Effectiveness of BCG vaccination against *Mycobacterium tuberculosis* infection in adults: a cross-sectional analysis of a UK-based cohort

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Summary statement

This analysis found BCG was associated with a lower prevalence of LTBI (measured via IGRA) in adults with recent exposure to active tuberculosis. These results suggest BCG may provide durable protection against Mtb infection as well as disease.
ABSTRACT

Background

BCG appears to reduce acquisition of *Mycobacterium tuberculosis* (*Mtb*) infection in children, measured using interferon-gamma release assays (IGRAs). We explored whether BCG vaccination continues to be associated with decreased prevalence of *Mtb* infection in adults.

Methods

We conducted a cross-sectional analysis of data from adult contacts of tuberculosis cases participating in a UK cohort study. Vaccine effectiveness (VE) of BCG, ascertained based on presence of a scar or vaccination history, against latent tuberculosis infection (LTBI), measured via IGRA, was assessed using multivariable logistic regression. The effects of age at BCG and time since vaccination were also explored.

Results

Of 3453 recent tuberculosis contacts, 27.5% had LTBI. There was strong evidence of an association between BCG and LTBI (aOR=0.70, 95% CI 0.56-0.87, p=0.0017) yielding a VE of 30%. VE declined with time since vaccination, but there was evidence that LTBI prevalence was lower amongst vaccinated individuals even >20 years after vaccination, compared with non-vaccinated participants.

Conclusion

BCG is associated with lower prevalence of LTBI in adult contacts of tuberculosis. These results contribute to growing evidence that suggests BCG may protect against *Mtb* infection.
as well as disease. This has implications for immunisation programmes, vaccine development and tuberculosis control efforts worldwide.

**Key words**

BCG; Bacille Calmette-Guérin vaccine; tuberculosis; vaccine effectiveness
INTRODUCTION

Tuberculosis (TB) is the leading cause of death from infectious disease worldwide.[1] The widely used Bacillus Calmette-Guérin (BCG) vaccine is the only licensed vaccine against Mycobacterium tuberculosis (Mtb).[2] Infant BCG vaccination has shown consistently high efficacy of 70-80% against childhood TB, namely meningitis and miliary TB.[3] The protective effect of BCG against adult pulmonary disease varies geographically,[4–6] which may in part be associated with varying exposure to Mtb or environmental mycobacteria,[7,8] which may mask or block protection induced by BCG.[4,9–11]

Until recently it was not possible to determine if BCG vaccination prevents acquisition of Mtb infection or only limits progression from latent TB infection (LTBI) to active disease. This was due to limitations of the tuberculin skin test (TST), which can be positive following BCG vaccination and, to a lesser extent, exposure to environmental mycobacteria.[12,13] More recently developed interferon-gamma release assays (IGRAs) are more specific for Mtb infection,[14] as they measure interferon-gamma release from T-lymphocytes stimulated with antigens not present in BCG or most environmental mycobacteria.[15] Since the protective effect of BCG against Mtb infection was first demonstrated[16], several observational studies have investigated this phenomenon. A meta-analysis of 14 observational studies in children aged <16 years with recent exposure to active TB found a vaccine effectiveness (VE) of 19% against Mtb infection. In the six studies which followed up children who were IGRA-positive, BCG was associated with a 58% reduction in the risk of active TB.[17]

Data on whether this protection against Mtb infection continues into adulthood, as it appears to against disease,[18,19] are limited. Several observational studies of adults have found weak evidence of protection by BCG against infection measured via IGRA.[20–25] There has been no investigation of the influence of age at vaccination on VE of BCG against LTBI in
adults, or of changes in protection over time. These issues are important as, in order to assess the role of BCG (or similar vaccines in development) in TB control programmes, the effect of BCG on the full spectrum of TB should be understood.[26] In this cross-sectional study, we used baseline data from a large United Kingdom (UK) cohort study of adults at risk of *Mtb* infection to determine the presence and durability of BCG protection against *Mtb* infection, assessed by IGRA, and the potential factors that influence VE.

**METHODS**

**Study design**

A cross-sectional study was carried out amongst participants recruited to the UK PREDICT study who were recent contacts of patients with active TB (‘contacts’). PREDICT was a prospective cohort study that aimed to assess the prognostic value of IGRA in predicting the development of active TB among individuals with, or at risk of, LTBI, as previously described.[27] 10045 TB contacts, as well as recent migrants, aged ≥16 years were recruited between January 2011 and July 2015. Participants with evidence of active TB at baseline were excluded, and migrants were excluded from this analysis as it was unclear when their primary infection occurred. Contacts were recruited at contact tracing appointments for TB screening in TB clinics (part of the routine public health management of TB in the UK).

After obtaining informed consent, study nurses completed a questionnaire with participants, including on demographic, social, medical and TB exposure history, took blood samples for IGRA testing, and administered a Mantoux TST (which was read 48-72 hours later).

Most recruitment sites were in London, with one clinic each in Birmingham and Leicester. To increase the probability that any detected LTBI was due to recent infection, participants who reported previous contact with active TB (prior to that resulting in recruitment) were
excluded. Participants who reported a previous TB diagnosis were also excluded from this analysis, as a positive IGRA may reflect their prior TB disease rather than current LTBI.

**Primary exposure, outcome and covariates**

The primary exposure of interest was previous BCG vaccination. Vaccination status was determined by inspection of both arms for a vaccination scar by a trained study or TB nurse, combined with a vaccination history and documentation from a personally-held vaccination record (e.g. the ‘red book’) if available. A positive response was recorded when a scar was observed or there was documented evidence of BCG administration, and a negative response recorded if no scar was seen. If participants thought they had been vaccinated but no scar was observed, the interviewer recorded ‘unsure’ and this was treated as missing. Participants who had received vaccination were asked the year of vaccination.

The outcome of interest was LTBI, measured via IGRA. LTBI was defined as a positive result on either or both of QuantiFERON-TB Gold In-Tube (QFT-GIT) and T-SPOT.TB. Those who were negative on both assays, or negative on one and indeterminate on the other, were considered not to have LTBI. Most participants had both IGRA performed, however a small number were only tested with QFT-GIT, and LTBI was determined based on the single assay. If both assays were indeterminate, the outcome was considered missing.

Self-reported questionnaire data included details of the TB exposure, country of birth, ethnicity (based on the Enhanced Tuberculosis Surveillance system categories[28]), smoking status (never or ever), social risk factors (none, or any of homelessness, imprisonment or use of controlled drugs), and medical details, including whether the participant had diabetes, HIV or other immunosuppression.

Age at vaccination was calculated as the difference between vaccination and birth year, and
dichotomised based on the ages of vaccination recommended in typical BCG vaccination polices (≤2 years to reflect infant vaccination, >2 years for vaccination in childhood and at older ages). Time since vaccination was calculated as age at recruitment minus the stated age at vaccination, and grouped into three categories to avoid data sparsity (≤10 years, 11-20 years, >20 years).[5] TB incidence in country of birth was obtained from WHO estimates for the year 2000.[29] Absolute latitude of country of birth, found to affect VE in previous studies[9], was calculated using average country latitude data from Google Public Data Explorer[30], and collapsed into 20° groups.[9,17]

**Statistical analysis**

To investigate the association between LTBI and BCG status (and all other covariates), cross-tabulation, unadjusted ORs and likelihood ratio tests (LRTs) were calculated. For variables with no natural reference group, the largest group was used as the baseline.

Multivariable analysis was performed using logistic regression and LRTs. Age group and sex were considered *a priori* confounders. Age group was treated as a categorical, rather than continuous, variable as this produced a better fit in bivariable analysis. Further confounding variables were included in the multivariable model based on the change-in-estimate method.

All variables that were associated with BCG status or LTBI on bivariable analysis with p≤0.2 (with none deemed to lie on the causal pathway) were added separately to the model. Any variable that resulted in a ≥10% relative change in the OR was kept in the model (with the variable that caused the largest change in the OR selected first if more than one variable caused a ≥10% change). All other variables were then individually re-added to the model until the addition of no further variables resulted in a 10% change in OR. All analyses used a ‘complete-case’ approach. Vaccine effectiveness for LTBI was calculated as VE=1-OR. This
OR is the prevalence odds ratio[31], which approximates the incidence rate ratio in cross-sectional studies.[32,33]

The roles of age at vaccination and time since vaccination on the association between BCG and LTBI were then explored. Two further multivariable logistic regression models were fitted separately (for age at BCG and time since BCG), using the same modelling strategy as above. The analysis of age at BCG was stratified by place of birth (UK or non-UK). Due to collinearity between age at vaccination and time since vaccination, analysis of time since BCG was stratified by age at BCG (≤2 years or >2 years).

Six sensitivity analyses of the primary multivariable model were performed: 1) with additional adjustment for smoking status and any social risk factor; 2) including adjustment for TB incidence of country of birth; 3) including only participants with concordant IGRAs; 4) using binomial regression with a log-link to directly estimate the prevalence ratio (PR), which may not be well approximated by the OR as the outcome was common[34]; 5) restricting the analysis to household contacts of active TB cases, who likely had the most defined single TB exposure[35]; 6) including participants who reported earlier contact with people with active TB. We also performed additional analyses using TST results to measure LTBI. Two cut-off criteria were used to define positivity: firstly, TST≥5mm[36]; and secondly, TST ≥5mm in BCG-naïve, or ≥15mm in BCG-vaccinated participants (which better predicts disease progression[27]).

To examine bias from missing data, observations with missing values were investigated for association with the outcome and exposure using cross-tabulation, together with multivariable analysis of factors associated with missing BCG status.

Analysis was conducted using Stata v15.0.
RESULTS

Participant inclusion

Of 10045 participants enrolled in the PREDICT study, 9515 had no evidence of active TB and did not report a prior history of TB. 4310 participants were recent TB contacts, of whom 857 had missing data on LTBI and/or BCG status, leaving 3453 participants in this cross-sectional study (Figure 1).

Baseline characteristics and bivariable analysis

Of 3453 participants, 86.9% (3000/3453) had received BCG vaccination. The median age was 32 years (interquartile range 25-43) and 50.0% were male. 2420/3444 (70.3%) were born outside the UK (Table 1).

The overall prevalence of LTBI was 27.5% (951/3453), 27.0% (809/3000) in those vaccinated and 31.4% (142/453) in the unvaccinated, yielding an unadjusted OR of 0.81 (95% CI 0.65-1.00, p=0.054) (Table 1). Characteristics associated with increased LTBI prevalence on univariate analysis were male sex, older age, being born outside the UK, some ethnicities, lack of immunosuppression, having diabetes, lower latitudes of country of birth, TB incidence in country of birth, and household TB exposure.

Multivariable analysis

3399 (98.4%) participants were included in the complete-case analysis. Apart from sex and age (included a priori), latitude of country of birth was the key confounding variable, shifting the OR away from the null, and the only covariate retained in the final model. After adjusting for sex, age group and latitude of country of birth, there was strong evidence of an association
between BCG and LTBI (OR 0.70, 95% CI 0.56-0.87, p=0.0017)(Table 2), thus the VE of BCG for LTBI in adult contacts of TB cases was 30% (95% CI 13-44%).

Sensitivity analyses produced largely similar results (Appendix 1). Additional analyses using TST results found that BCG was positively associated with LTBI using a 5mm TST threshold, and negatively associated using a stratified threshold based on BCG status (OR 0.50, 95% CI 0.40-0.63, p<0.001, Appendix 1).

There was no evidence of an association between missing LTBI data and BCG vaccination (OR 1.05, 95% CI 0.74-1.49, p=0.79). However those without data on BCG status were more likely to have LTBI (OR 1.33, 95% CI 1.09-1.63)(Appendix 2).

**Vaccine effectiveness by age at vaccination and time since vaccination**

Data on reported age at (and time since) vaccination were available for 2195 (73%) of 3000 BCG-vaccinated participants. Of the 641 people born in the UK, 497 (78%) were vaccinated aged >2 years. Of the 1554 people born outside the UK, 1268 (82%) were vaccinated aged ≤2 years (Appendix 3). Protection against infection was observed following both infant and older age vaccination, among those born within and outside the UK, after adjusting for age group, sex and latitude of country of birth (Table 3). There was no clear pattern by age at vaccination, as the confidence intervals for the adjusted ORs overlapped.

The association between BCG and LTBI, adjusted for age group, sex, ethnicity and country of birth, appeared to vary with time since vaccination in both age at vaccination strata (Table 4). In those vaccinated at age 2 or younger, the protective association was greater in those vaccinated 11-20 years ago (OR 0.55 [95% CI 0.33-0.90]) than those vaccinated >20 years ago (OR 0.78 [0.60-1.00]). As this was an adult cohort, there were no participants vaccinated ≤10 years ago in the group vaccinated in infancy. In participants vaccinated at age >2 years,
the protective association was greatest in those vaccinated ≤10 years ago (OR 0.31 [95% CI 0.15-0.63]), versus those vaccinated 11-20 and >20 years ago (OR 0.73 [0.48-1.10] and 0.67 [0.46-0.98] respectively). However there appeared to be evidence of protection more than 20 years later in both those vaccinated in infancy and those vaccinated in childhood and older ages, compared to those without BCG vaccination.

DISCUSSION

Principal findings

In this cross-sectional study, we found strong evidence of an association between BCG and LTBI in recent adult contacts of TB, with VE estimated as 30% (95% CI 13-44%). Protection against infection was seen following both infant and older age vaccination, among participants born within and outside the UK. The association appeared to differ by time since vaccination, in participants vaccinated at both ≤2 and >2 years of age. In those vaccinated aged ≤2 years, protection was seen in those vaccinated 11-20 years ago and, though less so, vaccinated >20 years ago. Among participants vaccinated at ages >2 years, the protective association was greater for those vaccinated <10 years ago than those vaccinated 10-20 years ago, where evidence of a protective effect was weak. In both groups, there remained evidence of some protection in participants vaccinated >20 years ago.

Strengths and limitations

To our knowledge, this is the largest adult study on the association between BCG and LTBI measured via IGRA in recent contacts of TB patients. The large sample size and rich dataset are key strengths. This enabled analysis by strata of age at BCG and time since vaccination and broad sensitivity analyses. Although the analysis of time since vaccination could not be adjusted for age at vaccination (and vice versa) due to collinearity, stratification helped
address this. Using both commercially-available IGRAs allowed a sensitivity analysis of those with concordant results, reducing the potential for outcome misclassification.

There are some limitations in a cross-sectional study. The observational design cannot prove causality, and there may be confounding by other factors such as health-seeking behaviour. Furthermore, as many participants were born in high-burden countries, some may have been exposed to \textit{Mtb} before vaccination. However, to increase the probability that vaccination preceded \textit{Mtb} exposure, we only included recent TB contacts without prior reported TB exposure. Also, most participants born outside the UK were vaccinated in infancy, limiting exposure to \textit{Mtb} before vaccination.

\textit{Measurement error}

Similar to prior studies, this study relied predominantly on BCG scar to measure vaccination. BCG does not always result in scar formation, but may still confer protection in these cases.\cite{35,37,38} Therefore some vaccinated participants may have been misclassified as non-vaccinated, if there was no documented evidence otherwise. This would be non-differential with respect to IGRA, potentially biasing our VE estimates towards the null. Data on vaccination year was also likely subject to recall error, but again this is likely non-differential with regards to outcome.

Most data on covariates was self-reported. Prevalence of HIV and smoking were relatively low, possibly reflecting social desirability biases. Residual confounding is also possible. For example, latitude of country of birth was an important confounder and may be a proxy measure of potential exposure to nontuberculous mycobacteria, as well as \textit{Mtb}, but does not take into account the time lived at that latitude. Similarly, TB incidence in country of birth is an incomplete measure of \textit{Mtb} exposure.
There is currently no gold standard for diagnosing LTBI, and a positive IGRA cannot distinguish between true ongoing latent *Mtb* infection with dormant yet viable bacteria and an immunological memory response following exposure to *Mtb*. Long-term follow-up studies (or development of a gold standard test for diagnosing LTBI) would help assess if IGRA does measure true infection preceding risk of disease. We found increased prevalence of TST reaction ≥5mm amongst vaccinated individuals, consistent with TST being affected by BCG. Stratified thresholds can improve the specificity of TST, as demonstrated by the protective association seen in our tiered 5/15mm analysis. However IGRA is a more sensitive and specific surrogate marker for *Mtb* infection in BCG-vaccinated individuals.[14,15]

**Missing data**

Twenty percent of otherwise eligible participants were excluded due to missing data on LTBI and/or BCG. Missing data on LTBI were predominantly due to logistic factors (e.g. failed blood collection), so likely missing completely at random. This is supported by the lack of association between missing outcome data and BCG vaccination, and is therefore unlikely to be an important source of bias.

BCG vaccination status was missing for 13% of participants, and these people were more likely to have LTBI. As it is harder to be certain of lack of vaccination, more unvaccinated participants may have been recorded as ‘unsure’ and therefore coded as missing (possibly leading to the association of missing BCG status with LTBI). However in these cases, when the missingness mechanisms are related to the exposure and covariates, but not the outcome, a logistic regression complete-case approach can still provide an unbiased estimate of the OR,[39] dependent on the model including the covariates with which missingness is related. While being non-UK born and of Pakistani ethnicity were associated with missing BCG status (and not included in the final model as they were not found to be important
confounders), these associations and numbers were small, so the overall bias of VE from missing BCG status is likely minimal.

**Comparison with existing literature**

The estimated VE of 30% is broadly consistent with other studies in adults.[20–25] Three studies in TB contacts had higher VE than this study (ORs 0.11-0.5), though these were small studies restricted to close contacts and had wide confidence intervals that crossed 1.[23–25] The lower VE in our analysis may reflect the limitations discussed above, which could have biased the estimate towards the null.

Although the confidence intervals overlapped, our results suggest a possible decline in protection with increased time since vaccination. This concurs with studies of the duration of protection against active TB.[5,18] Our finding that protection against infection was seen following both infant and older age vaccination is less consistent with other studies reporting that protection against active TB is greater when vaccination occurs at younger ages, in immunologically naïve subjects.[5,9,40] Our findings are likely influenced by several factors. We do not have data on why participants were vaccinated at particular ages. However, those born outside the UK and vaccinated aged >2 years are likely to have been vaccinated after moving to the UK, where they would have been offered school-aged BCG vaccination only after negative TST results under the UK’s school-based BCG program, discontinued in 2005.[41] Usually only infant vaccination programs are offered in high TB burden settings.

In addition, infant vaccination is less likely to result in scar formation compared with vaccination at older ages.[42] Therefore non-differential misclassification is more likely in those vaccinated earlier, leading to an underestimate of VE in the younger age group. Finally, measurement of these variables was susceptible to bias, due to missing data and recall errors.
for age at vaccination. These exploratory results should therefore be interpreted cautiously and confirmed in other studies, including with longitudinal design.

**Implications and future research**

This study suggests that BCG may protect against the acquisition of *Mtb* infection in adults and not only progression to disease.\[17,26\] This has implications for TB control strategies. The most recent WHO position paper on BCG reflects the growing evidence that BCG confers “a modest protective effect… against *Mtb* infection, representing a significant additional benefit of the BCG vaccine.”\[43\] Furthermore our data are consistent with evidence of durability of protection against disease,\[18,19\] which should be considered in cost-effectiveness and modelling studies by low-burden countries considering moving away from universal BCG vaccination to targeted vaccination of high-risk groups.\[43\]

The effect that BCG may have on wider transmission dynamics is unclear, though preliminary modelling studies suggest a vaccine that protects against *Mtb* infection would have a high population-level impact on TB incidence, across a range of exposure intensities.\[44\] Future modelling studies of TB transmission and burden should therefore include sensitivity analyses that account for some degree of protection against infection.\[43\]

Finally, these findings may contribute to understanding the mechanism of action of BCG. This is vital in the development and evaluation of new TB vaccines, since many vaccine candidates rely on a BCG-boosting strategy.\[45\] Novel vaccines must, and are starting to show they do, confer additional protection beyond the effect of BCG on both *Mtb* infection and disease progression.\[46\] Prevention of infection measured via IGRA is being examined as a shorter-term endpoint in efficacy trials of new TB vaccines, accelerating their assessment.\[47\] A recent trial of BCG revaccination versus vaccination with a novel subunit vaccine assessed vaccine efficacy using IGRA conversion as a measure of *Mtb* acquisition.
and sustained IGRA positivity to reflect sustained infection.[48] Our study suggests BCG-like vaccines that prevent infection may also provide long-term durability of protection.

Our study contributes to the growing evidence that suggests BCG can act partially by providing protection against *Mtb* infection as well as disease. This has important implications for immunisation programmes, vaccine development and assessment, and TB control efforts worldwide.
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We would also like to acknowledge Antonio Gasparini for his advice on the statistical methods.
TABLES AND FIGURES

Figure 1: Recruitment of participants to the PREDICT study and inclusion in cross-sectional study.
Table 1: Cross sectional study baseline characteristics and unadjusted ORs of their association with LTBI (n=3453).

<table>
<thead>
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<th>Variable</th>
<th>Group</th>
<th>Number positive for LTBI</th>
<th>Percentage positive for LTBI</th>
<th>Crude OR</th>
<th>95% CI</th>
<th>p value*</th>
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<td>0.60-0.81</td>
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<td>1.70</td>
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<td>80/211</td>
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<td>Smoking status (m=16)</td>
<td>Ever</td>
<td>207/822</td>
<td>25.2</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Never</td>
<td>741/2615</td>
<td>28.4</td>
<td>1.17</td>
<td>0.98-1.41</td>
<td>0.078</td>
</tr>
<tr>
<td>Latitude of country of birth (m=37)</td>
<td>&lt;20°</td>
<td>265/779</td>
<td>34.0</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>20-40°</td>
<td>455/1378</td>
<td>33.0</td>
<td>0.96</td>
<td>0.79-1.15</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;40°</td>
<td>221/1259</td>
<td>17.6</td>
<td>0.41</td>
<td>0.34-0.51</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TB incidence per 100 000 of country of birth (m=46)</td>
<td>≤10</td>
<td>26/115</td>
<td>22.6</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>11-40</td>
<td>200/1252</td>
<td>16.0</td>
<td>0.65</td>
<td>0.41-1.03</td>
<td></td>
</tr>
<tr>
<td></td>
<td>41-100</td>
<td>36/129</td>
<td>28.0</td>
<td>1.33</td>
<td>0.74-2.37</td>
<td></td>
</tr>
<tr>
<td></td>
<td>101-150</td>
<td>15/69</td>
<td>22.1</td>
<td>0.97</td>
<td>0.47-1.99</td>
<td></td>
</tr>
<tr>
<td></td>
<td>151-300</td>
<td>584/1621</td>
<td>36.0</td>
<td>1.93</td>
<td>1.23-3.02</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥300</td>
<td>77/222</td>
<td>34.7</td>
<td>1.82</td>
<td>1.08-3.05</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Setting of TB exposure (m=274)</td>
<td>Household</td>
<td>671/2149</td>
<td>31.2</td>
<td>1</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Non-household</td>
<td>204/1030</td>
<td>19.8</td>
<td>0.54</td>
<td>0.46-0.65</td>
<td></td>
</tr>
</tbody>
</table>
*Derived from likelihood ratio test

OR = odds ratio; LTBI = latent tuberculosis infection; n = number; CI = confidence interval; m = missing; UK = United Kingdom; HIV = human immunodeficiency virus
Table 2: Adjusted ORs for the association of LTBI and BCG vaccination from a multivariable logistic regression model (n=3399).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>Adjusted OR*</th>
<th>95% CI</th>
<th>p value**</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCG vaccination</td>
<td>No</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>0.70</td>
<td>0.56-0.87</td>
<td>0.0017</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>0.70</td>
<td>0.60-0.82</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age group (years)</td>
<td>16-25</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>26-35</td>
<td>1.31</td>
<td>1.07-1.61</td>
<td></td>
</tr>
<tr>
<td></td>
<td>36-45</td>
<td>1.55</td>
<td>1.23-1.97</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;45</td>
<td>1.38</td>
<td>1.10-1.74</td>
<td>0.0016</td>
</tr>
<tr>
<td>Latitude of country of birth</td>
<td>&lt;20°</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>20-40°</td>
<td>0.92</td>
<td>0.76-1.12</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;40°</td>
<td>0.42</td>
<td>0.34-0.52</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Adjusted for all other variables in the table

**Likelihood ratio test p value

OR = odds ratio; LTBI = latent tuberculosis infection; BCG = Bacillus Calmette-Guérin; n = number; CI = confidence interval.
**Table 3:** Crude and adjusted ORs for the association of LTBI and age at BCG vaccination, by place of birth.

<table>
<thead>
<tr>
<th>Birthplace</th>
<th>Age at BCG</th>
<th>Proportion with LTBI (%)</th>
<th>Crude OR (95% CI)</th>
<th>p value*</th>
<th>Adjusted OR** (95% CI)</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK (n=792)</td>
<td>No BCG</td>
<td>32/151 (21.2)</td>
<td>1</td>
<td>1</td>
<td>0.39 (0.19-0.77)</td>
<td>0.39</td>
</tr>
<tr>
<td></td>
<td>≤2 years</td>
<td>14/144 (9.7)</td>
<td>0.40 (0.20-0.79)</td>
<td>0.40</td>
<td>0.62 (0.38-1.00)</td>
<td>0.021</td>
</tr>
<tr>
<td></td>
<td>&gt;2 years</td>
<td>72/497 (14.5)</td>
<td>0.63 (0.40-1.00)</td>
<td>0.021</td>
<td>0.63 (0.38-1.00)</td>
<td>0.018</td>
</tr>
<tr>
<td>Non-UK (n=1854)</td>
<td>No BCG</td>
<td>110/300 (36.7)</td>
<td>1</td>
<td>1</td>
<td>0.83 (0.64-1.09)</td>
<td>0.123</td>
</tr>
<tr>
<td></td>
<td>≤2 years</td>
<td>434/1268 (34.2)</td>
<td>0.90 (0.69-1.17)</td>
<td>0.021</td>
<td>0.63 (0.44-0.90)</td>
<td>0.040</td>
</tr>
<tr>
<td></td>
<td>&gt;2 years</td>
<td>83/286 (29.0)</td>
<td>0.71 (0.50-1.00)</td>
<td>0.123</td>
<td>0.63 (0.44-0.90)</td>
<td>0.040</td>
</tr>
</tbody>
</table>

*Likelihood ratio test p value

**Adjusted for age group, sex and latitude of country of birth.

OR = odds ratio; LTBI = latent tuberculosis infection; UK = United Kingdom; BCG = Bacillus Calmette-Guérin; n = number; CI = confidence interval.
Table 4: Crude and adjusted ORs for the association of LTBI and years since BCG vaccination, by age of vaccination.

<table>
<thead>
<tr>
<th>Age at BCG</th>
<th>Years since BCG</th>
<th>Proportion with LTBI (%)</th>
<th>Crude OR (95% CI)</th>
<th>p value*</th>
<th>Adjusted OR** (95% CI)</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤2 years No BCG</td>
<td>≤2 years No BCG</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n=1867)</td>
<td>(n=1867)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤10</td>
<td>142/453 (31.4)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>11-20</td>
<td>27/160 (16.9)</td>
<td>0.44 (0.28-0.70)</td>
<td>0.55 (0.33-0.90)</td>
<td>0.55 (0.33-0.90)</td>
<td>0.026</td>
<td></td>
</tr>
<tr>
<td>&gt;20</td>
<td>423/1254 (33.7)</td>
<td>1.11 (0.89-1.40)</td>
<td>&lt;0.001</td>
<td>0.78 (0.60-1.00)</td>
<td>0.026</td>
<td></td>
</tr>
<tr>
<td>&gt;2 years No BCG</td>
<td>&gt;2 years No BCG</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n=1236)</td>
<td>(n=1236)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤10</td>
<td>12/106 (11.3)</td>
<td>0.28 (0.15-0.53)</td>
<td>0.31 (0.15-0.63)</td>
<td>0.31 (0.15-0.63)</td>
<td>0.0014</td>
<td></td>
</tr>
<tr>
<td>11-20</td>
<td>51/243 (21.1)</td>
<td>0.58 (0.40-0.84)</td>
<td>0.73 (0.48-1.10)</td>
<td>0.73 (0.48-1.10)</td>
<td>0.0014</td>
<td></td>
</tr>
<tr>
<td>&gt;20</td>
<td>92/434 (21.2)</td>
<td>0.59 (0.43-0.80)</td>
<td>&lt;0.001</td>
<td>0.67 (0.46-0.98)</td>
<td>0.0014</td>
<td></td>
</tr>
</tbody>
</table>

* Likelihood ratio test p value  
** Adjusted for age group, sex, ethnicity and country of birth (UK or non-UK)

OR = odds ratio; LTBI = latent tuberculosis infection; BCG = Bacillus Calmette-Guérin; n = number; CI = confidence interval; UK = United Kingdom.
REFERENCES


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POTENTIAL CONFLICTS OF INTEREST

All authors have completed the ICMJE Form for Disclosure of Potential Conflicts of Interest. CJ, JS and AJ report grants from the UK National Institute for Health Research during the conduct of the study. In addition, AJ reports grants from Wellcome Trust during the conduct of the study, and is a named inventor on patents pertaining to T cell-based diagnosis, including IGRA technologies. Some of these patents were assigned by the University of Oxford to Oxford Immunotec PLC resulting in royalty entitlements for the University of Oxford and AL. We declare no other relationships or activities that could appear to have influenced the submitted work.

AUTHOR CONTRIBUTIONS

Drs Katelaris, Gupta, and Abubakar have full access to all data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

Study concept and design: Mangtani, Jackson, Katelaris, Abubakar

Acquisition, analysis, and interpretation of data: Katelaris, Jackson, Mangtani, Abubakar

Statistical analysis: Katelaris, Jackson, Gupta

Drafting of the manuscript: Katelaris, Jackson, Mangtani

Critical revision of the manuscript for important intellectual content: All authors

Obtained funding: Abubakar, Lalvani, Drobniewski, Lipman
Administrative, technical, or material support: Jackson, Gupta, Southern
Supervision: Jackson, Mangtani, Abubakar

ETHICS APPROVAL

This study was approved by the LSHTM MSc Research Ethics Committee (reference #13431). Ethics approval for the PREDICT study was granted through the National Research Ethics Service (Brent Medical Ethics Committee, approval number 10/H0717/14) and is registered on clinicaltrials.gov (NCT01162265).

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TB = tuberculosis; LTBI = latent tuberculosis infection; BCG = Bacillus Calmette-Guérin.

* Contacts were defined as people with a cumulative duration of exposure to the index case (pulmonary or extra-pulmonary TB) of >8 hours in a confined space during the period of infectiousness.