Title: Exploring the effects of BCG vaccination in patients diagnosed with tuberculosis: observational study using the Enhanced Tuberculosis Surveillance system

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ABSTRACT

Background

Bacillus Calmette–Guérin (BCG) is one of the most widely-used vaccines worldwide. BCG primarily reduces the progression from infection to disease, however there is evidence that BCG may provide additional benefits. We aimed to investigate whether there is evidence in routinely-collected surveillance data that BCG vaccination impacts outcomes for tuberculosis (TB) cases in England.

Methods

We obtained all TB notifications for 2009-2015 in England from the Enhanced Tuberculosis surveillance system. We considered five outcomes: All-cause mortality, death due to TB (in those who died), recurrent TB, pulmonary disease, and sputum smear status. We used logistic regression, with complete case analysis, to investigate each outcome with BCG vaccination, years since vaccination and age at vaccination, adjusting for potential confounders. All analyses were repeated using multiply imputed data.

Results

We found evidence of an association between BCG vaccination and reduced all-cause mortality (aOR:0.76 (95%CI 0.64 to 0.89), P:0.001) and weak evidence of an association with reduced recurrent TB (aOR:0.90 (95%CI 0.81 to 1.00), P:0.056). Analyses using multiple imputation suggested that the benefits of vaccination for all-cause mortality were reduced after 10 years.

Conclusions

We found that BCG vaccination was associated with reduced all-cause mortality in people with TB although this benefit was less pronounced more than 10 years after vaccination. There was weak evidence of an association with reduced recurrent TB.

Keywords: Tuberculosis, BCG, Surveillance, Non-specific, Mortality

Highlights

- Found evidence of an association between BCG vaccination and reduced all-cause mortality in TB cases.
- Weaker evidence of an association between BCG vaccination and reduced repeat TB episodes in TB cases.
- There was little evidence of an association with other TB outcomes.
- There was weak evidence of associations between TB outcomes and age at, or years since, vaccination.

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.[2] However, the lack of a more effective vaccine and the emergence of drug-resistant TB strains means that BCG vaccination remains an important tool for reducing TB incidence and mortality rates.

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%.[3] It has been shown to highly efficacious in England and there is some evidence that efficacy increases with distance from the equator. Efficacy has been shown to be dependent on previous exposure, with unexposed individuals receiving the greatest benefit.[4] Unlike in adults, BCG has consistently been shown to be highly protective against TB and TB meningitis in children.[5,6] For this reason the majority of countries that use BCG, vaccinate at birth.[7,8] Adult vaccination is no longer common in the UK, where universal BCG vaccination of adolescents was stopped in 2005 in favour of a targeted neonatal programme aimed at high risk children.

Vaccination policy has been primarily based on reducing the incidence of TB disease, and mitigating disease severity, with little attention having been given to any additional effects of BCG vaccination on TB outcomes..[9,10] There is some evidence that BCG vaccination induces innate immune responses which may provide non-specific protection,[11] TB

patients with BCG scars were found to respond better to treatment with earlier sputum smear conversion,[12] and there is evidence to suggest that BCG vaccination is associated with reduced all-cause neonatal mortality[13,14] and both reduced TB[15] and all-cause[16] mortality in the general population. Given that the immunology behind TB immunity is not fully understood these findings suggest that BCG may play a more important role in improving TB outcomes than previously thought. 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. Where we found an association, we additionally explored the role of years since vaccination, and age at vaccination.

METHOD

Enhanced Tuberculosis Surveillance (ETS) system

We extracted all notifications from the Enhanced Tuberculosis Surveillance (ETS) system from January 1, 2009 to December 31, 2015. BCG vaccination status and year of vaccination have been collected since 2008. The outcomes we considered were: all-cause mortality, death due to TB (in those who died), recurrent TB, pulmonary disease, and sputum smear status. These outcomes were selected based on: their availability in the ETS; evidence from the literature of prior associations with BCG vaccination; associations with increased case infectiousness; or severe outcomes for patients.

All-cause mortality was defined using the overall outcome recorded in ETS, this is based on up to 36 months of follow up starting from date of starting treatment. Follow up ends when a case is recorded as completing treatment, with treatment status evaluated at 12, 24, and 36 months from starting treatment. Where the treatment start date was not available the notification date was used if appropriate. The date of death was validated against Office for National Statistics (ONS) data. Those that were lost to follow up, or not evaluated were treated as missing. In cases with a known cause of death, death due to TB was defined as those that died from TB, or where TB had contributed to their death. Cause of death was recorded by case managers. TB cases who had recurrent episodes were identified using probabilistic matching. Positive sputum smear status was given to cases that had a sputum sample shown to contain Acid-Fast Bacilli. A positive sputum smear status indicates that cases are more likely to be infectious. Cases were defined as having pulmonary TB if a positive sputum smear sample was recorded, if a positive culture was grown from a

pulmonary laboratory specimen, or if they were clinically assessed as having pulmonary TB.

Exposure variables relating to BCG

We included three exposure variables related to BCG: BCG status (vaccinated, yes/no), years since vaccination and age at vaccination.

BCG status was collected and recorded in ETS by case managers. Information on BCG vaccination status may have come from vaccination records, patient recall or the presence of a scar. When cases are uncertain, and there is no evidence of a scar, no BCG status is given. Year of vaccination was collected similarly. Years since BCG vaccination was defined as year of notification minus year of vaccination and categorised into two groups (0 to 10 and 11+ years). This was based on: evidence that the average duration of BCG protection is at least 10-15 years;[15] increasing recall bias with time since vaccination, and any association between years since vaccination and TB outcomes may be non-linear. Age at vaccination is defined in the online supplementary information.

Statistical Analysis

R was used for all statistical analysis.[17] The analysis was conducted in two stages. Firstly, we calculated proportions for all demographic and outcome variables, and compared vaccinated and unvaccinated TB cases using the χ^2 test. Secondly, we used logistic regression, with complete case analysis, to estimate the association between exposures and outcome variables, both with and without adjustment for confounders.

In the multivariable models, we adjusted for sex,[18–20] age,[21] Index of Multiple Deprivation (2010) categorised into five groups for England (IMD rank),[22,23] ethnicity,[18,24] UK birth status,[25,26] and year of notification. As the relationship between age and outcomes was non-linear, we modelled age using a natural cubic spline with knots at the 25%, 50% and 75% quantiles.

We conducted sensitivity analyses to assess the robustness of the results, by dropping each confounding variable in turn and assessing the effect on the adjusted Odds Ratios (aORs) of the exposure variable. We repeated the analysis excluding duplicate 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. To mitigate the impact of missing data we used multiple imputation, with the MICE package.[27] We imputed 50 data sets (for 20 iterations) using all outcome and explanatory variables included in the analysis as predictors along with Public Health England centre. The model results were pooled using the small sample method,[28] and effect sizes compared with those from the main 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 improved over time: 64.9% (20865/32154) of notifications included vaccination status for 2009 to 2012, increasing to 70% (13647/19491) from 2013 to 2015. The majority of cases that had a known vaccination

status were vaccinated (70.6%, 24354/34512), and where age and year of vaccination was known, the majority of cases were vaccinated at birth (60%, 5979/10066).

Vaccinated cases were younger than unvaccinated cases on average (median age 34 years (IQR 26 to 45) compared to 38 years (IQR 26 to 62)). A higher proportion of non-UK born cases were BCG vaccinated, (72.7%, 18297/25171) compared to UK born cases (65.2%, 5787/8871, P: < 0.001) and, of those vaccinated, 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). See table 1 for the breakdown of outcome variables table 2 for the breakdown of confounding variables.

1

2 ***Table 1:*** *Outcomes for individuals in England notified with tuberculosis between 2009-2015,*

3 *stratified by BCG vaccination status.*

Outcome	Total	Vaccinated	Unvaccinated	Unknown vaccine status
Total, all cases	51645	24354 {47}	10158 {20}	17133 {33}
All-cause mortality	45588 (88)	21685 (89)	9061 (89)	14842 (87)
No	43024 [*94*]	21291 [*98*]	8495 [*94*]	13238 [*89*]
Yes	2564 [*6*]	394 [*2*]	566 [*6*]	1604 [*11*]
Death due to TB (in those who died*)	1373 (3)	276 (1)	320 (3)	777 (5)
No	572 [*42*]	129 [*47*]	146 [*46*]	297 [*38*]
Yes	801 [*58*]	147 [*53*]	174 [*54*]	480 [*62*]
Recurrent TB	48497 (94)	23963 (98)	9991 (98)	14543 (85)
No	44869 [*93*]	22592 [*94*]	9256 [*93*]	13021 [*90*]
Yes	3628 [*7*]	1371 [*6*]	735 [*7*]	1522 [*10*]
Pulmonary TB	51432 (100)	24289 (100)	10121 (100)	17022 (99)
Extra-pulmonary (EP) only	24280 [*47*]	12085 [*50*]	4573 [*45*]	7622 [*45*]

Pulmonary, with or without EP	27152 [*53*]	12204 [*50*]	5548 [*55*]	9400 [*55*]
Sputum smear status	19551 (38)	9768 (40)	3910 (38)	5873 (34)
Negative	11060 [*57*]	5694 [*58*]	2231 [*57*]	3135 [*53*]
Positive	8491 [*43*]	4074 [*42*]	1679 [*43*]	2738 [*47*]

{% all cases}(% complete within vaccine status)[% *complete within category*],

* Death due to TB in those who died and where cause of death was known

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Table 2: *Confounders for individuals in England notified with tuberculosis between 2009-2015, stratified by BCG vaccination status.*

Confounder	Total	Vaccinated	Unvaccinated	Unknown vaccine status
Total, all cases	51645	24354 {47}	10158 {20}	17133 {33}
Age	51645 (100)	24354 (100)	10158 (100)	17133 (100)
Mean **[SD]**	40 **[19]**	36 **[16]**	44 **[22]**	45 **[20]**
Median **[25%, 75%]**	36 **[27, 52]**	34 **[26, 45]**	38 **[26, 62]**	41 **[29, 59]**
Sex	51535 (100)	24320 (100)	10136 (100)	17079 (100)
Female	22066 [*43*]	10791 [*44*]	4312 [*43*]	6963 [*41*]
Male	29469 [*57*]	13529 [*56*]	5824 [*57*]	10116 [*59*]
IMD rank (with 1 as most deprived and 5 as least deprived)*	43525 (84)	21240 (87)	8866 (87)	13419 (78)
1	16800 [*39*]	7779 [*37*]	3665 [*41*]	5356 [*40*]
2	13057 [*30*]	6836 [*32*]	2564 [*29*]	3657 [*27*]
3	6838 [*16*]	3459 [*16*]	1259 [*14*]	2120 [*16*]
4	4045 [*9*]	1893 [*9*]	836 [*9*]	1316 [*10*]
5	2785 [*6*]	1273 [*6*]	542 [*6*]	970 [*7*]
UK birth status	49820 (96)	24084 (99)	9958 (98)	15778 (92)
Non-UK Born	36988 [*74*]	18297 [*76*]	6874 [*69*]	11817 [*75*]

UK Born	12832 [*26*]	5787 [*24*]	3084 [*31*]	3961 [*25*]
Ethnic group	50416 (98)	24074 (99)	10024 (99)	16318 (95)
White	10194 [*20*]	3560 [*15*]	2695 [*27*]	3939 [*24*]
Black-Caribbean	1112 [*2*]	559 [*2*]	242 [*2*]	311 [*2*]
Black-African	8942 [*18*]	4620 [*19*]	1602 [*16*]	2720 [*17*]
Black-Other	462 [*1*]	261 [*1*]	80 [*1*]	121 [*1*]
Indian	12994 [*26*]	7176 [*30*]	2061 [*21*]	3757 [*23*]
Pakistani	8237 [*16*]	3512 [*15*]	1720 [*17*]	3005 [*18*]
Bangladeshi	2025 [*4*]	918 [*4*]	480 [*5*]	627 [*4*]
Chinese	601 [*1*]	289 [*1*]	101 [*1*]	211 [*1*]
Mixed / Other	5849 [*12*]	3179 [*13*]	1043 [*10*]	1627 [*10*]
Calendar year	51645 (100)	24354 (100)	10158 (100)	17133 (100)

{% all cases}(% complete within vaccine status)[% *complete within category*],

* Index of Multiple Deprivation (2010) categorised into five groups for England

All-cause mortality

In the univariable analysis the odds of death from any cause were lower for BCG vaccinated TB cases compared to unvaccinated cases, with an OR of 0.28 (95% CI 0.24 to 0.32, P: <0.001) (table 3, see supplementary table S1 for the full table); an association remained after adjusting for confounders, but was attenuated with an aOR of 0.76 (95% CI 0.64 to 0.89, P: 0.001). We estimate that if all unvaccinated cases had been vaccinated there would have been on average 19 (95% CI 9 to 29) fewer deaths per year during the study period

(out of 81 deaths per year on average in unvaccinated cases). Whilst there was evidence in univariable analyses to suggest all-cause mortality was higher in persons vaccinated more than 10 years prior to notification of TB and that all-cause mortality increased with increasing age group, these disappeared after adjusting for potential confounders (table 4, supplementary table S2).

Similar results to the multivariable analysis were found using multiply imputed data for the association between vaccination status and all-cause mortality (aOR: 0.76 (95% CI 0.61 to 0.94), P: 0.013), but not for time since vaccination with a greatly increased risk of all-cause mortality estimated for those vaccinated more than 10 years before case notification, compared to those vaccinated more recently (aOR: 12.19 (95% CI 3.48 to 42.64), (see online supplementary table S3, supplementary table S4)). For age at vaccination results for the multivariable analysis using multiply imputed data were comparable to those found using complete case analysis, except that there was some evidence that vaccination in adolescence, compared to under 1, was associated with increased, rather than decreased, all-cause mortality (aOR: 1.57 (95% CI 1.13 to 2.19), supplementary table S5).

Deaths due to TB (in those who died)

There was little evidence of any association between BCG vaccination and deaths due to TB (in those who died and where cause of death was known) in the univariable analysis (table 3). The adjusted point estimate indicated an association between BCG vaccination and reduced deaths due to TB (in those who died) although the confidence intervals remained wide with a similar result found using multiply imputed data (see online supplementary table S3). There were insufficient data to robustly estimate an association between deaths

due to TB (in those who died) and years since vaccination or age at vaccination (table 4, supplementary table S2).

Recurrent TB

In both the univariable and multivariable analysis there was some evidence that BCG vaccination was associated with reduced recurrent TB, although the strength of the evidence was weakened after adjusting for confounders (table 3). In the adjusted analysis, the odds of recurrent TB were lower for BCG vaccinated cases compared to unvaccinated cases, with an aOR of 0.90 (95% CI 0.81 to 1.00, P: 0.056). The strength of the evidence for this association was comparable in the analysis using multiply imputed data (see online supplementary table S3). There was little evidence in the adjusted analysis of any association between recurrent TB and years since vaccination (table 4) or age at vaccination (supplementary table S2).

Other Outcomes

After adjusting for confounders there was little evidence for any association between BCG vaccination and pulmonary disease or positive sputum smear status (table 3); similar results were found using multiply imputed data (see online supplementary table S3).

Table 3: *Summary of associations between BCG vaccination and all outcomes. Cases represents all notifications with complete data and a given BCG status, regardless of outcome. Cases with outcome is similarly defined but includes only cases with the specified outcome.*

Outcome	BCG vaccinated	Univariable				Multivariable			
		Cases*	Cases with outcome (%)	OR (95% CI)	P-value	Cases †	Cases with outcome (%)	aOR (95% CI)	P-value
All-cause mortality	No	9061	566 (6)	1	<0.001	7620	473 (6)	1	0.001
	Yes	21685	394 (2)	0.28 (0.24 to 0.32)		1837 3	334 (2)	0.76 (0.64 to 0.89)	
Death due to TB (in	No	320	174 (54)	1	0.786	270	143 (53)	1	0.177
	Yes	276	147 (53)	0.96 (0.69 to 1.32)		236	126 (53)	0.76 (0.51 to 1.13)	

those who died‡)									
Recurrent TB	No	9991	735 (7)	1	<0.001	8502	615 (7)	1	0.056
	Yes	23963	1371 (6)	0.76 (0.70 to 0.84)		20584	1177 (6)	0.90 (0.81 to 1.00)	
Pulmonary TB	No	10121	5548 (55)	1	<0.001	8595	4685 (55)	1	0.769
	Yes	24289	12204 (50)	0.83 (0.79 to 0.87)		20784	10342 (50)	0.99 (0.94 to 1.05)	
Sputum smear status - positive	No	3910	1679 (43)	1	0.187	3367	1435 (43)	1	0.730
	Yes	9768	4074 (42)	0.95 (0.88 to 1.02)		8351	3447 (41)	1.02 (0.93 to 1.11)	

OR (95% CI): unadjusted odds ratio with 95% confidence intervals,

aOR (95% CI): adjusted odds ratios with 95% confidence intervals,

* Univariable sample size for outcomes ordered as in table (% of all cases) = 30746 (60%), 596 (23%), 33954 (66%), 34410 (67%), 13678 (26%),

† Multivariable sample size with outcomes ordered as in table (% of all cases) = 25993 (50%), 506 (20%), 29086 (56%), 29379 (57%), 11718 (23%),

‡ Death due to TB in those who died and where cause of death was known

Table 4: *Summary of associations between years since vaccination and all outcomes in individuals who were vaccinated. The baseline exposure is vaccination* ≤ 10 *years before diagnosis compared to vaccination* $11+$ *years before diagnosis. Deaths due to TB (in those who died) had insufficient data for effect sizes to be estimated in both the univariable and multivariable analysis. Cases represents all notifications with complete data and a given BCG status, regardless of outcome. Cases with outcome is similarly defined but includes only cases with the specified outcome.*

Outcome	Years since BCG	Univariable				Multivariable			
		Cases*	Cases with outcome (%)	OR (95% CI)	P-value	Cases†	Cases with outcome (%)	aOR (95% CI)	P-value
All-cause mortality	≤ 10	718	5 (1)	1	0.004	554	4 (1)	1	0.897
	11+	8106	166 (2)	2.98 (1.22 to 7.28)		7171	148 (2)	0.91 (0.24 to 3.54)	
Death due to TB (in those who died‡)	≤ 10	2	2 (100)	1	-	2	2 (100)	1	-
	11+	108	59 (55)	*Insufficient data*		98	53 (54)	*Insufficient data*	

Recurrent TB	≤ 10	780	22 (3)	1	0.005	613	14 (2)	1	0.515
	11+	9172	451 (5)	1.78 (1.15 to 2.75)		8194	406 (5)	1.24 (0.63 to 2.44)	
Pulmonary TB	≤ 10	770	480 (62)	1	<0.001	601	382 (64)	1	0.309
	11+	9248	4757 (51)	0.64 (0.55 to 0.74)		8254	4232 (51)	0.87 (0.67 to 1.14)	
Sputum smear status - positive	≤ 10	157	81 (52)	1	0.941	122	61 (50)	1	0.920
	11+	3064	1590 (52)	1.01 (0.73 to 1.40)		2734	1405 (51)	1.02 (0.68 to 1.54)	

OR (95% CI): unadjusted odds ratio with 95% confidence intervals, aOR (95% CI): adjusted odds ratios with 95% confidence intervals,

* Univariable sample size for outcomes ordered as in table (% of vaccinated cases) = 8824 (36%), 110 (28%), 9952 (41%), 10018 (41%), 3221 (13%),

† Multivariable sample size with outcomes ordered as in table (% of vaccinated cases) = 7725 (32%), 100 (25%), 8807 (36%), 8855 (36%), 2856 (12%),

‡ Death due to TB in those who died and where cause of death was known

Sensitivity analysis

Dropping duplicate recurrent TB notifications increased the magnitude, and precision, of the effect sizes for recurrent TB, all-cause mortality, and deaths due to TB (in those who died) (see online supplementary table S6). 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 in adjusted analyses of an association between BCG vaccination and reduced recurrent TB, and evidence of an association with decreased all-cause mortality (see online supplementary table S6).

DISCUSSION

Using TB surveillance data collected in England we found that BCG vaccination, prior to the development of active TB, was associated with reduced all-cause mortality and fewer recurrent TB cases, although the evidence for this association was weaker. There was some suggestion that the association with all-cause mortality was due to reduced deaths due to TB (in those who died), though the study was underpowered to definitively assess this. We did not find evidence of an association between BCG status and positive smear status or pulmonary TB. Analysis with multiply imputed data indicated that notification 10+ years after vaccination was associated with increased all-cause mortality. In separate analyses, there was some evidence that vaccination at birth, compared to at any other age, was associated with reduced all-cause mortality, and increased deaths due to TB (in those who died).

This study used a large detailed dataset, with coverage across demographic groups, and standardized data collection from notifications and laboratories. The use of routine surveillance data means that this study would be readily repeatable with new data. The surveillance data contained multiple known risk factors, this allowed us to adjust for these confounders in the multivariable analysis, which attenuated the evidence for an association with BCG vaccination for all outcomes. However, there are important limitations to consider. The study was conducted within a population of active TB cases, therefore the association with all-cause mortality cannot be extrapolated to the general population. Additionally, vaccinated and unvaccinated populations may not be directly comparable because vaccination has been targeted at high-risk neonates in the UK since 2005. We

mitigated this potential source for bias by conducting a sensitivity analysis including only those eligible for the universal school age scheme, and whilst the strength of associations were attenuated there remained some evidence of improved outcomes. Sensitivity analysis excluding recurrent cases indicated their inclusion may have biased our results towards the null.

Variable data completeness changed with time, with both BCG vaccination status and year of vaccination having a high percentage of missing data, which may not be missing completely at random. We therefore checked the robustness of our results with multiple imputation including regional variability, however an unknown missing not at random mechanism, or unmeasured confounding may still have introduced bias. We found a greatly increased risk of all-cause mortality for those vaccinated more than 10 years ago in the analysis with multiply imputed data, compared to the complete case analysis. This is likely to be driven by a missing not at random mechanism for years since vaccination, with older cases being both more likely to have been vaccinated more than 10 years previously and to also have an unknown year of vaccination. The high percentage of missing data also means that we were likely to be underpowered to detect an effect of BCG vaccination on sputum smear status and deaths due to TB (in those who died), with years since vaccination, and age at vaccination likely to be underpowered for all outcomes. We were not able to adjust for either tuberculin skin test (TST) stringency, or the latitude effect, although we were able to adjust for UK birth status.[29] However, the bias induced by these confounders is likely to be towards the null, meaning that our effect estimates are likely to be conservative. We could also not adjust for the BCG strain each individual may have received, the BCG strain used may vary both temporally and geographically. Finally, BCG vaccination status,

and year of vaccination, may be subject to misclassification due to recall bias; validation studies of the recording of BCG status in the ETS would be required to assess this.

Little work has been done to assess the overall effect of BCG on outcomes for active TB cases although the possible non-specific effects of BCG are an area of active research.[14,30,31] Whilst multiple studies have investigated BCG's association with all-cause mortality, it has been difficult to assess whether the association continues beyond the first year of life.[31] The effect size of the association we identified between BCG and all-cause mortality in active TB cases was comparable to that found in a Danish case-cohort study in the general population (aHR: 0.58 (95% CI 0.39 to 0.85).[16] A recent systematic review also found that BCG vaccination was associated with reduced all-cause mortality in neonates, with an average relative risk of 0.70 (95% CI 0.49 to 1.01) from five clinical trials and 0.47 (95% CI 0.32 to 0.69) from nine observational studies at high risk of bias.[14] We found some weak evidence that BCG vaccination was associated with reduced deaths due to TB (in those who died), although our point estimate had large confidence intervals. Several meta-analyses have found evidence supporting this association,[6,15] with one meta-analysis estimating a 71% (RR: 0.29 95% CI 0.16 to 0.53) reduction in deaths due to TB in individuals vaccinated with BCG.[6] The meta-analysis performed by Abubakar et al. also found consistent evidence for this association, with a Rate Ratio of 0.22 (95% CI 0.15 to 0.33).[15] In contrast to our study, both of these meta-analyses estimated the protection from TB mortality in BCG vaccinated individuals rather than in BCG vaccinated cases who had died from any cause. Additionally, neither study explored the association between BCG vaccination and all-cause mortality or recurrent TB. This study could not determine the possible causal pathway for the association between BCG vaccination all-

cause mortality, and recurrent TB. These are important to establish in order to understand the effect of BCG vaccination on TB outcomes.

We found that BCG vaccination was associated with reduced all-cause mortality, with some weaker evidence of an association with reduced recurrent TB. A plausible mechanism for this association is that BCG vaccination improves treatment outcomes,[12] which then results in decreased mortality, and reduced recurrent TB. However, these effects may also be independent and for all-cause mortality may not be directly related to active TB. In this case, a possible mechanism for the association between BCG vaccination and all-cause mortality is that BCG vaccination modulates the innate immune response, resulting in non-specific protection.[11] For low incidence countries, where the reduction in TB cases has been used as evidence to scale back vaccination programs,[7] these results suggest that BCG vaccination may be more beneficial than previously thought. In countries that target vaccination at those considered to be at high risk of TB the results from this study could be used to help drive uptake by providing additional incentives for vaccination. The evidence we have presented should be considered in future cost-effectiveness studies of BCG vaccination programs.

Further work is required to determine whether years since vaccination and age at vaccination are associated with TB outcomes as this study was limited by low sample size, missing data for year of vaccination, and the relative rarity of some TB outcomes. However, due to the continuous collection of the surveillance data used in this analysis, this study could be repeated once additional data have been collected. If this study were to be repeated with a larger sample size particular attention should be given to the functional

form of any decay in protection from negative TB outcomes. Additionally, a larger sample size would allow investigation of the associations identified between TB outcomes and BCG vaccination stratified by pulmonary, extrapulmonary, and disseminated TB disease. Between country variations in the strength of associations could also be explored as a proxy to BCG strain using sub-group analysis. The results from this study require validation in independent datasets and the analysis should be reproducible in other low incidence countries that have similarly developed surveillance systems. If validated in low incidence countries, similar studies in medium to high incidence countries should be conducted because any effect would have a greater impact in these settings.

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Contributors

SA, HC, and EBP conceived and designed the work. SA undertook the analysis with advice from all other authors. All authors contributed to the interpretation of the data. SA wrote the first draft of the paper and all authors contributed to subsequent drafts. All authors approve the work for publication and agree to be accountable for the work.

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Conflicts of interest

HC reports receiving honoraria from Sanofi Pasteur, and consultancy fees from AstraZeneca, GSK and IMS Health, all paid to her employer.

Accessibility of data and programming code

The code for the analysis contained in this paper can be found at:
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