NIHR HTA Programme

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A. OBSERVATIONAL STUDY TO ESTIMATE THE CHANGES IN THE EFFICACY OF BCG WITH TIME SINCE VACCINATION

This study addresses HTA priority # 08/17: Duration of protection of BCG vaccination-new primary research

B.1 HOW THE PROJECT HAS CHANGED SINCE THE OUTLINE PROPOSAL WAS SUBMITTED

The objectives have changed slightly from the outline proposal.

(i) The outline proposal aimed to estimate the duration of efficacy of both infant and adolescent vaccination in high risk groups. The amended objectives explicitly measure (i) vaccine efficacy by time since infant vaccination in high risk groups and (ii) vaccine efficacy by time since adolescent school vaccination in the general population. We believe this will give separate, rigorous estimates of changes with time in efficacy in BCG vaccination programmes in infants and adolescents. In addressing referees' comments, it became clear to us that assessing the efficacy of adolescent vaccination in the general population avoided the problems caused by the fact that some children in high risk groups would have received vaccination at birth, some at school, and some not at all; and these differences might have been influenced by their degree of risk, leading to potential confounding. By choosing to estimate the duration of protection of adolescent BCG in the general population, we restrict this part of the study to a population at a much more homogenous risk of infection, avoiding the complication of previous BCG vaccination potentially related to their risk of infection.

(ii) The sample size has been amended to reflect the slight change in objectives and revised estimates of vaccine coverage.

(iii) The budget has increased to reflect the changes above and in response to the costing of more detailed preparatory studies.

C. PLANNED INVESTIGATION

1. RESEARCH OBJECTIVES:

To estimate the change in the efficacy of BCG with time since vaccination in preventing tuberculosis in today's UK population.

Primary objectives:

1.1 To estimate the efficacy of BCG vaccination when given in the first year of life ("infant BCG") **to high risk groups** in preventing tuberculosis in the following intervals since vaccination: 0 to 5, 6 to 12 and 13 to 17 years.

1.2 To estimate the efficacy of BCG vaccination when given at school age ("adolescent BCG") to the **general population** for preventing tuberculosis in the following intervals since vaccination: 10 to 14, 15 to 19 and 20 to 24 years.

1.3 To explore whether protection wanes with time since vaccination and to estimate the rate of change of protection with time since vaccination during the periods studied, in high risk groups and in the general population.

Health technologies being assessed:

BCG vaccination in the UK as given either

(i) to neonates in groups at high risk of tuberculosis (referred to in this proposal as infant BCG)

(ii) to schoolchildren in the general population (referred to in this proposal as adolescent BCG)

2. EXISTING RESEARCH

2.1 Tuberculosis epidemiology

Tuberculosis (TB) remains a significant and preventable cause of morbidity and mortality globally. Approximately 10% of infections with *M tuberculosis* progress to clinical disease[1]. The WHO estimates about one third of the world population is infected, and about 9 million new cases of TB and 1.6 million deaths from TB occur annually[2]. In the UK, after many decades during which both the risk of infection with *M tuberculosis* and the incidence of TB were decreasing, these have

increased steadily over the last two decades[3]. Since 2005 the numbers of reported TB has been stable at over 8000 cases per year. In London during this period rates of disease have increased in those aged 15-44 years [3]. The incidence of childhood TB, including miliary disease and meningitis, has remained stable[4,5].

Drug resistant TB has 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]. The percentage with multidrug resistance (MDR) has, however, remained stable at just under 1%. The prevalence of MDR TB among children is higher at about 2.3% of patients, although the numbers are small[5].

2.2 BCG vaccine efficacy 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 been given either to infant or to adolescents at school. The protection given by BCG at age 13 years against pulmonary tuberculosis in the UK is high, as shown by a trial initiated by the MRC in 1951[7] and in subsequent analyses of the efficacy of the vaccine given in the routine school immunisation programme[8]. However, there have been variable findings with respect to the efficacy against pulmonary disease of the vaccine in different countries or between different studies in the same country [9-11]. The efficacy 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[12, 13, 14]. Although WHO recommends not to re-vaccinate, mostly because of lack of evidence of efficacy, many countries implement re-vaccination programmes. Recent trials in Malawi and Brazil found no increase in efficacy associated with repeat BCG vaccination[15, 16,17].

In spite of evidence from the MRC trial that BCG gives good protection in the UK, there have been successive policy changes in BCG vaccination, prompted by changes in the epidemiology of TB and the cost-effectiveness of vaccination. 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 newborns of recent immigrants from countries with a high incidence of TB (e.g. Indian sub-continent and Africa) and for all refugees and-asylum seekers. It was also given to all newborns 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 migrants 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 newborn children of recent migrants from other countries with high incidence of tuberculosis[18].

There has been discussion regarding the need to continue BCG vaccination in the general population in the UK (and elsewhere) when the risk of TB was apparently decreasing, based primarily on the high number of vaccinations needed to prevent one case of tuberculosis[19]. 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 [20]. The IUATLD recommends BCG be discontinued if

- an efficient TB notification system is in place *and either*
- 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 passed all these criteria. The BCG vaccination policy for the UK was changed by the Department of Health in 2005. The school vaccination programme was stopped, and BCG vaccination was recommended to infants on a risk-based approach, in line with the IUATLD guideline. In the UK infants are eligible for vaccination if they have a parent/grandparent originating from a high 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 [21].

2.3 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[7]. 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 BCG adolescent vaccination programme in England [22]. There are no data regarding duration of 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 (yrs)			
		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
Vaccine efficacy (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 [23]. In a review of published studies conducted by two of the current applicants, the pooled estimate of protection after 10 years was 14% (95% CI –9% to 32%). 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 as a result 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.

An update of this systematic review of the duration of protection conferred by BCG against TB is about to be conducted by our group (HTA Project: 08/16/01 - Systematic Review and Meta-Analysis of the Current Evidence on the Duration of BCG Protection). It will include, as well as a systematic search for any other studies, the recent additional follow up of a BCG vaccine trial in American Indians (who were on average 7 years of age when vaccinated) in the 1930s which has reported protection lasting for several decades, as well as a cohort study in the control arm of the Brazilian BCG re-vaccination trial suggesting protection lasted 15 to 20 years[24-26].

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. We propose, therefore, to estimate the efficacy of BCG given to high risk infants in the UK up to 17 years after vaccination and the efficacy of BCG given to school-aged adolescents in the general population from 10 to 24 years after vaccination. If the study provides evidence of long duration of BCG protection, beyond 10 years, this will have a number of implications. They include estimates of the cost-effectiveness of BCG. The numbers of cases at different ages that would have occurred if all children were vaccinated compared to the number if not at all were vaccinated can be calculated using estimates of efficacy by time since vaccination, population age-specific incidence rates of tuberculosis and known newborn and school vaccine coverage by birth cohort. Others include: the number of vaccinations needed to prevent a case; the timing of vaccination for any new tuberculosis vaccine developed; i.e. provide the necessary

evidence for policies for immunization and, although not a formal evaluation of repeat vaccination, will give background data for possible re-immunization.

3. RESEARCH METHODS

Overview of studies proposed: Three preparatory studies and two matched case-control studies are proposed. The preparatory studies would support the conduct of the two matched case-control studies which will estimate the protective efficacy of BCG vaccine against TB for three time periods since vaccination. One of the case-control studies will estimate the efficacy of BCG given to infants in high risk groups (the results will be generalizable to high risk groups in the UK), for which a sample size of 481 cases and 481 frequency-matched controls will be required. The other case-control study will estimate efficacy for BCG given in adolescence to the general population (the results will be generalizable to the UK general population) and for which a sample size of 505 cases and 896 controls will be required (after refusals, non responses and exclusions for both studies). Cases will be those notified in the years 2003 to 2011. Controls will be recruited from the community from which cases have arisen. BCG vaccination status will be established based on BCG scar examination or photographs for independent review blind to case-control status and, if available, records. Records of past BCG vaccination are known to be incomplete and, if available, time consuming to retrieve from stored microfiches or manual files. BCG scar is a traditional way to establish past BCG vaccination and has high validity as an indicator of BCG vaccination in many populations[31]. Information on potential confounders will be collected from cases and controls including demographic and social variables. Clinical and microbiological information will be noted for cases.

3.1 PREPARATORY STUDY ONE: POLICY SURVEY

3.1.1 Objectives:

(i) To identify potential areas for the validation studies.

(ii) To clarify BCG vaccination policies (infant and adolescent) over time, including mode of vaccination (intra dermal, multi-puncture or jet injector) in potential study areas

(iii) To identify areas which still keep: (a) individual BCG vaccine records (either infant or adolescent) (b) individual records of PPD testing for the adolescent BCG programme (c) routine aggregated data on proportion of school children that tested PPD negative and proportion of those vaccinated for the adolescent BCG programme.

3.1.2 Methods

National and regional surveys on BCG policy conducted over the relevant periods, whether published or unpublished, will be identified and summarized. A list will be prepared of individuals who might have access to information on local policies regarding infant and adolescent BCG vaccination from 1968 to today, centrally, and at local level, including immunization coordinators of PCTs. These will be contacted to establish the history of local policies regarding infant and adolescent vaccination over the relevant time periods and whether individual records of infant and adolescent BCG vaccination were kept during the relevant periods. Information on infant and adolescent BCG vaccination policies by locality over time will be summarised in a table ("Operational table"). A mock version is presented below.

Table 2: Dummy operational table of BCG vaccine policies in selected study areas over time

	1970	75	80	85	90	95	…..
Adolescent programme							
District/PCT A	Ongoing	Ongoing	Ongoing	Interrupted 1985	Reinitiated 1990	Suspended	…
District/PCT B	Ongoing	Ongoing	Ongoing	Ongoing	Ongoing	Suspended	
……..							
Infant programme							
Hackney	Ethnic min	Universal	Universal	Universal	Universal	Universal	….
Wandsworth	Ethnic min	Ethnic min	Ethnic min	Ethnic min	Ethnic min	Ethnic min	

Areas will be selected for the validation study on whether records are kept locally. This preparation study is currently being conducted by the Health Protection Agency.

3.2 PREPARATORY STUDY TWO: PILOT STUDY

3.2.1 Objectives:

(i) To assess the feasibility of recruitment methods for cases and controls.
(ii) To estimate the response rate in cases and in matched controls.
(iii) To estimate BCG vaccination coverage in controls.
(iv) To estimate the proportion of cases and controls who can recall whether or not they received BCG vaccination. For those who were aged 13 years before the end of the school vaccination programme, we will establish the proportion that remembers whether or not they received BCG at school, and if they were PPD tested. For those who report that they were not vaccinated, we will establish the proportion that remembers if this was because of a positive PPD test.
(v) To field test the questionnaire.
(vi) To assess the usefulness of scar photographs.

3.2.2 Methods

Twenty cases in high risk groups and 20 cases in the general population will be contacted from areas identified early in the policy survey. Cases (or their relatives in the case of children) will be contacted and invited to participate in the studies if they meet the inclusion criteria (see below - under the general studies). Those accepting the invitation will be visited at home. During the visit, information will be collected and their arms examined and photographed for a scar, as described in the main project (see below). For each case we will note if translation was required. Matched controls will be contacted and the same process of consent followed. For those who agree to participate, interviews and scar examinations and photographs will be done as for cases. Reasons for refusals and duration of interviews will be noted for cases and controls. This field work will be conducted by the independent social and health research institute NatCen (National Centre for Social Reearch) supervised by the study nurse project manager, and analysed by the research statistician, in consultation with the co-applicants.

3.3 PREPARATORY STUDY THREE: VALIDATION OF EXPOSURE: BCG SCAR READING

Three forms of information are usually considered valid indications of a previous history of BCG vaccination: a scar, a convincing history, or records of BCG vaccination. For example the current Joint Committee on Vaccination and Immunisation (JCVI) recommendation is that BCG vaccination should not to be offered to children who already received BCG vaccination according to any of these three types of evidence [21]. This preparatory study will examine consistency between these forms of evidence in the cases and controls in areas where routine vaccination records have been kept.

3.3.1 Objectives:

(i) To compare information from scar reading, subject recall of vaccination, personally held vaccination records and centrally held vaccination records.
(ii) To compare information from recall of presence and timing of vaccination to that from personally or centrally held vaccination records.
(iii) To compare information on whether a positive PPD was the reason for not receiving adolescent BCG from recall and from centrally held individual vaccination records; and from aggregated data.

3.3.2 Methods

The study areas will be those identified in the policy study as suitable for the different aspects of the validation study i.e. areas where infant BCG vaccination records are available, areas where adolescent vaccination records/individual PPD results are available and areas with routine information on the proportion of children with PPD positive, negative not vaccinated and negative vaccinated. . Cases and controls living in these areas at the age at which BCG vaccination was offered will be listed and vaccination records for those cases and controls will be sought. Data on vaccination and

tuberculin testing result will be abstracted from the vaccination records (blind to case status, recall of BCG vaccination and scar reading). Information from scar reading, recall and records will be compared. In addition, the existence of routine statistics of proportion of children with a negative PPD test who were vaccinated by the school programme will be established and compared with that in controls in the relevant areas. The final analysis of the main study will be defined taking into account these results. For example, in defining the best indicator of past BCG vaccination to be used in the analysis (scar alone, recall alone, a combination of both) and in assessing the need for sensitivity analysis. The field work will be conducted by the study nurse project manager and analyses by the research statistician, in consultation with CoPIs.

3. 4. CASE CONTROL STUDY 1: CHANGES IN THE EFFICACY OF INFANT BCG WITH TIME SINCE VACCINATION IN HIGH RISK GROUPS

3.4.1 Setting:
The study will be conducted in high TB incidence areas selected during the policy survey.

3.4.2 Target population:
Children aged 0 to 17 years of age, with disease notified between 2003 and 2011, inclusive, and born in the UK in high risk groups.

3.4.3 Study population*:*
The population will be those born during 1986 to 2011, from ethnic minority groups (considered to be at higher risk of tuberculosis than the general population) for whom infant BCG vaccination was recommended. The study is restricted to areas with 30% or more resident ethnic minority from the 2001 general population census, for logistical ease in contacting community-based controls.

3.4.4 Measurement of disease status and of vaccination
Definition of outcome (Tuberculosis): tuberculosis (all forms) during the period 2003 to 2011 in the relevant age groups and years of birth.
Definition of exposure (BCG status):
BCG vaccination received during the first year of life (based on scar), validated where possible by records kept by participants and by routine services. The decision of how best to combine information from complementary sources will be taken after the validation study.

(i) Scar examination

WHO recommends, as does the UK Health department, that BCG be given in the left upper arm[21]. BCG vaccination in cases and in controls will therefore be ascertained by examination of the deltoid area of the left arm for presence of a BCG scar, by trained interviewers. If proven during the pilot to be possible, interviewers will be allocated subjects blind to case-control status so that examination for BCG scar is not influenced by knowledge of whether subject is a case or a control.

(ii) Reporting

Cases and controls will be interviewed in person. Interviewers will ask to see personal vaccination cards and ask parents and guardians of cases and controls whether the child received vaccination in the first year of life. No children will have been aged 13 years during a time when BCG vaccination was still being offered at school routinely but we will also ask parents and guardians if the children received BCG vaccination at schools as catch up.

3.4.5 Source of cases and of controls:
Cases of tuberculosis (both pulmonary and non-pulmonary) will be ascertained from the Health Protection Agency's Enhanced Tuberculosis Surveillance system (ETS) from the selected areas in the relevant age groups.
Controls: individuals without tuberculosis, randomly selected within the community from the same areas, frequency-matched to cases on year of birth.

3.4.7 Inclusion and exclusion criteria

Inclusion criteria for cases and controls:
(i) Subjects from ethnic minority background and born in the UK between 1986 and 2011;
Exclusion criteria for cases and controls:
(i) those born in areas where BCG was administered by multi-puncture or jet injector techniques (either of which is less likely to lead to scarring) and
Exclusion criteria for cases:
(i) Cases with HIV infection. Data will be stripped of all identifiers within the HPA before they are forwarded to the project statistician who does not have access to identifying information of cases and controls, which will be kept at HPA. The prevalence of HIV infection in the general population is too small to require doing the same for controls.

3.4.8 Addressing the issue of infection prior to BCG vaccination (latent tuberculosis)
It is thought that BCG is not effective when given to those already infected (a paper addressing the implication of this for estimates of vaccine efficacy was written by one of the applicants, PGS[27]). This is not a problem for neonatal BCG, as the risk of infection at birth is negligible. Infection after BCG vaccination is not a problem: it is one of the components of the development of tuberculosis evaluated in this study. The possibility that the risk of infection and risk of being vaccinated are clustered (leading to confounding) is the reason for the matching based on risk group, as described below.

3.4.9 Control of confounding and procedures for control recruitment.
The study aims to make cases and controls similar with respect to potential confounders. An ideal recruitment of cases and controls does not match for exposure –it allows for variation in exposure – but controls for variables that might be associated with both exposure (in this case BCG) and outcome (in this case tuberculosis), i.e., control for confounding.
The challenge in the study is to control for the variation in the policies for neonatal BCG vaccination and in incidence of tuberculosis over time, by area and by ethnic group. This is addressed by selecting controls that were under the same BCG policy and at similar risk of infection and disease. The majority of English health districts were already offering neonatal BCG vaccination within ethnic minority groups (considered to have a risk of tuberculosis higher than the average for the population). At the same time, BCG immunisation of 13 year old school-children was routine policy in England since 1953. In 2005, the national BCG-vaccination policy was changed from school-age to infant-vaccination targeting high-risk population groups, including ethnic minorities.

The key aspect seems to be what variables are associated with both risk of disease and risk of BCG vaccination for individuals that are born in the same district and time. Our impression is that (other than the policy of the district at the time) factors related to BCG and to tuberculosis are different. There is no data on whether BCG coverage varies with socio-economic status, but it is more likely that determinants of vaccination are related to service factors, for example hospital of birth and who in the district delivers BCG in infancy (chest clinics, maternity hospital itself etc); and these tend to be uniform in a district. Determinants of tuberculosis are likely to be related to socio economic status and time since last visit to high prevalence countries.

Data on determinants of BCG vaccination are sparse and we will only be sure after the start of the data collection. It is important to collect data on characteristics of cases and controls, and to assess or limit the extent of this potential problem. We will collect information on socio-economic status of cases and controls and will examine whether there is an association between socio-economic status and BCG vaccination within a particular district policy, examine whether the agreement in socio-economic status of cases and controls changes with time since vaccination, and if it does, control for such confounding using modelling techniques.

Procedures for recruitment of controls: We will recruit neighbourhood/community-based controls frequency matched to cases on year of birth and sex. They will be selected using a two stage probabilistic sampling scheme to provide a sample representative of the eligible population in the study area as well as maximum geographic representativeness of the study area. The primary sampling unit (PSU) will be the lower layer super-output area (LSOA). These are statistical levels of geography in England made of adjacent postcodes and designed to have similar population size and to be as socially homogenous as possible; each LSOA has an average population of 1500. We aim to recruit on average one control per

primary sampling unit (PSU), and we have estimated that approximately 7-8 dwellings need to be screened in each PSU to successfully find one control. In the first stage, LSOAs are selected with probability proportional to the number of resident ethnic minority population (from census 2001) without replacement; then 7 postcode units are randomly selected within each LSOA using simple random sampling, and one residential address is sampled in each postcode unit by simple random sampling. Only one individual is recruited per address.

3.4.10 Proposed Sample size

Sample size was calculated based on estimation of vaccine efficacy at each of three periods after vaccination, 0-5y, 6-12y and 13-17y. Based on a frequency-matched study with one control per case (with a 15% inflation in sample size to control for confounders) the number of case-control pairs required for a 90% power to detect a protective effect of at least 60% at the 5% level of significance for the age groups 0-5y and 6 to 12y was calculated to be 252 and 158 respectively. Uptake of infant BCG vaccination was estimated to be 90% and 80% for these two age groups respectively[29,31]. For the 13 to 17 year olds it was assumed that 60% would have been vaccinated in infancy with an efficacy of 50%, requiring 217 cases and 217 controls.

Table 3: Sample size required for each age group in case control study of BCG vaccination in infancy

Power90%at the 5% level of significance - 1 control per case				
Age at tuberculosis (years)	Assumed BCG Coverage	Assumed Vaccine efficacy	Number of cases required	Number of frequency matched controls required
0 to 5	90%	60%	252	252
6 to 12	80%	60%	158	158
13 to 17	60%	50%	217	217
Total subjects 627 cases and 627 controls				

3.4.11 Statistical Analysis

Case and controls will be classified into two levels of exposure, vaccinated at birth or not vaccinated at birth, based on the best information as defined by the validation study. A possibility would be to use documentary evidence of having received BCG if available and if not the presence of a BCG scar and potentially also reported BCG history. A logistic regression model will be built to estimate the odds ratio of tuberculosis associated with infant BCG vaccination for each of the three age groups defined (0-5y, 6-12y, and 13-17y), while controlling for frequency-matched variables (year of birth and sex) and other potential confounders. The odds ratio will be translated into the efficacy of BCG into that age group, and therefore at 0-5, 6-12 and 13 to 17 years since infant vaccination. Given vaccine is received at birth or in infancy before 1 year old in this group, age is collinear to time since vaccination and will be used as such. Interval specific VE will be estimated by fitting an interaction between BCG vaccination status and time since vaccination as a categorical variable in the model using the pre-specified intervals. These estimates will be plotted against time since vaccination for graphical inspection for change of efficacy in time. More formally, we will investigate (exponential change) evidence of decline in VE with time since vaccination (ie linear change on the log scale) by fitting an interaction between BCG vaccination status and time since vaccination as a continuous variable in the model; departure from log-linearity will also be investigated. If necessary, other statistical methods will be explored to describe the change in VE with time since vaccination, including weighted moving average and locally weighted polynomial regression (“LOESS”).

3.4.12 Proposed outcome measures
The summary output of this study will be presented in a table as below

Table 4: Dummy table of the estimated protective effect of BCG vaccine in years since vaccination in infancy

Population	Age at diagnosis of tuberculosis	Year of birth	Years since vaccination	Protection (95%CI)
			Neonatal BCG	
High risk	0 to 5	1998 to 2011	0-5	
High risk	6 to 12	1991 to 2005	6 to 12	
High risk	13 to 17	1986 to 1998	13 to 17	

The estimates of efficacy by time since vaccination from the weighted averages or LOESS will be presented numerically and in a graph.

3.5 CASE CONTROL STUDY 2: CHANGES IN THE EFFICACY OF ADOLESCENT BCG WITH TIME SINCE VACCINATION IN THE GENERAL POPULATION

3.5.1 Setting:
The study will be conducted in population groups with incidence of tuberculosis lower than population average.

3.5.2 Target population:
Adults aged 23 to 38 years with cases notified in 2003 to 2012 in the general population in the UK.

3.5.3 Study population:
The study will be in the White ethnic group population, born in 1965 to 1988 and aged 23 to 46 years when recruited to the study.

3.5.4 Measurements of disease status and of vaccination.
Definition of outcome (tuberculosis): tuberculosis (all forms) during the period 2003 to 2012 in the relevant age groups and years of birth.

Definition of exposure (BCG status): this is different from the study of infant vaccination, as it refers to adolescent vaccination.
BCG vaccination received as part of the school programme (based on scar and reporting of whether vaccinated at school), validated by records kept by participants and by routine services. The decision of how best to combine information from complementary sources will be taken after the validation study.
(i) Scar examination:
BCG vaccination in cases and in controls will be ascertained by trained interviewers as in case control study 1.
(ii) Reporting:
Cases and controls will be interviewed in person. Interviewers will ask to see personal vaccination cards and ask cases and controls whether they had received vaccination at school, and if not, if the reason was prior vaccination, and whether the subject received a PPD test, whether it was positive and the reason for lack of vaccination. It is expected that a very small proportion of adolescents will have been vaccinated on the thigh at their request (to avoid scars in the arms) and so this will be enquired.

3.5.5 Source of cases and controls
Cases of tuberculosis (both pulmonary and non-pulmonary) will be ascertained from the Health Protection Agency's Enhanced Tuberculosis Surveillance system (ETS) in the relevant age groups between 2003 and 2012.
Controls: individuals without tuberculosis, randomly selected within the community from which cases arose, frequency-matched to cases on year of birth.

3.5.7 Inclusion and exclusion criteria

Inclusion criteria for cases and controls:

(i) (i) Subjects from White ethnic group (risk of TB lower than population average) and born in the UK between 1965 and 1988;

Exclusion criteria for cases and controls:

(i) those born in areas where BCG was administered by multi-puncture or jet injector techniques (either of which is less likely to lead to scarring) and

(ii) Having tested positive to PPD at the school and therefore were excluded from BCG vaccination (according to subject or parental report).

Exclusion criteria for cases:

(i) Cases with HIV infection. Data will be stripped of all identifiers within the HPA before they are forwarded to the project statistician who does not have access to identifying information of cases and controls, which will be kept at HPA. The prevalence of HIV infection in the general population is too small to require doing the same for controls.

(ii) Cases whose contact address is an institution (e.g prisons) or with no contact details available

(iii) Vaccinated in infancy

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

The implications of infection prior to vaccination was discussed previously[27]. In this paper two situations are addressed: when BCG vaccine is given after a negative PPD test, or with no prior PPD test. In the UK, the school programme did test for PPD before vaccination and vaccinated only those who tested negative. The validation study will explore how well unvaccinated children recall the reason for lack of adolescent vaccination (prior positive PPD (assumed to be about 20% of notified cases and 10 % of notified controls[32]), refusal, not being present at the time of vaccination). Accuracy of recall by unvaccinated subjects will be explored in the validation study. Assuming that it is sufficiently accurate, all subjects not vaccinated because of prior positive PPD (cases or controls) will be excluded from the study. If accuracy is not very high modelling of risk of TB due to latent infection over time[33] will inform appropriate statistical adjustments and sensitivity analyses of estimates of the protection from BCG vaccines.

3.5.9 9 Restricting by ethnicity and procedures for control recruitment.

Restriction is used to make cases and control similar with respect to potential confounders. In this study, the population is the White ethnic group, whose risk of TB is lower than the general UK-born population. Also, until 2005, it was routine policy to offer and administer BCG to school-children in this population group.

Procedures for recruitment of controls: We will recruit neighbourhood/community-based controls frequency matched to cases on year of birth and sex only. They will be selected using a three- stage probabilistic sampling scheme to provide a sample representative of the eligible population in England as well as maximum geographic representativeness of the study area, while optimising logistical efficiency (to contact eligible controls). The primary sampling unit (PSU) will be the mid layer super-output area (MSOA) and the secondary sampling unit will be the lower layer super-output area (LSOA). LSOAs are statistical levels of geography in England made of adjacent postcodes and designed to have similar population size and to be as socially homogenous as possible; each LSOA has an average population of 1500; MSOAs consist of the grouping of 4 to 5 LSOAs. We aim to recruit on average one control per LSOA, and 3 LSOAs per MSOA. We have estimated that approximately 7-8 dwellings need to be screened in each PSU to successfully find one control. In the first stageMSOAs are selected without replacement with probability proportional to the resident population aged 25 to 49 years old (from ONS population estimates 2010); then three LSOAs are sampled within each selected MSOA with probability proportional to size of resident population. Finally, 7 postcode units are randomly selected within each LSOA using simple random sampling, and one residential address is sampled in each postcode unit by simple random sampling. Only one individual is recruited per address.

3.5.10 Proposed Sample size

Based on a frequency-matched study with two controls per case, we estimated we need 145 cases and 258 controls for 90% power at the 5% level of significance to detect at least an efficacy of 60% in the earlier interval since adolescent vaccination, and 260 cases and 463 controls to detect 50% protection in the later intervals respectively, with an estimated uptake of school aged BCG vaccination of 80%. Exclusion due to PPD positivity in the adolescent vaccination programme is assumed to be 20% in cases and 10% in controls, and the samples are inflated by 15% to account for adjustment on the frequency- matching variables.

Table 5: Sample size required for each age group in case control study of BCG vaccination in adolescence.

	Power 90%, precision 95%, 2 controls per case					
Years since adolescent BCG	Age at tuberculosis (years)	Assumed Coverage	Vaccine efficacy	Number of cases	Number of cases assuming 20% not vaccinated as PPD+ve	Number of controls assuming 10% not vaccinated as PPD +ve
10 to 14	23 to 27	80%	60%	116	145	258
15 to 19	28 to 32	80%	50%	208	260	463
20 to 24	33 to 37	80%	50%	208	260	463
	Total subjects 665 cases and 1183 controls				665	1183

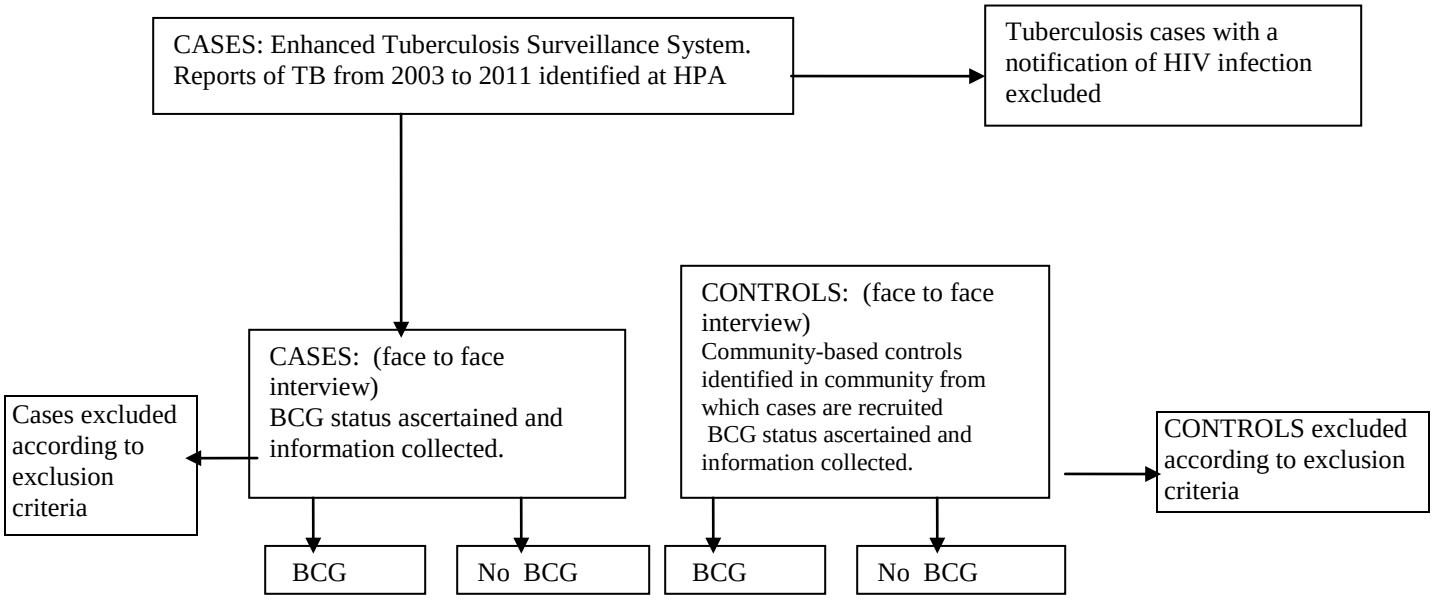
3.5.11 Statistical Analysis

Cases and controls will be classified as having received BCG in the school programme or not, following the same process as in case control 1. A logistic regression model will estimate the odds ratio of tuberculosis associated with adolescent BCG vaccination for each age group, which will be translated into the efficacy of BCG 10 to 14, 15 to 19 and 20 to 25 years since vaccination, while controlling for frequency-matched variables (year of birth and sex) and other potential confounders. Information on age at vaccination will be collected during the study and used to derive time since vaccination. Interval specific VE will be estimated by fitting an interaction between BCG vaccination status and time since vaccination as a categorical variable in the model using the pre-specified intervals. These estimates will be plotted against time since vaccination for graphical inspection for change of efficacy in time. More formally, we will investigate (exponential change) evidence of decline in VE with time since vaccination (ie linear change on the log scale) by fitting an interaction between BCG vaccination status and time since vaccination as a continuous variable in the model; departure from log-linearity will also be investigated. If necessary, other statistical methods will be explored to describe the change in VE with time since vaccination, including weighted moving average and a locally weighted polynomial regression ("LOESS"). These results will be added to the results from the case control study in high risk groups and presented as below (table 6):

Table 6: Dummy table of the estimated protective effect of BCG vaccine in years since vaccination

Population	Age at tuberculosis	Year of birth	Years since Infant BCG vaccination	Protection (95%CI)	Years since Adolescent BCG vaccination	Protection (95%CI)
High risk	0 to 5	1998 to 2011	0-5		na	-
High risk	6 to 12	1991 to 2005	6 to 12		na	-
High risk	13 to 17	1986 to 1998	13 to 17		na	-
General	23 to 27	1976 to 1988	Na	-	10 to 14	
General	28 to 32	1971 to 1983	Na	-	15 to 19	
General	33 to 38	1968 to 1978	Na	-	20 to 24	

D. FLOW DIAGRAM


CASES: Enhanced Tuberculosis Surveillance System. Reports of TB from 2003 to 2011 identified at HPA
Tuberculosis cases with a notification of HIV infection excluded
CONTROLS: (face to face interview)
Community-based controls identified in community from which cases are recruited
BCG status ascertained and information collected.
CONTROLS excluded according to exclusion criteria
CASES: (face to face interview)
BCG status ascertained and information collected.
Cases excluded according to exclusion criteria
BCG
No BCG
BCG
No BCG

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