

The duration of protection of school-age BCG vaccination in England: a population -based case-control study

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Key Words:	BCG Vaccine, Bacillus Calmette-Guerin, Effectiveness, Duration, tuberculosis, epidemiology

Title: The duration of protection of school-age BCG vaccination in England: a population -based case-control study.

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Abstract**Background**

Evidence of protection from childhood BCG against tuberculosis (TB) in adulthood, when most transmission occurs, is important for TB control and resource allocation.

Methods

We conducted a population-based case-control study of protection by BCG given to children aged 12 to 13 years against tuberculosis occurring 10 to 29 years later. We recruited UK-born white subjects with tuberculosis and randomly sampled white community controls. Hazard ratios and 95% confidence intervals were estimated using case-cohort Cox regression, adjusting for potential confounding factors, including socio-economic status, smoking, drug use, prison and homelessness. Vaccine effectiveness (VE=1-hazard ratio) was assessed at successive intervals more than 10 years following vaccination

Results

We obtained 677 cases and 1170 controls after a 65% response rate in both groups. Confounding by deprivation, education and lifestyle factors was slight 10-20 years after vaccination, more evident after 20 years. VE 10 -15 years after vaccination was 51% (95% CI 21, 69%) and 57% (CI 33, 72%) at 15-20 years. Subsequently BCG protection appeared to wane; 20-25 years VE=25% (CI -14%, 51%) and 25-29 years VE= 1% (CI -84%, 47%). Based on multiple imputation of missing data (in 17% subjects) VE estimated in the same intervals after vaccination were similar (56% (CI 33, 72%), 57% (CI 36, 71%), 25% (-10, 48%), 21% (-39, 55%).

Conclusions

School-age BCG vaccination offered moderate protection against tuberculosis for at least 20 years which is longer than previously thought. This has implications for assessing the cost-effectiveness of BCG vaccination and when evaluating new TB vaccines.

(250 words)

1
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3 **Key words:** BCG Vaccine, Bacillus Calmette-Guerin, Effectiveness, Duration, tuberculosis,
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5 epidemiology, prevention & control, England
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10
11 **Key messages**

- 12 • It is unclear if protection by school age BCG vaccination against TB continues in
13 adulthood when most transmission occurs
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- 15 • Using a case-control study design based on 677 cases and 1170 controls we found
16 about 50% protection that lasted 20 years and then waned
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- 18 • That BCG attributable protection against tuberculosis lasts longer than previously
19 thought affects its cost-effectiveness and has implications for the evaluation of new
20 TB vaccines.
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Background

Tuberculosis (TB) is a major, and potentially preventable, cause of morbidity and mortality globally with two to three billion of the world's population infected with *Mycobacterium tuberculosis*,¹ 10% of whom progress to clinical disease.² In 2015, 10.4 million people were estimated to have developed TB.¹ TB incidence increases sharply in young adults³ and most cases of pulmonary disease, the main source of onward transmission, occur in adults. Progress in developing new TB vaccines is slow and BCG is the only licensed TB vaccine.⁴ . The efficacy of BCG in preventing TB varies geographically, particularly for pulmonary TB, with limited evidence of protection in many tropical areas.^{5, 6} Recent evidence suggest that BCG may act in part by protecting against infection.⁷ A large UK trial in the 1950s showed good protection against TB for upto 15 years following BCG vaccination of secondary school-children,⁸ confirmed in observational studies to last at least 10 years after introduction into the UK national programme.⁹ Although there are few data on protection, more than 10 years after vaccination,^{10, 11} studies in Brazil,¹² in US Native-American populations¹³ and, more recently, in the Norwegian general population¹⁴ suggest BCG protection against TB can last longer. We aimed to provide confirmatory evidence of its durability in a case-control study of school-age BCG vaccination more than 10 years after vaccination in England. From the 1950s, BCG (based on the Danish strain^{15, 16}) was offered routinely to schoolchildren in the UK aged about 13 years, until the programme was discontinued in 2005.

Methods

From 2102 to 2014 cases and controls were invited to take part in face-to-face interviews and to be examined for a BCG scar. We assessed protection from BCG vaccination administered to children 10 to 30 years previously, in five-year intervals after vaccination and tested for trends over time by analysing time since vaccination on a continuous scale.

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3 Details of the study design are presented elsewhere¹⁷. In summary the study was restricted
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5 to persons of white ethnic group born in the UK. Other ethnic groups with a higher risk of TB
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7 were offered BCG in infancy. Cases were subjects living in England at diagnosis of a first TB
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9 episode notified between 2003 and 2012 to the Enhanced Tuberculosis Surveillance System
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11 (ETS) of Public Health England (PHE). Cases not known to be infected with HIV were
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13 included if they were between 23 and 38 years old at diagnosis (i.e. born between 1965 and
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15 1989, and aged 13 years between 1978 and 2002). Controls were UK-born subjects of white
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17 ethnic group without a previous history of tuberculosis, residing in England, selected from
18
19 the general population and frequency-matched to cases by birth cohort (in 5-year bands).
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21 For logistic efficiency, recruitment of population-based controls was based on three-stage,
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23 self-weighted, cluster sampling across England¹⁷.
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27 Experienced field interviewers carried out Computer-assisted Personal Interviews (CAPI),
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29 following training specific to the study including inspecting both arms of all subjects to
30
31 identify BCG vaccination scars. The training included scar reading of volunteers with and
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33 without scars and examination of photographs. Formal supervisory field visits and blind
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35 telephone recall interviews of at least 10% of study participants (selected at random) were
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37 conducted for quality control.
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41 No central databases of school vaccination records exist in the UK and records were not
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43 kept consistently in local child-health information systems. The classification of BCG
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45 vaccination status was based on a combination of participants self-reported history of BCG
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47 status (convincing history, probable history, no history) and scar inspection (present, not
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49 present, not examined). As BCG was a vaccine given in school at about 12-13 years and
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51 usually caused a pustule and then a scar, recall by cases and controls was considered likely
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53 to be good. However several had difficulties recalling whether or not they had had a
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55 tuberculin skin test (TST) (children were only eligible for BCG vaccination if they were
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57 considered TST negative). These subjects were not excluded from the analysis. Instead, we
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3 reviewed the impact of the likely proportion of unvaccinated participants who would have had
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5 a positive TST.
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9 Information on potential confounding factors, including demographic and social variables,
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11 was collected and compared in cases and controls. A measure of deprivation at the small
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13 area level (average 1,500 households) was obtained from Census data based on quintiles of
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15 the index of multiple deprivation (IMD) score in 2010.¹⁸ Education was assessed as highest
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17 education attainment and household crowding was calculated from current number of people
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19 in the household, number of rooms and bedrooms. Ever or never been in prison in the UK or
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21 elsewhere was noted, as was a history of being homeless for a week or more, and regular
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23 travel (defined as every few years or more often) and long stays (3 months or more) in high
24
25 TB burden regions. Smoking was categorised as never, ex- or current, under or over 20
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27 pack-years. Alcohol consumption was based on frequency as well as quantity of UK
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29 standard units and recreational drug use as only non-Class A drugs (e.g. cannabis or
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31 solvents) or also using class A drugs (e.g. cocaine and heroin). Information on smoking,
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33 alcohol, drug use, prison and homelessness was collected using a Computer-Assisted self-
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35 interview (CASI): interviewees entered the data on a laptop and then locked them to be
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37 inaccessible to the interviewer before returning the laptop.
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40 41 42 Ethics and consent

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44 The study was approved by the UK's NHS National Research Ethics Service Committee. We
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46 obtained signed informed consent from those willing to take part. Participants, irrespective
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48 of whether they completed the study or not, were given a £15 gift voucher as compensation
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50 for their time.
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Statistical methods

Cases and controls were compared across quintiles of the IMD score. We cross-tabulated history of BCG receipt and presence and absence of a BCG scar, assessing agreement using Cohen's kappa coefficient.

Hazard ratios (HR) for the association between BCG vaccination status and TB incidence were estimated using the case-cohort approach, with controls forming the sub-cohort.^{19, 20} Controls were considered representative samples from the underlying population, as they were sampled at random from the underlying population within which cases arose (frequency matched by birth cohort in 5 year bands). TB rates are very low in the underlying population. The above approach allowed efficient use of data on the controls at different ages over time, as well as flexible modelling of vaccine effectiveness by time since vaccination.²¹ Vaccine effectiveness (VE) was defined as $VE=1- HR$.

Based on a Cox regression model allowing a time-varying association between vaccination status and case-control status, each case was compared at its event time with all controls in the sub-cohort who were still at risk at that time (i.e. were interviewed at an age older than that of the case) and in the same year of birth stratum as the case. The time scale in these analyses was age, and vaccination status was a time-dependent variable. Self-reported age at vaccination, if available, was used to define vaccination status at a given age, otherwise the median age of 12 years in those reporting age at vaccination was assumed. The event time for cases was age at TB diagnosis, and the time of right censoring in controls was the age at interview for the study. Event times among cases were left-truncated on the day before the TB diagnosis date. Model parameters were estimated using a pseudo-partial likelihood analysis with robust standard errors as is required in a case-cohort analysis in which control groups are shared between cases^{19, 20}.

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3 HRs were estimated within successive time-since-vaccination intervals, respectively 10-15,
4 15-20, 20-25 and 25- 30 years after vaccination. Log HRs were also modelled as a smooth
5 function of time-since-vaccination. Flexible models based on restricted cubic splines were
6 compared, using the Akaike information criterion (AIC),²² with a model in which the log HR
7 for BCG vaccination was assumed to change linearly with time-since-vaccination.
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15 All Cox models used separate baseline hazards by year of birth, to take into account the
16 frequency-matching of controls by birth cohort. The baseline model was also adjusted for
17 sex. Deprivation level and educational level were considered to be potentially important
18 confounders and were added to the baseline model for separate analyses (partially adjusted
19 model). In addition, other potential confounders were added in a further fully adjusted model,
20 in which potential confounding variables were added one by one, and those judged to be
21 important (i.e. changing the estimated log HR for BCG vaccination by +/-0.25 of the standard
22 error of the log HR) were retained. Variables relating to lifestyle (smoking status, drinking
23 behaviour, drug use) were included as a block in this procedure. Any remaining variables
24 were then added again one by one to the model and assessed for retention as before.
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37 Analyses were conducted first for those who had complete data on the variables included in
38 the final model. In sensitivity analyses we fitted the baseline and partially adjusted models on
39 all individuals with complete data for the model in question. Analyses were repeated using
40 multiple imputation by chained equations to deal with missing data, under a 'missing at
41 random' (MAR) assumption.²³ (see details in Supplementary Methods available as
42 supplementary data at *IJE* online).
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51 **Results**

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53 Of 1602 potentially eligible cases, 1047 (65%) were contacted successfully. Of these, 60
54 were ineligible (not born in the UK or not white) and 53 had difficulties precluding
55 participation such as frailty. Of the remaining 934, 257 (28%) refused and 677 (72%) were
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3 enrolled¹⁷ Of those enrolled 534 (80%) had pulmonary disease, 85% bacteriologically
4 confirmed, the rest had extra-pulmonary disease of which 53% were laboratory confirmed.
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9 We recruited controls by sampling 9424 residential addresses. For 13% the address no
10 longer existed or no-one was at the address after repeated visits on different days and times.
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12 Among 8176 screened addresses 1790 (22%) had at least one eligible resident. We
13 recruited from these addresses 1170 controls, a 65% response rate¹⁷.
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19 The distribution of visits by time of day and by day of week was similar in cases and
20 controls¹⁷. The proportions of contactable cases was slightly lower for those living in more
21 deprived areas based on IMD quintiles. The proportion of addresses successfully screened
22 to identify eligible controls was similar across IMD quintiles. (see Supplementary Table 1,
23 available as supplementary data at *IJE* online). Among eligible cases contacted, the refusal
24 rate was slightly higher for those living in the least deprived quintiles. The proportion of
25 addresses successfully screened to identify eligible controls was similar across IMD
26 quintiles. Among subjects identified as eligible to be controls, the refusal rate was similar
27 across IMD quintiles, though slightly higher than in cases. (see Supplementary figure 1,
28 available as supplementary data at *IJE* online)
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42 Cases were, more likely to be male, more likely to be in the most deprived IMD quintile,
43 more likely to live in overcrowded households and had fewer educational qualifications than
44 controls (Table 1). Cases were more likely to report regular travel to or a long-term stay (≥ 3
45 months) in a high TB region. A higher proportion of cases than controls reported drinking at
46 a hazardous or harmful level and reported being a smoker. The proportion of cases reporting
47 having used class A drugs was twice as high as in controls. Similarly, a history of having
48 ever been in prison or homeless was more frequent in cases than controls.
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3 We were unable to trace NHS vaccination records for 96% of participants. For those traced
4 with BCG vaccination recorded, 94% (34/36) either recalled BCG vaccination or had a BCG
5 scar. For those traced and no BCG recorded, 71% had a BCG scar. Records were therefore
6 not used. As there was a good level of agreement between self-reported history and scar
7 inspection (86% agreement, kappa=0.6, $p < 0.001$)¹⁷, information on self-reported history and
8 scar examination were combined to classify the BCG status of participants, (as shown in
9 Table 2). Controls were more likely to have had BCG vaccination than cases.
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19 Estimated effects of BCG vaccine on TB according to time since vaccination, for each
20 model, are shown in Table 3. Area-level deprivation and education level met our retention
21 criterion and were included in the partially adjusted model. In the fully adjusted model, we
22 adjusted additionally for smoking, alcohol, use of controlled drugs, regular travel abroad to a
23 high TB region, history of homelessness and history of prison stays. The remaining variables
24 (long term travel abroad to a high TB region, average number of people per room, average
25 number of people per bedroom) did not meet our retention criterion.
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36 In the complete case analyses, fewer than 1% of individuals were excluded because
37 information was missing on BCG vaccination but a larger proportion were excluded because
38 of missing information on confounding variables (17% in the fully adjusted model). The
39 baseline model shows evidence of a moderate protective effect of BCG up to 25 years post
40 vaccination (Table 3). This was attenuated in the partially adjusted model: the protective
41 effect 20-25 years post vaccination was low. Results were similar, though with narrower
42 confidence intervals, when the baseline and partially adjusted models included all subjects
43 with complete data for those models (see Supplementary Table 2, available as
44 supplementary data at *IJE* online). Based on the fully adjusted model, there was good
45 evidence of a protective effect of BCG 10 to 15 years (HR 0.49 95% CI 0.31,0.79) and 15 to
46 20 years (HR 0.43 95% CI 0.28,0.67) since vaccination. The protective effect was lower after
47 20 years: and 20 to 25 years (HR 0.75 95% CI 0.49,1.14) and 25 to 29 years (0.99 95% CI
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3 0.53,1.84) since vaccination. These estimates correspond to a VE of 51%, 57%, 25%, and
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5 1%, 10- 15, 15- 20, 20- 25 and 25- 29 years since vaccination, respectively
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9 The results based on multiple imputation of the missing data also indicated lower protection
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11 more than 20 years after BCG vaccination (Table 3). Estimated VEs were 56%, 57%, 25%
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13 and 21%, 10-15, 15- 20, 20-25 and 25-29 years since vaccination.
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17 The association between BCG vaccination and log hazard of TB modelled using restricted
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19 cubic splines with 3 knots at 15, 20 and 25 years post-vaccination did not fit the data better
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21 than the linear model (based on the AIC). Results from analyses based on the simpler linear
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23 model suggested an estimated 7% (95% CI: 0.2% to 12%) increase in the log of the HR with
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25 each year from 10 years post-vaccination (Figure 1). The results using multiple imputation
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27 were similar to those from the complete case analysis, suggesting some protective effect of
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29 the vaccine up to about 25 years post-vaccination. The spline model suggested a fairly
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31 constant level of vaccine effectiveness up to around 17 years post vaccination, and then a
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33 steeper reduction in the VE after that (see Supplementary Figure 2, available as
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35 supplementary data at *IJE* online).
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38 39 **Discussion**

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41 Based on a large, population-based case-control study there was about a 50% protection
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43 against TB between 10 and 20 years following school-age BCG vaccination, with little
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45 evidence of good protection after 20 years. Although numbers were small there appeared to
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47 be subsequent waning in protection. Results from complete-case analyses and multiple
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49 imputation to deal with missing data were consistent.
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53 We had a moderately good response rate from cases and controls recruited to represent the
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55 children born in the UK in the general population. As we were able to locate few vaccination
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57 records we relied upon self-report of BCG vaccination and inspection of participants for BCG
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3 scars to ascertain BCG vaccination status. The correspondence between the histories and
4 the scar inspections was good. There was some confounding in estimating the protective
5 effect of BCG, due to lower BCG uptake in poorer subjects who had a higher risk of TB, but
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7 we were able to control for this in the analysis.
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13 A limitation in our approach was the inability to assess and exclude subjects who had a
14 positive tuberculin skin test (TST) in the school vaccination programme, who would have
15 been ineligible for vaccination. Retrospective ascertainment of results of TST testing based
16 on recall was not feasible, and participants' recall could not be validated in the absence of
17 records. Persons who have a positive response to a TST are known to be at higher risk of
18 TB during the first few years after testing. However follow-up data from the British MRC BCG
19 trial in adolescents showed that, in that low transmission setting, the risk of TB in participants
20 with a positive TST test declined over time, and was similar to that of subjects who were TST
21 negative at baseline by about 10 years after enrolment^{24,25} (see figure 11 in ref¹⁷ for details).
22 Thus, not taking account of the TST results is unlikely to bias the association between BCG
23 vaccination and TB beyond 10 years after vaccination. Also extrapolation from modelling
24 work,²⁶ suggests that, in our study, the prevalence of tuberculin positivity in the white
25 population would have been no greater than 4% at the time and age of screening for
26 vaccination.
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44 Other limitations include the possibility that subjects taking part are more likely to have been
45 vaccinated than those not contactable or who had refused. Cases were somewhat harder to
46 contact than controls. Together with a higher response rate in cases than in controls, this
47 might if anything, have acted to underestimate the protective effect of BCG. After 20 years a
48 protective effect could no longer be detected after adjustment for confounding in the baseline
49 model. Control for a wide range of confounders made little difference to the hazard ratio 10
50 to 20 years after vaccination suggesting that if there were any other unmeasured
51 confounders or residual confounding they may have limited effect.
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5 This study provides evidence that adds to that from the original UK MRC trial, in which
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7 protection of 63% was reported 10 to 15 years after vaccination (with wide 95% confidence
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9 intervals, 17 to 84%). In that trial there was no evidence of protection 15 to 20 years after
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11 vaccination but the numbers of cases were small and the confidence interval consequently
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13 very wide (VE 9%, 95% CI <0 to 71%).²⁴ The apparent waning of protection after 20 years
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15 has also been seen in Norway where moderately good protection was noted for 10-19 years
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17 after childhood BCG (VE 58% (CI 27%,76%), and lower protection 20-29 years after
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19 vaccination (VE 38%, CI -32 to 71%).¹⁴ In a Brazilian cohort protection in 15-20 year olds
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21 after infant BCG vaccination was 39% (9-58%), but with no data in older individuals.²⁷ Other
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23 evidence for the duration of protection in high prevalence settings is limited. A protective
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25 effect was noted in a case-control study in Saudi Arabian 15-24 year olds after infant BCG
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27 vaccination (VE 67%, 95% CI 55-77%), but not in 25 to 34 year olds (VE 20%, CI -6 to
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29 37%).²⁸ In contrast in an extended follow up of a BCG trial in US Native-Americans
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31 protection up to 60 years was reported.¹³ However it is unclear if such a long follow up might
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33 have acted to select those at lower risk of TB. The above studies also do not indicate
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35 whether the protective effect of BCG in childhood is more durable, when it is assumed
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37 immune responses are better, than in infancy.

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41 It has been suggested that in high transmission settings and areas closer to the equator,
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43 masking of the effect of BCG occurs by infection or sensitisation by environmental
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45 mycobacteria increasingly providing, over time, some protection in the unvaccinated.^{5, 6, 29, 30}
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47 The studies so far on durability of BCG have limited information with which to assess the role
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49 of masking.
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54 In summary, our case-control study suggests BCG vaccination in UK-born adolescents
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56 provided protection against tuberculosis for at least 20 years. BCG at school age may have
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58 helped in the control of TB, including reducing the risk of multidrug resistant disease as
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3 those vaccinated around 13 years of age have been protected into adulthood. WHO's End
4 TB strategy notes the importance of continuing infant BCG vaccination in high prevalence
5 settings.^{31, 32} We suggest also including a recommendation for childhood vaccination when
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7 infant vaccination has not been given. Our finding of longer duration of BCG protection may
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9 be helpful for countries assessing the cost-effectiveness of BCG in the prevention of
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11 tuberculosis. It also has implications for assessing new vaccines against tuberculosis, which
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13 should desirably provide protection which is greater than that from BCG and which might also
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15 be expected to provide lasting protection, although assessment of the latter would, in the
16
17 short term, have to be based on immunological characteristics.
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37
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39
40 data-management. PM, PND and LR provided academic leadership and other authors
41
42 provided academic expertise and advice at key points. PND and RK carried out data
43
44 cleaning and merging of data across sources. RK devised and carried out the analyses with
45
46 assistance from PND. Additional expertise was provided in statistics and presentation of the
47
48 results (JS); BCG epidemiology and study design (PF, PS); TB epidemiology in England,
49
50 BCG vaccine records, and public health (IA, JW DE and ML), and estimating PPD positivity
51
52 levels in the general population (EV). PM and PND wrote a first draft with RK. All authors
53
54 contributed to this paper.
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References

1. World Health Organization. Global tuberculosis report 2016 2016 30th December 2016. Available from: <http://apps.who.int/iris/bitstream/10665/250441/1/9789241565394-eng.pdf?ua=1>.
2. Comstock GW, Livesay VT, Woolpert SF. The prognosis of a positive tuberculin reaction in childhood and adolescence. *Am J Epidemiol*. 1974 Feb;99(2):131-8
3. Public Health England. Tuberculosis in England 2016 (presenting data to end of 2015)2016 [cited 2016. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/555343/TB_Annual_Report_2016_GTW2309.pdf.
4. Kaufmann SH, Lange C, Rao M, Balaji KN, Lotze M, Schito M, et al. Progress in tuberculosis vaccine development and host-directed therapies--a state of the art review. *The Lancet Respiratory medicine*. 2014 Apr;2(4):301-20
5. Fine PEM. Variation in protection by BCG: Implications of and for heterologous immunity. *Lancet*. 1995;346(8986):1339-45
6. Mangtani P, Abubakar I, Ariti C, Beynon R, Pimpin L, Fine PE, et al. Protection by BCG vaccine against tuberculosis: a systematic review of randomized controlled trials. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. 2014 Feb;58(4):470-80
7. Roy A, Eisenhut M, Harris RJ, Rodrigues LC, Sridhar S, Habermann S, et al. Effect of BCG vaccination against *Mycobacterium tuberculosis* infection in children: systematic review and meta-analysis. *BMJ*. 2014;349:g4643
8. Hart PD, Sutherland I. BCG and vole bacillus vaccines in the prevention of tuberculosis in adolescence and early adult life. Final report to the Medical Research Council 5535. *British Medical Journal*. 1977;2(6082):293-5
9. Sutherland I. Effectiveness of BCG vaccination in England and Wales in 1983. *Tubercle*. 1987;68(2):81-92

10. Sterne JA, Rodrigues LC, Guedes IN. Does the efficacy of BCG decline with time since vaccination? *Int J Tuberc Lung Dis*. 1998;2(3):200-7
11. Abubakar I, Pimpin L, Ariti C, Beynon R, Mangtani P, Sterne JA, et al. Systematic review and meta-analysis of the current evidence on the duration of protection by bacillus Calmette-Guerin vaccination against tuberculosis. *Health Technol Assess*. 2013 Sep;17(37):1-372
12. Barreto ML, Cunha SS, Pereira SM, Genser B, Hijjar MA, Ichihara MY, et al. Neonatal BCG protection against tuberculosis lasts for 20 years in Brazil 1251. *International journal of tuberculosis and lung disease*. 2005;9(10):1171-3
13. Aronson NE, Santosham M, Comstock GW, Howard RS, Moulton LH, Rhoades ER, et al. Long-term efficacy of BCG vaccine in American Indians and Alaska Natives: A 60-year follow-up study. *JAMA : the journal of the American Medical Association*. 2004 May 5;291(17):2086-91
14. Nguipdop-Djomo P, Heldal E, Rodrigues LC, Abubakar I, Mangtani P. Duration of BCG protection against tuberculosis and change in effectiveness with time since vaccination in Norway: a retrospective population-based cohort study. *Lancet Infect Dis*. 2016 Feb;16(2):219-26
15. Gorak-Stolinska P, Weir RE, Floyd S, Lalor MK, Stenson S, Branson K, et al. Immunogenicity of Danish-SSI 1331 BCG vaccine in the UK: comparison with Glaxo-Evans 1077 BCG vaccine. *Vaccine*. 2006 Jul 17;24(29-30):5726-33
16. Office TNA. Procurement of Vaccines by the Department of Health 2003 12th October 2016 [30 p.]. Available from: <https://www.nao.org.uk/wp-content/uploads/2003/04/0203625.pdf>.
17. Mangtani PN-D, P; Keogh,R; Trinder,L; Smith,P;Sterne,J; Abubakar,I; Vynnycky,E; Watson,J; Elliman,D; Lipman,M; Rodrigues,LC. NIHR/HTA study 08/17/01: Observational study to estimate the changes in the effectiveness of bcg with the time since vaccination for preventing tuberculosis in the uk. *Health Technol Assess*. 2017 [In Press]

- 1
2
3 18. Office for National Statistics. The English Indices of Deprivation 2010 2011. Available
4 from: <https://www.gov.uk/government/statistics/english-indices-of-deprivation-2010>.
5
6
7 19. Keogh RH, Cox DR. Case-subcohort studies. Case-control studies: Cambridge
8 University Press; 2014. p. 191-211.
9
10 20. Prentice RL. A case-cohort design for epidemiologic cohort studies and disease
11 prevention trials. *Biometrika*. 1986;73(1):1-11
12
13 21. Keogh RH, Mangtani P, Rodrigues L, Nguipdop Djomo P. Estimating time-varying
14 exposure-outcome associations using case-control data: logistic and case-cohort analyses.
15 *BMC Med Res Methodol*. 2016;16:2
16
17 22. Information Theory and an Extension of the Maximum Likelihood Principle. Second
18 International Symposium on Information Theory. Akaike H, editor. Budapest Akademiai
19 Kiado; 1973.
20
21 23. Sterne JA, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, et al. Multiple
22 imputation for missing data in epidemiological and clinical research: potential and pitfalls.
23 *BMJ*. 2009;338:b2393
24
25 24. Hart PD, Sutherland I. BCG and vole bacillus vaccines in the prevention of
26 tuberculosis in adolescence and early adult life. Final report to the Medical Research
27 Council. *British Medical Journal*. 1977;2(6082):293-5
28
29 25. Fourth report to the Medical Research Council by its Tuberculosis Vaccines Clinical
30 Trials Committee. BCG and vole bacillus vaccines in the prevention of tuberculosis in
31 adolescence and early adult life. *Bulletin of the World Health Organization*. 1972;1972. 46:3-
32 85
33
34 26. Vynnycky E, Fine PE. The annual risk of infection with *Mycobacterium tuberculosis* in
35 England and Wales since 1901. *Int J Tuberc Lung Dis*. 1997 Oct;1(5):389-96
36
37 27. Barreto ML, Cunha SS, Pereira SM, Genser B, Hijjar MA, Yury Ichihara M, et al.
38 Neonatal BCG protection against tuberculosis lasts for 20 years in Brazil. *Int J Tuberc Lung*
39 *Dis*. 2005 Oct;9(10):1171-3
40
41
42
43
44
45
46
47
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56
57
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2
3 28. Al Kassimi FA, Al Hajjaj MS, Al Orainey IO, Bamgboye EA. Does the protective effect
4 of neonatal BCG correlate with vaccine-induced tuberculin reaction? 639. American Journal
5 of Respiratory and Critical Care Medicine. 1995;152(5 I):1575-8
6
7
8
9 29. Palmer CE, Long MW. Effects of infection with atypical mycobacteria on BCG
10 vaccination and tuberculosis. AmRevRespirDis. 1966;94(4):553-68
11
12
13 30. Valadas E. Nontuberculous mycobacteria: clinical importance and relevance to
14 bacille Calmette-Guerin vaccination. ClinInfectDis. 2004;39(4):457-8
15
16
17 31. Uplekar M, Weil D, Lonroth K, Jaramillo E, Lienhardt C, Dias HM, et al. WHO's new
18 end TB strategy. Lancet. 2015 May 2;385(9979):1799-801
19
20
21 32. Organization WH. Documentation for World Health Assembly 67 Geneva: WHO;
22 2014 [02.04.2017]. Available from: [http://apps.who.int/gb/ebwha/pdf_files/WHA67/A67_11-
24 en.pdf](http://apps.who.int/gb/ebwha/pdf_files/WHA67/A67_11-
23 en.pdf)
25
26
27 33. Rehm J, Greenfield TK, Walsh G, Xie X, Robson L, Single E. Assessment methods
28 for alcohol consumption, prevalence of high risk drinking and harm: a sensitivity analysis. Int
29 J Epidemiol. 1999 Apr;28(2):219-24
30
31
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Table 1 Characteristics of study participants by case and control status

Characteristic	Cases		Controls	
	(n=677)	%	(n=1170)	%
Birth Cohort				
1965-1969	65	9.6	174	14.9
1970-1974	178	26.3	312	26.7
1975-1979	215	31.8	260	22.2
1980-1989	219	32.4	424	36.2
Sex				
Female	341	50.4	700	59.8
Male	336	49.6	470	40.2
Quintiles of LSOA-level Index of Multiple Deprivation				
1 (least deprived)	63	9.3	234	20.0
2	99	14.6	234	20.0
3	109	16.1	234	20.0
4	130	19.2	234	20.0
5 (most deprived)	276	40.8	234	20.0
Highest educational (academic, professional and or vocational) qualification				
None	132	19.5	75	6.4
O Levels or equivalent ^a	207	30.6	363	31.0
A Levels or equivalent ^b	91	13.4	246	21.0
Degree level or equivalent ^c	216	31.9	455	38.9
Missing	31	4.6	31	2.7
Average number of people per room				
Less than or equal to 1	634	93.7	1144	97.8
Greater than 1	26	3.8	24	2.1
Missing	17	2.5	2	0.2
Average number of people per bedroom				
Less than or equal to 1	385	56.9	705	60.3
Greater than 1	275	40.6	463	39.6
Missing	17	2.5	2	0.2
TB infection risk from regular travels abroad				
Low ^d	618	91.3	1099	93.9
High ^e	58	8.6	71	6.1
Missing	1	0.2	0	0.0
TB infection risk from long-term (≥ 3 months) stays abroad				
Low ^d	607	89.7	1113	95.1
High ^e	70	10.3	57	4.9
Alcohol drinking^f				
Very low/no risk	166	24.5	329	28.1
Low risk	346	51.1	632	54.0
Hazardous risk	36	5.3	68	5.8
Harmful risk	41	6.1	25	2.1
Missing	88	13.0	116	9.9
Tobacco smoking				
Never smoker	188	27.8	499	42.7
Ex-smoker	62	9.2	135	11.5
Smoker: <20 pack-years	308	45.5	422	36.1
Smoker: ≥20 pack-years	99	14.6	85	7.3
Missing	20	3.0	29	2.5
Drug misuse/abuse^g				
No drug use	379	56.0	847	72.4
Class B and/or C use only	69	10.2	108	9.2
Class A use	217	32.1	188	16.1

Missing	12	1.8	27	2.3
History of homelessness				
Never been homeless for >1 week	553	81.7	1091	93.2
Ever been homeless for >1 week	117	17.3	68	5.8
Missing	7	1.0	11	0.9
History of prison stay^h				
Never detained	590	87.2	1119	95.6
Ever detained in the UK or abroad	82	12.1	35	3.0
Missing	5	0.7	16	1.4

^aO Levels, GCEs, or GCSEs (any grades), City & Guilds Craft/Ordinary Level or NVQ Level 1 or 2

^bA Levels, SCE Higher, ONC/ONT/BEC/TEC, City & Guilds Advanced Final Level or NVQ Level 3

^cDegree Level, Teaching qualification, HNC/HND, BEC/TEC Higher or BTEC Higher

^dRegular travel (i.e. every few years or more often) or long-term (>3 months) stay to Eastern Europe, Caribbean, or none of the places specified

^eRegular travel (i.e. every few years or more often) or long-term (≥3 months) stays to Africa or Asia

^fAlcohol drinking based on combination on drinking frequency and quantity in UK standard units, and cut-offs by gender as proposed by Rehm et al³³. Cut-offs for hazardous and harmful drinking respectively (20g/day and 40g/day) in women and (40g/day and 60g/day) in men. Subjects who stopped drinking 5 years or more ago classified as low risk.

^gClass B and C examples included benzodiazepines, cannabis, qat, glue, gas, solvents, and amphetamines. Class A drug examples included ecstasy, cocaine, crack, heroin, LSD, magic mushrooms

^h72/82 (88%) cases and 33/35 (94%) controls with history of prison stay report only ever been in prison in the UK and not abroad.

Table 2: BCG vaccination status based on a combination of self-report and scar reading, among 677 cases and 1170 controls

Self-reported history	Scar inspection	Cases	Controls	Assigned vaccination status	Cases	Controls
		(n=677)	(n=1170)			
Convincing ^a BCG	Present	391 (57.8%)	776 (66.3%)	"Vaccinated"	473 (69.9%)	933 (79.7%)
Convincing BCG	None	57 (8.4%)	117 (10%)			
Convincing BCG	NI	22 (3.2%)	29 (2.5%)			
Probable ^a BCG	Present	3 (0.4%)	11 (0.9%)	"Likely vaccinated" ^b	33 (4.9%)	78 (6.7%)
Probable BCG history	None	3 (0.4%)	18 (1.5%)			
Probable BCG history	NI	0 (0%)	3 (0.3%)			
No BCG history	Present	16 (2.4%)	27 (2.3%)	"Not vaccinated"	163 (24.1%)	154 (13.2%)
Unsure	Present	14 (2.1%)	30 (2.6%)			
No BCG history	None	135 (19.9%)	122 (13.4%)			
No BCG history	NI	19 (2.8%)	20 (1.7%)	Missing	8 (1.2%)	5 (0.4%)
Unsure	None	9 (1.3%)	12 (1.0%)			
Unsure	NI	8 (1.2%)	5 (0.4%)			

NI: not inspected
^aIf there was recall of being given BCG at school and either a clear recall of a prior tuberculin skin test (TST) test or a pustule or scarring post vaccination, this was categorised as a convincing history, if only recall of BCG at school it was categorised as probable.
^bsensitivity analysis moving this category to the vaccinated did not change the effect estimate of the association between BCG and TB and had small numbers, they were therefore assigned to the vaccinated category in the rest of the results

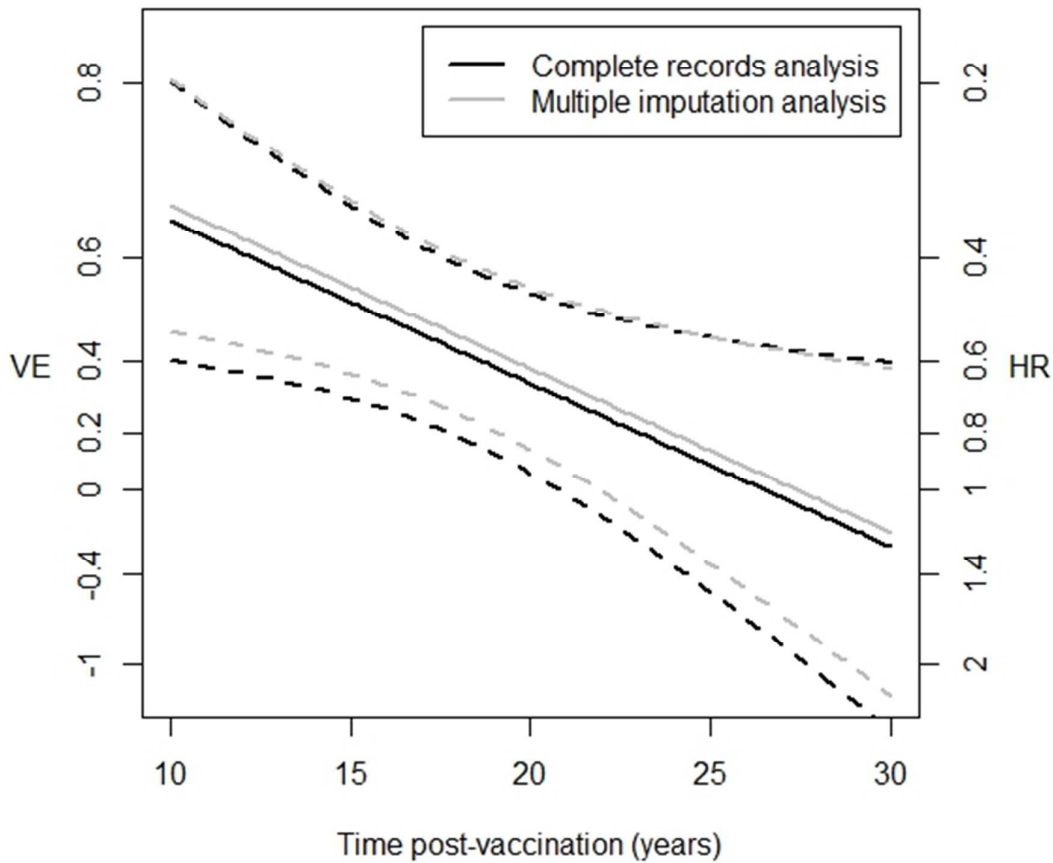
Table 3. Results from complete case analyses (based on the 532 cases and 993 controls used in the fully adjusted model) and from analyses of 677 cases and 1170 controls based on multiple imputation

	Baseline model ^a		Partially adjusted model ^b		Fully adjusted model ^c	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
Complete case analyses						
Unvaccinated	1 (ref)		1 (ref)		1 (ref)	
Vaccinated 10-15 years ago	0.43 (0.28,0.66)	<0.001	0.49 (0.31,0.79)	0.004	0.49 (0.31,0.79)	0.003
Vaccinated 15-20 years ago	0.34 (0.23,0.50)	<0.001	0.41 (0.27,0.63)	<0.001	0.43 (0.28,0.67)	<0.001
Vaccinated 20-25 years ago	0.56 (0.39,0.80)	0.001	0.69 (0.46,1.02)	0.065	0.75 (0.49,1.14)	0.174
Vaccinated 25-29 years ago	0.70 (0.40,1.24)	0.225	0.88 (0.48,1.59)	0.660	0.99 (0.53,1.84)	0.970
Analyses based on multiple imputation						
Unvaccinated			1 (ref)		1 (ref)	
Vaccinated 10-15 years ago			0.43 (0.29,0.67)	<0.001	0.44 (0.28,0.67)	<0.001
Vaccinated 15-20 years ago			0.42 (0.29,0.62)	<0.001	0.43 (0.29,0.64)	<0.001
Vaccinated 20-25 years ago			0.70 (0.49,1.00)	0.049	0.75 (0.52,1.10)	0.141
Vaccinated 25-29 years ago			0.71 (0.42,1.19)	0.195	0.79 (0.45,1.39)	0.406

^aThe baseline model is stratified on birth cohort and adjusted for sex ^bThe partially adjusted model is additionally adjusted for confounding variables area-level deprivation and educational level. ^cThe fully adjusted model has additional adjustment for lifestyle confounding variables (tobacco smoking, alcohol drinking and misuse/abuse of controlled drugs), history of homelessness, history of prison stays, TB infection risk from regular travels abroad.

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Figure 1: Results from modelling the time-varying effect of the vaccine as a linear function of time (on a log scale)



Legend figure 1

The left-hand vertical axis shows the vaccine effectiveness (VE) and the right-hand vertical axis shows the hazard ratio (HR), both on the log scale. Results are based on the fully adjusted model. The dashed lines show the 95% confidence bounds