Title: Beneficial effects of BCG vaccination in outcomes for patients with TB: observational study using the Enhanced Tuberculosis surveillance system 2009-2015

Sam Abbott, Hannah Christensen, Maeve K Lalor, Mary Ramsay, Ellen Brooks-Pollock

13 April 2017

**Authors:**

Sam Abbott, PhD student, School for Social and Community Medicine, University of Bristol, Bristol BS8 2BN, United Kingdom, [sam.abbott@bristol.ac.uk](mailto:sam.abbott@bristol.ac.uk), 01173310185,

Hannah Christensen, Lecturer, School for Social and Community Medicine, University of Bristol, Bristol, United Kingdom

Maeve K Lalor, Epidemiologist, TB section, Public Health England, London, United Kingdom

Mary E Ramsay, Head of Immunisation, Hepatitis and Blood safety department, Public Health England, London, United Kingdom

Ellen Brooks-Pollock, Lecturer, School for Social and Community Medicine, University of Bristol, Bristol, United Kingdom

**Correspondence to:** Sam Abbott

**WORD COUNT:** **Title** 20 (20), **Abstract** 248 (250), **Paper** 3537 (3500) [Excluding Boxes and Sections after the discussion]

##### PAGEBREAK

**ABSTRACT**

**Background**

Bacillus Calmette–Guérin (BCG) is one of the mostly widely-used vaccines. However, little attention has been given to the indirect benefits of BCG. We aimed to quantify the effects of BCG vaccination on outcomes for individuals with notified TB in England.

**Methods**

We obtained all TB notifications for 2009-2015 in England from the Enhanced Tuberculosis surveillance system. We considered seven outcomes: pulmonary disease, smear status, drug resistance, multiple episodes, all-cause mortality, TB mortality, and successful treatment. We used logistic regression to investigate each outcome with BCG vaccination, years since vaccination and age at vaccination, adjusting for potential confounders.

**Results:** We found evidence of an association between BCG vaccination and all-cause mortality (aOR: 0.76 (95% CI 0.64 to 0.89), P: 0.001), increased successful treatment (aOR: 1.14 (95% CI 1.02 to 1.26), P: 0.018), reduced multiple episodes (aOR: 0.90 (95% CI 0.81 to 1.00), P: 0.055) and reduced TB mortality (aOR: 0.76 (95% CI 0.51 to 1.13), P: 0.179). We also found evidence that vaccination after 10 years, compared to more recent vaccination, was associated with increased all-cause mortality, decreased successful treatment, and reduced multiple episodes.

**Conclusions:** We found beneficial effects of BCG vaccination on outcomes for TB cases, specifically reduced all-cause mortality, increased successful treatment, and decreased multiple episodes; these effects were reduced when cases were notified 10+ years after vaccination. Further validation studies are required to assess the strength of these associations, but public health policy and evaluation should consider these additional potential benefits of BCG vaccination.

**Keywords:** Tuberculosis, BCG, vaccination, surveillance

**What is the key question?**

Recent evidence has shown that BCG may prevent infection, predict sputum conversion and reduce mortality in neonates; it is not understood what other roles BCG may play in TB control, or to what extent these results can be generalised to all TB cases.

**What is the bottom line?**

This analysis suggests that vaccination with BCG is associated with improved outcomes for TB patients including reduced all-cause mortality, increased successful treatment, and decreased multiple episodes.

**Why read on?**

This study uses a well developed national surveillance system to assess the effect of BCG vaccination on outcomes for a large cohort of active TB cases.

##### PAGEBREAK

**INTRODUCTION**

Bacillus Calmette–Guérin (BCG) is one of the mostly widely-used vaccines and the only vaccine that protects against tuberculosis (TB) disease. BCG was first used in humans in 1921 and was introduced into the WHO Expanded Program on Immunization in 1974 [1]. BCG vaccination has been controversial due to its variable efficacy, and possibility of causing a false positive result with the standard skin test for TB. However the failure of other TB vaccines and the emergence of drug-resistant TB strains means that the use of BCG vaccination for TB control is being reconsidered of.

BCG’s primary mode of action is to directly prevent the development of active, symptomatic disease. Its efficacy in adults is context specific, with estimates ranging between 0% and 78% [2]. Efficacy has been shown to be dependent on previous exposure, with unexposed individuals receiving the greatest benefit. Unlike in adults, BCG has consistently been shown to be highly protective against TB and TB meningitis in children [3] [4]. For this reason, the majority of countries that use BCG vaccinate at birth [5] and adult vaccination is being phased out in many countries, such as the UK where universal vaccination of 13 year olds was stopped in 2005 in favour of a targeted programme aimed at high risk children at birth.

Little attention has been given to the indirect benefits of BCG [6] and TB control is primarily based on prompt treatment of symptomatic individuals. However, BCG vaccination has been shown to protect against infection as well as disease [7], TB patients with BCG scars were found to respond better to treatment with early sputum smear conversion [8], and there is evidence to suggest that BCG vaccination is associated with reduced childhood mortality [9]. Given that the immunology behind TB immunity is not well understood, these findings suggest that BCG may be able to play a more important role in TB control than previously thought, by improving patient outcomes. We aimed to quantify the effects of BCG vaccination on outcomes for individuals with notified TB in England using routinely collected surveillance data to provide evidence for appropriate public health action and provision.

**METHOD**

**Enhanced Tuberculosis Surveillance (ETS) system**

We extracted all notifications from the Enhanced Tuberculosis Surveillance (ETS) system from Jan 1, 2009 to Dec 31, 2015. Notification of TB is mandatory in England and the Public Health England ETS system continuously collects clinical, demographic and microbiological data on all notified cases of TB. Data collection began in 2000 and was expanded with additional variables including BCG vaccination status and year of vaccination, with the launch of a web based system in 2008 [10]. We considered seven TB outcomes which were selected due to their association with increased case infectiousness or poor consequences for patients (Table 1)

**Table 1:** Summary of outcome definitiions

|  |  |
| --- | --- |
| Outcome | Definition |
| Pulmonary disease (Pulmonary, with or without Extra-pulmonary/Extra-pulmonary only) | Cases that present with pulmonary TB (regardless of extra-pulmonary TB status). |
| Smear status (Positive/Negative) | Status of sputum sample tested for Acid-Fast Bacilli. |
| Drug resistance (Yes/No) | Resistance to any, or multiple, first line anti-TB drugs (isoniazid, rifampicin, pyrazinamide or ethambutol). |
| Multiple episodes (Yes/No) | Notifications with evidence of a previous TB diagnosis, all additional notifications for an individual already present in the data set were flagged as recurrent prior to anonymisation. |
| All-cause mortality (Yes/No) | Assessed via follow up at 12 and 24 months; mortality is defined as cases with an overall outcome of died, and survival is defined as those that completed treatment, were still on treatment, and stopped treatment. Those that were lost to follow up, or not evaluated were treated as missing. |
| TB mortality (Yes/No) | For cases with a known cause of death TB mortality is defined as those that died directly from TB, or where TB had contributed to their death. |
| Successful treatment (Yes/No) | For cases that had a recorded date of starting treatment and at least 12 months of follow up, with their outcome recorded at the latest available follow up. Those that completed treatment are defined as successfully treated; treatment failure is defined as those that stopped treatment, were lost to follow up, those that died during follow up up directly from TB, or where TB contributed to their death, and those who were still on treatment. Those that were not evaluated were treated as missing. |

**Exposure variables relating to BCG**

We calculated years since BCG vaccination, from year of vaccination and year of notification. Years since BCG vaccination was highly skewed, therefore we categorised this into to and 11+ years based on evidence that the average duration of protection is 10-15 years [11]. We calculated age at vaccination from the reported age of the notified individual and their year of vaccination. Age at vaccination has a bi-model distribution with modes at 0 and 12 years, therefore for analysis we categorised this into to , to , to and 16+ years. This also captures the current UK policy of vaccination at birth, historic policy of vaccination at 13-15 years and catch up vaccination for high risk children [12].

**Statistical Analysis**

R was used for all statistical analysis [13]. For individuals with known BCG status we calculated proportions for all demographic and outcome variables, and compared vaccinated and unvaccinated TB cases using the test. We used logistic regression to estimate the association between exposures and outcome variables. All variables from the univariable analysis were included in the multivariable analysis. In the multivariable models, we adjusted for sex [14] [15] [16], age [17], Index of Multiple Deprivation (2010) categorised into five groups for England (IMD rank) **???**, ethnicity [14] [18], UK birth status [19] [20], and year of notification. The relationship between age and outcomes was non-linear, therefore we modelled age using a natural cubic spline with knots at 25%, 50% and 75%. We tested for potential interaction effects between BCG vaccination, and exposure variables using likelihood ratio tests, adjusting for the effect of testing all interactions by using a bonferroni correction for each TB outcome. To clarify the effect of interactions with age, as the coefficients of a spline cannot easily be interpreted, we transformed it into a categorical variable when included as an interaction, with boundaries as follows to , to and .

We conducted a number of sensitivity analyses to assess the robustness of our results. We assessed the robustness of our results by dropping each variable in turn and assessing the effect on the aORs of the exposure variable. We repeated the principal analysis, dropping recurrent cases, and restricting the study population to those eligible for the BCG schools scheme (defined as UK born cases that were aged 14 or over in 2004) to assess the comparability of the BCG vaccinated and unvaccinated populations. We assessed the sensitivity of the definition of successful treatment by repeating the analysis with follow up restricted to 12 months. There was a high degree of missing data for some variables; we therefore did an analysis after multiple imputation of the missing exposure and outcome data using the MICE package [21]. We imputed 50 data sets (for 20 iterations) using all exposures and outcomes as predictors along with Public Health England centre, the model results were then pooled using the small sample method [22], and effect sizes compared with those from the principal analysis.

**RESULTS**

**Description of the data**

There were 51,645 TB notifications between 2009-2015 in England. Reporting of vaccination status and year of vaccination improves over time; 64.9% (20865/32154) of notifications include vaccination status for 2009 to 2012, increasing to 70% (13647/19491) from 2013 to 2015. The majority of cases that have a known vaccination status were vaccinated (70.6%, 24354/34512), and where age and year of vaccination is known, the majority of cases were vaccinated at birth (60%, 5979/10066).

Vaccinated cases were on average younger than unvaccinated cases, with the median age of vaccinated cases being 34 (IQR 26 to 45) compared to 38 (IQR 26 to 62) in the unvaccinated cases. Vaccine coverage was higher in non-UK born cases, (72.7%, 18297/25171) compared to in UK born cases (65.2%, 5787/8871) and a higher proportion of non-UK born cases were vaccinated at birth compared to UK born cases (68%, 4691/6896 vs. 40.5%, 1253/3096 respectively, P: < 0.001). Vaccine coverage was highest for cases notified in the East Midlands (76.5%, 1296/1694) and the East of England (76.1%, 1529/2010) and lowest in the South-East (50%, 568/1136). Table 2 summarises the number of notified cases for each outcome stratified by BCG vaccinations status, see the Supplementary Information for the breakdown of confounding variables.

##### PAGEBREAK

**Table 2:** Summary of outcome variables stratified by BCG vaccination status.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Demographic Characteristics | Total | Vaccinated | Unvaccinated | Unknown vaccination status |
| Total, all cases | 51645 | 24354 {47.2} | 10158 {19.7} | 17133 {33.2} |
| Drug resistance | 30650 (59.3) | 14315 (58.8) | 5888 (58.0) | 10447 (61.0) |
| No | 28314 [*92.4*] | 13180 [*92.1*] | 5463 [*92.8*] | 9671 [*92.6*] |
| Yes | 2336 [*7.6*] | 1135 [*7.9*] | 425 [*7.2*] | 776 [*7.4*] |
| Multiple episodes | 48497 (93.9) | 23963 (98.4) | 9991 (98.4) | 14543 (84.9) |
| No | 44869 [*92.5*] | 22592 [*94.3*] | 9256 [*92.6*] | 13021 [*89.5*] |
| Yes | 3628 [*7.5*] | 1371 [*5.7*] | 735 [*7.4*] | 1522 [*10.5*] |
| Positive sputum smear | 19551 (37.9) | 9768 (40.1) | 3910 (38.5) | 5873 (34.3) |
| Negative | 11060 [*56.6*] | 5694 [*58.3*] | 2231 [*57.1*] | 3135 [*53.4*] |
| Positive | 8491 [*43.4*] | 4074 [*41.7*] | 1679 [*42.9*] | 2738 [*46.6*] |
| All-cause mortality | 45588 (88.3) | 21685 (89.0) | 9061 (89.2) | 14842 (86.6) |
| No | 43024 [*94.4*] | 21291 [*98.2*] | 8495 [*93.8*] | 13238 [*89.2*] |
| Yes | 2564 [*5.6*] | 394 [*1.8*] | 566 [*6.2*] | 1604 [*10.8*] |
| TB mortality | 1373 (2.7) | 276 (1.1) | 320 (3.2) | 777 (4.5) |
| No | 572 [*41.7*] | 129 [*46.7*] | 146 [*45.6*] | 297 [*38.2*] |
| Yes | 801 [*58.3*] | 147 [*53.3*] | 174 [*54.4*] | 480 [*61.8*] |
| Successful treatment | 44128 (85.4) | 21713 (89.2) | 8731 (86.0) | 13684 (79.9) |
| No | 3792 [*8.6*] | 1518 [*7.0*] | 748 [*8.6*] | 1526 [*11.2*] |
| Yes | 40336 [*91.4*] | 20195 [*93.0*] | 7983 [*91.4*] | 12158 [*88.8*] |
| Pulmonary TB | 51432 (99.6) | 24289 (99.7) | 10121 (99.6) | 17022 (99.4) |
| Extra-pulmonary only | 24280 [*47.2*] | 12085 [*49.8*] | 4573 [*45.2*] | 7622 [*44.8*] |
| Pulmonary, with or without EP | 27152 [*52.8*] | 12204 [*50.2*] | 5548 [*54.8*] | 9400 [*55.2*] |
| {% all cases}(% complete within vaccine status)[% *complete within category*] | | | | |

##### PAGEBREAK

**Univariable regression**

In the univariable analysis we found that compared to unvaccinated cases for BCG vaccinated cases the odds of death were 72% (95% CI 68% to 76%) lower, the odds of successful treatment were 25% (95% CI 14% to 37%) higher, the odds of multiple episodes were 24% (95% CI 20% to 30%) lower, and that the odds of pulmonary TB were 17% (95% CI 13% to 21%) lower (Table 3). There was some evidence that BCG vaccination was associated with reduced drug resistance, and with reduced positive sputum smear status, and little evidence of an association between BCG vaccination and TB mortality.

Restricting the analysis to vaccinated cases only, there was evidence that compared to being vaccinated 10 years ago, vaccination 11+ years ago was associated with reduced pulmonary TB, decreased successful successful treatment, increased multiple episodes, and increased all-cause mortality (Table 4). We also found some evidence that age at vaccination impacted TB outcomes (Table 5). We found evidence that vaccination at any other age other than birth was associated with increased all-cause mortality, increased pulmonary TB status, and increased positive sputum smear status. There was some evidence that vaccination at any age other than at birth was associated with reduced TB mortality, and little evidence that age at vaccination was associated with any other outcome.

**Multivariable regression**

After adjusting for possible confounders for multiple episodes, all-cause mortality and successful treatment the effect sizes were attenuated but there remained some evidence of associations with BCG vaccination (Table 3); with the odds of death being 24% (95% CI 11% to 36%) less, the odds of successful treatment being 14% (95% CI 2% to 26%) higher, and the odds of multiple episodes being 10% (95% CI NA% to NA%) lower for BCG vaccinated cases compared to unvaccinated cases. There was some evidence that BCG vaccination was associated with reduced TB mortality, and little evidence of any other association.

Restricting the analysis to vaccinated cases only, there was little evidence for any association between years since vaccination and TB outcomes, except for successful treatment (Table 4). For which, there was some evidence that cases vaccinated years before vaccination, compared to those vaccinated more recently, had reduced successful treatment. We found that the evidence for any association between age at vaccination and TB outcomes was attenuated in the multivariable analysis (Table 5). However, there was some evidence of an association between vaccination at birth, compared to at any other age, and a reduction in pulmonary TB. There was also some evidence that vaccinating at to , compared to at birth was associated with, decreased all-cause mortality, and reduced drug resistance.

##### PAGEBREAK

**Table 3:** Summary of associations between BCG vaccination and all outcomes

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Outcome | OR (95% CI) | P-value | aOR (95% CI) | P-value |
| Drug resistance | 1.11 (0.99 to 1.24) | 0.086 | 0.93 (0.82 to 1.06) | 0.301 |
| Multiple episodes | 0.76 (0.70 to 0.84) | <0.001 | 0.90 (0.81 to 1.00) | 0.055 |
| Positive sputum smear | 0.95 (0.88 to 1.02) | 0.187 | 1.02 (0.93 to 1.11) | 0.730 |
| All-cause mortality | 0.28 (0.24 to 0.32) | <0.001 | 0.76 (0.64 to 0.89) | 0.001 |
| TB mortality | 0.96 (0.69 to 1.32) | 0.786 | 0.76 (0.51 to 1.13) | 0.179 |
| Successful treatment | 1.25 (1.14 to 1.37) | <0.001 | 1.14 (1.02 to 1.26) | 0.018 |
| Pulmonary TB | 0.83 (0.79 to 0.87) | <0.001 | 0.99 (0.94 to 1.05) | 0.769 |
| OR (95% CI): unadjusted odds ratio with 95% confidence intervals, aOR (95% CI): adjusted odds ratios with 95% confidence intervals | | | | |

**Table 4:** Summary of associations between years since vaccination and all outcomes in individuals who are vaccinated - the baseline exposure is vaccination years ago compared to vaccination years ago

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Outcome | OR (95% CI) | P-value | aOR (95% CI) | P-value |
| Drug resistance | 1.15 (0.69 to 1.93) | 0.585 | 1.08 (0.55 to 2.15) | 0.816 |
| Multiple episodes | 1.78 (1.15 to 2.75) | 0.009 | 1.24 (0.63 to 2.44) | 0.525 |
| Positive sputum smear | 1.01 (0.73 to 1.40) | 0.941 | 1.02 (0.68 to 1.54) | 0.920 |
| All-cause mortality | 2.98 (1.22 to 7.28) | 0.016 | 0.91 (0.24 to 3.54) | 0.896 |
| TB mortality | 0.00 (0.00 to Inf) | 0.988 | 0.00 (0.00 to Inf) | 0.994 |
| Successful treatment | 0.46 (0.29 to 0.71) | <0.001 | 0.63 (0.33 to 1.21) | 0.167 |
| Pulmonary TB | 0.64 (0.55 to 0.74) | <0.001 | 0.87 (0.67 to 1.14) | 0.310 |
| OR (95% CI): unadjusted odds ratio with 95% confidence intervals, aOR (95% CI): adjusted odds ratios with 95% confidence intervals | | | | |

##### PAGEBREAK

**Table 5:** Summary of associations between age at vaccination and all outcomes in individuals who are vaccinated - the baseline exposure is vaccination at birth compared to vaccination from 1 to < 12, 12 to < 16, and 16+ years of age.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Outcome | Age group (years) | OR (95% CI) | P-value | aOR (95% CI) | P-value |
| Drug resistance | < 1 | 1 | 0.535 | 1 | 0.195 |
|  | 1 to < 12 | 1.07 (0.84 to 1.36) |  | 1.07 (0.82 to 1.39) |  |
|  | 12 to < 16 | 0.83 (0.61 to 1.14) |  | 0.69 (0.45 to 1.05) |  |
|  | ≥ 16 | 1.06 (0.66 to 1.70) |  | 1.05 (0.58 to 1.89) |  |
| Multiple episodes | < 1 | 1 | 0.463 | 1 | 0.246 |
|  | 1 to < 12 | 1.01 (0.80 to 1.26) |  | 0.84 (0.65 to 1.09) |  |
|  | 12 to < 16 | 0.84 (0.63 to 1.12) |  | 0.70 (0.48 to 1.02) |  |
|  | ≥ 16 | 1.22 (0.81 to 1.85) |  | 0.82 (0.49 to 1.37) |  |
| Positive sputum smear | < 1 | 1 | <0.001 | 1 | 0.862 |
|  | 1 to < 12 | 1.20 (1.01 to 1.42) |  | 0.96 (0.79 to 1.17) |  |
|  | 12 to < 16 | 1.97 (1.62 to 2.40) |  | 1.06 (0.81 to 1.39) |  |
|  | ≥ 16 | 1.26 (0.91 to 1.75) |  | 0.93 (0.63 to 1.37) |  |
| All-cause mortality | < 1 | 1 | <0.001 | 1 | 0.127 |
|  | 1 to < 12 | 3.60 (2.43 to 5.34) |  | 1.36 (0.85 to 2.16) |  |
|  | 12 to < 16 | 3.86 (2.51 to 5.91) |  | 0.81 (0.45 to 1.46) |  |
|  | ≥ 16 | 8.17 (5.01 to 13.32) |  | 1.41 (0.76 to 2.63) |  |
| TB mortality | < 1 | 1 | 0.118 | 1 | 0.543 |
|  | 1 to < 12 | 0.30 (0.11 to 0.87) |  | 0.36 (0.08 to 1.51) |  |
|  | 12 to < 16 | 0.46 (0.14 to 1.50) |  | 0.40 (0.06 to 2.52) |  |
|  | ≥ 16 | 0.31 (0.09 to 1.12) |  | 0.35 (0.06 to 2.16) |  |
| Successful treatment | < 1 | 1 | 0.671 | 1 | 0.531 |
|  | 1 to < 12 | 0.88 (0.71 to 1.09) |  | 1.00 (0.78 to 1.27) |  |
|  | 12 to < 16 | 1.00 (0.77 to 1.30) |  | 1.28 (0.89 to 1.83) |  |
|  | ≥ 16 | 0.90 (0.59 to 1.36) |  | 1.15 (0.69 to 1.90) |  |
| Pulmonary TB | < 1 | 1 | <0.001 | 1 | 0.005 |
|  | 1 to < 12 | 1.23 (1.12 to 1.36) |  | 1.15 (1.02 to 1.29) |  |
|  | 12 to < 16 | 2.36 (2.09 to 2.67) |  | 1.09 (0.92 to 1.29) |  |
|  | ≥ 16 | 1.77 (1.45 to 2.15) |  | 1.47 (1.15 to 1.88) |  |
| OR (95% CI): unadjusted odds ratio with 95% confidence intervals, aOR (95% CI): adjusted odds ratios with 95% confidence intervals | | | | | |

##### PAGEBREAK

**Sensitivity analysis**

We repeated the principal analysis using multiply imputed data; for BCG vaccination the evidence of any association was attenuated (Supplementary Information). However, there was still some evidence of an association with reduced multiple episodes (aoR: 0.91 (95% CI 0.80 to 1.03)), decreased all-cause mortality (aoR: 0.78 (95% CI 0.62 to 0.97)), and increased successful treatment (aoR: 1.13 (95% CI 0.98 to 1.30)). For years since vaccination there was some evidence that vaccination 11+ years prior to notification, compared to vaccination within 10 years, was associated with reduced multiple episodes (aoR: 0.78 (95% CI 0.58 to 1.06)), increased all-cause mortality (aoR: 9.93 (95% CI 2.40 to Inf)), and decreased successful treatment (aoR: 0.59 (95% CI 0.40 to 0.87)). For age at vaccination there was some evidence that vaccination in adolescence was associated with increased all-cause mortality (aoR: 1.58 (95% CI 1.18 to Inf)), and with reduced mortality due to TB (aoR: 0.38 (95% CI 0.19 to 0.77)). There was also some evidence that vaccination in adulthood was associated with increased successful treatment (aoR: 1.45 (95% CI 1.14 to 1.83)), and that vaccination for children (aoR: 1.37 (95% CI 1.18 to 1.59)), and adolescence (aoR: 1.12 (95% CI 1.04 to 1.21)) was associated with increased pulmonary TB.

Dropping recurrent cases increased the magnitude, and precision, of the effect sizes for multiple episodes, all-cause mortality, TB mortality, and successful treatment. Restricting the analysis to only cases that were eligible for the BCG schools scheme reduced the sample size of the analysis (from an initial study size of 51645, of which 12832 were UK born, to 9943 cases that would have been eligible for the BCG schools scheme), with this reduced sample size there was strong evidence of beneficial associations for multiple episodes, and all-cause mortality and some evidence of an association with successful treatment. Restricting the definition of successful treatment to 12 months of follow up reduced the magnitude of the effect size (aOR: ) and the strength of the evidence (P: ) of an association with BCG vaccination.

**Interactions between each exposure variable and the confounders**

After correcting for multiple testing there was evidence of interactions between BCG vaccination and multiple confounding variables, for several TB outcomes (Supplementary Information). For multiple episodes there was evidence of interactions between age (P: 0.001), ethnic group (P: 0.014), UK birth status (P: 0.047), and BCG vaccination; with little evidence for any other interaction. There was evidence that the association between BCG vaccination and reduced multiple episodes was restricted to the age group (aOR: 0.68 (95% CI 0.52, to 0.88)), to the white ethnic group (aOR: 0.62 (95% CI 0.49, to 0.77)), and to the UK born population (aOR: 0.71 (95% CI 0.58, to 0.87)). Whilst there was some evidence of interactions for sputum smear status, and pulmonary TB this is not readily interpretable as the evidence of any association in the principal analysis was limited. There was little evidence for interactions between confounding variables and any other TB outcome.

**DISCUSSION**

**Principal findings**

We present data from an analysis of routinely collected TB surveillance data collected in England between Jan 1, 2009 and and Dec 31, 2015, which considered the evidence for beneficial effects of BCG vaccination on outcomes for TB cases. Our data suggests that BCG vaccination, prior to the development of active TB, is linked to more positive outcomes for TB cases than previously thought.

Our results show that BCG vaccination was associated with a reduction in all-cause mortality, multiple episodes, and an increase in successful treatment. There was some evidence that the association with all-cause mortality was confined to TB mortality. We found little evidence in the surveillance data that BCG status was associated with drug resistance, positive smear status or pulmonary TB.

We found little evidence that vaccination after 10 years, compared to more recent vaccination, was associated with any TB outcome; except for decreased successful treatment. An analysis with multiply imputed data supported the association with decreased successful treatment, as well as indicating associations with reduced multiple episodes, and increased all-cause mortality. Additionally, we found some evidence that vaccination at birth, compared to at any other age was associated with reduced pulmonary TB. In the analysis with multiply imputed data there was some evidence that vaccination at birth was associated with reduced all-cause mortality, and with increased successful treatment.

**Strengths and Weaknesses of the study**

As the ETS system only contains data on notified TB cases it is not representative of the general English population. Therefore any research question must be limited to outcomes for tuberculosis patients only. Specifically this means that an estimation of the effect of BCG vaccination on all-cause mortality is not possible for the general population. In addition to this the BCG vaccinated and unvaccinated populations may not be directly comparable because vaccination has been offered to high risk neonates since 2005. However we have attempted to adjust for this by including confounding variables that are related to TB risk, and by conducting a sensitivity analysis of the population that were eligible for the schools scheme. This was limited by low sample size, but the magnitude of the effect sizes were comparable. However, as with all observational studies this study may contain additional unmeasured confounding.

There is the potential for misclassification bias both within the ETS system, and within several of our constructed outcome variables. The data set contains 3628 cases with multiple episodes; evidence from the literature shows that risk of recurrent tuberculosis is maximised between 1-5 years [23]. To account for this we repeated our principal analysis dropping those flagged as recurrent cases, this resulted in the magnitudes of the effect sizes increasing, which indicates that the inclusion of recurrent cases may have biased our analysis towards the null.

As the ETS system is compiled using routine surveillance data, it is likely that not all TB cases are notified and are therefore missing from the ETS system [25]. Additionally, some level of missing data is inevitable for all variables due to the routine nature of the ETS system. The proportion of missing data varies across variables, but has decreased as the ETS system has been developed [26], it is also likely that the degree of under-reporting has also decreased. For the years that it has been collected nationally BCG vaccination status has a high percentage of missing data (33.2%, 17133/51645), as does year of vaccination (58.7%, 14288/21522), which may introduce bias and reduce the precision of our analysis. As our results are comparable when repeated with imputed data there is little evidence that any of the outcomes, exposure, or confounding variables bias the collection of data. However the potential for a unknown missing not at random mechanism, or unmeasured confounding, means that we cannot conclude that our results are unbiased. We have attempted to account for this in part by including Public Health England centre in the imputation model, as it is likely that data collection differs across regions.

Whilst the initial size of the study population was large, the high percentage of missing data on those BCG vaccinated means that we were likely to be underpowered to detect an effect on drug resistance, sputum smear status, and TB mortality. In addition as a high proportion of those with known vaccination status were missing year of vaccination both year of vaccination, and age at vaccination are likely to be underpowered for all adjusted analysis (Supplementary Information). However, as the data used in this study is routinely collected these issues may be able to be addressed as more data is collected.

**Strengths and Weaknessess in relation to other studies**

As this study used routinely collected surveillance data we could not account for unmeasured confounding, or deal with the structural biases in the data to the same level as previous studies [27]. Additionally, as this study was conducted in a single population we cannot account for biases introduced by unmeasured population demographics, unlike previous meta-analysis approaches [7]. However, the ETS system is a robust national surveillance system that has been operational for over a decade, with a similar structure and reporting methods. This means that our study has the benefit of large amounts of high quality demographic information about each notified TB case. We were also able to assess multiple outcomes and exposure variables, providing initial evidence for possible associations. Whilst the assessment of multiple outcomes was hypothesis driven it does increase the likelihood of a type 1 error, however this is mitigated by the collinearity of many of the outcome measures.

**Meaning of the study**

This study indicates that BCG vaccination is associated with positive outcomes for active tuberculosis including, reduced all-cause mortality, increased successful treatment and reduced incidence of multiple episodes. It also indicates that these effects may vary across demographic subgroups for multiple episodes. There is some support in the literature for reduced mortality in neonates resulting from BCG vaccination [15], however an RCT study was unable to detect an effect in populations of neonates [31] and there is some discussion that designing a study to adequately detect this effect may be challenging [32], although this is a current area of research. There is also some evidence for other non-specific benefits of BCG vaccination such as improving innate immune response [33].

**Generalisability of the study results**

As this study is population-based it will yield effect measures that are generalisable to other populations of TB cases. We have conducted sensitivity analysis on the comparability of the BCG vaccination and unvaccinated populations, and found weak evidence of any changes in the magnitude of the estimated effect sizes.

**Unanswered questions and future research**

This study provides initial evidence of several beneficial associations between BCG vaccination and TB outcomes, to validate these results further statistical analysis is required using independent data sets, or a future validation study using the ETS as more data is collected. Our results indicate that BCG vaccination may be more effective in preventing negative outcomes than previously thought; this evidence should be considered in future cost effectiveness studies.

**Acknowledgements**

Lucy Thomas, and Dominik Zenner.

**Funding**

SEA was funded by the National Institute for Health Research Health Protection Research Unit (NIHR HPRU) in Evaluation of Interventions at University of Bristol in partnership with Public Health England (PHE). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR, the Department of Health or Public Health England.

**Conflicts of interest**

* statements needed

**Accessibility of data and programming code**

The code for the analysis contained in this paper can be found at: *link not yet available*

##### PAGEBREAK

## References

1 The World Health Organization. BCG Vaccine. *Weekly epidemiological record* 2004;**79**:27–48.

2 Mangtani P, Abubakar I, Ariti C *et al.* Protection by BCG Vaccine Against Tuberculosis: A Systematic Review of Randomized Controlled Trials. *Clinical Infectious Diseases* 2014;**58**:470–80. doi:[10.1093/cid/cit790](https://doi.org/10.1093/cid/cit790)

3 Rodrigues LC, Diwan VK, Wheeler JG. Protective effect of BCG against tuberculous meningitis and miliary tuberculosis: a meta-analysis. *International journal of epidemiology* 1993;**22**:1154–8.<http://www.ncbi.nlm.nih.gov/pubmed/8144299>

4 Colditz GA, Brewer TF, Berkey CS *et al.* Efficacy of BCG Vaccine in the Prevention of Tuberculosis. *JAMA* 1994;**271**:698. doi:[10.1001/jama.1994.03510330076038](https://doi.org/10.1001/jama.1994.03510330076038)

5 Zwerling A, Behr MA, Verma A *et al.* The BCG World Atlas: a database of global BCG vaccination policies and practices. *PLoS medicine* 2011;**8**:e1001012. doi:[10.1371/journal.pmed.1001012](https://doi.org/10.1371/journal.pmed.1001012)

6 Fine PE. Herd immunity: history, theory, practice. *Epidemiologic reviews* 1993;**15**:265–302.<http://www.ncbi.nlm.nih.gov/pubmed/8174658>

7 Roy a, Eisenhut M, Harris RJ *et al.* Effect of BCG vaccination against Mycobacterium tuberculosis infection in children: systematic review and meta-analysis. *Bmj* 2014;**349**:g4643–3. doi:[10.1136/bmj.g4643](https://doi.org/10.1136/bmj.g4643)

8 Jeremiah K, Praygod G, Faurholt-Jepsen D *et al.* BCG vaccination status may predict sputum conversion in patients with pulmonary tuberculosis: a new consideration for an old vaccine? *Thorax* 2010;**65**:1072–6. doi:[10.1136/thx.2010.134767](https://doi.org/10.1136/thx.2010.134767)

9 Higgins JPT, Soares-weiser K, López-lópez JA *et al.* Association of BCG , DTP , and measles containing vaccines with childhood mortality : systematic review. doi:[10.1136/bmj.i5170](https://doi.org/10.1136/bmj.i5170)

10 Kruijshaar M, Charlotte Anderson DIAFC. Tuberculosis in the UK, Annual report on tuberculosis surveillance and control in the UK 2007. *PHE Publications* Published Online First: 2007. doi:[10.1136/thx.50.6.703](https://doi.org/10.1136/thx.50.6.703)

11 Abubakar I, Pimpin L, Ariti C *et al.* Systematic review and meta-analysis of the current evidence on the duration of protection by bacillus Calmette-Guérin vaccination against tuberculosis. *Health technology assessment (Winchester, England)* 2013;**17**:1–372, v–vi. doi:[10.3310/hta17370](https://doi.org/10.3310/hta17370)

12 Public Health England. The Green Book. 2013;391–409.

13 R Core Team. R: A Language and Environment for Statistical Computing. 2016.<https://www.r-project.org/>

14 Parslow R, El-Shimy N a, Cundall DB *et al.* Tuberculosis, deprivation, and ethnicity in Leeds, UK, 1982-1997. *Archives of disease in childhood* 2001;**84**:109–13. doi:[10.1136/adc.84.2.109](https://doi.org/10.1136/adc.84.2.109)

15 Roth A, Sodemann M, Jensen H *et al.* Tuberculin reaction, BCG scar, and lower female mortality. *Epidemiology (Cambridge, Mass)* 2006;**17**:562–8. doi:[10.1097/01.ede.0000231546.14749.ab](https://doi.org/10.1097/01.ede.0000231546.14749.ab)

16 Aaby P, Nielsen J, Benn CS *et al.* Sex-differential and non-specific effects of routine vaccinations in a rural area with low vaccination coverage: An observational study from Senegal. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 2014;**109**:77–84. doi:[10.1093/trstmh/tru186](https://doi.org/10.1093/trstmh/tru186)

17 Teale C, Goldman JM, Pearson SB. The association of age with the presentation and outcome of tuberculosis: a five-year survey. *Age and ageing* 1993;**22**:289–93.

18 Abubakar I, Laundy MT, French CE *et al.* Epidemiology and treatment outcome of childhood tuberculosis in England and Wales: 1999-2006. *Archives of disease in childhood* 2008;**93**:1017–21. doi:[10.1136/adc.2008.139543](https://doi.org/10.1136/adc.2008.139543)

19 French CE, Antoine D, Gelb D *et al.* Tuberculosis in non-UK-born persons, England and Wales, 2001-2003. *International Journal of Tuberculosis and Lung Disease* 2007;**11**:577–84.

20 Djuretic T, Herbert J, Drobniewski F *et al.* Antibiotic resistant tuberculosis in the United Kingdom : 2002;477–82.

21 Van Buuren S, Groothuis-Oudshoorn K. Multivariate Imputation by Chained Equations. *Journal Of Statistical Software* 2011;**45**:1–67. doi:[10.1177/0962280206074463](https://doi.org/10.1177/0962280206074463)

22 Barnard J, Rubin DB. Miscellanea. Small-sample degrees of freedom with multiple imputation. *Biometrika* 1999;**86**:948–55. doi:[10.1093/biomet/86.4.948](https://doi.org/10.1093/biomet/86.4.948)

23 Millet JP, Shaw E, Orcau À *et al.* Tuberculosis Recurrence after Completion Treatment in a European City: Reinfection or Relapse? *PLoS ONE* 2013;**8**:1–8. doi:[10.1371/journal.pone.0064898](https://doi.org/10.1371/journal.pone.0064898)

24 Moosazadeh M, Bahrampour A, Nasehi M *et al.* The incidence of recurrence of tuberculosis and its related factors in smear-positive pulmonary tuberculosis patients in Iran: A retrospective cohort study. *Lung India* 2015;**32**:557. doi:[10.4103/0970-2113.168113](https://doi.org/10.4103/0970-2113.168113)

25 Pillaye J, Clarke A. An evaluation of completeness of tuberculosis notification in the United Kingdom. *BMC Public Health* 2003;**3**:31.

26 PHE. Tuberculosis in the UK: 2014 report. *PHE Publications* 2014.

27 Hart PDA, Sutherland IAN. BCG and vole bacillus vaccines in the prevention of tuberculosis in adolescence and early adult life. *Bulletin of the World Health Organization* 1972;**46**:371–85. doi:[10.1136/bmj.2.6082.293](https://doi.org/10.1136/bmj.2.6082.293)

28 Rieckmann A, Villumsen M, Sørup S *et al.* Vaccinations against smallpox and tuberculosis are associated with better long-term survival: a Danish case-cohort study 1971–2010. *International Journal of Epidemiology* 2016;**94**:dyw120. doi:[10.1093/ije/dyw120](https://doi.org/10.1093/ije/dyw120)

29 Sankoh O, Welaga P, Debpuur C *et al.* The non-specific effects of vaccines and other childhood interventions: The contribution of INDEPTH Health and Demographic Surveillance Systems. *International Journal of Epidemiology* 2014;**43**:645–53. doi:[10.1093/ije/dyu101](https://doi.org/10.1093/ije/dyu101)

30 Aaby P, Benn CS. Saving lives by training innate immunity with bacille Calmette-Guerin vaccine. *Proceedings of the National Academy of Sciences* 2012;**109**:17317–8. doi:[10.1073/pnas.1215761109](https://doi.org/10.1073/pnas.1215761109)

31 Aaby P, Roth A, Ravn H *et al.* Randomized trial of BCG vaccination at birth to low-birth-weight children: Beneficial nonspecific effects in the neonatal period? *Journal of Infectious Diseases* 2011;**204**:245–52. doi:[10.1093/infdis/jir240](https://doi.org/10.1093/infdis/jir240)

32 Fine PEM, Smith PG, Evans SJW. Non-specific effects of BCG? *Journal of Infectious Diseases* 2012;**205**:515. doi:[10.1093/infdis/jir760](https://doi.org/10.1093/infdis/jir760)

33 Kleinnijenhuis J, Quintin J, Preijers F *et al.* Bacille Calmette-Guerin induces NOD2-dependent nonspecific protection from reinfection via epigenetic reprogramming of monocytes. *Proceedings of the National Academy of Sciences of the United States of America* 2012;**109**:17537–42. doi:[10.1073/pnas.1202870109](https://doi.org/10.1073/pnas.1202870109)

##### PAGEBRE