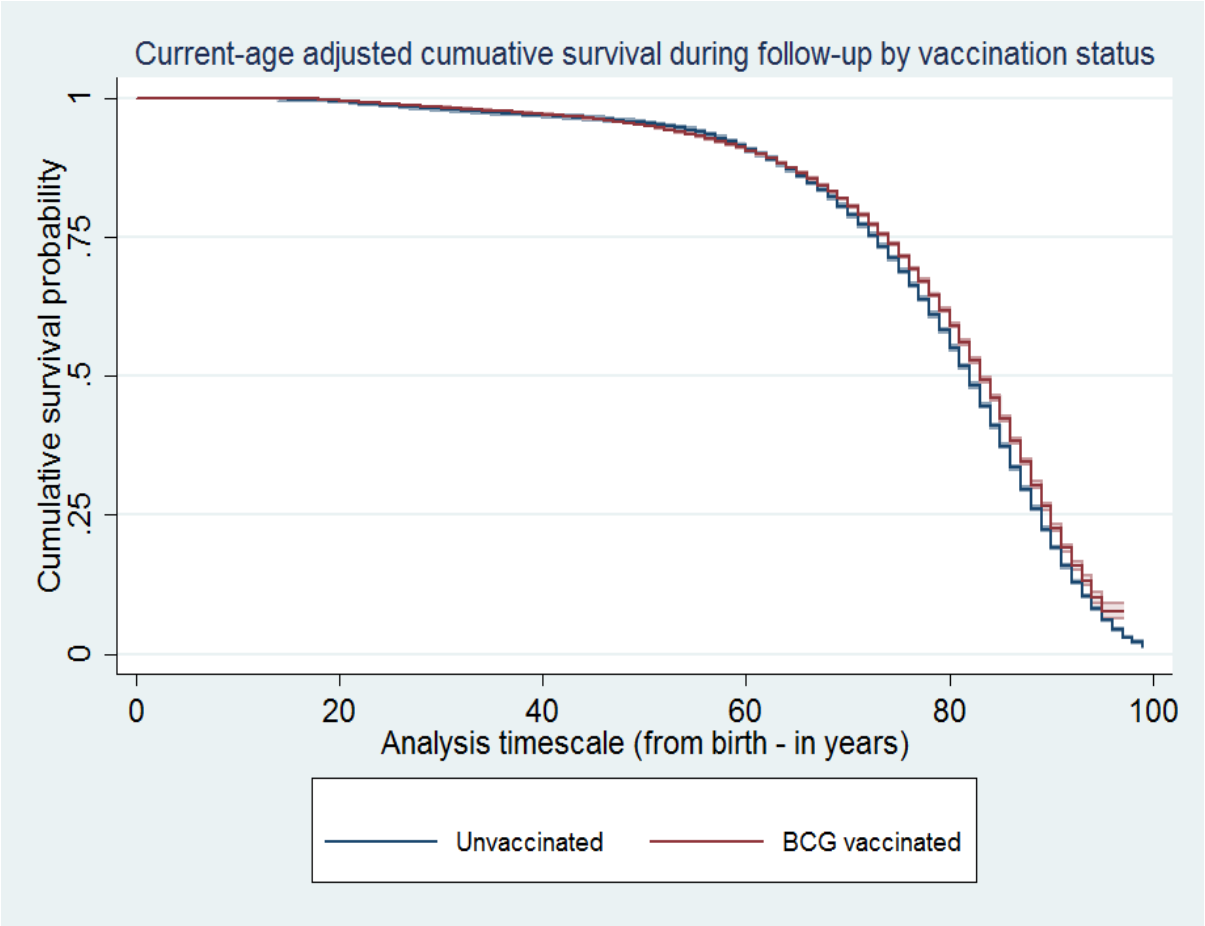
Manuscript:

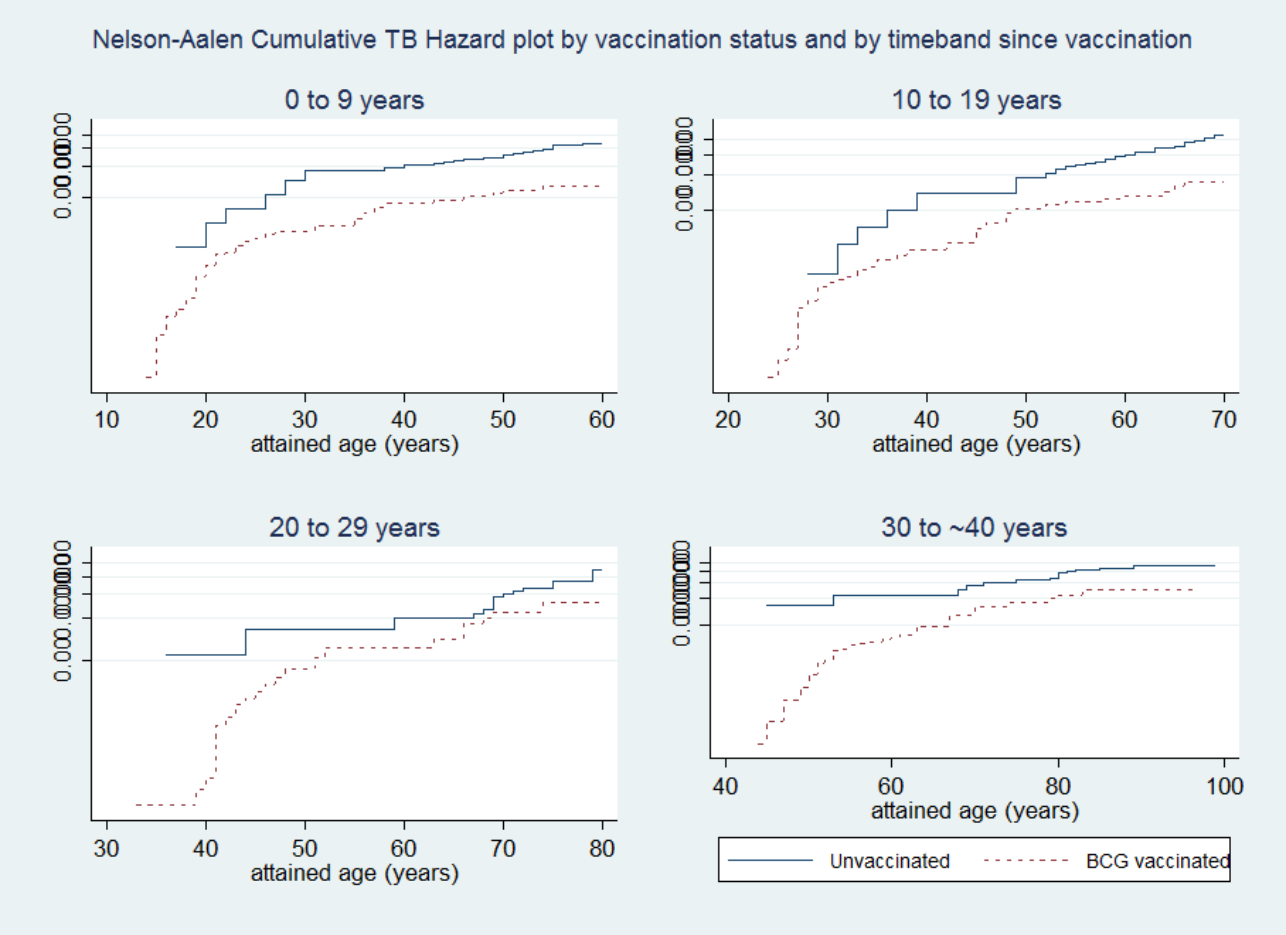
Duration and change in BCG effectiveness against tuberculosis with time since vaccination: evidence from a Norwegian population-based cohort study.

Online–Only Supplements



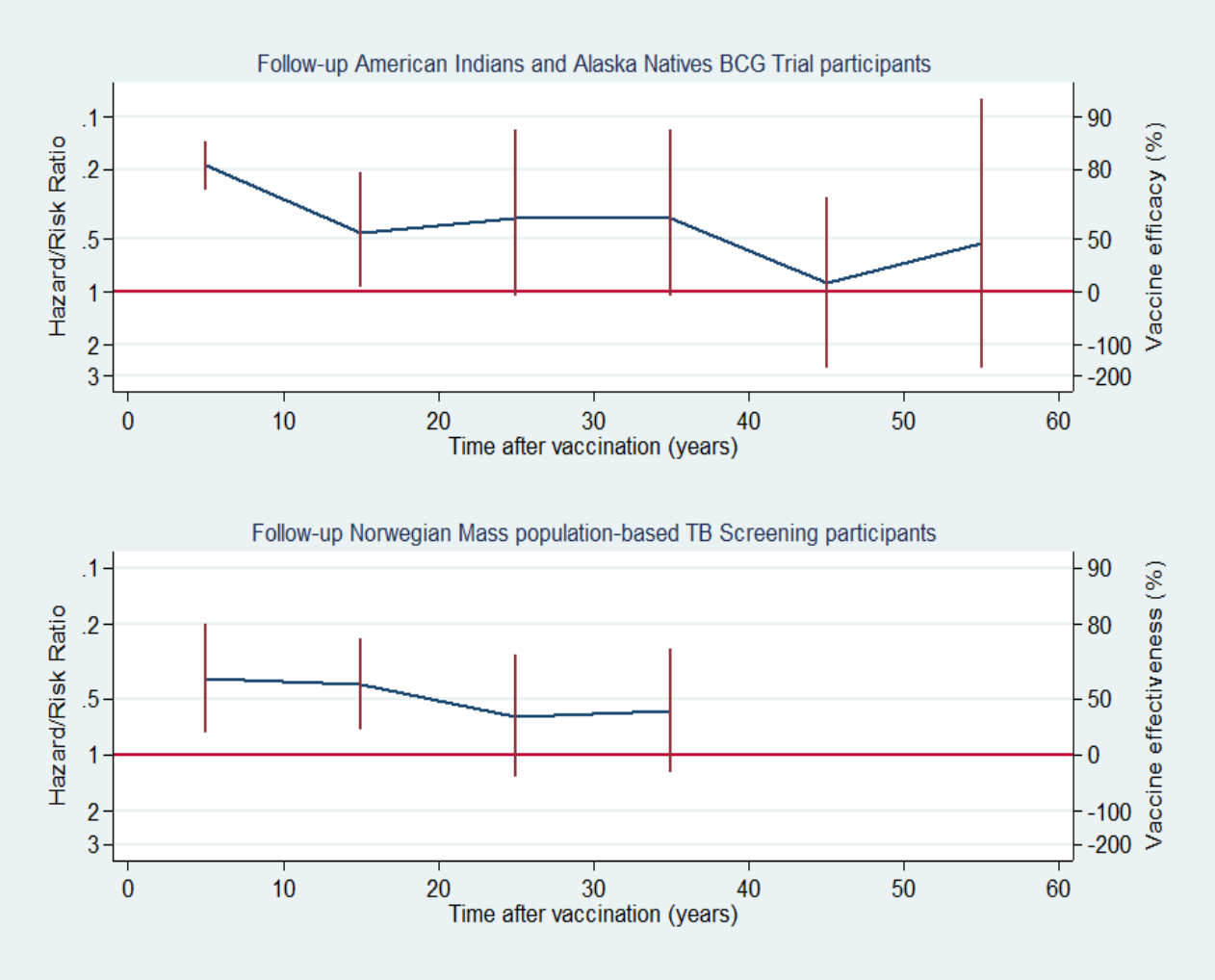
<u>eFigure1</u>: Age-adjusted cumulative survival probability during follow-up by vaccination status

The graph suggests that the age-adjusted survival is broadly similar between the BCG vaccinated and unvaccinated subjects, in spite of the age difference at start of follow-up. This supports the fact that analysis using a Cox model adjusted for age as a time updated variable (i.e. fitting the model on the age (in years) time scale) provided a reasonable control for confounding by age.



eFigure 2: Nelson-Aalen Cumulative Hazard plot by vaccination status

The solid blue and dashed red lines respectively represent cumulative TB hazards in unvaccinated and BCG vaccinated subjects for successive 10-year bands since vaccination, after adjustment for current age. The Nelson-Aalen plots of cumulative hazard by vaccination status for each time band suggest that overall, there is no gross violation of the proportionality assumption.



<u>eFigure 3</u>: BCG effectiveness against all tuberculosis - results from Norwegian cohort compared to 60-year follow-up of American Indians and Alaska Natives BCG Trial[1] *(Vertical bars represent 95% confidence intervals; TB cases occuring in first 2 years after screening are excluded)*

eTable 1: Age-adjusted association of baseline characteristics to risk of all type of tuberculosis among unvaccinated study participants

	TB rate per 100,000pyr (# / pyrs)	Hazard Ratio (95%CI)
Sex		
Female	2.2 (47/2126580)	-
Male	5.6 (56/1005338)	2.46 (1.67;3.62)
Marital status		
Married	3.1 (77/2451020)	-
Single/Other	3.8 (26/680898)	0.85 (0.54;1.36)
Education level of head of household[1]		
Lower secondary or less	3.3 (65/1953514)	-
Higher secondary	3.1 (33/1073866)	0.92 (0.61;1.40)
Tertiary / Vocational / Post-2ry	4.8 (5/104538)	1.41 (0.46;3.52)
Type of Municipality at entry (Urban/Rural)		
Rural	2.9 (39/1363433)	-
Urban	3.6 (64/1768485)	1.26 (0.84;1.87)
Number of residents in household at entry		
0-2	4.0 (27/674049)	-
3-4	2.9 (46/1565386)	0.73 (0.45;1.18)
5-6	3.3 (24/723736)	0.82 (0.47;1.43)
7+	3.6 (6/168747)	0.87 (0.36;2.13)
Occupation category of head of household at entry		
Manufacture, construction, mining	3.4 (45/1314856)	-
Technical, scientific, humanities	2.7 (5/185927)	0.79 (0.31;1.98)
Administration, sales, services	2.9 (13/444628)	0.86 (0.46;1.59)
Agriculture, forestry, fishing	3.2 (20/623615)	0.94 (0.56;1.60)
Trade, transport, communication	3.3 (17/510265)	0.97 (0.56;1.70)
Military, Other	5.7 (3/52627)	1.64 (0.51;5.28)
Annual TB rates 1965		
<20per100000	3.4 (53/1550626)	-
20-25per100000	3.5 (23/649109)	1.03 (0.63;1.68)
26+per100000	2.9 (27/932183)	0.83 (0.52;1.33)

All Hazard Ratios adjusted for current age

[1] In absence of detailed information on income for all members of the household and given the fact we used census data from 1960 and 1970, the head of household was defined for practical purpose as (husband if married (or own if husband is unemployed)), father if <21 or in school (or mother if father is unemployed or not available) or own otherwise). This is as close as we could to definitions in place in Norway in the 1960-70s (oldest person in household – Keilman – Household Statistics in Europe – consequences of different definitions http://www.ssb.no/a/histstat/aap/aap_befolkning_199203.pdf retrieved on 03Dec2013).

eTable 2: BCG Effectiveness per stratum and adjusted for age and potential baseline confounders

	BCG vaccine		No BCG vaccine		Stratum-specific age adjusted VE (%) (95%CI)[2]	p-value (test homogeneity)	Bivariable adjusted VE (%) (95%CI)
Characteristics	**# TB**	**Rate[3]**	**# TB**	**Rate[3]**			
Overall ('Crude')	157	1.3	103	3.3	64 (52 to 73)		64 (52 to 73)
Sex							
Female	73	1.1	47	2.2	59 (38 to 73)		
Male	84	1.5	56	5.6	70 (56 to 80)	0.25	65 (54 to 74)
Marital status							
Married	37	1.2	77	3.1	63 (44 to 75)		
Single/Other	120	1.3	26	3.8	62 (40 to 75)	0.91	62 (49 to 72)
Education level of head of household at entry							
Lower secondary or less	93	1.5	65	3.3	52 (32 to 66)		
Higher secondary	55	1.1	33	3.1	72 (54 to 94)	0.02	61 (49 to 71)
Tertiary / Vocational / Post-2ry	9	0.9	5	4.8	89 (65 to 99)		
Type of Municipality of Residence							
Rural	66	1.3	39	2.9	60 (38 to 74)		
Urban	91	1.3	64	3.6	51 (50 to 76)	0.63	63 (51 to 72)
Number of residents in household at entry							
0-2	12	1.5	27	4.0	56 (09 to 78)		
3-4	57	1.0	46	2.9	64 (46 to 76)	0.94	63 (50 to 72)
5-6	63	1.4	24	3.3	66 (41 to 81)		
7+	25	1.7	6	3.6	59 (-8 to 85)		
Occupation category of head of household at entry							
Manufacture, construction, mining	53	1.1	45	3.4	69 (51 to 80)		
Technical, scientific, humanities	8	0.8	5	2.7	80 (23 to 95)		
Administration, sales, services	14	0.9	13	2.9	69 (24 to 87)	0.74	64 (52 to 73)
Agriculture, forestry, fishing	38	1.7	20	3.2	58 (19 to 78)		
Trade, transport, communication	35	1.7	17	3.3	49 (3 to 73)		
Military, Other	9	2.1	3	5.7	54 (-56 to 87)		
County-level Annual TB rates 1965							
<20per100000	58	1.1	53	3.4	69 (53 to 80)		
20-25per100000	30	0.9	23	3.5	74 (53 to 86)	0.06	63 (51 to 72)
26+per100000	69	1.8	27	2.9	39 (0 to 64)		

[2] VE = Vaccine effectiveness; 95%CI = 95% Confidence Interval

[3] Rate of tuberculosis per 100,000 person-years

eTable 3: BCG vaccine effectiveness against all TB with 5-year bands break down for initial 20 years after vaccination

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
0-4 years								
Unvaccinated	9/406289	2.2 (1.2;4.3)						
BCG vaccinated	19/1463866	1.3 (0.8;2.0)	0.65 (0.26;1.60)	35 (-60 to 74)	0.35	0.79 (0.31;2.02)	21 (-102 to 69)	0.62
0-4 years (excluding TB events occurring in first 2 years)								
Unvaccinated	7/406285	1.7 (0.8;3.6)						
BCG vaccinated	9/1463850	0.6 (0.3;1.2)	0.52 (0.18;1.49)	48 (-49 to 82)	0.22	0.58 (0.19;1.76)	42 (-76 to 81)	0.34
5-9 years								
Unvaccinated	20/405715	4.9 (3.2;7.6)						
BCG vaccinated	27/1456931	1.9 (1.3;2.7)	0.33 (0.17;0.66)	67 (34 to 83)	0.002	0.39 (0.19;0.83)	61 (17 to 81)	0.01
10-14 years								
Unvaccinated	19/398866	4.8 (3.0;7.6)						
BCG vaccinated	24/1444728	1.7 (1.1;2.5)	0.36 (0.18;0.72)	64 (28 to 82)	0.004	0.43 (0.21;0.89)	57 (11 to 79)	0.02
15-19 years								
Unvaccinated	25/385974	6.5 (4.4;9.6)						
BCG vaccinated	21/1429846	1.5 (1.0;2.3)	0.33 (0.17;0.64)	67 (36 to 83)	0.001	0.43 (0.21;0.89)	57 (11 to 79)	0.02
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 (0.28;1.31)	38 (-31 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)	0.71 (0.35;1.46)	29 (-46 to 65)	0.35	0.58 (0.27;1.23)	42 (-23 to 73)	0.16

Crude means adjusted only for current age (in years) (Cox model fitted on age timescale)
Fully adjusted for current age, calendar time, and baseline characteristics

eTable 4: BCG Vaccine Effectiveness against Pulmonary TB

Time since vaccination	# PTB 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	78/3131442	2.5 (2.0;3.1)	-					
BCG vaccinated	121/12424654	1.0 (0.8;1.2)	0.36 (0.26;0.49)	64 (51 to 74)	<0.001	0.45 (0.30;0.68)	55 (32 to 70)	<0.001
0-9 years								
Unvaccinated	20/811781	2.5 (1.6;3.8)						
BCG vaccinated	32/2920511	1.1 (0.8;1.5)	0.43 (0.22;0.85)	57 (15 to 78)	0.02	0.43 (0.20;0.92)	57 (8 to 80)	0.03
0-9 years (excluding TB events occurring in first 2 years)								
Unvaccinated	19/811779	2.3 (1.5;3.7)						
BCG vaccinated	26/2920500	0.9 (0.6;1.3)	0.36 (0.18;0.74)	64 (26 to 82)	0.005	0.33 (0.15;0.73)	67 (27 to 85)	0.006
10-19 years								
Unvaccinated	38/784707	4.8 (3.5;6.7)						
BCG vaccinated	36/2874390	1.3 (0.9;1.7)	0.31 (0.18;0.54)	69 (46 to 82)	<0.001	0.37 (0.20;0.68)	63 (32 to 80)	0.002
20-29 years								
Unvaccinated	11/704697	1.6 (0.9;2.8)						
BCG vaccinated	22/2794270	0.8 (0.5;1.2)	0.67 (0.30;1.50)	33 (-50 to 70)	0.33	0.50 (0.21;1.19)	50 (-19 to 79)	0.12
30+ years								
Unvaccinated	9/830257	1.1 (0.6;2.1)						
BCG vaccinated	31/3835483	0.8 (0.6;1.1)	0.79 (0.34;1.87)	21 (-87 to 66)	0.60	0.60 (0.24;1.46)	40 (-46 to 76)	0.26

**'Crude' HRs are in fact 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=0.012

eTable 5: Distribution of baseline characteristics in BCG vaccinated subjects with date of BCG available and missing and aged 13 years or less in 1962

	BCG date recorded (N=297,905)	BCG date missing (N=24957)
Sex		
Female (%)	163634 (54.9%)	11535 (46.2%)
Male (%)	134271 (45.1%)	13422 (53.8%)
Marital status		
Married	78321 (26.7%)	2414 (9.7%)
Single/Other	216162 (73.3%)	22266 (89.2%)
Missing	3422 (1.1%)	277 (1.1%)
Education level of head of household		
Lower secondary or less	151968 (51.0%)	12459 (49.9%)
Higher secondary	120522 (40.4%)	10864 (43.5%)
Tertiary / Vocational / Post-secondary	24383 (8.2%)	1486 (6.0%)
Missing	1032 (0.4%)	148 (0.6%)
Type of Municipality at entry (Urban/Rural)		
Urban	171916 (57.7%)	15791 (63.3%)
Rural	125580 (42.2%)	9109 (36.5%)
Missing	409 (0.1)	57 (0.2%)
Number of residents in household at entry		
0-2	21002 (7.0%)	2073 (8.3%)
3-4	132790 (44.6%)	11165 (44.7%)
5-6	109416 (36.7%)	8785 (35.2%)
7+	34276 (11.6%)	2876 (11.5%)
Missing	421 (0.1%)	58 (0.2%)
Occupation category of head of household at entry		
Manufacture, construction, mining	119232 (40.0%)	9724 (39.0%)
Technical, scientific, humanities	24814 (8.3%)	1989 (8.0%)
Administration, sales, services	38234 (12.8%)	3889 (15.6%)
Agriculture, forestry, fishing	54497 (18.3%)	3449 (13.8%)
Trade, transport, communication	49356 (16.6%)	4417 (17.7%)
Military, Other	10136 (3.4%)	1300 (5.2%)
Missing	1636 (0.6%)	189 (0.8%)
Annual TB rates 1965		
<20per100000	127961 (43.0%)	10705 (42.9%)
20-25per100000	78637 (26.4%)	4152 (16.6%)
26+per100000	91300 (30.6%)	10097 (40.4%)

The date of vaccination was missing in 173,384/940,584 (18.4%) subjects, some of whom would have been vaccinated after 1962 hence eligible for the study. As mentioned in the methods section, individuals aged 13 years or more after 1962 were more likely to have been vaccinated as soon as they became eligible (i.e. when they turned 13-14 years). 24,957/173,384 (14%) people with missing BCG date were 13 years old or less in 1962, and therefore included in a sensitivity analysis making the pragmatic assumption that they received BCG when aged 13 years. The distribution of baseline characteristics in these subjects, including socio-demographic and other TB risk factors is presented in the supplementary table 4 above.

eTable 6: Sensitivity analysis of BCG effectiveness against all TB

Time since vaccination	Adjusted HR (95%CI)	p-value	VE (%) (95%CI)
Complete data analysis results			
0 to 9 years	0.49 (0.26;0.93)	0.03	51 (7 to 74)
0 to 9 years excl TB in first 2 years	0.39 (0.20;0.76)	0.006	61 (24 to 80)
10 to 19 years	0.42 (0.24;0.73)	0.002	58 (27 to 76)
20 to 29 years	0.62 (0.29;1.32)	0.22	38 (-32 to 71)
30 to ~40 years	0.58 (0.27;1.24)	0.16	42 (-24 to 73)
Pragmatic Assumption*: BCG vaccinated subjects with missing value for year of vaccination were vaccinated when they reached 13 years old if did so after 1962			
0 to 9 years	0.48 (0.25;0.91)	0.025	52 (9 to 75)
0 to 9 years excl TB in first 2 years	0.38 (0.19;0.75)	0.005	62 (25 to 81)
10 to 19 years	0.44 (0.25;0.76)	0.003	56 (24 to 75)
20 to 29 years	0.62 (0.29;1.33)	0.22	38 (-33 to 71)
30 to ~40 years	0.56 (0.26;1.20)	0.13	44 (-20 to 74)
Multiple Imputation using Predictive Mean Matching			
0 to 9 years	0.68 (0.37;1.25)	0.22	32 (-25 to 63)
0 to 9 years excl TB in first 2 years	0.50 (0.26;0.98)	0.04	50 (2 to 74)
10 to 19 years	0.42 (0.25;0.73)	0.002	58 (27 to 75)
20 to 29 years	0.59 (0.28;1.26)	0.17	41 (-26 to 72)
30 to ~40 years	0.55 (0.26;1.17)	0.12	45 (-17 to 74)

**Under the pragmatic assumption, 24957 BCG vaccinated subjects with year of vaccination missing are included in analysis, as detailed in eTable 5.*

eTable 7: Sensitivity Analysis of BCG effectiveness against Pulmonary Tuberculosis

Time since vaccination	Adjusted HR (95%CI)	p-value	VE (%) (95%CI)
Complete data analysis			
0 to 9 years	0.43 (0.20;0.92)	0.03	57 (8 to 80)
0 to 9 years excl TB in first 2 years	0.33 (0.15;0.73)	0.006	67 (27 to 85)
10 to 19 years	0.37 (0.20;0.68)	0.002	63 (32 to 80)
20 to 29 years	0.50 (0.21;1.19)	0.12	50 (-19 to 79)
30 to ~40 years	0.60 (0.24;1.46)	0.26	40 (-46 to 76)
Pragmatic Assumption*: BCG vaccinated subjects with missing value for year of vaccination were vaccinated when they reached 13 years old if did so after 1962			
0 to 9 years	0.42 (0.32;0.90)	0.026	58 (10 to 68)
0 to 9 years excl TB in first 2 years	0.32 (0.15;0.71)	0.005	68 (29 to 85)
10 to 19 years	0.38 (0.21;0.71)	0.002	62 (29 to 79)
20 to 29 years	0.51 (0.21;1.20)	0.12	49 (-20 to 79)
30 to ~40 years	0.57 (0.23;1.41)	0.22	43 (-41 to 77)
Multiple Imputation using Predictive Mean Matching			
0 to 9 years	0.62 (0.30;1.30)	0.20	38 (-30 to 70)
0 to 9 years excl TB in first 2 years	0.46 (0.21;0.99)	0.05	54 (1 to 79)
10 to 19 years	0.37 (0.20;0.66)	0.001	63 (34 to 80)
20 to 29 years	0.49 (0.21;1.15)	0.10	51 (-15 to 79)
30 to ~40 years	0.57 (0.23;1.40)	0.22	43 (-40 to 77)

**Under the pragmatic assumption, 24957 BCG vaccinated subjects with year of vaccination missing are included in analysis, as detailed in eTable 5.*

References

1. Aronson NE, Santosham M, Comstock GW, et al. Long-term efficacy of BCG vaccine in American Indians and Alaska Natives: A 60-year follow-up study. *JAMA : the journal of the American Medical Association.* 2004;291(17):2086-2091.