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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

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Key words: BCG Vaccine, Bacillus Calmette-Guerin, Effectiveness, Duration, tuberculosis, epidemiology, prevention & control, England, ethnic groups

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List of Abbreviations & Acronyms

BAME - Black and Asian Minority Ethnic

BCG – Bacillus Calmette Guerin

CAPI - Computer-Assisted Personal Interview

CASI - Computer-Assisted Self-Interview

CHIS - Child Health Information System

CI – confidence interval

EM - environmental mycobacterial

ETS – enhanced tuberculosis surveillance system

HPA - Health Protection Agency

HR – hazard ratio

HSE - Health Survey for England

HTA – Health Technology Assessment Programme

IMD - Indice of Multiple Deprivation

IUATLD – International Union Against Tuberculosis and Lung Disease

LSHTM – London School of Hygiene & Tropical Medicine

LSOA - Lower level Super-Output Areas

MDR – multi drug resistant

MRC – Medical Research Council

MSOA - Mid-level Super-Output areas

Mtb - Mycobacterium tuberculosis

NatCen - National Centre for Social Research

NatSAL - National Survey of Sexual Attitudes and Lifestyles

NHS – National Health Service

NIHR – NHS National Institute for Health Research

NRES - National Research Ethics Service

ONS – Office for National Statistics

PCT – Primary Care Trust

PHE – Public Health England

PPB - persons per bedroom

PPD – purified protein derivative

PPR - persons per room

PPS – probability proportional to size

R&D - Research and Development

SRS - simple random sampling

TB – tuberculosis

TST - tuberculin skin test

UK – United Kingdom

USA – United States of America

VE – vaccine efficacy

WHO – World Health Organization

Abstract

Background

Until recently evidence that BCG protection lasted beyond 10 years was limited. In the last few years, studies in Brazil and in USA (Native Americans) suggested that BCG protection against tuberculosis in childhood can last for several decades. The UK's universal school-age BCG vaccination programme was stopped in 2005, and the programme of selective vaccination of high-risk (usually ethnic minority) infants was enhanced.

Objectives

To assess the duration of protection from infant and school-aged BCG vaccination against TB in the UK.

Methods

Two case-control studies of the duration of protection of BCG vaccination were conducted: the first on minority ethnic groups who were eligible for infant BCG vaccination 0-19 years earlier and the second on white subjects eligible for school-aged BCG 10 to 29 years earlier. TB cases were selected from notifications to the UK national Enhanced Tuberculosis Surveillance System (ETS) from 2003 to 2012. Population based controls frequency matched for age were recruited . BCG vaccination status was established from BCG records, scar reading, and BCG history. Information on potential confounders was collected in computer-assisted interviews. Vaccine effectiveness was estimated as a function of time since vaccination, using a case-cohort analysis based on Cox regression.

Results

In the infant BCG study, vaccination status used vaccination records, as recall was poor and concordance between records and scar reading limited. A protective effect was seen up to 10 years following infant vaccination (under 5 years after vaccination VE 66% (95%CI 17% to 86%); 5 to 10 years VE 75%, (95%CI 43 to 89%)) but weak evidence of an effect 10-15 years after vaccination (VE 36%, (95%CI negative to 77%, p=0.396)). The analyses of the protective effect of infant BCG vaccination were adjusted for confounders, including birth cohort and ethnicity.

After school-aged BCG vaccination, a 48% protection (95% CI 17 to 68%) was found 10 to 15 years after vaccination, and 55% (95% CI 30 to 71%) 15 to 20 years after vaccination, beyond which time protection appeared to wane. Ascertainment of vaccination status was based on self-reported history and scar reading.

Conclusions

Infant BCG vaccination protection in a population at high risk for TB was shown to last for at least 10 years and in the white population school-age vaccination protection lasts for at least 20 years.

The evidence may inform TB vaccine programmes (e.g. timing of administration of improved tuberculosis vaccines, if they become available) and cost effectiveness studies.

Limitations

The difficulty in examining vaccination sites in older females in the high-risk ethnic-minority study population and the sparsity of vaccine record data in the later periods precluded robust assessment of protection from BCG more than 10 years after vaccination.

Future work,

Methods to deal with missing record data in the infant study could be explored including use of scar reading.

Funding details

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During the conduct of the study JS, IA and LR received other funding from NIHR; IA and LR have also received funding from the MRC. PM received funding from the BBSRC.

Word count: current 500; max 500

Scientific summary

Background

Until recently there was no evidence that protection against TB by BCG lasted more than 10 years. In the last few years, studies in Brazil and in US (Native Americans) have suggested that BCG protection against tuberculosis can last for several decades in some populations. These findings were interesting and we conducted this research to add to this body of evidence and to determine its relevance to the UK.

Establishing the duration of protection from BCG vaccination against TB is of relevance given the higher disease risks in young adults and the increase with age in the proportion of tuberculosis cases that are pulmonary, the main source of onward transmission. We carried out two case-control studies of the duration of protection of BCG vaccination: one of infant BCG vaccination and one of school-aged BCG vaccination . The studies took advantage of

the UK's long standing universal school-aged BCG vaccination programme, and the changes in 2005, when school-aged vaccination was discontinued and the programme of selective vaccination of high risk (usually ethnic minority) infants was enhanced.

Methods

We carried out two case-control studies in England of cases of tuberculosis and population-based controls, frequency-matched for age. One involved those in minority ethnic groups who were eligible for infant BCG vaccination 1-19 years earlier. The other involved those who were UK born and white who were eligible for school-aged BCG 10 to 29 years earlier. TB cases included in both studies were drawn from among those notified in the years 2003 to 2012 to the UK national Enhanced Tuberculosis Surveillance System (ETS). Controls were recruited from the community in the areas where sampled cases had arisen. BCG vaccination status was established based on BCG records when available, scar reading (inspection of both arms), and BCG history (recall of vaccination). Information on potential confounders (including demographic and social variables) was collected from cases and controls in face-to-face computer-assisted interviews. We studied vaccine effectiveness as a function of time since vaccination, using a case-cohort analysis based on Cox regression.

Results

In the study of infant BCG, vaccination status was based on available vaccination records, as there was poor concordance between vaccination records and either a history of BCG vaccination or scar reading. For infant vaccination, in the subset with vaccine records, a protective effect was seen up to 10 years following vaccination (under 5 years since vaccination VE 66% [95%CI 12% to 85%]; 5 to 10 years VE 76%, [95%CI 44 to 89%] but with weak evidence of an effect 10-15 years after vaccination (VE 36%, (95% CI negative to 76%, p=0.361)). The analyses of the protective effect of infant BCG vaccination were adjusted for several confounding variables, including birth cohort and ethnicity. Adjusting only for ethnicity, sex and birth cohort, for which there were less missing data (on covariates), gave weak evidence of effectiveness (VE 50% (95% CI negative to 78%, p=0.096)) 10 to 15 years after vaccination. The high infant BCG vaccine uptake in this high-risk ethnic minority study population and the sparsity of vaccine record data in the later periods precluded further assessment. These results may be modified when methods to deal with missing data are further explored.

After school-aged BCG vaccination a protective effect of 51% (95% CI 21 to 69%) was found 10 to 15 years after vaccination, and 57% (95% CI 33 to 72%) 15 to 20 years after vaccination, beyond which time protection appeared to wane. Ascertainment of vaccination status was based on self-reported history and scar reading.

Conclusions

Although the findings for infant BCG vaccination in a population at high risk for TB are insufficient to conclude that the protection extends beyond 10 years, the evidence is stronger for a moderate protective effect up to for 20 years after school-aged BCG vaccination in the native white population. The findings are consistent with the limited literature available.

This new evidence may be useful for decisions on TB vaccine programmes (e.g. timing of administration of improved tuberculosis vaccines, if they become available) and for cost effectiveness studies.

Word count: 670

Plain English summary

It was believed that the protection given by BCG vaccination against tuberculosis lasted only ten years. This was used to define policy in the UK. Recently there were some studies suggesting that it could last longer. We studied how the protection changes with time since vaccination in two situations – when BCG was given to infants at higher risk of tuberculosis, the current policy, and also when given at school-age (UK policy until 2005). We found protection from infant BCG vaccination lasted for 10 years, but robust data could not be obtained to establish vaccination status in some subjects. For vaccine given at school-age, we found that protection was substantial for at least 20 years after vaccination (51% from 10 to 15 years after vaccination, and 57% from 15 to 20 years after vaccination).

Background

Tuberculosis epidemiology

Tuberculosis (TB) remains a significant and preventable cause of morbidity and mortality globally. Approximately 10% of infections with *Mycobacterium tuberculosis* progress to clinical disease.[1] The WHO estimates over two billion of the world's population is infected. In 2014, 9.6 million people developed symptoms of TB disease and 1.5 million died from it.[2] In the UK, after many decades during which both the risk of infection with *M. tuberculosis* and the incidence of TB decreased, the last decade of the 20th century and the first decade of the 21st century saw a steady rise.[3] From 2005 to 2011, numbers remained stable at around 8000 cases per year in England. It then declined reaching 6520 in 2014, but England still has the highest rates in Western Europe.[4] There has been no decline in TB rates amongst the UK born population overall; the incidence of childhood TB, including miliary disease and meningitis, in UK born children has however started to fall. TB continues to be concentrated in urban areas with much higher rates in the most deprived areas and in non-UK born populations.[5] Drug resistant TB had increased among culture confirmed cases in the UK (the percentage resistant to any first line drug increased from 5.6% in 1998 to 7.5% in 2005), mainly due to a rise in isoniazid resistance[6] and has remained stable[5]. However, the percentage with multidrug resistance (MDR) has started to fall and is under 1.4%, although complex long-term treatment requirements and poor completion rates make such outcomes an ongoing concern.

BCG vaccine effectiveness and UK policies on BCG vaccination in relation to the changing epidemiology in the UK.

BCG vaccination is widely used and globally over 100 million doses are given annually. In the UK, the vaccine has mainly been given either to infants or to adolescents at school. The protection against pulmonary tuberculosis in the UK is high, when BCG is given to tuberculin negative school children at around age 13 years. This was shown by a trial initiated by the MRC in 1951[7] and in subsequent analyses of the effectiveness of the vaccine given in the routine school immunisation programme.[8] However, there have been variable findings with respect to the effectiveness against pulmonary disease of the vaccine in different countries or between different studies in the same country.[7,9,10] The effectiveness of BCG given in infancy (to prevent pulmonary tuberculosis, miliary tuberculosis and tuberculous meningitis) has been found to be consistently high in all countries where it has been measured.[11,12] Although WHO recommends not to re-vaccinate, mostly because of lack of evidence of the efficacy of revaccination, many countries implement re-vaccination programmes. Trials in Malawi and more recently in Brazil found none to a modest increase in effectiveness associated with repeat BCG vaccination.[13,14]

Although the MRC trial of adolescent vaccination with BCG demonstrated high protection in the UK, there have been several subsequent policy changes with respect to BCG vaccination in the UK, prompted by changes in the epidemiology of TB. In brief, from 1953 BCG vaccine was given to tuberculin negative ("PPD negative") school children at age 10-13 years, as part of the national vaccination programme. In 1972, as the proportion of cases of TB in ethnic minorities increased, BCG vaccination in infancy was recommended for new-borns of recent immigrants from countries with a high incidence of TB (e.g. Indian sub-continent and Africa) as well as all refugees and-asylum seekers. It was also given to all new-borns in some areas (Health Districts/ Primary Care Trusts (PCTs)) with high TB incidence.

In 1991, a survey was conducted in the UK on how well the policies for BCG vaccination in the first year of life were implemented. At that time, five districts offered BCG to all new born children; 31 to none; and 148 to infants born to those in ethnic groups from the Indian subcontinent, Africa, West Indies, China, Middle East and Southeast Asia. Of the 184 districts, 120 reported that they offered vaccine to the new-born children of recent migrants from other countries with high incidence of tuberculosis.[15]

There was discussion on whether BCG vaccination in the general population should be discontinued when the risk of TB decreased based primarily on the high number of vaccinations needed to prevent one case of tuberculosis, in the UK and worldwide.[16] The International Union against Tuberculosis and Lung Disease (IUATLD) developed a set of criteria for the discontinuation of mass BCG programmes in low prevalence populations.[17] The IUATLD recommends BCG be discontinued if:

An efficient TB notification system is in place and

- ✓ The average annual notification rate of smear positive pulmonary tuberculosis is less than 5 per 100,000, or
- ✓ The average annual notification rate of tuberculous meningitis in children under five years of age has been less than 1 per 10 million population over the previous five years, or
- ✓ The average annual risk of infection is less than 0.1 percent.

The UK met all these criteria and BCG vaccination policy for the UK was changed by the Department of Health in 2005 to the current policy.[18] The school vaccination programme was stopped, and BCG vaccination was recommended to infants on a risk-based approach, in line with the IUATLD guidelines. In the UK infants are eligible for vaccination if they have a parent/grandparents originating from a high TB incidence country and any infant is also eligible if born in a part of the UK with a high incidence of tuberculosis (>40 per 100,000).

Some occupational groups, and uninfected contacts of TB cases, are also recommended to receive BCG vaccination.[19]

Evidence for the duration of BCG protection

In the UK, the efficacy of BCG by time since vaccination of adolescents at school was estimated in the MRC trial as follows: 84% during the first five years after vaccination, 68% between 5 and 10 years since vaccination and 63% between 10 to 15 years.[7] Although all these estimates were statistically significantly different from zero, the number of cases 10 to 15 years post-vaccination was small, and there was a wide 95% confidence interval on the efficacy estimate (17% to 84%). There were too few cases between 15 and 20 years after vaccination to assess efficacy. Protection by time since vaccination, with 95%CIs (calculated by us based on the trial data presented in the paper) is given in table 1. The level of protective effect in the first ten years after vaccination was confirmed in a subsequent cohort analysis of data from the school-aged BCG vaccination programme in England.[8] There are no data regarding long-term protection post-infant BCG in high-risk groups.

Table 1: Numbers of cases of TB at different intervals since BCG vaccination in vaccinated and unvaccinated groups in the MRC trial among 13-year old schoolchildren.

Trial group	**No. of participants**	**Time since vaccination (years)**			
		0-5	**5-10**	**10-15**	**15-20**
Negative reaction to tuberculin unvaccinated	12867	160	67	16	5
Negative reaction to tuberculin BCG vaccinated	13598	27	22	7	6
Negative reaction to tuberculin vole bacillus vaccinated	5817	12	11	2	1
Total negative vaccinated with either vaccine	19415	39	33	9	7
BCG Vaccine effectiveness (95% CI)		**84% (77-89)**	**68% (51-79)**	**63% (17-84)**	**9% (-187 to 71)**

The HTA stated, and we agree, that it is not known how long BCG protection lasts, particularly in different age and population groups, and this hinders the development of evidence-based policies. Until recently there was little evidence of protection lasting beyond ten years after vaccination at any age. In a review of published studies conducted by two of the current authors, the pooled estimate of protection after 10 years was 14% (95% CI – 9% to 32%).[20] Considerable heterogeneity was observed between studies in the annual change in BCG vaccine efficacy with time since vaccination. There was no relation between average annual change in efficacy and overall efficacy. As with most vaccines, immunological memory may wane with time, leading to a lower level of protection. Other

explanations proposed include decreasing susceptibility among the unvaccinated because of continued exposure to environmental mycobacteria or an increase in the proportion of disease caused by reactivation or re-infection, against which BCG may not protect.[21]

An update of this systematic review of the duration of protection conferred by BCG against TB has been conducted by our group (HTA Project: 08/16/01 - Systematic Review and Meta-Analysis of the Current Evidence on the Duration of BCG Protection).[22] It included, as well as a systematic search for any other studies, the recent additional follow-up of a BCG vaccine trial in Native Americans (who were on average 7 years of age when vaccinated) in the 1930s, which has reported protection lasting for several decades,[23] as well as a cohort study in the control arm of the Brazilian BCG re-vaccination trial suggesting protection lasted 15 to 20 years.[24]

There is, however, evidence from some countries of poor protection by BCG in adult life, and much of the existing research is of uncertain relevance to the UK. The aims of this research project were to estimate the duration of protection of BCG given to high-risk infants in the UK and separately to school-aged children in the general population. If the study provides evidence of long duration of BCG protection, beyond 10 years, this will have several implications. They include changes to estimates of the cost-effectiveness of BCG, the number of vaccinations needed to prevent a case, the possible characteristics of new BCG-like vaccines and the timing of vaccination for any new tuberculosis vaccine developed i.e. provide the necessary evidence for vaccination policies as well as inform research and development of new TB vaccines.

Research Objectives:

Estimate the change in the effectiveness of BCG with time since vaccination in preventing tuberculosis in today's UK population.

Primary objectives:

1. To estimate the effectiveness of BCG vaccination when given in the first year of life ("infant BCG") to high risk groups in preventing tuberculosis in five-year intervals since vaccination in the infant programme.

2. To estimate the effectiveness of BCG vaccination when given in adolescence ("school-aged BCG") to the general population for preventing tuberculosis in five-year intervals since vaccination starting at 10 years since vaccination.

3. To explore whether protection wanes with time since vaccination, in high-risk groups and in the general population.

Health technologies assessed:

BCG vaccination in the UK as given either

1. To infants at higher risk of TB (referred to in this report as infant BCG)

2. To schoolchildren in the general population (referred to in this report as school-aged BCG)

Methods

Overview

Two main observational analytic studies aiming to estimate the effectiveness of BCG vaccine against TB by time since vaccination were conducted; we also conducted three supporting studies. The two main studies were case control studies aimed at (1) estimating the effectiveness of BCG given to infants in high risk groups (results generalizable to high risk groups in the UK), and (2) estimating the effectiveness of BCG given in school-age to the general population (results generalizable to the UK population). The three supporting studies were (1) a survey of BCG vaccination policy in England, (2) A pilot study for the main observational studies, and (3) a validation study of the BCG scar reading.

In the two case-control studies, TB cases included in the study were sampled among those notified in the years 2003 to 2012 to the UK national Enhanced Tuberculosis Surveillance System (ETS). Controls were recruited from the community in the areas where sampled cases had arisen. BCG vaccination status was established based on BCG records when available, scar reading (inspection of both arms), and BCG history (recall of vaccination). Information on potential confounding variables (including demographic and social variables) was collected from cases and controls in a face-to-face computer-assisted interview conducted by trained staff from the National Centre for Social Research (NatCen), a leading centre for independent social research with over 40 years' experience in nation-wide surveys. Clinical and microbiological information, including type of disease for cases was retrieved from the ETS.

Ethics

The protocol for all studies, information leaflets and data collection tools were reviewed and approved by the NHS National Research Ethics Service (NRES) Committee – London and South East (REC Reference 11/H1102/11) and LSHTM Observational / Interventional Research Ethics Committee (LSHTM Ethics reference 5996). NHS (R&D) permission was obtained with Public Health England (formerly the Health Protection Agency) as the "NHS participating organisation".

We report first on the policy survey (one of the supporting studies), then on the two main observational studies.

SURVEY OF INFANT-BCG VACCINATION POLICIES IN ENGLAND

Background

There appeared to be widespread variation at the local level, in the implementation of the recommendations for infant BCG vaccinations, as well as vaccine delivery pathways.

A survey of both past and current vaccination policies was conducted to support the main studies by assessing what infant-BCG provision was in place prior to 2005 in local areas; and to identify and engage with services or individuals on the delivery pathway who managed or had access to vaccination records.

Methods

We designed a standardised, mostly close-ended structured questionnaire, covering both the historical and current BCG vaccination policy in and outside infancy, eligibility criteria and their documentation, delivery pathways and constraints to service delivery. The questionnaire was tested by asking Immunisation Coordinators from four London Primary Care Trusts (PCT) to complete them and they were then adjusted accordingly.

We carried out a questionnaire-based survey of all 152 PCTs - the then local administrative areas for health care services in England between November 2010 and March 2011. We also checked PCT websites and related NHS sources for publically available documents to assess agreement with the questionnaire data received. Details of the survey are published as a peer-reviewed paper.[25]

We also obtained the source data (original questionnaires / tables) from previous BCG policy surveys from the investigators in order to complement information on historical infant vaccination policies.

Results

Questionnaires were returned from 85% (129/152) of the PCTs in England. There were no differences in TB notification rates between responding and non-responding PCTs. We found publically available current BCG policy documents for 114 (88%) of the 129 PCTs from which responses were obtained. Two (2%) PCTs were excluded from subsequent analysis because their BCG policies could not be determined clearly from their responses.

Current BCG vaccination policy

The agreement with publically available BCG policy documents was high, with only three (2%) PCTs reporting policies that were different from the information in these documents. Details of the findings are given elsewhere.[25] In summary, the new policy for the delivery of infant BCG in high risk groups had been implemented in all PCTs but with considerable heterogeneity in the organization of the delivery of the vaccine and some difficulties in the

identification of eligible children. Sixteen (13%) of the 127 PCTs reported universal infant vaccination and 111 (87%) selective infant vaccination. PCTs with selective infant policy most frequently vaccinated on postnatal wards (51/102, 50%) whereas PCTs with universal infant vaccination most frequently vaccinated in community clinics (9/13, 69%; p=0.011). All (100%) PCTs that vaccinated primarily on postnatal wards did so during the infants' first month of life whereas only 13/37 (35%) PCTs that mainly vaccinated in community clinics did so in the infants' first month of life (p<0.001).

Past (pre-2005) BCG vaccination policy

Prior to 2005, the national policy was to vaccinate all TST-negative schoolchildren aged 11 to 14 years. The tuberculin test was performed by school nurses, who also administered the vaccine in eligible children. However, the 1983 survey of BCG vaccination policies reported that five health authorities had stopped their routine BCG vaccination programme for schoolchildren (two in 1974 and one each in 1977, 1980 and 1983), and replaced it with selective infant-BCG vaccination targeting immigrants.[26, 27] By 1992, at least 15 health authorities in England and Wales had stopped their routine schoolchildren BCG vaccination programme, mostly in areas with very low TB notification rates.[15] The later survey also found that 18 health authorities offered BCG to selected groups at school entry, mostly recent immigrants, although this was offered in only 2 of the 15 districts that discontinued BCG for schoolchildren.[15]

Infant-BCG vaccination pre-2005

The survey of BCG policies in 1983 found that six of the 201 health districts in England and Wales had universal infant-BCG program, while a further 98 health districts already had some form of selective infant-BCG vaccination programme, mostly targeting immigrants' new-borns and/or neonatal TB contacts.[26, 27] The 1992 survey reported that out of the 184 health districts surveyed, five had universal infant-BCG vaccination, and 148 had a selective infant-BCG vaccination programme (including 14 of the 15 districts where schoolchildren vaccination was discontinued).[15] The main groups targeted in areas with selective policies were infants from ethnic minorities (all 148 districts) and recent immigrants from high TB burden countries (120 districts), as well as infants from families with history of TB (40 districts). This survey also found that only one of the 31 health districts with no infant-BCG programme had an estimated population of Indian sub-continent origin greater than 10%.

Overall, previous surveys suggest that about half of health districts in England and Wales already offered BCG to ethnic minority infants by 1983, with over 80% doing so by 1992, including nearly all areas with an estimated population from the Indian subcontinent origin of more than 10%.

BCG administration

In 1983, 152/201 (76%) health districts vaccinated using a syringe and needle exclusively, whereas 14 used a jet injector, and 25 used either of these methods at the discretion of the provider. Two districts used the multi-puncture method.[27] By 1992, 163/169 (96%) health district still implemented routine schoolchildren vaccination using a needle and syringe, with three using multiple-puncture and one using a jet injector. All districts offering infant-BCG administered it using a syringe and needle.[15]

Discussion

The data for this survey were collected during and in the aftermath of a major reorganisation of the National Health Service (NHS). This complicated access to key informants as staff and responsibilities were not clear or certain, and also implies that potential implications of the recent NHS reorganisation for BCG vaccination policies at the local level are not now reflected in this document.

Implication of findings for the main studies

One of the main features of BCG vaccination policies in England highlighted by this and previous surveys is the substantial heterogeneity in infant-BCG policies between health areas, as well as the changes over time. However, the constant patterns relevant to the main studies are that:

1. Up to 1992, over 90% of health districts still had a routine universal schoolchildren vaccination programme. Given that the birth cohorts eligible for the main study of BCG in the general population are subjects born in 1965-1989, it is reasonable to assume that most of the target population had similar opportunities/exposure to the schoolchildren vaccination programme.

2. From 1983, more than 50% of health districts had an infant-BCG program with ethnic minorities in its prime population target, increasing to over 80% by 1992. Furthermore, all but one districts with >10% residents with Indian subcontinent origin (the majority minority ethnic group in England and Wales) had an infant-BCG program.

OBSERVATIONAL STUDIES OF BCG EFFECTIVENESS WITH TIME SINCE VACCINATION IN ENGLAND

Objectives:

The primary objectives of these two studies were respectively:

1. To estimate the effectiveness of BCG vaccination when given in the first year of life ("infant BCG") to high risk groups in preventing tuberculosis in five-year intervals since vaccination after infancy.

2. To estimate the effectiveness of BCG vaccination when given at school-age ("school-age BCG") to the general population for preventing tuberculosis in five-year intervals since vaccination starting 10 years after vaccination.

For both exposures, to explore whether protection wanes with time since vaccination.

Methods

Study design and study areas:

Participants to both studies were recruited using a case-control design. For logistical efficiency, the recruitment for the infant BCG study was restricted to areas of England with 30% or greater resident Black and Asian Minority Ethnic (BAME), based on the 2001 general census. These communities are geographically clustered. The school-age BCG study was across England, reflecting the much larger geographical spread of TB cases in the target population. A pilot study to test methods for recruiting controls was first conducted.

Pilot study

The main objectives for the pilot study were:

1. To estimate the response rate for cases in order to refine the sampling strategy

2. To assess the feasibility of the control recruitment strategy (nominated controls)

3. To field-test the operating procedures and the questionnaire

A total of 115 subjects with previous TB diagnosis notified to the ETS were selected and invited to take part, 58 for the infant BCG study and 57 for the school-age BCG study. Those successfully recruited were invited to nominate up to five non-relative acquaintances of roughly similar age, gender and broad ethnic background residing in the fieldwork area, to serve as 'controls'

Study main exposure and primary outcome

Infant BCG study:

Main exposure: BCG vaccination given in infancy to subjects at higher risk of TB disease (study population restricted to BAME populations as they were the main target of

vaccination programme), as recommended by UK Department of Health guidelines (Green Book).[19]

Primary outcome: Level and duration of BCG-derived protection against any notified tuberculosis disease up to 19 years after vaccination.

School-age BCB study:

Main exposure: BCG vaccination given to tuberculin skin test (TST) negative schoolchildren as part of the UK universal school BCG vaccination programme until 2005 when it was discontinued.

Primary outcome: Duration and level of BCG-derived protection against any notified tuberculosis disease from 10 to 29 years after school-age vaccination

Participants

Infant BCG study:

Cases were UK-born subjects from BAME background with a confirmed first TB episode diagnosed and notified to Public Health England (PHE, formally Health protection Agency HPA) Enhanced Tuberculosis Surveillance System (ETS) between 2003 and 2012, aged between 1 and 19 years at the time of diagnosis (i.e. born between 1984 and 2012), and residing in the study area at the time of diagnosis. The BAME backgrounds included those from high TB burden settings. They were any Black or South Asians (including from India, Pakistan, Bangladesh, Nepal, Bhutan, Maldives, Sri Lanka, including those whose families were originally from these backgrounds but who migrated to Britain from other regions, for example the Caribbean, east or southern Africa).

Controls were population based UK-born subjects from the same target BAME backgrounds, residing in the same study area as cases, from the same birth cohorts as cases (i.e. born between 1984 and 2012), and with no previous episode of TB. Controls were frequency matched to cases within 5 year birth cohorts.

Exclusion criteria: Cases with known HIV infection were not included in the study. This criterion was not applied to controls because the prevalence of HIV infection in the general population from which they are sampled was small. Cases and controls from BAME backgrounds other than those targeted (e.g. Chinese, Japanese, Korean, etc.) were not included.

School-age BCG study:

Cases were UK-born subjects from White ethnic background with a confirmed first TB episode diagnosed and notified to Public Health England (PHE, formally Health protection Agency HPA) Enhanced Tuberculosis Surveillance System (ETS) residing in England at the time of diagnosis between 2003 and 2012 and aged between 23 and 38 years at the time of

diagnosis (i.e. born between 1965 and 1989). School-age BCG was routinely offered to schoolchildren aged about 13 years (range 10-15 years), so the age range of cases would allow measurement of the effect of the vaccine between about 10 to 29 years after vaccination.

Controls were UK-born subjects from White ethnic background residing in England, from the same birth cohorts as cases (i.e. born between 1965 and 1989), and with no previous episode of TB. Controls were frequency matched to cases on 5-year birth cohort.

Exclusion criteria: Cases with known HIV infection were not included. This criterion was not applied to controls because the prevalence of HIV infection in the general population from which they are sampled was small.

Sample size:

The sample size calculations for both studies was based on assumptions on expected BCG vaccine uptake, and minimum level of Vaccine Effectiveness (VE) for successive time band since vaccination for the different populations. All calculations were for a frequency-matched case-control study design, with 90% power and 5% significance level. Numbers were inflated by 15% to allow for post-recruitment exclusions due to ineligibility and loss of power after controlling for confounding variables. For the infant BCG study, at a ratio of case to control of 1:1, we estimated the required sample to be 627 cases and 627 controls. For the school-age BCG study, the number of eligible cases available to be invited was limited, hence the sample size was estimated for an average ratio of up to 2 controls per case, for a total of 665 cases and 1183 controls. A ratio of up to 2 controls per case in the school-age BCG study was applied to mitigate the effect on statistical efficiency in, of an expected low case recruitment rate based on the results of the pilot study; however, the intention was to recruit as many cases as possible. The detailed sample size estimates for each study are presented in tables 2 and 3.

Table 2 Sample size estimates for the infant BCG study

Age at TB diagnosis	**time since vaccination**	**Assumed BCG uptake**	**Min VE to be detected**	**Frequency-matched design with ratio of 1 control per 1 case**	
				Case	Control
0 to 5 yrs	0 to 5 yrs	90%	60%	252	252
6 to 12 yrs	6 to 12 yrs	80%	60%	158	158
13 to 17 yrs	13 to 17 yrs	60%	50%	217	217
Total number in 'infant-BCG sample'				627	627

Table 3 Sample size estimates for the school-age BCG study

Age at TB diagnosis	**time since vaccination**	**Assumed BCG uptake**	**Min VE to detect**	**Frequency-matched design with ratio of 2 controls per 1 case**	
				Case	Control
23 to 27 yrs	10 to 14 yrs	80%	60%	116 (145)	232 (258)
28 to 32 yrs	15 to 19 yrs	80%	50%	208 (260)	416 (463)
33 to 37 yrs	20 to 24 yrs	80%	50%	208 (260)	416 (463)
Total number in 'schoolchildren-BCG sample'				532 (665)	1064 (1183)

It was possible that about 10% controls and 20% cases would not be eligible (discarded) because tuberculin positive (PPD +), hence number in brackets were the actual recruitment target taking this into account

Study sampling:

Cases selection: For both studies, eligible TB cases were identified from the ETS database based on the date of diagnosis and reported date of birth, residential address at the time of diagnosis and self-reported ethnic background. Cases with a reported previous TB episode, or with a previous notification of TB in the database were not included. For the infant study, cases were included if they resided in the study area (defined to include small areas where 30% or more of the population were BAME). For the school-aged study the study area included all of England.

Controls selection: This was amended after the pilot. We required community-based controls, who represented the population in which the cases occurred. We had two potential strategies for this: the first, which was lower cost but high risk, was nominated controls. We piloted this strategy to recruit individually matched controls among non-relative acquaintances nominated by cases. The pilot study indicated that nominated controls were not feasible: people were either reluctant to nominate friends or reported that they did not have friends of eligible age or ethnicity. The control recruitment strategy was thus changed to our second choice strategy (more resource intensive but lower risk): a self-weighted multi-stage stratified sample of the target populations across the area from which cases were recruited. A multi-stage sampling was preferred to a straightforward simple random sampling in order to ensure wider geographical coverage of respective study areas, while maintaining reasonable clustering of field data collection for optimal logistical efficiency:

For the infant BCG study, we used a two-stage self-weighted sampling design:

Based on previous work by the Health Survey for England[28,29] and the 2001 census,[30] we estimated screening on average 12 residential addresses would provide one eligible (based on BAME and birth cohort) control successfully recruited from the community. A total of 7750 addresses were selected probability proportional to size (PPS) of the eligible BAME population in the study area: geographical areas with 30% or more BAME residents based on the 2001 census. Inter-census estimates were not thought to be as robust and not available by small areas.

The first stage consisted of sampling the Lower level Super-Output Areas (LSOAs) with 30% or more resident BAME population by PPS. LSOAs are designed to have a fairly socially homogeneous population of an average 1500 residents each.[31] A total of 2,659/32,482 (8.2%) LSOAs had 30% or more BAME residents, accounting for 50% (2,027,398/4,024,287) of the total BAME population in England. The study area also included 60% of all eligible TB cases in these groups notified to the ETS.

The second stage was a simple random sampling (SRS) of seven (7) residential addresses within each LSOA selected in the first stage. This was done using the Small-user Postal Address File. To ensure equal geographical spread of selected addresses within the LSOA, we randomly sampled seven distinct postcode units in each LSOA, then one address per postcode unit. Postcode units each have on average 15 residential addresses, and LSOAs count on average 30 postcode units each.

Overall, 1107 LSOAs were sampled with PPS out of 2659 with ≥30% BAME residents, and in each selected LSOA, 7 residential addresses were selected using SRS.

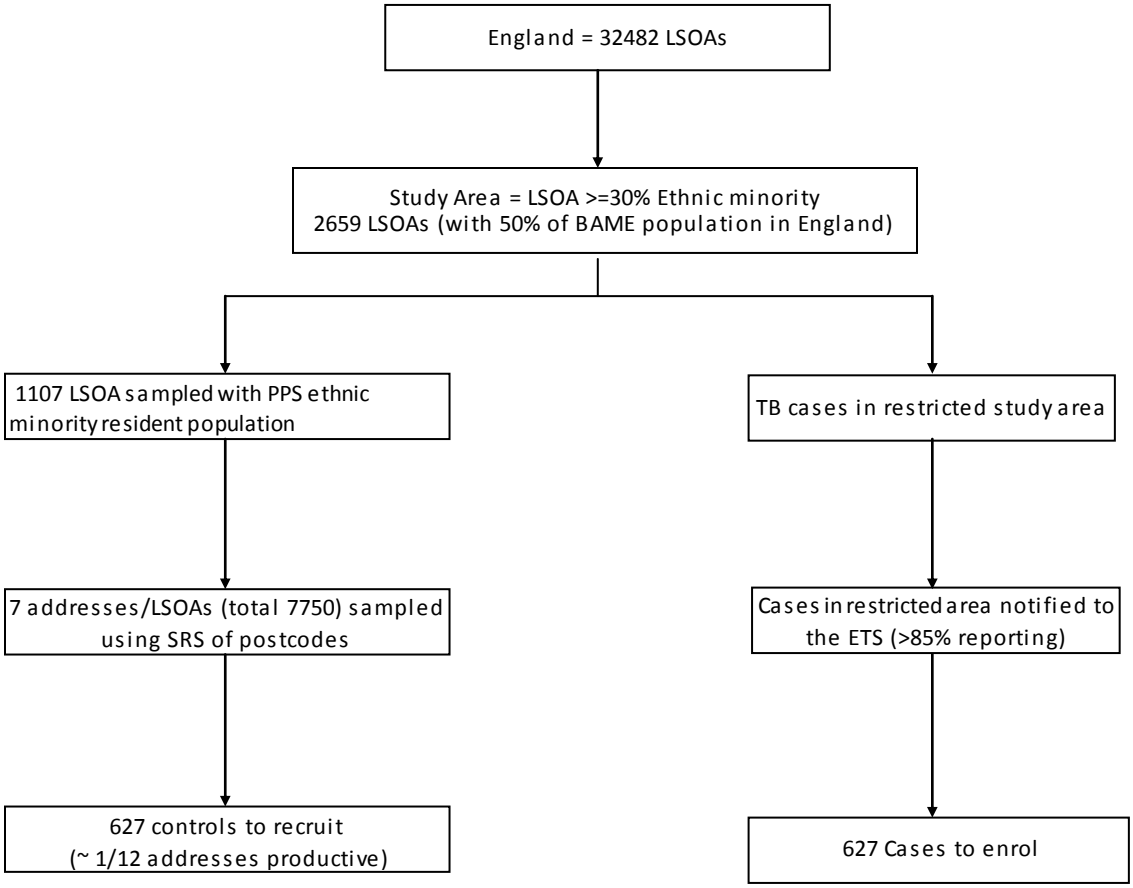

Figure 1 Summary of sampling strategy for the infant BCG study

For the school-age BCG study, we used a three-stage self-weighted sampling design to reflect the much wider study area (whole of England):

We estimated that a total of about 9500 residential addresses would have to be screened to meet our target, based on an average of one eligible control successfully recruited from every 7-8 addresses screened based again on the HSE and census data broken down by age and ethnicity.

The first stage was the selection of 449 Mid-level Super-Output areas (MSOA) out of a total of 6781 in England, with probability proportional to the size (PPS) of their 2010 mid-year estimates of population aged 25-49 years.[32] MSOAs consist of contiguous LSOAs, constrained by the 2003 local authority boundaries; each has a minimum population of 5,000, average 7,200 inhabitants.[31]

The second stage was the random selection of three LSOAs in each MSOA, by PPS;

The third stage was the selection of seven residential addresses from each LSOA by SRS using the same procedure as for the infant-BCG study above.

In total, we selected 449/6781 MSOAs, and a total of 1347 LSOAs across England (3 per MSOA). Seven randomly sampled addresses were screened in each LSOA, for a total of 9423 addresses screened for eligible controls.

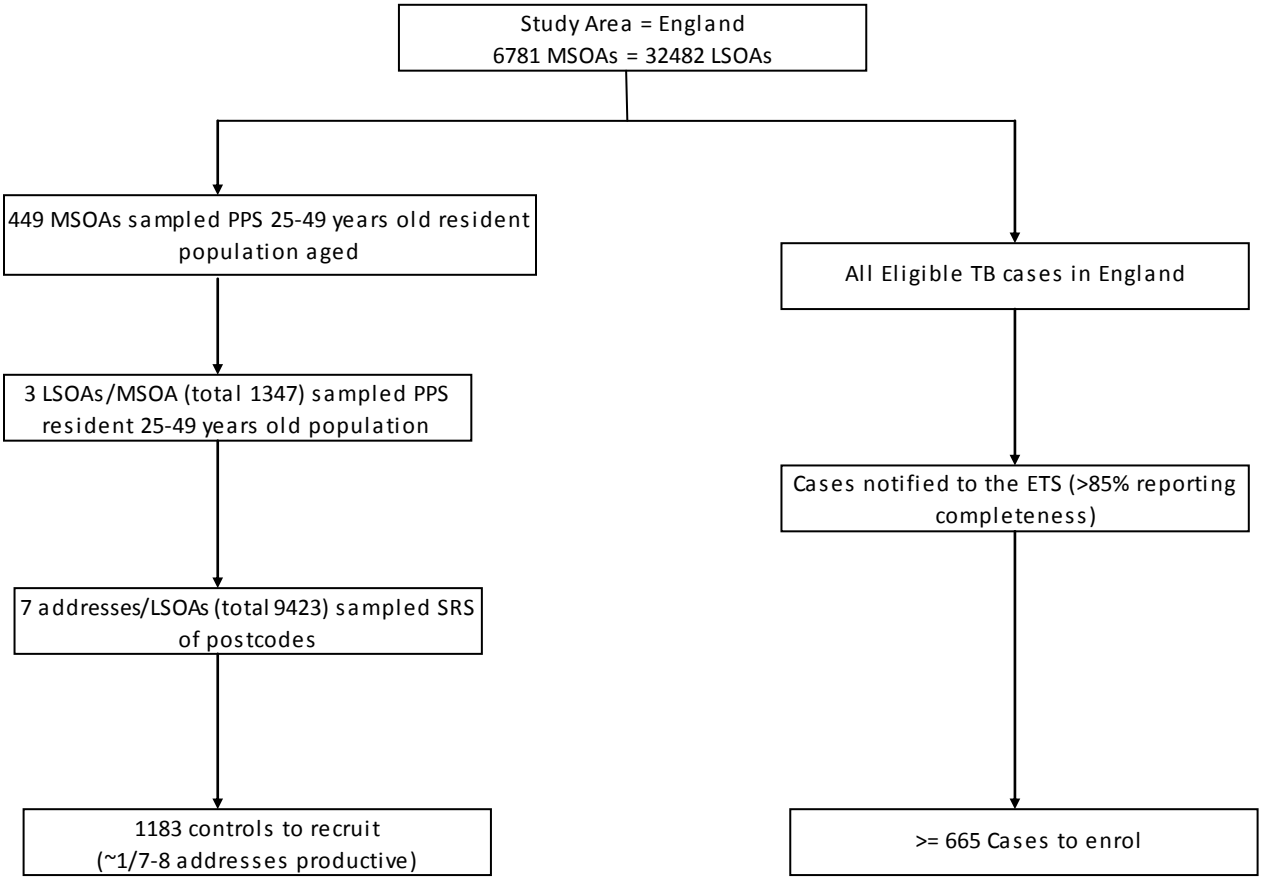

Figure 2: Summary of sampling strategy for the school-age BCG study

Data sources:

Data for the studies were obtained from four main sources:

Face to Face interviews: the core study data, including indicators of BCG status (vaccination history, inspection of both arms for vaccination scar, and personally held vaccination record or card e.g. the Red book) were collected in the community through Computer-assisted Personal Interviews (CAPI) by trained and experienced field interviewers. This data source will be called in this document CAPI data.

Surveillance register: Clinical information for TB cases was obtained from the Public Health England's (PHE) Enhanced Tuberculosis Surveillance system (ETS). This data source will be called in this document ETS data.

NHS vaccination records: Information on BCG vaccination records held by the NHS was requested from, and manually searched for, in the Child Health Information Systems (CHIS) of NHS Primary Care Trusts (PCTs) as well as NHS Community Care Trusts in areas in which participants have resided at the time when eligible for vaccination. This data source will be called in this document NHS records

Other: Small area-level (LSOA) Indices of Multiple Deprivation (IMD) – a proxy-measure for socio-economic status - were obtained from the ONS English Indices of Deprivation 2010,[33] by linkage using study participants' residential postcodes. Local annual TB rates in the area of residence (local authorities 1988-90 and PCTs 2005-2007) when eligible for vaccination were obtained from PHE historical data.

Study variables

Indicators of vaccination status

Data were collected on four indicators of BCG status, respectively history (recall from parent or respondent), the inspection of both arms for BCG scar by the interviewer following a standardised procedure, personal vaccination record (Red book) or card, and NHS vaccination records. All four indicators were incomplete and had strengths and limitations for the two different studies:

- ✓ **Vaccination history:**
    - For the infant BCG study, the information was collected from parents or subjects (if older and living away from home, but they were encouraged to check with their parents over the phone). Subjects were, of course, not able to remember vaccination in the first year of life, and parents' report was subject to considerable recall bias because BCG vaccination was confused with any of the several other vaccinations given in infancy.
    - For the school-age BCG study, BCG history was less likely to be affected by recall error, as BCG was the sole vaccine routinely given at school in all children aged around 13 years (at an age when they can recall).

- ✓ **Inspection for BCG scar:** Interviewers were trained to recognise a BCG scar and inspected both arms for BCG vaccination scars after consent was obtained. Higher refusal rates were noted by young/teenager female cases with family origins in Africa and Pakistan.
- ✓ **Personal vaccination record:** Study participants were encouraged to look for any vaccination record or card ahead of the interview. The most common personally-held vaccination record, (commonly known as the "Red book"), was introduced in England in the mid-1990s, thus, these records were missing for older participants to the infant BCG study. No participants to the school-age BCG study had hand held records.
- ✓ For the infant study, vaccination was checked through the **Child Health Information System (CHIS)** in local area health trusts. There were several practical challenges: the decentralisation of primary health care in the NHS, with heterogeneity in how data are stored and procedures to request authorisations between trusts; the major NHS reform that coincided with our study period which meant that not every care trust could be successfully contacted to check their records; the fact that CHIS records are also discarded or archived by regulatory requirements when individuals reach an older age, varying from 21 to 25 years depending on the area. Any such records need only to be kept to 25 years of age before they can be destroyed.
- ✓ For the school-age BCG study, there was **no central database of school vaccination records**, and this information was inconsistently recorded in the CHIS. NHS vaccination records were therefore not available for nearly all participants.

Tuberculosis events:

Information on date of notification of TB event, as well as reported date when symptoms started and date of diagnosis for all cases was retrieved from the ETS. We also extracted data on the site of disease, as well as checking that no previous TB episode was reported. Controls were asked for any past TB diagnosis, and their details were also checked against the ETS for any notified TB.

Other variables / potential confounders:

- ✓ Basic demographics, including date of birth, sex, and ethnic background (CAPI): ethnic background was self-assessed, choosing from the standard ONS categories in the latest UK general population census.
- ✓ Education level (CAPI): for the infant BCG study, we collected information on education level of both parents, and for the school-age BCG study, we collected information on own education level.

- ✓ Small-area level deprivation index: The postcode of cases at the time of diagnosis as well as that of controls was used to obtain the LSOA-level indices of multiple deprivation (IMD) scores and ranks, a proxy-measure of socio-economic status. The IMD, a composite measure of deprivation generated by the ONS, combines scores in 7 deprivation domains (income, employment, health and disability, education, skills and training, crime, and living environment).[33]
- ✓ Household crowding (CAPI): information was collected on the number of residents in the household, and the number of rooms in general (excluding kitchen and bathroom) and the number of bedrooms. This was used to generate two commonly used measures of crowding, the number of persons per room (PPR) and the number of persons per bedroom (PPB).[34,35]
- ✓ Background risk of TB: We collected data on broad world region of origin of parents and grandparents, as well as frequent travel and/or prolonged stays (≥3 months) to parts of the world with high TB burden.
- ✓ Lifestyle/behaviour risk factors (CAPI): For the school-age BCG study, participants were also asked about potential risk behaviours, including history of tobacco smoking, alcohol abuse, drug misuse, stays in prison and homelessness.
- ✓ Other: information was collected on areas of residence of participants between birth and age 14 years. These data were used to retrieve historical average TB notification rates in those areas at relevant time periods as a proxy-measure of the local TB epidemiology.

Ethics and consent

Eligible subjects were given detailed information on the relevant study via an information leaflet and a dedicated webpage, with the opportunity to ask clarification questions. For those willing to take part in the studies, we obtained up to three separate informed consents, respectively for (i)the face to face interview, (ii) the inspection of both arms for BCG characteristic scar (and photographs for about 25%), and (iii) permission for us to contact the NHS using their personal details to check their vaccination records for BCG. Subjects aged less than 16 years old provided an assent, with formal consent obtained from their parent or legal guardian.

All subjects contacted for this study were given the option to opt-out following the initial invitation, in which case no further contact was attempted by the field worker. Subjects could also freely withdraw from the study at any stage, including during the interview, or even afterwards by telephone and their data deleted.

Participants to the study were given a £15 gift voucher as compensation for their time, irrespective of whether they completed the interview or withdrew their consent at any stage.

Field procedures and data collection

The pilot study for the recruitment of cases and nominated controls was carried-out in September and October 2011.

The main change after the pilot was the approach to control recruitment, described above. After preparations for the new approach to control recruitment were complete, the main data collection was conducted from February 2012 to September 2014.

Cases were sent information letters inviting them to take part to the study, and offered the opportunity to request further information or opt out either by telephone, or by returning an opt-out slip. Controls were sent similar advance information letters with opt-outs as above to the residential addresses selected for screening.

Trained interviewers attempted contact with both the invited cases and selected control residential addresses with a standard visit schedule, including week and weekend days, and morning, afternoon and evening visits. For controls, the residents at sampled addresses were first screened for eligibility. If required at the door, a translation screening card with 17 of the most common other languages spoken in England was used to ask which language was their first language together with a show-card asking for their help with the study in their first language. Eligible controls were provided information on the study. Informed consent was obtained from all those eligible and willing to participate to the study before face-to-face interviews were conducted.

Study participants aged 16 years and older were directly interviewed. Parents or those with parental responsibilities were interviewed for those aged 0 to 15 years. For the infant BCG study where some parents from BAME were not fluent in English, translation (from up to 17 most commonly spoken foreign languages in England) was offered if requested.

All interviews were carried out by experienced staff from NatCen, a leading independent social research non-for profit organisation that routinely conduct other large-scale national surveys (e.g. Health Survey for England (HSE), National Survey of Sexual Attitudes and Lifestyles (NatSAL) etc.). All interviewers undertook a day's training specifically for this study before taking part in any field work, including prior homework and intensive practical training on inspection of both arms to identify BCG vaccination scars. The training of scar reading included photos and volunteers with and without scars.

Monitoring and quality control during field data collection included formal supervisory field visits of individual interviewers and blind telephone recall of at least 10% randomly selected

study participants, checking for quality of face-to-face interviews, compliance with protocols and procedures for interviewing, as well as other specific instructions.

The CAPI included a standardised pre-tested questionnaire with only close-ended questions, and a pre-set standard script that interviewers had to read. Part of the questionnaire for the school BCG study collected sensitive data on lifestyle behaviour on tobacco, alcohol and controlled substance use, and previous stay in prison via a Computer-Assisted self-interview (or CASI), during which the interviewee entered the data themselves then locked the data to be inaccessible to the interviewer before returning the laptop to them.

Information on a range of other potential confounding variables was collected during the interview, including indicators of socio-economic status, education level, household crowding, lifestyle behaviours etc.

Analysis

Data cleaning and descriptive analysis

For both studies, data from the different data sources were merged, cleaned and checked using consistency and range checks. The distribution of quantitative variables was examined and they were transformed into categorical variables as required (IMD scores, birth year). The distribution of covariates and any missing data on them were summarised by case and control status.

Definition of vaccination status

Infant BCG study

After exploration of completeness, agreements between the different indicators of vaccination status were assessed. Based on the assessment we judged that BCG status was best defined using combinations of observed vaccination records as described in table 4 below. Briefly, the recording of BCG in either the Red book or NHS record was used as evidence of previous BCG vaccination. Subjects were classified as unvaccinated only if both records were available, and there was no BCG recorded in both records. The date of BCG vaccination was taken as that reported in the vaccination records.

Table 4: Definition of BCG status for the infant BCG study using both vaccination records

Red Book	**NHS Record**	**BCG vaccination status (definition 1)**
BCG Recorded	BCG Recorded	**Vaccinated**
BCG Recorded	BCG not recorded	
BCG not recorded	BCG Recorded	
BCG not recorded	BCG not recorded	**Not vaccinated**
BCG not recorded	Missing	Treated as missing
Missing	BCG not recorded	
Missing	Missing	Missing

School-age BCG study

After checking for completeness, BCG vaccination status was based on the two indicators available, i.e. self-reported history and scar inspection. Self-reported history was based on recall of TST testing prior to vaccination and subsequent BCG vaccination; participants' self-reported BCG history was therefore classified into three categories:

- ✓ Convincing history of BCG vaccination: subjects who recalled the TST testing, and subsequent BCG vaccination 48 to 72 hours later, or post-vaccination soreness, pustule and/or scar.
- ✓ Probably BCG vaccinated: those who reported receiving BCG at school, but do not recall the TST testing and/or the post-vaccination soreness, pustule or scar.
- ✓ Not vaccinated: subjects who reported never receiving BCG vaccination.

Self-reported history was combined with the result of inspection of the arms for a scar to define BCG vaccination status as detailed in the Table 5 below. Briefly, subjects with a convincing self-reported history of BCG, or a probable history and a scar were classified as vaccinated. Those with a history of no BCG vaccination and no scar at inspection, or either, were classified as not vaccinated.

Those with history of vaccination reported the age when they were vaccinated, but the exact date of vaccination was not available, so a date of vaccination was assigned randomly by sampling dates within the year corresponding to the age at vaccination (excluding the school-holiday months of July and August), using a uniform distribution. For those in which the age of vaccination was not available (e.g. "possibly vaccinated" based on scar), the age at vaccination was assigned to be age 12 years, which was the median age at vaccination among those for whom age at vaccination was available.

Table 5 Definition of BCG vaccination status for the school-age BCG study

Self-reported history	**Scar inspection**	**BCG vaccination status**
Convincing BCG history	Scar present	"Vaccinated"
Convincing BCG history	No scar	
Convincing BCG history	Not inspected	
Probable BCG history*	Scar present	
Probable BCG history*	No scar	
Probable BCG history*	Not inspected	
No BCG history	Scar present	
Unsure	Scar present	
No BCG history	No scar	"Not vaccinated"
No BCG history	Not inspected	
Unsure	No scar	
Unsure	Not inspected	Missing

Association between time since BCG vaccination and risk of TB

We investigated the association between time since vaccination and the risk of TB in two steps:

- ✓ Firstly we estimated the association for successive time-since-vaccination intervals of approximately 5 years, respectively 1-5, 5-10,10-15,15-19 years after vaccination for the infant BCG study, and 10-15,15-20, 20-25, and 25-29 years after vaccination for the school-age BCG study.
- ✓ Secondly, we modelled vaccine effectiveness smoothly as a function of time-since-BCG.

Statistical methods

The data were analysed using the case-cohort approach,[36,37] in which controls formed the 'sub-cohort', i.e. the set of potential controls for each case. This provided an efficient analysis approach for the data which made best use of data for controls throughout the time they were at risk, and allowed flexible modelling of vaccine effectiveness by time since vaccination.[38] This approach was appropriate because our controls were sampled at random from the underlying population within which cases arose (with frequency matching on year of birth) and because the outcome (TB) is rare in the underlying population (with annual TB notification rates in our study populations in the 10s per 100,000); the controls can therefore be considered approximately as random samples from the underlying population within each of the frequency-matching strata.

Under our selected approach, each case is compared at its event time with all controls in the sub-cohort who are still at risk at that time and who are in the same stratum as the case. The statistical analyses assume an underlying Cox proportional hazards model, the parameters of which were estimated using a pseudo-partial likelihood analysis with robust standard errors; the latter is necessary in case-cohort analyses to account for the 'shared' control groups between cases.

Follow-up started for all participants from the 1st birthday (when most would have had an opportunity to receive infant BCG vaccination). In both studies, the basic model for vaccine effectiveness was stratified by year of birth, and adjusted for sex. Allowing separate baseline hazards within each year of birth was used to account for frequency-matching of controls on year of birth. For the infant BCG study, given that not only the risk of TB in each ethnic group is different but also the age distribution of cases is different, the baseline hazard was also allowed to vary by ethnic group. Other covariates were then added in turn in the basic model to assess potential confounding effect by examining changes in the point estimates and the standard errors, and a final multivariable model was built.

We present results as hazard ratios (HRs) and corresponding 95% confidence intervals (95% CI). Vaccine effectiveness (VE) estimates can be computed as VE = 1 – HR).

We modelled vaccine effectiveness smoothly as a function of time-since-BCG using two methods. Firstly, we used a restricted cubic spline with 3 knots, with the knots reflecting the time intervals of each study. Secondly, we fitted a simpler model in which the log hazard ratio associated with BCG vaccination was assumed to change linearly with time. The results were displayed graphically as smooth curves, including 95% confidence limits. The results from the linear model were also tabulated.

Handling of missing data

Results presented in this report are based on 'complete case' analyses. Individuals with missing information on vaccination status (according to our definitions) are excluded from analyses. Individuals with missing data on adjustment variables are excluded from models that include those variables. Results from models, which include different adjustment variables, are compared by fitting the simpler models on both the maximum possible number of individuals for the model in question and on the subset of individuals on which more fully adjusted models are fitted.

Given the presence of some missing data especially for vaccine records, further analyses including use of scar information and possibly multiple imputation will be explored. They are not part of this report.

Results

Main results from Pilot study

The response rates were estimated respectively as 61% for the infant BCG study cases and 35% for the school-age BCG cases (table 6). The refusal rates were similar between the two studies and consistent with community-based studies (about 10%), and the difference was mainly due to non-contact, notably because of address changes. It was not unexpected as the target population for the school-age BCG study included more young and middle-age adults of working age, hence likely to be more mobile.

Table 6: Response rate in cases:

Outcome	**Infant BCG Sample**	**School-age BCG Sample**
Total Invited	58	57
Could not be contacted (%)	17 (29%)	32 (56%)
Contacted but refused to take part (%)	7 (12%)	6 (11%)
Successfully recruited (%)	**34 (61%)**	**19 (35%)**

Less than 1 in 4 infant BCG study cases and 1 in 3 school-age BCG study cases were willing and/or able to nominate 2 or more potential controls, and respectively 29% and 26% were unable to suggest any acquaintance (table 7). Furthermore, of the total nominated acquaintances, we were only able to recruit 46% (17/34) for the infant BCG study and 35% (8/23) for the school-age BCG study . A further challenge was the time needed to recruit each control, as nominated acquaintances (when more than one) could not all be contacted concomitantly.

Table 7 Results of nominated control strategy

Number of controls nominated per case recruited	**Infant BCG Sample (n=34)**	**School-age BCG Sample (n=19)**
0	10 (29%)	5 (26%)
1	16 (47%)	8 (42%)
2 to 5	8 (24%)	6 (32%)

The data collection tools and study procedures worked well and required only minor alterations.

Conclusion from pilot study:

The two main conclusions from the pilot study were:

1. Nomination of acquaintances to recruit controls was unlikely to be effective in this context. The low recruitment of nominated controls by cases was partly due to the paucity of friends of similar age as well as not wanting to risk any potential disclosure of past health issues. We decided instead to use the alternative already planned, community-based controls.

2. The low recruitment of cases in the school-BCG study (35% of those invited) suggested a reduction in the number of cases expected to be recruited even by inviting all those eligible and notified to the ETS. This led us to adjust the sample size by increasing the ratio of controls per case from 1 control per case to 2 controls per case.

Results: Concordance between different measures of BCG vaccination

These results are based on eligible participants successfully recruited to the respective studies, as detailed in the subsequent sections. For the infant BCG study, it was found that participants had difficulties distinguishing BCG vaccination in infancy from other childhood vaccines. As the information of self-reported vaccination was clearly of poor quality, the three other BCG indicators were examined: scar inspection, personally-held records (red book or vaccination card), and NHS vaccination records. For the school-age BCG study, the quality of recall was better, probably because vaccination was offered at an older age, i.e. to schoolchildren aged 12-13 years on average.

Availability of information on indicators of BCG status

In the infant BCG study, respectively 15% of cases and 10% of controls declined scar inspection. Red books were available in 48% cases and 57% controls, and NHS records were found for 52% cases and 40% controls (table 8).

In the school-age BCG study, self-reported history was available in over 95% of participants, and scar inspection was done in more than 90% of subjects. Vaccination records were unavailable for over 95% of subjects, and thus could not be used (table 9).

Table 8 Available information on various BCG indicators by case and control in the infant BCG study

Variable	Cases (n=744)	%	Controls (n=694)	%
Red book and vaccination card				
Available: BCG vaccination not recorded	156	21.0	152	21.9
Available: BCG vaccination recorded	203	27.3	241	34.7
Not available	385	51.7	301	43.4
NHS record				
Available: BCG vaccination not recorded	100	13.4	72	10.4
Available: BCG vaccination recorded	286	38.4	209	30.1
Not available	358	48.1	413	59.5
Scar inspection				
BCG scar present	207	27.8	174	25.1
No BCG scar	422	56.7	451	65.0
Not inspected	115	15.5	69	9.9

Table 9 Available information on various BCG indicators by case and control in the school-age BCG study

Variable	Cases (n=677)	%	Controls (n=1170)	%
Self-reported BCG history				
History of BCG	170	25.1	169	14.4
No history of BCG	476	70.3	954	81.5
Do not remember	31	4.6	47	4.0
Scar inspection				
Interviewer did not find a BCG scar	204	30.1	269	23.0
Interviewer found a BCG scar	424	62.6	844	72.1
Not inspected	49	7.2	57	4.9
Red book and vaccination card				
Available: BCG vaccination not recorded	29	4.3	59	5.0
Available: BCG vaccination recorded	6	0.9	12	1.0
Not available	642	94.8	1099	93.9
NHS record				
Available: BCG vaccination not recorded	20	2.9	27	2.3
Available: BCG vaccination recorded	16	2.4	20	1.7
Not available	641	94.7	1123	96.0

Agreement between NHS and BCG records, and scar and records in the infant BCG study

The agreement in BCG vaccination between NHS records and Red book was poor (table 11), suggesting different patterns of incompleteness in the two types of records (i.e. it was unlikely that the absence of BCG in one record equated to no vaccination). We found that 40% (35/88) of subjects with no BCG in their NHS records were vaccinated according to their red book, and 67% (110/163) of those with no BCG in their red book were vaccinated according to their NHS record.

Table 10 Agreement between NHS and BCG records in the infant BCG study

	BCG in red book					
BCG in NHS Record	Overall		Cases		Controls	
	No	Yes	No	Yes	No	Yes
No	53 (14.6%)	35 (9.9%)	35 (17.4%)	18 (9.0%)	18 (11.5%)	17 (10.8%)
Yes	110 (30.8%)	160 (44.8%)	61 (30.3%)	87 (43.3%)	49 (31.2%)	73 (46.5%)
Kappa	0.15		0.20		0.09	

The data also suggested that for infant vaccination scar inspection was not very specific as compared to vaccination records (table 12). Respectively of those with no BCG in their Red book only 42% (111/262) subjects had no scar, and of subjects with no BCG in their NHS records, only 40% (58/146) had no scar on inspection. This proportion was slightly higher when we combined records and considered no BCG in both records as our best evidence of unvaccinated status; 53% (23/43) of those thus classified as unvaccinated had no scar at inspection.

Table 11 Concordance between scar inspection and vaccination records[1] in the infant BCG study, overall and by case and control status

Scar inspection	**Red book**		**NHS records**		**Combined records**	
	BCG recorded	BCG not recorded	BCG recorded	BCG not recorded	BCG recorded	No BCG in both
Cases	**n = 182**	**n = 130**	**n = 248**	**n = 80**	**n = 351**	**n = 28**
Scar present	128 (70.3%)	76 (58.5%)	183 (73.8%)	47 (58.7%)	252 (71.8%)	14 (50%)
Scar absent	54 (29.7%)	54 (41.5%)	65 (26.2%)	33 (41.3%)	99 (28.2%)	14 (50%)
Controls	**n = 226**	**n = 132**	**n = 188**	**n = 66**	**n = 346**	**n = 15**
Scar present	184 (81.4%)	75 (56.8%)	152 (80.8%)	41 (62.1%)	280 (80.9%)	6 (40%)
Scar absent	42 (18.6%)	57 (43.2%)	36 (19.2%)	25 (37.9%)	66 (19.1%)	9 (60%)
Overall	**n = 408**	**n = 262**	**n = 436**	**n = 146**	**n = 697**	**n = 43**
Scar present	312 (76.5%)	151 (57.6%)	335 (76.8%)	88 (60.3%)	532 (76.3%)	20 (46.5%)
Scar absent	96 (23.5%)	111 (42.4%)	101 (23.2%)	58 (39.7%)	165 (23.7%)	23 (53.5%)

[1]*Subjects are vaccinated if BCG reported in either record. They are unvaccinated if both records and available and neither have BCG reported.*

Agreement between BCG history and scar in the school-age BCG study

There was good agreement between self-reported history of BCG and scar inspection among participants to the school-age BCG study (kappa=0.6; table 10)

Table 12 Agreement between BCG self-reported history and scar in school-age BCG study

	Self-reported history of BCG vaccination					
Scar inspection	Overall		Cases		Controls	
	Yes	No	Yes	No	Yes	No
Scar Present	1181 (70.5%)	43 (2.6%)	394 (65.1%)	16 (2.6%)	787 (73.5%)	27 (2.5%)
No scar	195 (11.6%)	257 (15.3%)	60 (9.9%)	135 (22.3%)	135 (12.6%)	122 (11.4%)
Kappa	0.60		0.69		0.52	

Interpretation:

Our information about BCG vaccination was clearly better in the school vaccination than for infant vaccination.

For the infant BCG study, it appears that no single indicator of BCG status was good enough to be used on its own to define BCG vaccination status, our main exposure. There was some suggestion that combining information from both records was helpful. For the school-age study, data were available on two main indicators, respectively self-reported history and scar inspection, and there was good agreement between both measures. This suggested they could be combined to better define BCG vaccination status.

Results: Infant BCG study

Overview of recruitment

Recruitment of cases

Of 1390 potentially eligible cases from the ETS invited to take part in the study, it was possible to contact 1138. Of these 6% were also excluded either because they were not

born in the UK, they were away as reported by a household member, or during interview were noted to have been vaccinated because of contact with a case of TB. Of the 1076 subjects contacted and eligible, 797 (74%) subjects were enrolled.

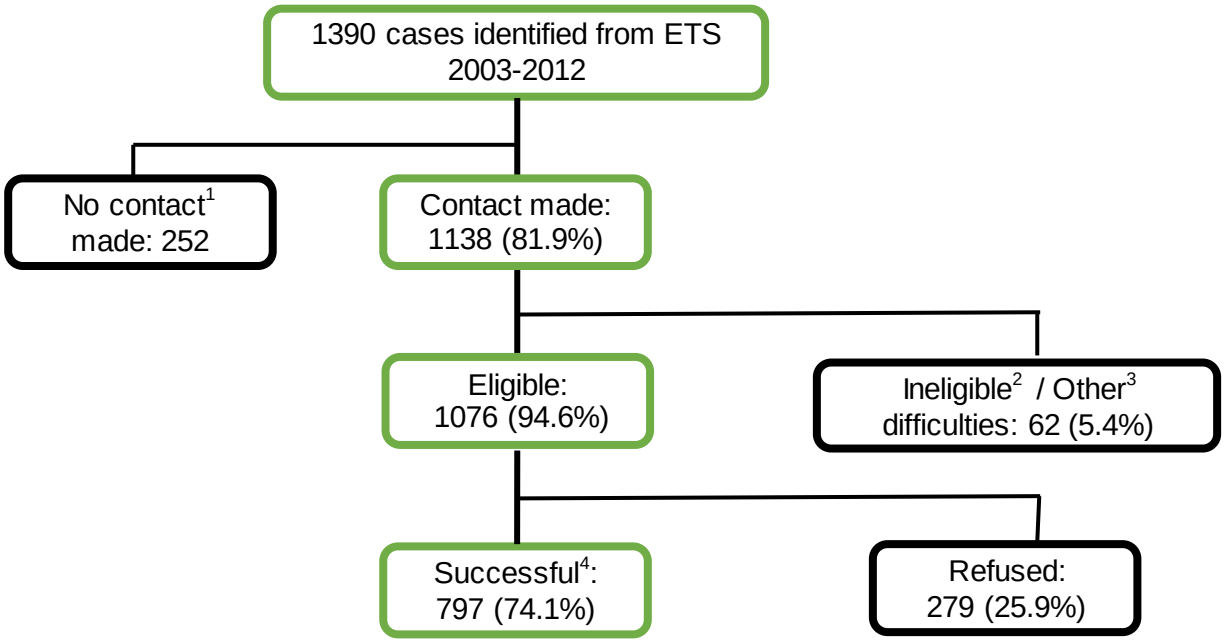

Figure 3 Overview of infant BCG cases recruitment

[1]No contact because changed addresses (142), no contact with anybody at address provided (87), moved out of England to other parts of UK (10), moved abroad (8), unspecified (5).
[2]Ineligible (29) because not born in the UK (20), not BAME (2) reported contact with TB case in red book and consistent with date TB diagnosis in ETS (2), unspecified (5).
[3]Other difficulties (33) include away or in hospital during the survey (22), too frail to take part (5) and various other reasons (6).
[4]Note 797 cases successfully recruited, but 53 not included in analysis because developed TB before chance of getting infant BCG (i.e before 1st birthday)

Recruitment of controls

We sampled 7755 residential addresses, of which 1089 (14%) could not be screened to establish eligibility for the study because addresses could not be located or were inaccessible, or where no contact could be established following the standard visit pattern of visiting more than once on different days and more than once at different times. Among the 6666 addresses that were screened, 1073 (16%) had at least one eligible resident, with 694 (65%) eligible subjects successfully recruited to the control group.

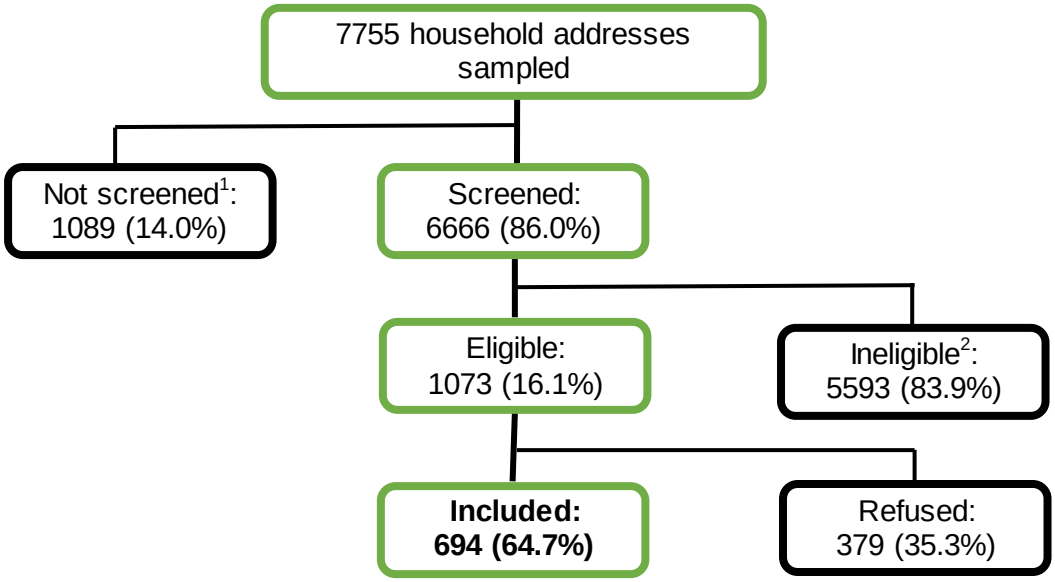

Figure 4 Overview of infant BCG study recruitment of controls

[1]Not screened because no contact with anybody at address provided after several visits following pre-set visit pattern.
[2]Ineligible include 4861 addresses screened with no eligible subjects and 719 addresses either with non-residential, vacant, derelict or demolished buildings.

Comparison of recruitment between cases and controls

The proportion of cases that could be contacted was fairly comparable across quintiles of area-level indices of multiple deprivation (IMD) (table 13). Among those contacted and eligible, the refusal rate did not vary much by quintile of area-level IMD. Similarly, the proportion of addresses successfully screened was similar across quintiles of IMD. Among subjects identified as eligible to be controls, the refusal rate had a similar trend as in cases, but was consistently higher in controls than cases.

Table 13: contact and refusal rates in infant BCG study by area-level indices of deprivation quintiles and case/control status

	Cases		**Controls**	
	Cases invited to participate		**Addresses screened for eligible**	
IMD quintiles	**Total**	**Contacted**	**Total**	**Screened**
Least deprived	159	134 (84%)	1556	1377 (88%)
2	219	174 (79%)	1559	1379 (88%)
3	273	217 (79%)	1544	1305 (84%)
4	330	283 (86%)	1547	1307 (84%)
Most deprived	407	328 (91%)	1549	1298 (84%)
	Eligible cases contacted		**Eligible controls contacted**	
IMD quintiles	**Eligible**	**Refusal**	**Eligible**	**Refusal**
Least deprived	125	38 (30%)	217	82 (38%)
2	160	42 (26%)	223	87 (38%)
3	205	55 (27%)	186	65 (35%)
4	271	67 (25%)	197	71 (36%)
Most deprived	312	76 (24%)	250	74 (30%)

The distribution of visits by time of the day and by day of the week was also comparable in cases and controls (figure 6).

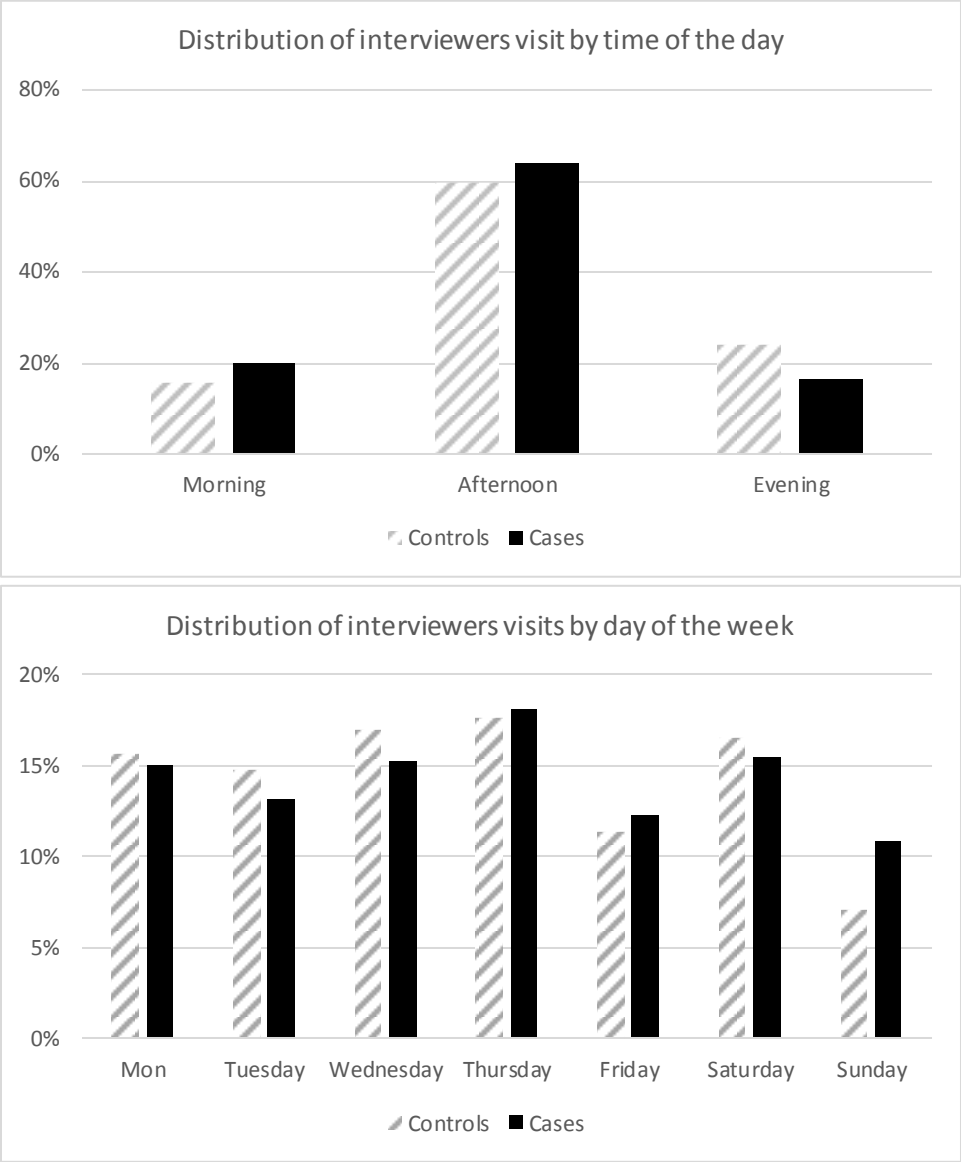

Figure 5 Distribution of interviewers visits by time of the day, and day of the week in invited cases and sampled control addresses for the infant BCG study

Fifty-three subjects who had developed TB in their 1st year of life were censored (i.e. exited the study) before the start of 'follow-up', as some may have developed TB before full opportunity for infant-BCG vaccination (which could have been offered at any point before age one year), hence they were not included in the analysis. Table 14 shows the number of cases by age-range at the time of TB diagnosis and birth cohort.

Table 14 Distribution of cases and controls in the infant BCG study by time-intervals since vaccination

	Number of cases[1] by birth cohort and age-range (in years) at time of TB diagnosis, and number of controls[2] from the same birth cohort					
Birth cohort		**Total**	**1-4**	**5-9**	**10-14**	**15-19**
1985-1989	**Cases**	54	-	-	9	45
	Controls	67	0	0	33	67
1990-1994	**Cases**	188	-	2	72	114
	Controls	130	0	55	130	130
1995-1999	**Cases**	202	3	59	109	31
	Controls	151	61	151	151	90
2000-2004	**Cases**	189	93	73	17	-
	Controls	168	168	168	56	0
2005-2011	**Cases**	117	103	14	-	-
	Controls	178	178	67	0	0

[1]Note that the study included cases notified between 2003 and 2012 and aged 1 to 19 years at time of diagnosis; therefore some birth cohorts do not contribute cases in some follow-up time (left-truncation. e.g. birth cohort 1985-1989 would be aged 13-19 years at start of 'follow-up' in 2003, so will not include subjects from the birth cohort who developed TB at age 1-12 years)

[2]Controls could contribute observation time to more than one period since vaccination (see methods section for details)

Descriptive statistics by case and control status

The distribution of cases and controls by sex and birth cohort did not appear substantially different although there were more cases with Pakistani and Black African ethnic background (63%) than controls (44%) (Table 15). The distributions of TB cases by area-level deprivation quintiles and highest level of parental education were consistent with the known relationship between TB and deprivation, with increasing proportion of cases in the more deprived quintiles, and having parents with fewer educational qualifications. The proportion of cases from overcrowded households was also higher than in controls. The distribution of other variables was fairly similar. In addition, nearly 95% of study participants had a place of residence in infancy or early childhood where infant BCG vaccination was offered, and was similar in cases and controls.

Table 15 Characteristics of subjects in the infant BCG study by case and control status

Characteristic	Cases[1] (n=744)	%	Controls (n=694)	%
Birth Cohort				
1985-1989	54	7.3	67	9. 6
1990-1994	188	25.3	130	18.7
1995-1999	202	27.1	151	21.8
2000-2004	183	24.6	168	24.2
2005-2011	117	15.7	178	25.7
Sex				
Female	417	56.1	350	50.4
Male	327	43.9	344	49.6
Ethnicity				
Indian + mixed	146	19.6	172	24.8
Bangladeshi + mixed	55	7.4	79	11.4
Pakistani + mixed	323	43.4	206	29.7
Other Asian + mixed	27	3.6	51	7.4
Black African + mixed	150	20.2	97	14.0
Other Black + mixed	43	5.8	89	12.8
Quintiles of LSOA-level Index of Multiple Deprivation				
1 (least deprived)	86	11.6	139	20.0
2	105	14.1	140	20.2
3	182	24.5	139	20.0
4	199	26.7	141	20.3
5 (most deprived)	172	23.1	135	19.5
Parental highest educational (academic, professional and or vocational) qualification				
None	263	35.3	154	22.2
O Levels or equivalent[2]	214	28.8	160	23.0
A Levels or equivalent[3]	88	11.8	89	12.8
Degree level or equivalent[4]	142	19.1	270	38.9
Missing	37	5.0	21	3.0
Average number of people per room				
Less than or equal to 1	524	70.4	569	81.8
Greater than 1	191	25.7	126	18.2
Missing	29	3.9	0	0.0
Average number of people per bedroom				
Less than or equal to 1	104	14.0	168	24.2
Greater than 1	610	82.0	526	75.8
Missing	32	4.0	0	0.0
TB infection risk from regular travels abroad				
Low[5]	453	60.9	434	62.5
High[6]	289	38.8	260	37.5
Missing	2	0.3	0	0.0
TB infection risk from long-term stays abroad				
Low[5]	637	85.6	618	89.1
High[6]	106	14.3	76	10.9
Missing	1	0.1	0	0.0
Infant BCG vaccination policy in health district / primary care trust of residence up to age 4 years old				
None	34	4.5	39	5.6
Selective	502	67.5	420	60.5
Universal	186	25.0	206	29.7
Missing	22	3.0	29	4.2
3-year average TB notification rate in local authority or PCT of residence in childhood				
<20 per 100,000	172	23.1	177	25.5
20 to 39 per 100,000	394	53.0	299	43.1
40 per 100,000 or higher	178	23.9	216	31.1
Missing	0	0.0	2	0.3

[1]53 cases with TB in their first year of life exit before the start of follow-up at the 1st birthday
[2]O Levels, GCEs, or GCSEs (any grades), City & Guilds Craft/Ordinary Level or NVQ Level 1 or 2
[3] A Levels, SCE Higher, ONC/ONT/BEC/TEC, City & Guilds Advanced Final Level or NVQ Level 3
[4]Degree Level, Teaching qualification, HNC/HND, BEC/TEC Higher or BTEC Higher
[5] Regular 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
[6] Regular travel (i.e. every few years or more often) or long-term (>3 months) stays to Africa or Asia

Indicators of vaccination status

We examined our main definition of BCG vaccination status combining information from the Red book and NHS records (see table 4). The distribution of BCG status according to these definitions by case and control status is presented in table 16. The detailed uptake in cases and controls is presented in table 17, for each interval of time since vaccination and by birth cohort stratum; in the analysis, we stratified by year of birth.

Table 16: BCG vaccination status in the infant BCG study based on combination of Red book and NHS records

Red Book	**NHS Record**	**BCG vaccination status (def 1)**	**Cases (n=744)**	**Controls (n=694)**
BCG Recorded	BCG Recorded	Vaccinated	402 (54.0%)	377 (54.3%)
BCG Recorded	BCG not recorded			
BCG recorded	Missing			
BCG not recorded	BCG Recorded			
Missing	BCG Recorded			
BCG not recorded	BCG not recorded	Not vaccinated	35 (4.7%)	18 (2.6%)
BCG not recorded	Missing	Missing	60 (8.1%)	85 (12.3%)
Missing	BCG not recorded		47 (6.3%)	37 (5.3%)
Missing	Missing	Missing	200 (26.9%)	177 (25.5%)

Association between time since BCG and all TB: complete case analysis

Table 17 Distribution of observed vaccination status (definition: combined BCG records) by cases and corresponding sub-cohort of controls in the infant BCG study

	Vaccination status in cases by birth cohort and age-range (in years) at time of TB diagnosis, and in controls[1] from the same birth cohort					
		Uptake by time since vaccination (in years)				
Birth cohort		**Total**	**1-5**	**5-10**	**10-15**	**15-19**
1985-1989	Cases vaccinated	16/17 (94%)	0	0	2/3	14/14
	Controls vaccinated	15/16 (94%)	0	0	6/7	15/16
1990-1994	Cases vaccinated	78/85 (92%)	0	1/1	27/31	50/53
	Controls vaccinated	46/48 (96%)	0	19/21	46/48	46/48
1995-1999	Cases vaccinated	118/125 (94%)	3/3	38/39	62/67	15/16
	Controls vaccinated	86/90 (95%)	40/41	86/90	86/90	46/49
2000-2004	Cases vaccinated	107/121 (88%)	56/62	42/49	9/10	0
	Controls vaccinated	97/102 (96%)	97/102	97/102	24/27	0
2005-2011	Cases vaccinated	83/89 (93%)	73/78	10/11	0	0
	Controls vaccinated	133/139 (96%)	133/139	48/53	0	0
Total for each time since BCG, across birth cohorts	Cases vaccinated		132/143 (92.3%)	91/100 (91.0%)	100/111 (90.1%)	79/83 (95.2%)
	Controls vaccinated		270/282 (95.7%)	250/266 (94.0%)	162/172 (94.2%)	107/113 (94.7%)

1Note: Controls could be used more than once hence columns by time since vaccination for controls will not add up to the column totals for controls (see methods section for details)

Potential confounding variables

There was little evidence of variation in vaccine uptake with covariates in the study dataset. There was some evidence of different uptake by ethnic background, and of higher vaccine uptake in participants from crowded household (table 18). We did not find strong correlation between covariates.

The analyses were stratified by year of birth and ethnic background, thus allowing for the change in TB rates with age, as well as the known variation in TB rates between ethnic groups.[39] The latter also accounted for any differential uptake in vaccine between ethnic

groups. In the multivariable analysis, we adjusted for those variables associated with vaccine uptake as well as other potential confounders, as detailed in the methods section.

Table 18 Association between vaccine uptake (based on combined records) and covariates in the control group of the infant BCG study

	# vaccinated (%)	OR	95% CI	p-val
Sex				
Female (n=193)	182 (94.3%)	1		0.286
Male (n=202)	195 (96.5%)	1.68	(0.64, 4.44)	
Birth Cohort				
1985-1989 (n=16)	15 (93.7%)	1		0.997
1990-1994 (n=48)	46 (95.8%)	1.53	(0.13, 18.1)	
1995-1999 (n=90)	86 (95.6%)	1.43	(0.15, 13.7)	
2000-2004 (n=102)	97 (95.1%)	1.29	(0.14, 11.8)	
2005-2011 (n=139)	133 (95.7%)	1.48	(0.17, 13.11)	
Ethnic group				
Indian (n=96)	93 (96.9%)	1		0.007
Bangladeshi (n=50)	48 (96.0%)	0.77	(0.13, 4.8)	
Pakistani (n=133)	131 (98.5%)	2.11	(0.35, 12.9)	
Other Asian (n=30)	30 (100%)	-	-	
Black African (n=56)	50 (89.3%)	0.27	(0.06, 1.12)	
Other Black (n=30)	25 (83.3%)	0.16	(0.04, 0.72)	
Area-level deprivation quintiles				
Least deprived (n=78)	74 (94.9%)	1		0.56
2 (n=79)	77 (97.5%)	2.08	(0.37, 11.7)	
3 (n=73)	68 (93.1%)	0.73	(0.19, 2.8)	
4 (n=80)	78 (97.5%)	2.11	(0.37, 11.8)	
Most deprived (n=85)	80 (94.1%)	0.86	(0.22, 3.3)	
People per bedroom				
<1 PPB (n=75)	67 (89.3%)	1		0.011
>1 PPB (n=320)	310 (96.9%)	3.70	(1.41, 9.73)	
Highest parental education level				
None (n=90)	87 (96.7%)	1		0.56
O Levels (n=87)	82 (94.2%)	0.56	(0.13, 2.4)	
A Levels (n=52)	51 (98.1%)	1.76	(0.18, 17.4)	
Degree (n=160)	151 (94.4%)	0.58	(0.15, 2.2)	

Table 19: Complete case analysis of the association between time since vaccination and risk of TB using combined records in the infant BCG study

	Base[1] model (Based on 417 cases and 382 controls)			**Base[1] model restricted to subjects with no missing data on covariates** (Based on 379 cases and 378 controls)			**Multivariable[2] adjusted model** (Based on 379 cases and 378 controls)		
	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
Unvaccinated	1 (ref)			1 (ref)					
Vaccinated: 1-5 yrs	0.38	(0.17,0.86)	0.021	0.43	(0.18,1.03)	0.058	0.34	(0.15,0.78)	0.011
Vaccinated: 5-10 yrs	0.37	(0.15,0.88)	0.025	0.32	(0.13,0.79)	0.014	0.25	(0.11,0.56)	0.001
Vaccinated: 10-15 yrs	0.50	(0.22,1.13)	0.096	0.68	(0.28,1.66)	0.396	0.64	(0.24,1.68)	0.361
Vaccinated: 15-20 yrs	1.25	(0.28,5.64)	0.775	2.06	(0.33,12.91)	0.440	2.26	(0.34,15.10)	0.400

[1]Base model is stratified on year of birth and ethnic group, and additionally adjusted for sex
[2]The multivariable model is additionally adjusted for people-per-bedroom, area-level deprivation quintiles, and highest parental educational level

The results of the complete case analysis (i.e. using only subjects with vaccine records) are presented in table 19. Good evidence of a protective effect of the vaccine was noted in the < 5 year time period and in the 5-10 year period before and after adjusting for confounding (HR_{adj}=0.34 95%CI 0.14,0.78:p=0.011 and HR_{adj} 0.25 95%CI 0.11,0.57:p=0.001 respectively). The evidence for a protective effect of the vaccine in the time period 10-15 years was weaker both in the baseline analysis but more so in the adjusted analysis ($HR_{baseline}$ 0.5 95%CI 0.22,1.13: p=0.096 and HR_{adj} 0.64 95%CI 0.24,1.68: p=0.361). Examination in a baseline analysis of the effect of vaccination on the smaller number of records used in the multivariable analysis suggested that this lack of evidence of an effect was the result of chance (sampling error), rather than the effect of controlling for confounding. Evidence was lacking for a protective effect 15 to 20 years after infant vaccination in both models based on the small numbers available. Confidence intervals were wide, ranging in the baseline analysis from 0.28 to 5.64.

Trends in the association between time since BCG vaccination and risk of TB

Table 20 shows the results from modelling the association between BCG vaccination and log hazard of TB as a linear function of time since vaccination, centred at 5 years post-vaccination. The results are displayed graphically in figure 7. The model suggests an 12% increase in the HR with each year post-vaccination, though this was only of borderline statistical significance (95% CI: -1% to 26%). We also explored the trend in time using restricted cubic splines with 3 knots, respectively at 5, 10 and 15 years post-vaccination. The results were similar to those found using the linear model and are not shown here. The results suggest a statistically significant protective effect of the vaccine up to about 10 years post-vaccination, with a gradual reduction in the protective effect up to that time. After 10 years post-vaccination, the confidence bounds are wide and there is insufficient information to draw conclusions about the vaccine effectiveness.

Table 20: Association between BCG status and risk of TB in the infant BCG study as a smooth function of time since vaccination, using the multivariable adjustment model.

	HR	**95% CI**	**p-val**
Unvaccinated	1 (ref)		
HR at 5-years post-vaccination	0.32	(0.16,0.64)	0.001
Multiplying factor for each year increase in time-since-vaccination	1.12	(0.99,1.26)	0.062

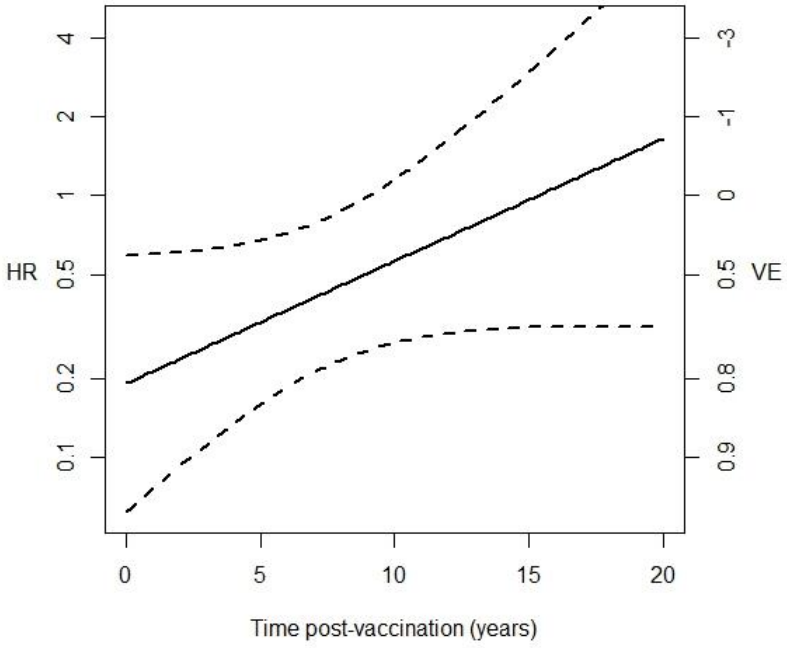

Figure 6**:** Results from modelling the time-varying effect of the vaccine as a linear function of time (on the log scale) in the infant BCG study

The left-hand vertical axis shows the hazard ratio (HR) and the right-hand vertical axis shows the vaccine effectiveness (VE), both on the log scale. Results are based on the multivariable adjusted model.

Results: School-age BCG study

Overview of recruitment

Recruitment of cases

A total of 1602 potentially eligible cases were identified from the ETS and invited to take part in the study, of whom 1047 (65%) were successfully contacted. About 11% were not included either because they were ineligible or due to other difficulties (figure 8). Of those contacted and eligible, 257 (28%) declined to participate and 677 (72%) subjects were enrolled.

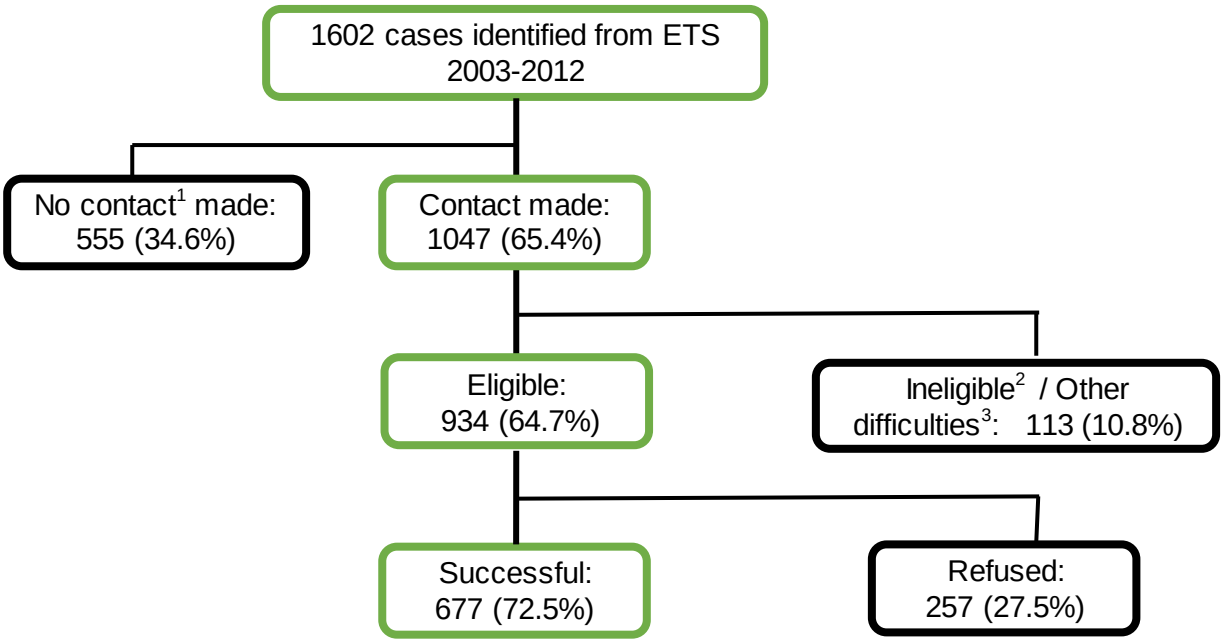

Figure 7 Overview of school-age BCG study cases recruitment

[1]No contact because changed addresses (353), no contact with anybody at address provided (165), moved out of England to other parts of UK (10), moved abroad (12), inaccessible (6), unspecified (9).
[2]Ineligible (60) because not born in the UK (13), not White (23), reported vaccination at later age and following contact with TB case in red book and consistent with date TB diagnosis in ETS (4), unspecified (20).
[3]Other difficulties (53) include away or in hospital during the survey (23), too frail to take part (20), who had died (6), other reasons (4).

Recruitment of controls

We sampled 9424 residential addresses, of which 1248 (13%) could not be screened because the address no longer existed or no-one was at the household after several visits to establish whether any of the residents was eligible for the study (figure 8). Among the 8176 addresses that were screened, 1790 (22%) had at least one eligible resident, with 1170 (65%) eligible subjects successfully recruited to the control group.

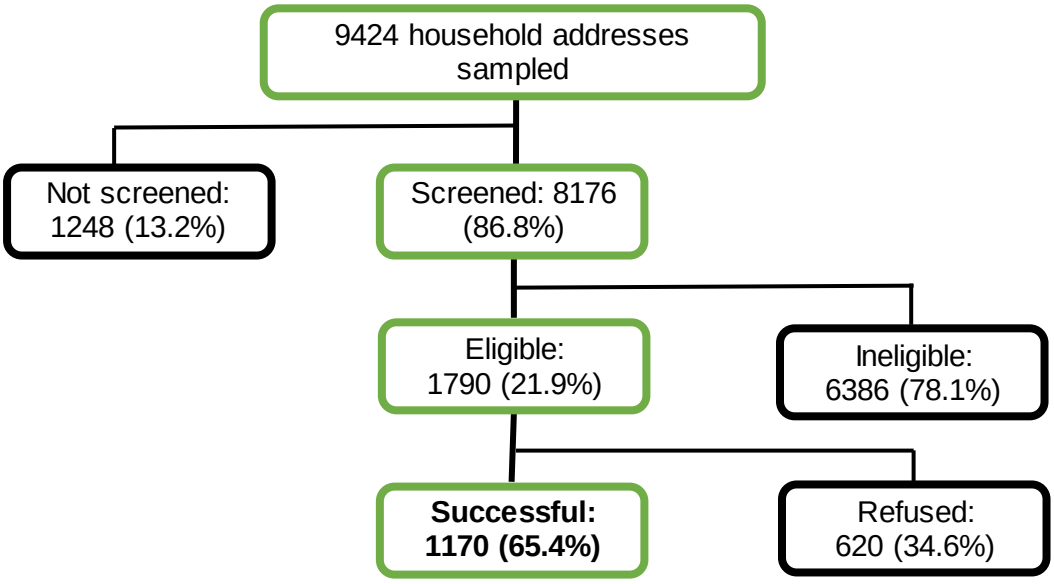

Figure 8 Overview of school-age BCG study recruitment of controls

[1]No screened because no contact with anybody at address provided after several visits following pre-set visit pattern.
[2]Ineligible include 5692 addresses screened with no eligible subjects and 694 addresses either with non-residential, vacant, derelict or demolished buildings.

Comparison of recruitment between cases and controls

The proportion of cases that could be contacted was slightly lower in the more deprived quintiles of area-level indices of multiple deprivation (table 21). Among those contacted and eligible, the refusal rate was slightly lower in the lower quintiles of area-level IMD. The proportion of addresses to identify eligible controls successfully screened was similar across quintiles of IMD. Among subjects identified as eligible to be controls, the refusal rate was similar across quintiles and was slightly higher in controls than cases.

Table 21: Comparison of recruitment in school-age BCG study cases and controls

	Cases		**Controls**	
	Cases invited to participate		**Addresses screened for eligible**	
IMD quintiles	**Total**	**Contacted**	**Total**	**contacted**
Least deprived	165	119 (72%)	1889	1634 (87%)
2	218	157 (72%)	1885	1599 (85%)
3	233	148 (64%)	1886	1631 (86%)
4	394	254 (64%)	1886	1659 (88%)
Most deprived	575	357 (62%)	1878	1653 (88%)
	Eligible cases contacted		**Eligible controls contacted**	
IMD quintiles	**Eligible**	**Refusal**	**Eligible**	**Refusal**
Least deprived	107	35 (33%)	429	155 (36%)
2	146	36 (25%)	363	130 (36%)
3	137	35 (26%)	358	127 (35%)
4	217	63 (29%)	359	113 (31%)
Most deprived	316	86 (27%)	281	95 (34%)

The distribution of visits by time of the day and by day of the week was comparable in cases and controls (figure 9).

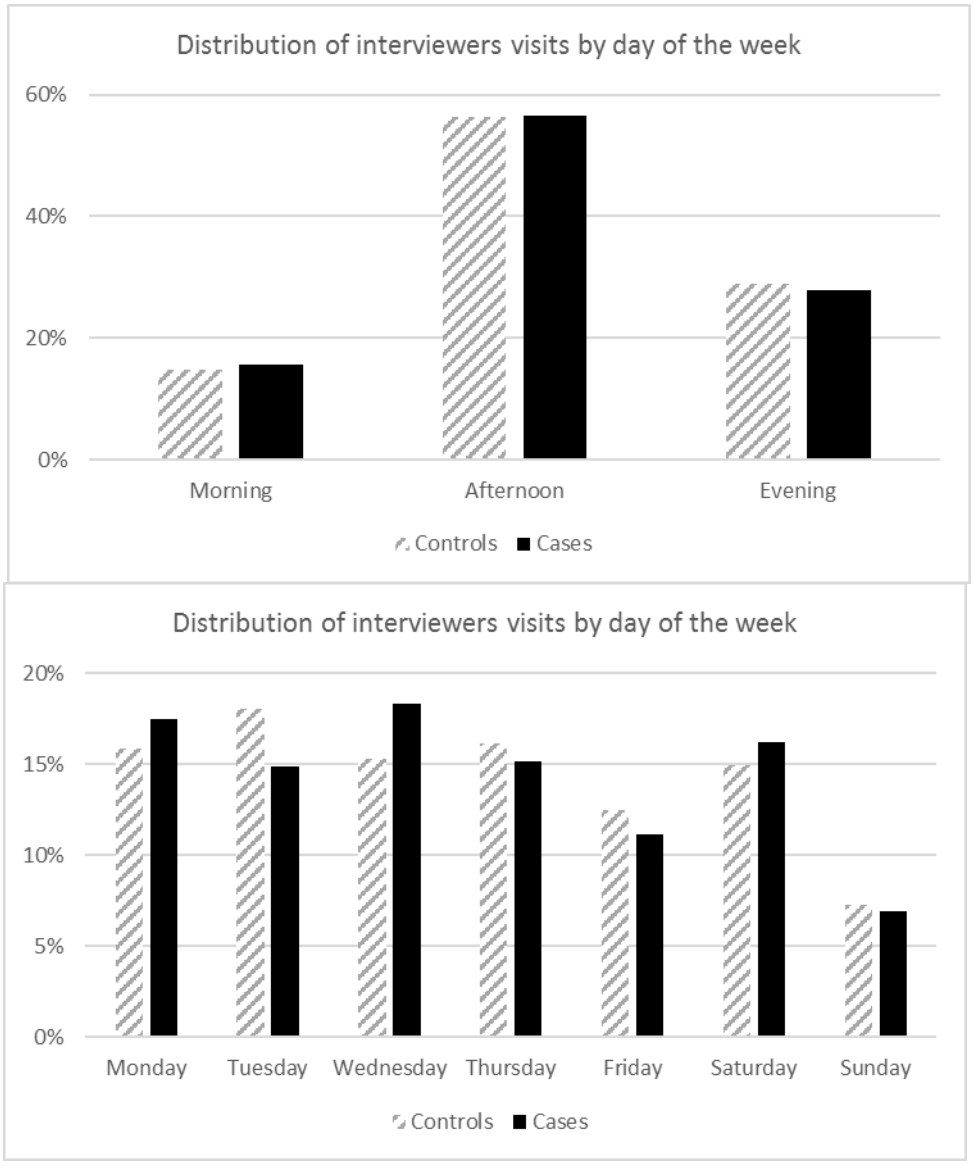

Figure 9 Distribution of interviewers' visits by time of the day, and day of the week in invited cases and sampled control addresses for the school-age BCG study

We found that retrospective ascertainment of results of TST testing was challenging in the school-aged BCG vaccine study, with very poor recall and with no record to support or validate participants' self-reports. Further investigation of the literature indicated that the initially high TB risk in those who were PPD positive dropped to be the same as those PPD negative unvaccinated (figure 12). Thus, we included all those unvaccinated irrespective of PPD status prior to the offer of school-aged BCG vaccination.

Descriptive statistics by case and control status

The cases were slightly younger than controls and more likely to be male (table 22). The distributions of cases compared to controls by area-level deprivation quintiles and highest level of education were consistent with the known association of TB with deprivation, with a higher proportion of cases in the most deprived quintile, and with fewer educational qualifications compared to controls. The proportion of cases from overcrowded households was also slightly higher than controls. Cases were slightly more likely to have had regular travel to a high-risk area and somewhat more likely to have had a long term stay in a high risk area. A higher proportion of cases than controls reported drinking at a hazardous or harmful level and reported being a smoker. A much higher proportion of cases than controls reported having used class A drugs. Cases were also more likely than controls to report a history of homelessness for a week or more, and prison detention in the UK or abroad.

Table 22 Characteristics of study participants in school-age BCG study by case and control status

Characteristic	Cases (n=677)	%	Controls (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	32.3	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[1]	207	30.6	363	31.0
A Levels or equivalent[2]	91	13.4	246	21.0
Degree level or equivalent[3]	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	2.0
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[4]	618	91.3	1099	93.9
High[5]	58	8.6	71	6.1
Missing	1	0.1	0	0.0
TB infection risk from long-term stays abroad				
Low[4]	607	89.7	1113	95.1
High[5]	70	10.3	57	4.9
Alcohol drinking[6]				
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	2.2
Missing	88	13.0	116	9.9
Tobacco smoking				
Never smoker	188	27.8	499	42.6
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	2.9	29	2.5
Drug misuse/abuse[7]				
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	32.0	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[8]				
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

[1]O Levels, GCEs, or GCSEs (any grades), City & Guilds Craft/Ordinary Level or NVQ Level 1 or 2
[2] A Levels, SCE Higher, ONC/ONT/BEC/TEC, City & Guilds Advanced Final Level or NVQ Level 3
[3]Degree Level, Teaching qualification, HNC/HND, BEC/TEC Higher or BTEC Higher
[4]Regular 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
[5]Regular travel (i.e. every few years or more often) or long-term (>3 months) stays to Africa or Asia
[6]Alcohol drinking based on combination on drinking frequency and quantity in UK standard units, and cut-offs by gender as proposed by Rehm et al.(IJE 1999) [40]. 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.
[7]Class 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
[8]72/82 (88%) cases and 33/35 (94%) controls with history of prison stay report only ever been in prison in the UK and not abroad.

Indicators of vaccination status

The availability of the various indicators of BCG status is presented in table 23. As noted, earlier in table 12 page 40, self-report of BCG vaccination at school was judged to be more accurate than a self or parental report of infant BCG vaccination. Both personal and NHS records were missing for over 90% study participants in the school-aged BCG vaccination study and insufficient to allow any formal assessment of the validity of either of these measures. There was however, a good level of agreement between self-reported history and scar inspection. These two indicators were therefore combined to define BCG status in this study (table 24).

Table 23 Availability of BCG indicators in school-age BCG study by case and control status

	Cases (n=677)	**Controls (n=1170)**
BCG history		
Vaccinated	470 (69.4%)	922 (78.8%)
Probably vaccinated	6 (0.9%)	32 (2.7%)
Not vaccinated	170 (25.1%)	169 (14.4%)
Missing	31 (4.6%)	47 (4.0%)
Scar inspection		
Scar present	424 (62.6%)	844 (72.1%)
Scar absent	204 (30.1%)	269 (23.0%)
Not inspected	49 (7.2%)	57 (4.9%)
Personal vaccination record		
BCG recorded	6 (0.9%)	12 (1.0%)
BCG not recorded	29 (4.3%)	59 (5.0%)
No personal record	642 (94.8%)	1099 (94.0%)
NHS vaccination records		
BCG recorded	16 (2.4%)	20 (1.7%)
BCG not recorded	20 (2.9%)	27 (2.3%)
NHS record missing	641 (94.7%)	1123 (96.0%)

Table 24: BCG vaccination status in school-age BCG study based on combination of self-report and scar reading

Self-reported history	**Scar inspection**	**BCG vaccination status**	**Cases (n=677)**	**Controls (n=1170)**
Convincing BCG history	Scar present	"Vaccinated"	473 (69.9%)	933 (79.7%)
Convincing BCG history	No scar			
Convincing BCG history	Not inspected			
Probable BCG history	Scar present			
Probable BCG history	No scar	"likely vaccinated"*	33 (4.9%)	78 (6.7%)
Probable BCG history	Not inspected			
No BCG history	Scar present			
Unsure	Scar present			
No BCG history	No scar	"Not vaccinated"	163 (24.1%)	154 (13.2%)
No BCG history	Not inspected			
Unsure	No scar			
Unsure	Not inspected	Missing	8 (1.2%)	5 (0.4%)

**sensitivity 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*

Association between time since BCG and all TB: complete case analysis

Table 25 Distribution of observed vaccination status in school-age BCG study (combined BCG history and scar) by cases and corresponding sub-cohort of controls

	Vaccination status in cases by birth cohort and age-range (in years) at time of TB diagnosis, and in controls[1] from the same birth cohort					
		Uptake by time since vaccination (in years)				
Birth cohort		**Total**	**10-15**	**15-20**	**20-25**	**25-29**
1965-1969	Cases vaccinated	51/64 (79.7%)	-	-	32/39	19/25
	Controls vaccinated	147/173 (85.0%)	0	0	124/144	147/173
1970-1974	Cases vaccinated	136/174 (78.2%)	-	28/34	93/120	15/20
	Controls vaccinated	262/311 (84.2%)	0	208/259	262/311	262/311
1975-1979	Cases vaccinated	161/212 (75.9%)	33/46	66/81	61/84	1/1
	Controls vaccinated	231/259 (89.2%)	231/259	231/259	231/259	55/64
1980-1989	Cases vaccinated	158/219 (72.2%)	121/159	37/59	0/1	-
	Controls vaccinated	371/422 (87.9%)	371/422	236/259	48/55	0
Total for each time since BCG, across birth cohorts	Cases vaccinated		154/205 (75.1%)	131/174 (75.3%)	186/244 (76.2%)	35/46 (76.1%)

1Note: Controls could be used more than once hence columns by time since vaccination for controls will not add up to the column totals for controls (see methods section for details)

Table 26 Complete case analysis of the association between time since vaccination and risk of TB using various definitions for BCG status in the school-age BCG study

	Base[0] model (based on 669 cases and 1165 controls)			**Partially[1] adjusted model** (based on 638 cases and 1134 controls)			**Fully[2] adjusted model** (based on 532 cases and 993 controls)			**Base[0] model fitted on same subset as included in fully[2] adjusted model** (based on 532 cases and 993 controls)			**Partially[1] adjusted model fitted on same subset as included in Fully[2] adjusted model** (based on 532 cases and 993 controls)		
	HR	**95% CI**	**p-val**	**HR**	**95% CI**	**p-val**	**HR**	**95% CI**	**p-val**	**HR**	**95% CI**	**p-val**	**HR**	**95% CI**	**p-val**
Unvaccinated	1 (ref)			1 (ref)			1 (ref)			1 (ref)			1 (ref)		
Vaccinated: 10-15 yrs ago	0.400	(0.274,0.584)	0.000	0.419	(0.272,0.644)	0.000	0.49	(0.31,0.79)	0.003	0.43	(0.28,0.66)	<0.001	0.49	(0.31,0.79)	0.004
Vaccinated: 15-20 yrs ago	0.346	(0.246,0.487)	0.000	0.390	(0.264,0.575)	0.000	0.43	(0.28,0.67)	<0.001	0.34	(0.23,0.50)	<0.001	0.41	(0.27,0.63)	<0.001
Vaccinated: 20-25 yrs ago	0.554	(0.404,0.759)	0.000	0.640	(0.448,0.916)	0.015	0.75	(0.49,1.14)	0.174	0.56	(0.39,0.80)	0.001	0.69	(0.46,1.02)	0.065
Vaccinated: 25-29 yrs ago	0.565	(0.342,0.932)	0.025	0.772	(0.453,1.315)	0.341	0.99	(0.53,1.84)	0.97	0.70	(0.40,1.24)	0.225	0.88	(0.48,1.59)	0.66

[0]Base model is stratified on birth cohort and adjusted for sex
[1]The partially adjusted model is additionally adjusted for confounding variables area-level deprivation and educational level.
[2]The fully adjusted model is further adjusted for confounding variables area-level deprivation and educational level, lifestyle 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.

There was strong evidence of a protective effect of the vaccine in each of the 5 year periods from 10 to 20 years post-vaccination (table 26). Results from the model fully adjusted for confounders provided evidence of a protective effect 10 to 15 (HR_{adj} 0.49 95% CI 0.31,0.79:p=0.003) and 15 to 20 years later (HR_{adj} 0.43 95% CI 0.28,0.67:p<0.001) compared to after 20 years. Numbers were too small to assess the effect from 20 to 25 years but there was a suggestion of a protective effect.

These results are based on a complete case analysis (ie based on subjects with no missing data). Taking into account missing information may be explored in the future.

Trends in the association between time since BCG vaccination and risk of TB

Table 27 shows the results from modelling the association between BCG vaccination and log hazard of TB as a linear function of time since vaccination, centred at 10 years post-vaccination. The results are displayed graphically in figure 11. The model suggests a 7% increase in the HR with each year post-vaccination, and this was statistically significant (95% CI: 0.2% to 12%). We also explored the trend in time using restricted cubic splines with 3 knots, respectively at 15, 20 and 25 years post-vaccination. The results were similar to those found using the linear model and are not shown here.

Table 27 Association between BCG status and risk of TB as a smooth function of time since vaccination in the school-age study

	Partially Adjusted model[1]			**Fully Adjusted model[2]**		
	HR	**95% CI**	**p-val**	**HR**	**95% CI**	**p-val**
Unvaccinated	1 (ref)			1 (ref)		
HR at 10-years post-vaccination	0.310	(0.188,0.511)	0.000	0.374	(0.215,0.652)	0.001
Multiplying factor for each year increase in time-since-vaccination	1.07	(1.00,1.12)	0.015	1.057	(1.002,1.116)	0.042

[1]*The partially adjusted model is stratified on birth cohort and adjusted for confounding variables sex, area-level deprivation and educational level.*

[2]*The fully adjusted model is further adjusted for confounding variables area-level deprivation and educational level, lifestyle 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*

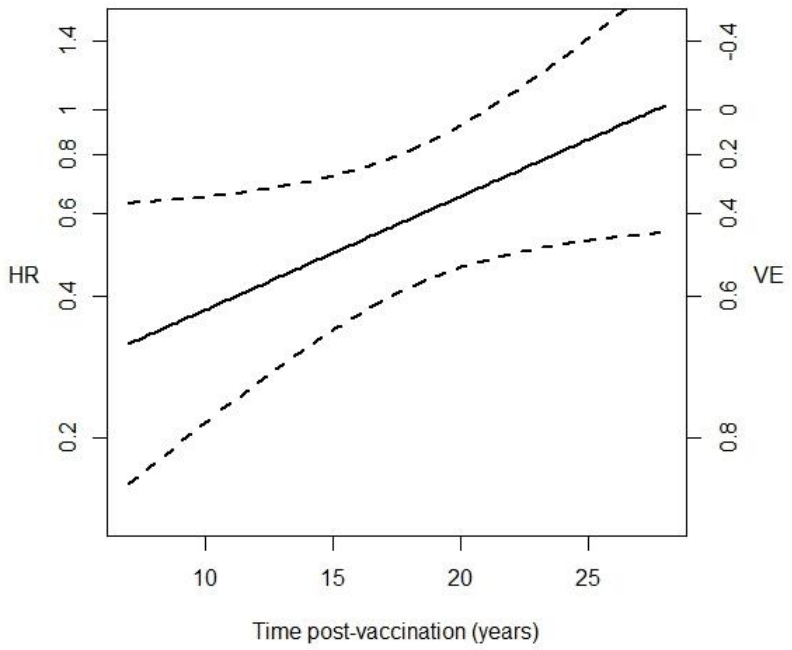

Figure 10: Results from modelling the time-varying effect of the vaccine as a linear function of time (on the log scale) in the school-age study

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

The results showed a statistically significant protective effect of the vaccine up to about 23 years post-vaccination, with a gradual reduction in the protective effect up to that time. The

protective effect of the vaccine appears to reduce more steeply after about 20 years post-vaccination. However, we had only a relatively small number of cases with more than 25 years post-vaccination and thus have insufficient evidence to assess protection beyond that time.

Discussion

These results from our studies of the duration of protection of BCG vaccination indicate that protection persists for at least 10 years for infant vaccination and for at least 20 years for school-age vaccination. After school-aged BCG vaccination a protective effect of 48% (95% CI 17 to 68%) was seen 10 to 15 years after vaccination, and 55% (95% CI 30 to 71%) 15 to 20 years after vaccination beyond which protection appeared to wane. For infant BCG vaccination a protective effect was seen up to 10 years since vaccination (less than 5 years after vaccination VE 66%, 95%CI 17% to 86%; 5 to 10 years VE=75%, 95%CI 43 to 89%) but with less evidence of an effect 10-15 years later (VE=36%, 95%CI negative to 77%, p=0.396). These results for the infant BCG study were based on subjects for whom vaccine records were available in the analysis adjusted for several confounders including birth cohort and ethnicity. By adjusting only for ethnicity and birth cohort, slightly more records with complete data could be included, giving weak evidence of a 50% VE (95% CI negative to 78%, p=0.096) 10 to 15 years after infant BCG vaccination. The higher than expected infant BCG vaccine uptake in this high-risk ethnic minority study population and sparsity of vaccine record data in the later time periods precluded further assessment.

Although the findings for infant BCG vaccination in a population at high risk for TB are insufficient to assess protective effect beyond 10 years, the evidence is much stronger for a moderate protective effect for up to 20 years after school-aged BCG vaccination in the native white population. The study findings are consistent with recent findings from Norway[41] and from Brazil,[24] and provides additional evidence to that from the seminal MRC trial in which protection of 63% was seen 10 to 15 years after vaccination with wide confidence intervals (17 to 84%) with absence of evidence of protection 15 to 20 years after vaccination (VE 9% 95% CI negative to 71).[7]

BCG vaccine composition or changes in administration was not considered to be an important source of variation over the study period. Although the liquid Danish BCG was replaced in the UK in the 1960s' by Glaxo freeze dried BCG (Glaxo 1077 vaccine strain developed by Glaxo from the Danish Strain and produced in the UK by Evans-Medeva), a study comparing both showed non inferiority[42,43].[41,42] From 2002 the UK was only able to source BCG from Denmark's Statens Serum Institute (SSI vaccine also based on the Danish Strain 1331) [44,45].[43,44] A recent systematic review of the BCG vaccine trials by our research group also suggested protection did not vary in relation to vaccine strain.[10] Multipuncture vaccination use was limited. In our analysis of policy we noted that the 1983 survey indicated 76% of districts used intradermal BCG vaccination, which increased in the 1992 survey to 96% of districts. No data are available comparing protection using multipuncture versus intradermal vaccination but sensitisation based on TST testing was similar.[46] [44]

We had a good response rate in both studies and were successfully able to recruit population-based controls to represent both the children born in the UK to populations from high TB burden settings and the general population. We were unable to link to vaccine records for most of the school-aged BCG subjects despite their willingness to consent to such linkage. Self-reported history of BCG and scar were used instead to measure BCG uptake having been found to have good agreement with each other (this agreement was not observed, by contrast in those offered BCG in infancy). Although interviewers were not blind to case control status or to knowledge of a history of BCG vaccination before scar reading, they were specifically trained to identify a BCG scar that included tests based on examining volunteers with and without scars, 10% of interviews selected at random were checked by senior staff and standardised reporting was required. The reason for the study, limited information on duration of protection, was known from BCG, hence it is unclear if interviewers would have been more biased in one direction than the other when reading a BCG scar. There was some confounding due to lower BCG uptake in poorer subjects who had a higher risk of TB. We were however able to control for this.

We were able to evaluate the effectiveness of BCG in BAME population groups despite initial concern that this group would be difficult to assess. Consent was obtained to link to vaccine records but could only be retrieved for about a half of subjects from either NHS administrative areas or patient held records. There was a considerable lack of agreement between the different sources of information on infant BCG vaccination. Information on self-reported BCG uptake in the infant study was also found to be a poor measure of vaccination, and scar reading was poorly concordant with vaccine records where available. Red book and NIH records also had poor concordance, indicating that BCG vaccination was being noted in one record but not necessarily the other. We also noted a higher refusal rate for reading a BCG scar in some BAME young adult female cases who were not comfortable having their upper arms examined than controls. For both these reasons, we therefore used vaccine records where available, despite not having information on uptake for about 40% of subjects. Future work may include exploring approaches that could include scar information, despite the relatively poor specificity of scar reading noted in this study to reduce the level of missing information on vaccination status in the infant vaccination study.

Addressing the issue of prior infection as the reason for not receiving BCG vaccination

A theoretical limitation in the school-aged BCG analysis study was the inability to assess and exclude from the controls those with prior positive tuberculin skin tests. Retrospective ascertainment of results of TST testing based on recall was clearly not feasible, and there was no record to validate participants' memory recall. Under the routine school vaccination programme, prior infection by *Mycobacterium tuberculosis* (Mtb) or sensitization by environmental mycobacterial (EM) was investigated through TST, and such subjects were not offered BCG. These subjects are usually not included in studies measuring the effect of BCG in the short-term, as there is evidence that the risk of TB is higher in skin test positive

subjects during the first few years after infection. Their inclusion would thus act to overestimate the protective effect of BCG vaccination. It is also thought that BCG does not confer protection in TST positive subjects. However, follow-up data from the British MRC BCG trial in adolescents show that—at least in settings with low transmission—the risk of TB in participants who were positive to TST declined over time, and was similar to that of subjects who were TST negative at baseline by about 10 years after enrolment (see figure 12).[7,47] Thus, TST was thought unlikely to play a major role when measuring the association between BCG vaccination and TB beyond 10 years after vaccination as in our study. Extrapolation of earlier modelling work by one of the authors of the paper[48] and this document, also suggested the prevalence of tuberculin positivity in the white population in general would have been around 4% at the time of screening for vaccination.

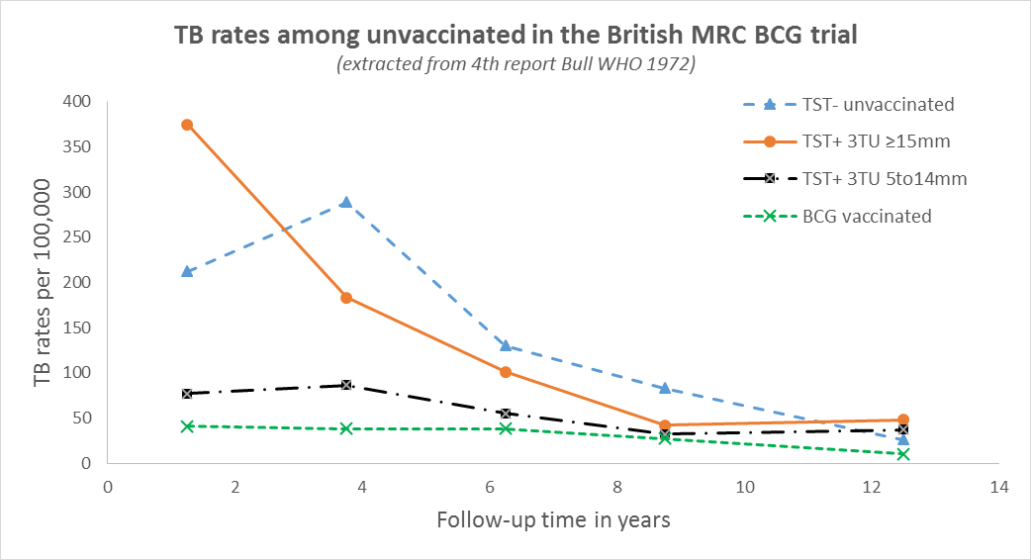

Figure 11 Comparison of TB rates in BCG vaccinated and unvaccinated by TST status at start of follow-up in the British MRC BCG trial in Adolescents

(Figure based on data from the British MRC trial published in 4th Report Bull WHO 1972)[47]

Conclusions

In summary, our two observational studies suggest BCG vaccination provides longer lasting protection than previously described, particularly for BCG vaccination at school-age where we were able to use scar and history as measures of BCG uptake. Protection was noted for more than two decades after vaccination, but to wane 20 to 25 years after vaccination. The findings are consistent with the limited data emerging from other trials and observational studies[22] as well as a more recent Norwegian historical cohort study of the duration of protection of BCG vaccine.[41] BCG at school-age may thus have helped in the control of TB including the potential for developing multidrug resistant disease as those vaccinated at about 13 years of age have moved into adulthood.

Our current analysis of the infant BCG study, based on just over 50% of the subjects with vaccine records and complete information on covariates, was able to confirm the known protective effect of infant BCG vaccination against TB for up to 10 years after vaccination adjusting for confounders. Numbers were however too sparse after 10 years to provide robust evidence of VE for this time period. Vaccine coverage was higher than expected in those with records. Further exploratory analyses to deal with missing records could include multiple imputation of missing BCG vaccination status amongst other sensitivity analyses. This assessment might inform a review of the incidence levels when countries are recommended to suspend BCG vaccination, estimates of cost effectiveness of BCG in prevention of tuberculosis, and have implications for testing and scheduling of new vaccines against tuberculosis which will need to give better protection than BCG and as durable. We also recommend more systematic recording of BCG uptake at the population level by ethnic group using the Child Health Information System and linkage to TB events to help provide ongoing data to assess protection and duration of protection over the life course.

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Contributions

LR and PM co-designed and co-wrote the proposal. PM provided the managerial lead for the project with PND. PM, PND and LR provided academic leadership and other co-applicants provided valued academic expertise and advice at key points. RK devised and carried out the analyses with assistance from PND and LT. PND, LT and RK carried out data cleaning and merging of data across sources. Additional expertise was provided in statistics (JS), BCG epidemiology and study design (PF, PS), TB epidemiology, the ETS, BCG vaccine records, public health policy and clinical aspects (IA, JW DE and ML), and exploring PPD positivity levels in the general population (EV). PND co-wrote a first draft of the report with PM and RK. All authors contributed to the final report.

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