Title:

Duration and change in BCG effectiveness against tuberculosis with time since vaccination: evidence from a Norwegian population-based cohort study.

Authors:

Nguipdop-Djomo Patrick*, MD, *Department of Infectious Disease Epidemiology - Faculty of Epidemiology and Population Health, & TB Centre, London School of Hygiene and Tropical Medicine, London, United Kingdom*

Heldal Einar, PhD, *Norwegian Institute of Public Health, Oslo, Norway*

Rodrigues Laura Cunha, PhD, Professor, *Department of Infectious Disease Epidemiology - Faculty of Epidemiology and Population Health, & TB Centre, London School of Hygiene and Tropical Medicine, London, United Kingdom*

Abubakar Ibrahim, PhD, Professor, *Institute of Epidemiology and Health & Centre for Infectious Disease Epidemiology, Faculty of Population Health Sciences, University College London, London, United Kingdom*

Mangtani Punam, MD, *Department of Infectious Disease Epidemiology - Faculty of Epidemiology and Population Health, & TB Centre, London School of Hygiene and Tropical Medicine, London, United Kingdom*

**Corresponding Author: Contact: patrick.nguipdop-djomo@lshtm.ac.uk*
Room G12, LSHTM, Keppel Street, London WC1E 7HT, United Kingdom
Tel. +44 20 7927 2475

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Abstract

Background: Little is known about how long the Bacillus Calmette-Guerin (BCG) vaccine protects against tuberculosis (TB). We assessed its long-term vaccine effectiveness (VE).

Methods: Historical cohort study based on tuberculin skin test (TST) and BCG information from participants to Norway mandatory mass TB screening and BCG vaccination programme, linked to the National TB Register, Population and Housing Censuses and the Population Register for emigrations and deaths. TST negative subjects aged 12-50 years and eligible for BCG vaccination were followed-up to the first TB episode or December 2011. The main outcomes were all and pulmonary tuberculosis. Cox regressions were used to estimate VE by time since vaccination, adjusted for age, calendar time, county-level TB rates, demographic and socio-economic indicators.

Findings: Follow-up was on average over 40 years, for 83,421 unvaccinated and 297,905 BCG vaccinated subjects, with 260 TB episodes. Tuberculosis rates were 3·3 per 100,000 person-years in unvaccinated and 1·3 per 100,000 person-years in vaccinated subjects. The adjusted average VE over 40-year follow-up was 49%(95%CI: 26%,65%); although the evidence was less strong after 20 years [up to 9 years, VE =61%(95%CI: 24%,80%), 10-19 years, 58%(27%,76%), 20-29 years, 38%(-32%,71%), and 30-40 years, 42%(-24,73%)]. VE against pulmonary TB for the same time intervals were respectively 67%(27%,85%), 63%(32%,80%), 50%(-19%,79%) and 40%(-46%,76%).

Interpretation: Findings are consistent with long-lasting BCG protection but waning of VE with time.

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Introduction

Bacillus Calmette-Guerin (BCG), the sole Tuberculosis (TB) vaccine licensed for use in human populations, is an important part of TB control efforts.[1] It provides on average 86% protection against miliary and meningeal TB in children.[2-4] BCG also protects against pulmonary tuberculosis (PTB), although its effect varies geographically and appears higher further from the equator, [5-7] ranging for instance from no evidence of protection in the Indian TB prevention Trial up to 78% efficacy in the British MRC trial.[7] Reasons for such variability, discussed elsewhere,[7,8] note good efficacy if vaccination is done prior to infection with *Mycobacterium tuberculosis* (Mtb) or sensitization by environmental mycobacteria.[7,9] BCG may also protect against TB infection,[10,11] suggesting a greater contribution to TB control than previously assumed, though our understanding of the immunological basis of BCG-derived protection remains limited.[12]

BCG is one of the commonest vaccines, but the duration of effect against TB is unclear, even though this information may influence vaccination policies. The substantial decline in TB incidence in the 1980-90s led several countries to move from universal vaccination of infants (most Western European countries) or schoolchildren (e.g. United Kingdom, Norway) to targeted vaccination of infants at higher risk of TB;[13] it is unclear if BCG protection will last until young adulthood when the risk of pulmonary TB and transmission to others is higher. A better understanding of long-term changes in BCG protection may also be useful not only to develop and test new TB vaccines, but also to adapt vaccination schedules. BCG-booster vaccine candidates are designed on the premises of enhancing weak or waned pre-existing BCG-derived protection.[14] Other TB vaccine candidates (recombinant BCG or other attenuated) are empirically inspired or derived from BCG,[14] and the performance of BCG may inform their potential effect.

A recent systematic review[15] suggests BCG protection may last up to 15 years. There is little information beyond that, because studies have either relatively short follow-up, or have few events if follow-up is long. The follow-up of participants to the Native American and Alaska Natives BCG trial found significant BCG protection up to 40 years after vaccination;[16] although these findings have not yet been confirmed elsewhere. We took the opportunity of an historical population cohort from Norway on which well-preserved information on tuberculin skin testing (TST) and BCG status was available, with reliable linkage to good TB surveillance from 1962 to 2011, to assess BCG effectiveness over 40 years in the general population and a different setting.

Methods

Study design and population

This was a historical population-based cohort study targeting TST negative subjects aged 12 to 40-50 years, to whom intradermal BCG vaccination was offered as part of the mandatory nationwide Norwegian tuberculosis mass-screening programme between the late 1940s and 1975.[17-19] Participants were screened for tuberculosis in mobile units – including chest radiography (CXR) and tuberculin skin testing (TST) using the adrenalin von Pirquet (aP) method,[18] which was standard in Norway until 2004. Screening campaigns were repeated every 2 to 10 years depending on local TB incidence. Overall attendance was 80-85%, the rest did not attend because they had been screened in other program (~5% e.g. as a miliary recruit), ill or temporary absent (5-10%) or reason unknown (~5%).[17] TST negative school leavers (13-14 years) were also offered vaccination through the annual school screening program.

Only Norwegian-born subjects aged 12 and over were included in the study, limited to those screened during the last round from 1962 to 1975 when data were computerized and all TB cases were compulsorily notified to a central TB Register (established 1962). We excluded subjects who had TB before or in the year of screening, and those with unknown TST and BCG status. Those aged under 12 years were not included because they were not offered BCG routinely, unless they had been in contact with a TB case. There was no specific exclusion of immunocompromised subjects; immunosuppression was not a specific contraindication for BCG vaccination as factors such as HIV infection and most immunosuppressant drugs were not yet present or widely used.

Also, there is also no clear reason why occurrence of these factors (if any) during the years of follow-up should influence TB rates in vaccinated and unvaccinated persons differently.

Tuberculin testing and BCG vaccination

Tuberculin skin testing by the aP method was done using Danish Old Tuberculin (OT), at a concentration corresponding to about 70% of the international standard from 1947 to 1953, and subsequently doubled from 1954 to improve sensitivity.[19] A positive reaction was defined by induration ≥4mm. BCG was manufactured at the Bergen State BCG Laboratory using the Swedish-Gothenburg strain.[20] Liquid BCG was used until 1959, progressively replaced by freeze-dried BCG between 1959 and 1973,[21] with standardization between the two formulations done by routinely comparing post-vaccination TST induration size in schoolchildren.[22] From 1973 BCG was provided from Statens Serum Institute, Copenhagen.

Follow-up and data sources

Participants accrued person-years from entry (TST negative at screening 1962-75) until the first episode of tuberculosis, emigration, death or end of follow-up (December 2011). Tuberculosis was ascertained through linkage to the National Tuberculosis Register, and censoring by death or emigration was checked in the population register. Prophylactic treatment for Latent TB infection (LTBI) was seldom used in Norway before 2002 and was therefore not a concern. Data sources were linked directly using the Birth Number (BN), a unique 11-digit personal identifier allocated to all Norway residents at birth or immigration, and used across administrative databases.

The screening database contained information on fact, date and results of CXR and TST, and BCG vaccination. BCG status was ascertained from health cards (~87%) subjects, scar examination (~7%) and self-reported vaccination history (~6%).

The National Tuberculosis Register provided the TB notifications since 1962,[23,24] and county-level TB-rates. Its completeness was estimated at 95% in 2008, based on crosschecking carried out since 1975 with Rifampicin prescriptions and laboratory results.[23,25]

Census data (1960 and 1970) provided information on potential confounders, including birth date , gender and marital status, and proxy-measures for socio-economic position (head-of-household education level and occupation, number of residents in household, urban/rural category of place of residence) at enrolment.

Quantitative variables were transformed into categories: five-year average annual TB rates at county-level in 1961-65[26] (proxy for local epidemiology) was classified in three levels (respectively <20, 20-25 and 26+ per 100,000); head-of-household's education level was grouped in lower secondary or less (up to 10th grade), higher secondary (11th to 13th grade), and post-secondary, vocational or tertiary; head of household's occupation was grouped by sectors shown to be related to TB infection risk in Norway,[27] respectively manufacturing, construction, mining and blasting, technical, scientific, humanities and arts, administration/management, sales and services, agriculture, forestry and fishing, trade transportation and communication, miliary and other; household size was grouped in four categories (0-2, 3-4, 5-6, and 7+ residents).

Ethical clearance was obtained from the Norwegian Research Ethics Committee.

Statistical methods

Hazard ratios (HRs) and 95% confidence intervals (95%CI) comparing respectively the overall and time specific (5- and 10-year intervals) TB rate in BCG vaccinated to unvaccinated subjects were computed by fitting Cox regression models to the data. Age-specific TB risk was adjusted for as a time-updated variable; demographic and socio-economic factors, and calendar time (in 10-year bands from 1960, to account for secular changes over the long follow-up) were also taken into account. Less than 3% subjects had missing data on any covariate; they were excluded from analyses. Starting with a model only including BCG status fitted on the age timescale, we added calendar time then potential confounders in turn based on descending order of magnitude of confounding at bi-variable analysis. We also checked their effects on overall vaccine effectiveness (VE) as well as any collinearity with vaccination status. Time-specific HRs were obtained by fitting an interaction between split follow-up time and BCG status. We also assessed statistical evidence of log-linear change in HR (thus VE) between time intervals and departure from linearity. P-values were obtained using Wald and Likelihood-ratio tests as appropriate. The proportional hazard assumption was assessed graphically using Nelson-Aalen cumulative hazard plots. BCG vaccine effectiveness (VE) and 95%CI were obtained using the formula [VE(%) = (1 – $HR_{v/u}$)x100]. We repeated analyses for pulmonary tuberculosis (PTB). Statistical analyses were done using Stata® 13. In this paper 'crude' HR/VE refer to estimates only adjusted for current age.

Missing date of vaccination and sensitivity analysis:

We performed two sensitivity analyses: (1) to TST stringency (by excluding subjects who developed TB in first two years after screening, likely already infected but not yet reactive to TST), and (2) to missing information on year of vaccination (missing in 18% BCG vaccinated across the database, of whom a proportion would have been vaccinated after 1962 and eligible for the study). Two approaches were used for the latter: firstly assuming all were vaccinated as soon as they reached age of eligibility and secondly, using predictive mean matching (PMM) multiple imputation by chained equations[28] (appropriate for truncated quantitative data, in our case the year of vaccination limited to 1948 to 1975 during the mass screening). Ten imputed datasets were generated using a PMM imputation model including all baseline covariates and the age-adjusted cumulative TB hazard. The analyses above were repeated on each imputed dataset restricted to eligible subjects (i.e. enrolled in 1962-75), and the imputed HRs were obtained by combining estimates across datasets using Rubin's rules[29].

Role of the funding source:

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, writing of the report, or approval of the manuscript of the study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Study sample and Baseline characteristics

About 77% of 1,739,996 subjects registered in the database were aged 12 to 50 years, of which 23% (306,318/1,334,686) were TST positive unvaccinated; 91·7% of TST negative were vaccinated, but the date of vaccination was missing in 18·4% (173,384/940,584). The study sample, restricted to those enrolled in 1962-75, included 83,421 TST negative unvaccinated and 297,905 BCG vaccinated subjects (figure 1).

The distribution of baseline characteristics is presented in table 1. BCG vaccinated were more likely to be male and be younger at enrolment than unvaccinated. The head-of-household's education level was also higher among vaccinated (48% higher secondary or above, vs 36% in unvaccinated), although the distribution of occupational groups were similar between groups. Finally a higher proportion of BCG vaccinated (49%) lived in households with 5 or more residents than unvaccinated (27%). The distribution of other baseline characteristics was otherwise broadly similar between groups.

Median follow-ups (in years) were respectively 44 (IQR=41-46) for vaccinated and 41 (IQR=32-49) for unvaccinated subjects. Censoring by emigration was negligible (<1%), and age-adjusted overall survival was comparable between groups (supplement eFigure 1).

Age-adjusted TB rates were comparable across categories for most baseline characteristics (supplement eTable 1), except gender where maleTB rates were more than twice that of females (HR=2·46; 95%CI=1·67,3·62). There was no interaction between baseline variables and BCG VE, except weak evidence for education level (relatively lower VE in lower education level) and county-level TB rates (relatively lower VE in counties with incidence >25/100,000). Stratified analyses were consistent with only weak confounding by individual baseline variables (supplement eTable 2).

BCG effectiveness against all tuberculosis

Overall 260 first episodes of TB were reported, of which 103 cases/3,131,917 person-years (pyrs) in unvaccinated (rate=3·3 per 100,000 pyrs), and 157 cases/12,425,272 pyrs in BCG vaccinated (crude rate 1·3 per 100,000 pyrs), corresponding to an age-adjusted HR=0·36 (0·27,0·48), and VE of 64% (52%,73%) . After adjusting for calendar time and baseline covariates, HR was 0·51 (0·35,0·74), thus an average adjusted VE of 49% (26%,65%) over 40 years (table 2). The baseline covariates had little confounding effect (supplement eTable 2), with most confounding due to calendar time.

Adjusted BCG VE was 51% (7%,74%) in the first 10 years post-vaccination (61% (24%,80%) when excluding the first 2-year TB episodes), and remained 58% (27%,76%) 10-19 years post-vaccination, subsequently dropping to 38% (-32%,71%) then 42% (-24,73%) respectively at 20-29 and 30-40 years. There was weak evidence that change in HRs between time intervals was not log-linear (p=0·015). Detailed results are presented in table 2. A further breakdown of VE in 5-year bands for the first 20 years after vaccination is provided in supplement eTable 3. Estimates remained similar, except in the first 10 years, when VE is lower at 21% (42% when excluding the first 2-year TB episodes) in the first 5 years post-vaccination, than 5-10 years (61%).

The Nelson-Aalen cumulative hazard plots did not show severe deviation from the proportionality assumption (Supplement eFigure 2).

BCG effectiveness against pulmonary tuberculosis

The adjusted VE against PTB over 40 years was 55% (32%,70%). Effectiveness against PTB by time since vaccination were respectively 0-9 years, 57% (8%,80%) (67% (27%,85%) when excluding the first 2-year TB episodes), and 10-19 years, 63% (32%,80%). VE was 50% (-19%,79%) and 40% (-46%,76%) respectively 20-29 and 30-40 years post-vaccination (figure 3; details in Supplement eTable 4). There was some statistical evidence that change in HRs between time interval was not log-linear (p=0·012).

Missing date of BCG vaccination

Time specific VE estimated either assuming those with missing BCG date were vaccinated as soon as they reached the eligible age, or using PMM imputation were consistent with the complete data analysis beyond the first 10 years after vaccination. Sensitivity estimates for the first 10 years were lower and less precise than the complete data (Supplement eTables 5, 6 and 7).

Discussion

Our study shows that BCG on average was associated with halving the risk of TB over a 40-year period after vaccination. When examined by decades, we found that BCG was associated with about 60% reduction in the risk of TB during the first two decades after vaccination. The VE was roughly 40% between 20 and 40 years post-vaccination, albeit the evidence was less strong. The vaccine's association with reduced risk of TB also appeared stronger against pulmonary tuberculosis, the infectious form of the disease. These results are only the second, to our knowledge, to present evidence in support of BCG protection against tuberculosis over a period of 40 years or longer, and the first in a European population.

The advantages of our study included the large sample size, good documentation of the TST and BCG vaccination status, and linkage to 50 years of good routine tuberculosis surveillance and various administrative databases. The study also had limitations: relatively few cases in each time period, due to low TB rates in Norway since the 1960s[30,31] (due to an effective nationwide TB control program in the 1940-70s and improvement in living conditions);[27] the lower stringency of TST compared to trials (people were tested only once at each screening round, and the aP test may have been less sensitive than the Mantoux test,[32] whereas some trials used higher tuberculin doses and 2-stage testing[5,7]); this would cause non-differential inclusion of some TST positives and, thus underestimating vaccine efficacy. The lower VE estimate in the first 5 years is consistent with this hypothesis. The higher VE obtained when excluding TB cases in the first 2-year suggests TST sensitization was more often due to infection with Mtb than environmental mycobacteria.

There is potential for selection bias and confounding. Those who declined vaccination may have had a higher TB risk than the general population, leading to an overestimate of the VE. The information available did not support this; age-adjusted all-cause mortality and loss of follow-up through emigration were comparable to vaccinated, as were most baseline socio-demographic characteristics. The unvaccinated group was however on average older than vaccinated so likely to have been exposed to higher risk of TB earlier in their life; however, these were also subjects who remained TST negative at several successive screening rounds, and therefore more likely to be selected for lower risk of TB. We therefore consider the study underestimates BCG effectiveness. Nonetheless, we acknowledge that in our study, as in most observational studies, there is a potential for residual confounding, including from unmeasured confounders.

Our estimates of BCG effectiveness in the first 5 years were lower than previously estimated in similar populations. BCG effectiveness was about 90% using data from Norway routine school vaccination programme[21] although they used a case-population approach known to slightly overestimate VE. Trials in the UK, USA and Canada yielded VEs of 70-80%.[5,15,33] The difference may partly be attributed to lower stringency of TST and selection through repeated screening of unvaccinated subjects at lower risk of TB, both discussed earlier; similarly low VE was reported in an earlier trial without stringent tuberculin testing prior to randomization.[34] Another factor may be that revaccination may have been captured in the database as a first vaccination; revaccination was not uncommon in subjects TST negative in spite of previous vaccination.[18,19] Post-vaccination TST induration is not correlated to BCG efficacy[35] and the current evidence suggests that revaccination has none to at most modest boosting effect on BCG-derived immunity.[36,37] In such revaccinated subjects, the VE at start of follow-up may have already declined since their first vaccination, thus underestimating VE.

BCG effect beyond 5 years was consistent with literature reports from similar settings. VE 5-10 years post-vaccination was comparable to estimates in cohorts from Norway[21] and France,[38] and consistent with the Native American[16] and the British-MRC[5] BCG trials. The overlap between our estimates and these two trials continued 10-15 years post-vaccination, although the latter had higher point estimates and narrower confidence intervals, consistent stringent TST and complete case ascertainment. The other trials in the northern hemisphere above the tropic had too few TB episodes beyond 10 years to measure VE.[15] The Native American trial measured BCG efficacy 15-20 years post-vaccination at 52% (28%,68%),[16] the sole trial with enough data beyond 15 years. This is comparable to our present findings, as well as those of Gernez-Rieux et al. who reported VE=51% over the same interval in a French cohort.[38] Overall, the VE estimated in our study over the first 20 years post-vaccination appear consistent with the literature.

In a recent systematic review, only the Native American trial was found to have measured BCG effectiveness beyond 20 years after vaccination.[15] The 60-years follow-up measured average VE of 55% (31%,77%), similar to ours over 40 years, with estimates 20-30 and 30-40 years post-vaccination of about 62% (-5%,88%)[16]. By comparison (Supplement eFigure 3), our average VE over 40-years follow-up was 55% (32%,70%), with VE 20-30 and 30-40 years after vaccination respectively of 38% (-31%,71%) and 42% (-23%,73%). We had less power than the Native American trial beyond 20 years, because of the very high TB incidence in their trial population, but both studies found persistence of BCG protection against tuberculosis beyond 20 years after vaccination.

BCG VE appeared to wane beyond the first 20 years post-vaccination, although the low study power precluded statistical evidence. A similar trend was noted in the Native American trial, and is consistent with the recent review on duration of BCG protection.[15] Two hypotheses may explain decline in VE estimates with time, notably reduction in the unvaccinated subjects' susceptibility or waning in the vaccinated subjects' immunity. Cross-immunity from sensitization by environmental mycobacteria among unvaccinated subjects may progressively 'mask' persistent BCG effect, therefore giving the false impression of declining VE. The decline may also be caused by waning of BCG-derived immunological memory, one of the premises for development of BCG booster vaccines.[14] The two hypotheses are not mutually exclusive and both may have played some role in our observations.

Overall, our results are consistent with the hypothesis of a long-lived BCG-derived immunity, adding to the evidence that BCG vaccination of subjects not yet infected by Mtb, nor sensitized by environmental mycobacteria, may confer some protection against tuberculosis for over 20 years.[15] Besides the emerging evidence that BCG may also protect against Mtb infection,[10,11] a longer duration of protection would imply that the vaccine is more cost-effective than previously estimated. In the absence of any new and more effective TB vaccine, the first pillar of the World Health Organization's (WHO) new "End TB Strategy" recognizes the potential contribution of continued BCG vaccination of individuals at higher risk of TB to their vision of a "world free of tuberculosis",[39,40]; a contribution that is strengthened by BCG's longer protection. Furthermore, given how widely BCG has been used across the world and the possibility that it may interact with future TB vaccines, it would be important to account for such long-lived effect during the development of new TB-vaccines.

Contributors: IA conceived the study. PN-D prepared the research protocol with input from all authors. PN-D did all statistical analyses under the supervision of EH, LCR, and PM, and drafted the initial report. All authors interpreted results and contributed to the final report.

Conflict of interest statement: LCR, PM, and IA are coinvestigators in a separate study of a similar question in another setting (England) funded by a grant from the UK National Institute for Health Research during the conduct of this study. IA reports grants from the UK National Institute for Health Research and British Medical Research Council for other tuberculosis-related research during the conduct of this study. PN-D and EH declare no competing interests.

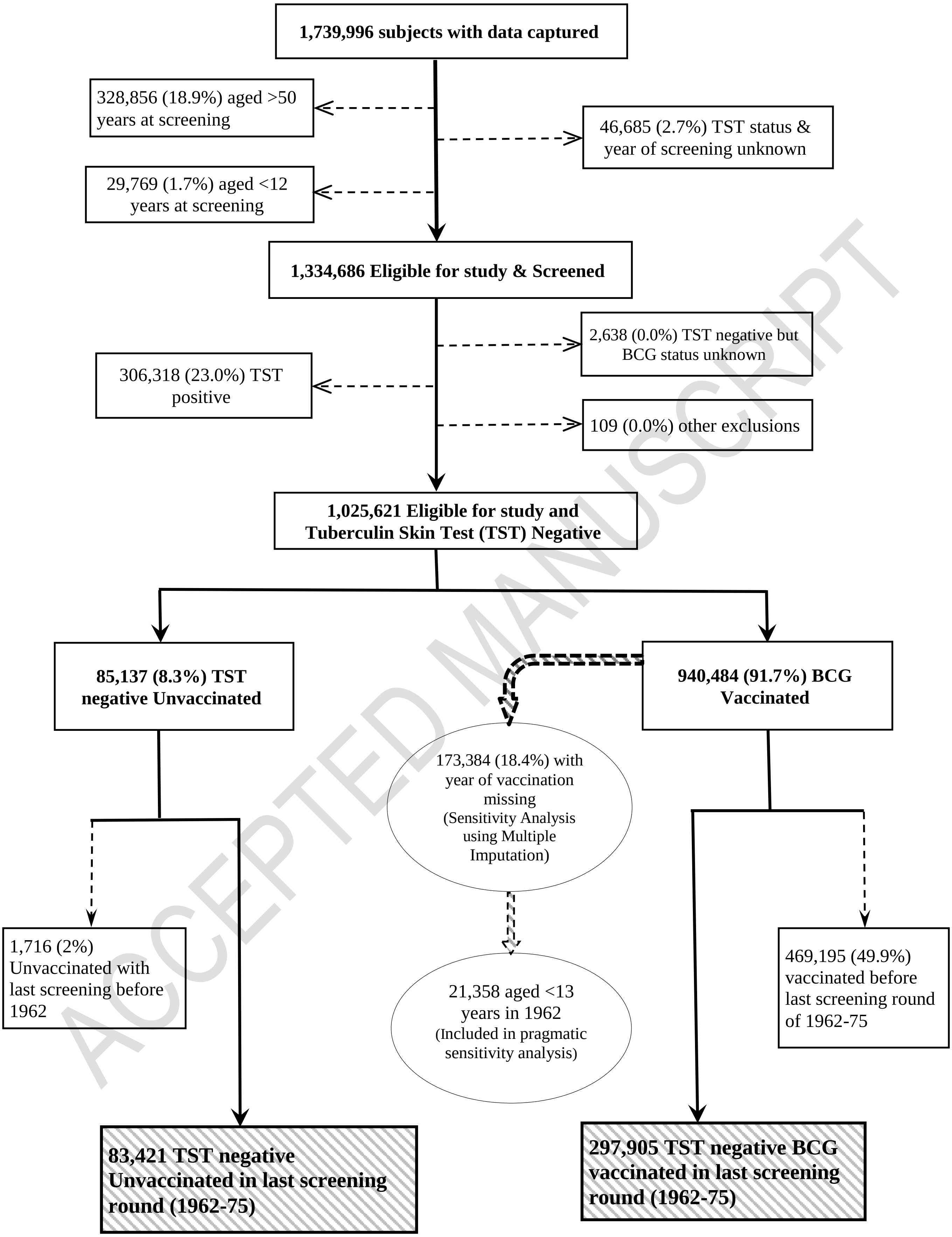

Figure 1: Flowchart from the population cohort to the study sample[1]

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[1] *Broken single lines depicts excluded subjects and solid arrows are those included in analyses. The thick lines are subjects included in sensitivity analyses*

Table 1: Baseline characteristics of study participants

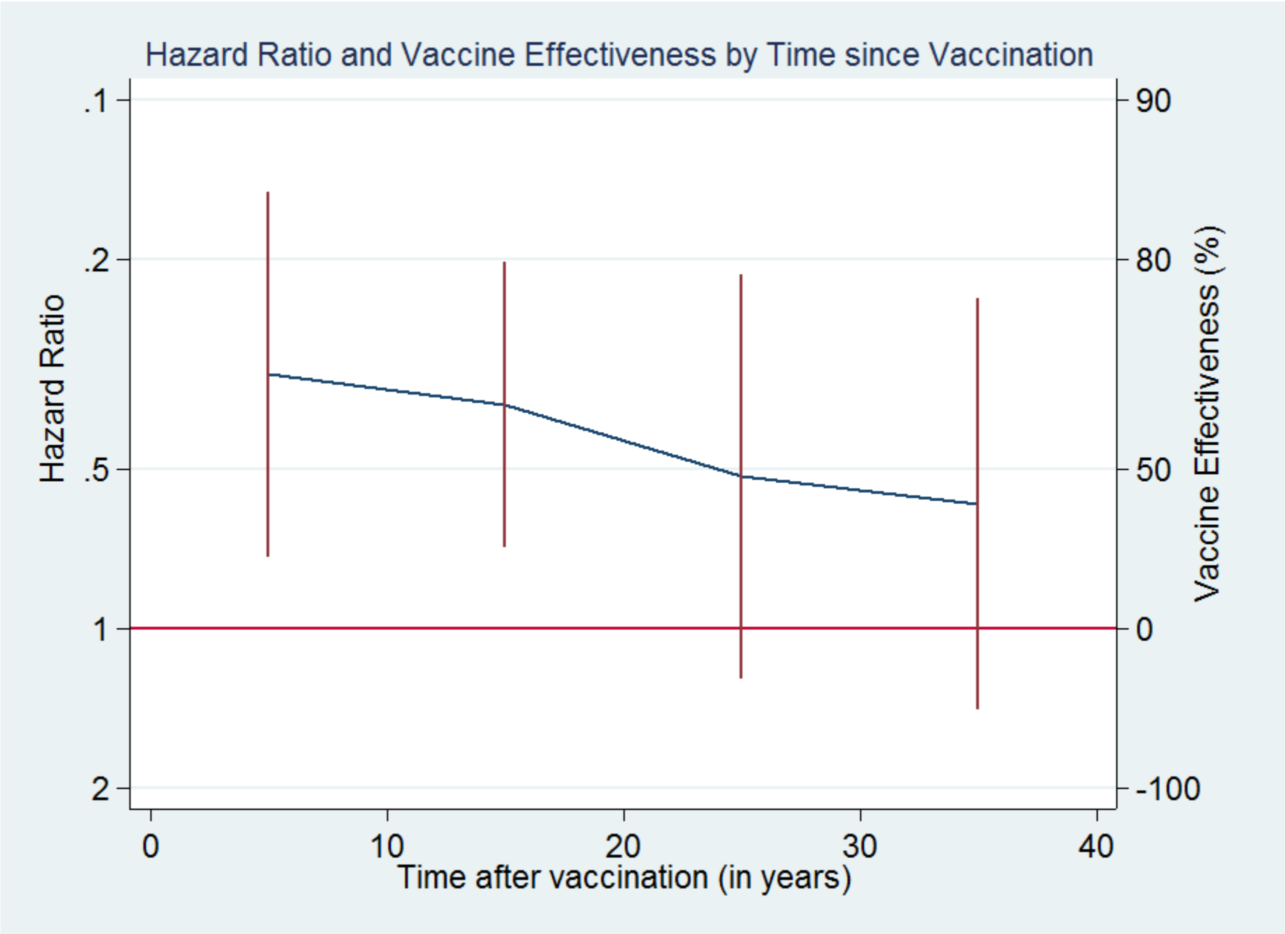
	BCG vaccine (N = 297905)	**No BCG vaccine (N = 83421)**
Sex		
Female (%)	163634 (55%)	54340 (65%)
Male (%)	134271 (45%)	29081 (35%)
Age at entry category		
12-15 years old (%)	145366 (49%)	3171 (4%)
16-20 years old (%)	67990 (23%)	6251 (7%)
21-30 years old (%)	29989 (10%)	5943 (7%)
31-40 years old (%)	27217 (9%)	21315 (26%)
41+ years old (%)	27343 (9%)	46741 (56%)
Birth cohort (year of birth)		
1910-1919	5026 (2%)	38771 (46%)
1920-1929	30566 (10%)	26813 (32%)
1930-1939	25371 (9%)	7272 (9%)
1940-1949	67809 (23%)	5930 (7%)
≥1950	169133 (57%)	4635 (6%)
Marital status		
Married	78321 (26%)	63932 (77%)
Single/Other	216162 (73%)	18455 (22%)
Missing	3422 (1%)	1034 (1%)
Education level of head of household		
Lower secondary or less	151968 (51%)	52554 (63%)
Higher secondary	120522 (40.6%)	27430 (33%)
Tertiary / Vocational / Post-secondary	24383 (8%)	2652 (3%)
Missing	1032 (0·4%)	785 (1%)
Type of Municipality at entry (Urban/Rural)		
Rural	125580 (42%)	36765 (44%)
Urban	171916 (58%)	46489 (56%)
Number of residents in household at entry		
0-2	21002 (7%)	19504 (23%)
3-4	132790 (45%)	41137 (49%)
5-6	109416 (37%)	18292 (22%)
≥7	34276 (11%)	4319 (5%)
Occupation category of head of household at entry		
Manufacture, construction, mining	119232 (40%)	34571 (41%)
Technical, scientific, humanities	24814 (8%)	4653 (6%)
Administration, sales, services	38234 (13%)	11475 (14%)
Agriculture, forestry, fishing	54497 (18%)	17025 (20%)
Trade, transport, communication	49356 (17%)	13178 (16%)
Miliary, Other	10136 (3%)	1438 (2%)
Missing	1636 (1%)	1081 (1%)
5-year average annual tuberculosis notification rate for 1961-65, per 100,000 person-years		
<20per100000	127961 (43%)	41976 (50%)
20-25per100000	78637 (26%)	17310 (21%)
≥26per100000	91300 (31%)	24135 (29%)
Follow-up*		
Median follow-up (IQR[£]) (years)	**44 (41-46)**	**41 (32-49)**
Total Follow-up (person-years)	**12425273**	**3131918**
First TB episodes and crude rate		
# All first TB episodes (rate per 100,000 pyrs)	157 (1.3)	103 (3.3)
# Pulmonary TB first episode (rate per 100,000 pyrs)	121 (1.0)	78 (2.5)

<u>Table 2</u>: BCG Vaccine Effectiveness against all TB

Time since vaccination	# TB cases/pyears	Rate (per 100,000pyears)	'Crude' HR* (95%CI)	Crude VE* (95%CI) (%)	p-value	Adjusted HR~ (95%CI)	Adjusted VE~ (%)(95%CI)	p-value
Overall								
Unvaccinated	103/3131917	3.3 (2.7;4.0)	-					
BCG vaccinated	157/12425272	1.3 (1.1;1.5)	0.36 (0.27;0.48)	64 (52 to 73)	<0.001	0.51 (0.35;0.74)	49 (26;65)	<0.001
0-9 years (including TB events in first 2 years after screening)								
Unvaccinated	29/812004	3.6 (2.5;5.1)						
BCG vaccinated	46/2920797	1.6 (1.2;2.1)	0.45 (0.25;0.80)	55 (20 to 75)	0.006	0.49 (0.26;0.93)	51 (7 to 74)	0.03
0-9 years (excluding TB events occurring in first 2 years after screening)								
Unvaccinated	27/812000	3.3 (2.3;4.8)						
BCG vaccinated	36/2920781	1.2 (0.9;1.7)	0.41 (0.23;0.76)	59 (24 to 77)	0.005	0.39 (0.20;0.76)	61 (24 to 80)	0.006
10-19 years								
Unvaccinated	44/784840	5.6 (4.2;7.5)						
BCG vaccinated	45/2874574	1.6 (1.2;2.1)	0.35 (0.21;0.58)	65 (42 to 79)	<0.001	0.42 (0.24;0.73)	58 (27 to 76)	0.002
20-29 years								
Unvaccinated	15/704774	2.1 (1.3;3.5)						
BCG vaccinated	29/2794374	1.0 (0.7;1.5)	0.72 (0.36;1.43)	28 (-43 to 64)	0.35	0.62 (0.29;1.32)	38 (-32 to 71)	0.22
30-~40 years								
Unvaccinated	15/830300	1.8 (1.1;3.0)						
BCG vaccinated	37/3835528	1.0 (0.7;1.3)	0.72 (0.35;1.46)	28 (-46 to 65)	0.36	0.58 (0.27;1.24)	42 (-24 to 73)	0.16

**'Crude' HRs are adjusted for current age (in years) (Cox model fitted on age timescale)*

~Fully adjusted for current age, calendar time, and baseline characteristics; Test for log-linear trend in HRs by timeband p=0.015



<u>Figure 2</u>: BCG Effectiveness against Pulmonary Tuberculosis by time since vaccination
(Vertical bars represent 95% confidence intervals; TB cases occuring in first 2 years after screening are excluded)

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