and suspected ALRI across multiple countries. Design strengths include the size and geographic scope of standardized individual-level survey data used, inclusion of a secondary cohort to ensure robustness of results, use of health-card data rather than self-report for vaccination status, and accounting for baseline differences in vaccine uptake using propensity weighting and sensitivity analysis were used to examine and account for vaccination status. Despite these strengths, several study limitations should be considered. First, although inverse probability weighting and sensitivity analysis were used to examine and account for vaccine uptake being associated with other health-related factors, residual confounding from unknown determinants of BCG use could still have occurred. Second, use of self-reported symptoms to define suspected ALRI rather than clinical, radiographic, and laboratory findings could have led to disease misclassification. Even though the use of a rapid breathing history as a clinical marker for ALRI has up to 90% sensitivity compared with physician-made diagnosis, sensitivity decreases with age, particularly among children ≥36 months of age.45 Furthermore, although ALRI was defined in our study as having both cough and respiratory distress, children could still have had concomitant upper respiratory infection. Third, while BCG is typically administered at birth, mothers who sought vaccination for their children after birth could have been more attentive to ALRI symptoms asked during the survey. Finally, our study did not evaluate the impact of BCG on ALRI-related mortality. If children who survived because of BCG exhibited significantly different patient characteristics than those who did not live, then generalizing our results to those at highest risk of ALRI-associated mortality could be difficult. Depending on the biological mechanisms through which BCG confers protection, bias would likely be greatest among survey participants reporting the longest time since vaccination.

**CONCLUSIONS**

Our study supports the association of BCG vaccination with ALRI and suggests DTP vaccination may play a key role in amplifying this effect. Additional research is needed to clarify biological mechanisms underlying the association between BCG and suspected ALRI, including a more detailed examination of BCG’s effect on specific types of suspected ALRI and whether risk reductions in tuberculosis may be contributing to this effect.

**ACKNOWLEDGMENTS**

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DOI: 10.1542/peds.2013-2218 originally published online December 30, 2013;

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