Infant BCG vaccination and risk of pulmonary and extrapulmonary tuberculosis throughout the life course: a systematic review and individual participant data meta-analysis

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Summary

Background BCG vaccines are given to more than 100 million children every year, but there is considerable debate regarding the effectiveness of BCG vaccination in preventing tuberculosis and death, particularly among older children and adults. We therefore aimed to investigate the age-specific impact of infant BCG vaccination on tuberculosis (pulmonary and extrapulmonary) development and mortality.

Methods In this systematic review and individual participant data meta-analysis, we searched MEDLINE, Web of Science, BIOSIS, and Embase without language restrictions for case-contact cohort studies of tuberculosis contacts published between Jan 1, 1998, and April 7, 2018. Search terms included "mycobacterium tuberculosis", "TB", "tuberculosis", and "contact". We excluded cohort studies that did not provide information on BCG vaccination or were done in countries that did not recommend BCG vaccination at birth. Individual-level participant data for a prespecified list of variables, including the characteristics of the exposed participant (contact), the index case, and the environment, were requested from authors of all eligible studies. Our primary outcome was a composite of prevalent (diagnosed at or within 90 days of baseline) and incident (diagnosed more than 90 days after baseline) tuberculosis in contacts exposed to tuberculosis. Secondary outcomes were pulmonary tuberculosis, extrapulmonary tuberculosis, and mortality. We derived adjusted odds ratios (aORs) using mixed-effects, binary, multivariable logistic regression analyses with study-level random effects, adjusting for the variable of interest, baseline age, sex, previous tuberculosis, and whether data were collected prospectively or retrospectively. We stratified our results by contact age and *Mycobacterium tuberculosis* infection status. This study is registered with PROSPERO, CRD42020180512.

Findings We identified 14 927 original records from our database searches. We included participant-level data from 26 cohort studies done in 17 countries in our meta-analysis. Among 68 552 participants, 1782 (2·6%) developed tuberculosis (1309 [2·6%] of 49 686 BCG-vaccinated participants *vs* 473 [2·5%] of 18 866 unvaccinated participants). The overall effectiveness of BCG vaccination against all tuberculosis was 18% (aOR 0·82, 95% CI 0·74–0·91). When stratified by age, BCG vaccination only significantly protected against all tuberculosis in children younger than 5 years (aOR 0·63, 95% CI 0·49–0·81). Among contacts with a positive tuberculin skin test or IFNγ release assay, BCG vaccination significantly protected against tuberculosis among all participants (aOR 0·81, 95% CI 0·69–0·96), participants younger than 5 years (0·68, 0·47–0·97), and participants aged 5–9 years (0·62, 0·38–0·99). There was no protective effect among those with negative tests, unless they were younger than 5 years (0·54, 0·32–0·90). 14 cohorts reported on whether tuberculosis was pulmonary or extrapulmonary (n=57 421). BCG vaccination significantly protected against pulmonary tuberculosis among all participants (916 [2·2%] in 41 119 vaccinated participants *vs* 334 [2·1%] in 16 161 unvaccinated participants; aOR 0·81, 0·70–0·94) but not against extrapulmonary tuberculosis (106 [0·3%] in 40 318 vaccinated participants *vs* 38 [0·2%] in 15 865 unvaccinated participants; 0·96, 0·65–1·41). In the four studies with mortality data, BCG vaccination was significantly protective against death (0·25, 0·13–0·49).

Interpretation Our results suggest that BCG vaccination at birth is effective at preventing tuberculosis in young children but is ineffective in adolescents and adults. Immunoprotection therefore needs to be boosted in older populations.

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Introduction

The BCG vaccine is around 100 years old and is one of the most widely used vaccines globally.[1] The vaccine has a well established safety profile[2,3] and is considered highly cost-effective in most settings, especially in low-income countries with a high tuberculosis burden.[4] However, there is considerable debate about the impact that BCG vaccination has on tuberculosis, particularly among older children and adults.[1,5,6]

There are several crucial unanswered questions about BCG vaccination that have important implications for global tuberculosis epidemics and the development of supplemental vaccines. Whether BCG vaccination protects against pulmonary tuberculosis is unclear. There has been wide variability in estimates of the effectiveness of the BCG vaccine against pulmonary tuberculosis,[3,5,6] with some studies showing strong protection and others showing none. Several reasons for this heterogeneity have been proposed, such as sensitisation by environmental mycobacteria, the timing of BCG administration, and stringent tuberculosis testing.[3,6–8] Additionally, there is a paucity of data on the impact of BCG vaccination on mortality during childhood,[9,10] with several studies having been done in the pre-chemotherapeutic era, producing heterogeneous results.[11,12] More recent studies suggest potential sex-specific differences in the effectiveness of BCG vaccination.[13,14]

In addition, the duration of protection against tuberculosis offered by BCG vaccination remains controversial. In the 1950s, a large randomised trial in the UK found that participants still had protection against tuberculosis 15 years after BCG vaccination.[15] By contrast, a randomised trial of 250 000 participants done in Chengalpattu, India, found that the effect of infant BCG vaccination appeared to wane by 12·5 years of age.[16] Other studies have shown BCG vaccination to offer sustained protection against tuberculosis into adulthood among US Native American and Norwegian populations.[17,18] These inconsistent results regarding the effectiveness of BCG vaccination in protecting against tuberculosis in later life have created controversy and confusion.

To attempt to improve our understanding of the effectiveness and longevity of BCG vaccination, we convened a large data consortium group of longitudinal cohort studies of tuberculosis-exposed contacts done during the past 20 years. Our primary aim was to investigate the age-specific impact of BCG vaccination at birth on all forms of tuberculosis and on pulmonary

Research in context

Evidence before this study

The BCG vaccine is around 100 years old and among the most widely used vaccines globally. We searched PubMed for relevant articles without language restrictions published between database inception and April 1, 2022, using the search term "BCG" together with "tuberculosis", restricting to title and abstract fields. We found that previous studies have shown heterogeneous results and there is still considerable debate about BCG vaccination and its impact on tuberculosis and death. Estimates for the protection offered by BCG vaccination for the prevention of pulmonary tuberculosis have ranged from 0% in a trial from south India to 80% in a trial from the UK. The majority of previously published studies examining the effect of BCG vaccination were done in settings with low tuberculosis burden and are now more than 50 years old.

Added value of this study

In this systematic review and meta-analysis comprising individual-level data from 68 552 participants from 17 countries, we found that the overall effectiveness of infant BCG vaccination against all tuberculosis was 18%. When stratified by age, BCG vaccination only significantly protected against all tuberculosis in children younger than 5 years. BCG vaccination significantly protected against tuberculosis among all participants, participants younger than 5 years, and participants aged 5–9 years with positive tuberculin skin tests or IFNγ release assays, but not among those without positive tests, unless they were younger than 5 years. In contrast to some previous studies, BCG vaccination was protective against pulmonary tuberculosis (19% effectiveness), but this effect was only seen in children younger than 3 years (42% effectiveness) when stratified by age. Protection against all tuberculosis and pulmonary tuberculosis was greater in female participants than in male participants. Among 18 175 participants followed up for mortality, BCG vaccination was significantly protective against death for participants younger than 15 years, but not for participants aged 15 years or older. Importantly, almost all cohort studies included in our analysis were done in the past 10 years in settings with a high tuberculosis burden, such as India, South Africa, China, Viet Nam, Indonesia, Uganda, The Gambia, and Brazil. We therefore provide a novel assessment of the effectiveness of BCG vaccination against tuberculosis from a broad selection of high-burden countries.

Implications of all the available evidence

Our findings from this multicohort collaboration indicate that BCG vaccination is effective at preventing tuberculosis and death in children, but not adults. These results, combined with those from several historical trials, suggest that protective immunity against *Mycobacterium tuberculosis* should be boosted after childhood.

and extrapulmonary disease specifically. In addition, we aimed to investigate the relationship between infant BCG vaccination and the prevention of death.

Methods

Search strategy and selection criteria

This systematic review and individual participant data meta-analysis follows Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines[19] for individual patient data meta-analyses and uses the same data collection and data collation methods as our previously published systematic review and individual-participant meta-analysis investigating the development of tuberculosis among children closely exposed to a tuberculosis case.[20]

Briefly, we searched MEDLINE, Web of Science, BIOSIS, and Embase without language restrictions for case-contact cohort studies of tuberculosis contacts published between Jan 1, 1998, and April 7, 2018. The 20-year timeframe was chosen on the basis of the expected availability of individual participant data. Because one of the primary study outcomes in our previous meta-analysis[20] was incident tuberculosis, we restricted our search to cohort studies only—case-control studies and outbreak reports were excluded. Search terms included "mycobacterium tuberculosis", "TB", "tuberculosis", and "contact" and can be found in full in the appendix (p 4). We reviewed other systematic reviews and review articles of contact tuberculosis investigations[21–24] and inspected their reference lists for eligible articles. We included data that were unpublished (found through discussions with authors and experts in the field), data deposited in data storage repositories, conference abstracts, and dissertations if eligible. Because our search terms were broad in nature and our search was expansive, we developed a list of exclusionary words (appendix pp 5–10), ruling out articles if these words were present in their titles. We tested the exclusionary words approach for accuracy by implementing the exclusionary algorithm on a random list of 100 titles that were also manually screened for eligibility to our study. To be eligible for inclusion in the individual participant data meta-analysis, an article's dataset needed to include: follow-up for tuberculosis of a minimum of 6 months; individuals with household or close exposure to an individual with tuberculosis; information on the age and sex of the contact; and study start and follow-up dates. We did not restrict the age of participants, but studies assessing incident tuberculosis without dates or follow-up times were excluded and data on children were required. We excluded studies that did not provide information on BCG vaccination or were done in countries that did not recommend BCG vaccination at birth (including studies from countries that did not recommend BCG vaccination at birth might have led to selection bias). We classified a country's policy on BCG vaccination by using the 2020 BCG World Atlas.[25]

Two reviewers (LM and OC) conducted the searches and independently reviewed the articles for eligibility in two stages. First, they evaluated titles and abstracts and then they reviewed the full text. Only articles that did not contain any exclusionary words in their titles were reviewed. At each stage, the two reviewers discussed discrepancies and re-evaluated articles until a consensus was reached. Individual participant data were requested from authors of all eligible studies. All data were appropriately deidentified before sharing; therefore, the project was deemed exempt from further review by Stanford University's institutional review board. We also collected national tuberculosis incidence data from WHO databases for each included study done after 1990 as a proxy for local tuberculosis rates. The study protocol can be found online.

Study definitions

Participants were characterised as being exposed to tuberculosis if they were reported to be a close contact (either living in the same household or having substantial interaction outside the household) of a person with microbiologically or radiologically diagnosed pulmonary tuberculosis. Investigators from each study defined exposure and index case diagnoses; we used the study definitions assigned to each cohort (appendix p 34). Tuberculosis infection was defined by a positive QuantiFERON-TB Gold In-Tube test (IFNγ nil value ≥0·35 IU/mL), T-SPOT.TB test (nil spots minus antigen spots ≥8), or tuberculin skin test (≥10 mm induration). We used each study's classification of tuberculosis. Prevalent tuberculosis was defined as any diagnosis of tuberculosis at the initial visit or within 90 days of baseline evaluation, as per the conventional definition.[21] Incident tuberculosis was defined as a new tuberculosis case diagnosed more than 90 days after the initial evaluation. Further information on the algorithms used to diagnose tuberculosis, the diagnostic tests that were used in each study, and tuberculosis diagnosis at baseline and follow-up for each study can be found in the appendix (pp 35–36). Countries were classified into income levels by use of World Bank 2020 definitions (high-income, upper-middle-income, lower-middle-income, and low-income countries). We used each study's classification of BCG vaccination, which was based on a BCG vaccine scar, vaccination records, or both.

Data analysis

Individual participant data for a prespecified list of variables, including the characteristics of the exposed participant (contact), the index case, and the environment (appendix p 37), were requested from authors of all eligible studies. We pooled individual participant-level data from all included cohorts. Our analysis had two primary aims: (1) to estimate the overall and age-specific effectiveness of BCG vaccination in preventing pulmonary,

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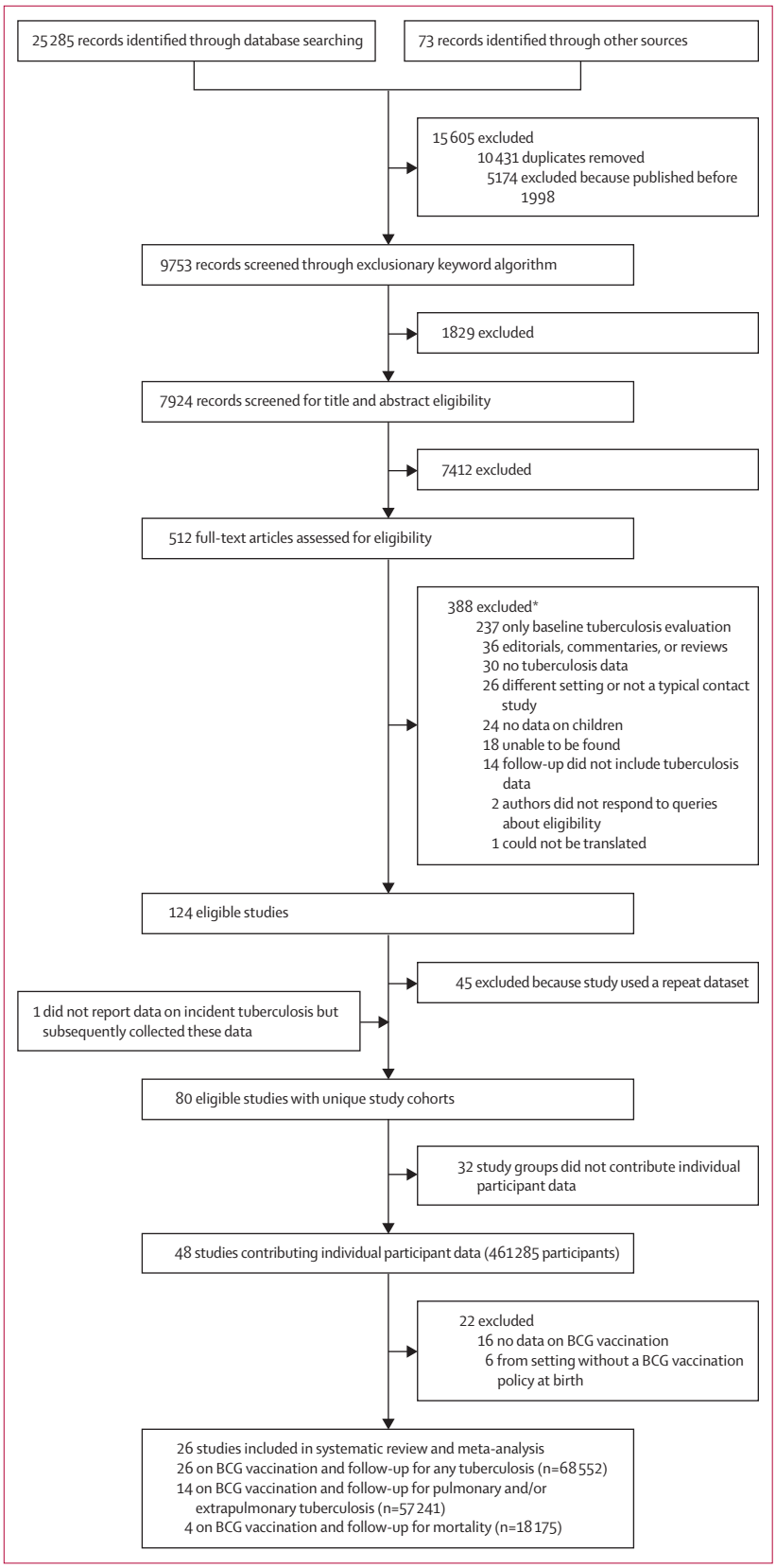

Figure 1: **Study selection**
*Excluded articles could have more than one reason for exclusion. Only one reason for exclusion is listed for each excluded article.

extrapulmonary, or any tuberculosis episode and (2) to estimate the overall and age-specific mortality benefits of BCG vaccination. Therefore, our primary outcome was a composite of diagnosed prevalent and incident tuberculosis in contacts exposed to tuberculosis. Secondary outcomes were pulmonary tuberculosis, extrapulmonary tuberculosis, and mortality. For these analyses, we derived adjusted odds ratios (aORs) using mixed-effects, binary, multivariable logistic regression analyses with study-level random effects. We assumed a conditional Bernoulli distribution of the response given the random effects. Models were adjusted for the variable of interest, baseline contact age, contact sex, contact previous tuberculosis, and whether data were collected prospectively or retrospectively, as fixed effects. In our analyses, we considered age as a proxy for time since vaccination.

We first compared vaccinated and unvaccinated participants by the secondary characteristics of age, sex, *Mycobacterium tuberculosis* infection status, previous tuberculosis, and HIV infection, generating aORs. For our main analysis of all tuberculosis, we stratified by age, sex, and tuberculosis infection status (a composite of tuberculin skin test and IFNγ release assay status). We did a range of secondary multivariable regression analyses of all tuberculosis, further stratifying by preventive therapy, index HIV status, index smear status, index cavitary status, WHO region, country income status, and tuberculosis infection status separately by test (tuberculin skin test or IFNγ release assay).

For our pulmonary and extrapulmonary tuberculosis outcomes, we stratified by age, sex, and tuberculosis infection status (composite tests). For our mortality outcome, we only stratified by age; four age groups were used (rather than six in the other analyses) due to the low number of outcomes. We also grouped participants younger than 15 years and participants aged 15 years or older in analyses of risk per year. We further evaluated whether adjustment (rather than stratification) for tuberculosis infection status at baseline had an impact on the relationship between tuberculosis (pulmonary and extrapulmonary) and BCG vaccination.

Between-study heterogeneity was assessed by use of the I^2 statistic. Two reviewers (LM and OC) independently assessed the quality of each study using a modified rubric of the Newcastle–Ottawa scale.[26] Each study was judged on a 9-point scale using three broad criteria: the selection of participants (4 points), the comparability of cohorts (2 points), and the ascertainment of the outcome of interest (3 points). High quality was defined by a score of greater than 6, moderate quality by a score of 4–6 points, and low quality by a score of 3 points or fewer.[27] We used Stata,

	Number of cohorts	BCG-vaccinated participants	Non-BCG-vaccinated participants	All participants
Outcomes analysed				
All tuberculosis	26	49 686	18 866	68 552
Pulmonary tuberculosis	14	41 118	16 161	57 279
Extrapulmonary tuberculosis	14	40 315	15 868	56 183
Mortality	4	16 780	1395	18 175
Contact characteristics				
Age group				
<5 years	23	9225/49 686 (18·6%)	1312/18 866 (7·0%)	10 537/68 552 (15·4%)
5–9 years	21	9936/49 686 (20·0%)	1289/18 866 (6·8%)	11 225/68 552 (16·4%)
10–14 years	19	7847/49 686 (15·8%)	1190/18 866 (6·3%)	9037/68 552 (13·2%)
15–24 years	11	7984/49 686 (16·1%)	2628/18 866 (13·9%)	10 612/68 552 (15·5%)
25–34 years	11	5159/49 686 (10·4%)	3006/18 866 (15·9%)	8165/68 552 (11·9%)
≥35 years	11	9535/49 686 (19·2%)	9441/18 866 (50·0%)	18 976/68 552 (27·7%)
Sex				
Female	26	26 421/49 600 (53·3%)	11 208/18 752 (59·8%)	37 629/68 352 (55·1%)
Male	26	23 179/49 600 (46·7%)	7544/18 752 (40·2%)	30 723/68 352 (44·9%)
TST or IGRA positive	25	13 543/33 474 (40·5%)	3121/7068 (44·2%)	16 664/40 543 (41·1%)
Living with HIV	15	233/15 119 (1·5%)	87/3693 (2·4%)	320/18 812 (1·7%)
Previous tuberculosis	17	1274/33 812 (3·8%)	542/17 746 (3·1%)	1816/51 288 (3·5%)
Median follow-up, years	26	2·0 (1·0–2·3)	2·0 (1·9–2·1)	2·0 (1·2–2·1)
Study characteristics				
Prospective study design	20	38 020/49 686 (76·5%)	17 658/18 866 (93·6%)	55 678/68 552 (81·2%)
Latitude				
0° to <10°	5	3470/49 686 (7·0%)	846/18 866 (4·5%)	4316/68 552 (6·3%)
10° to <20°	9	31 680/49 686 (63·8%)	16 154/18 866 (85·6%)	47 834/68 552 (69·8%)
20° to <30°	8	13 024/49 686(26·2%)	935/18 866 (5·0%)	13 959/68 552 (20·4%)
30° to <40°	4	1363/49 686 (2·7%)	930/18 866 (4·9%)	2293/68 552 (3·3%)
≥40°	1	149/49 686 (0·3%)	1/18 866 (<0·1%)	150/68 552 (0·2%)
Country income status*				
High	1	9241/49 686 (18·6%)	170/18 866 (0·9%)	9411/68 552 (13·7%)
Upper-middle	13	16 075/49 686 (32·4%)	3573/18 866 (18·9%)	19 648/68 552 (28·7%)
Lower-middle	4	16 253/49 686 (32·7%)	11 670/18 866 (61·9%)	27 923/68 552 (40·7%)
Low	6	8117/49 686 (16·3%)	3453/18 866 (18·3%)	11 570/68 552 (16·9%)
High WHO tuberculosis burden†	14	21 966/49 686 (44·2%)	13 662/18 866 (72·4%)	35 628/68 552 (52·0%)
WHO region*				
African region	10	9144/49 686 (18·4%)	3656/18 866 (19·4%)	12 800/68 552 (18·7%)
Region of the Americas	9	14 563/49 686 (29·3%)	2642/18 866 (14·0%)	17 205/68 552(25·1%)
Eastern Mediterranean region	0	..	..	..
South-East Asia region	4	1989/49 686 (4·0%)	461/18 866 (2·4%)	2450/68 552 (3·6%)
Western Pacific region	3	23 841/49 686 (48·0%)	12 106/18 866 (64·2%)	35 947/68 552 (52·4%)
European region	1	149/49 686 (0·3%)	1/18 866 (<0·1%)	150/68 552 (0·2%)

Data are n or n (%) or median (IQR) unless otherwise specified. Denominators vary due to missing data. IGRA=IFNγ release assay. TST=tuberculin skin test. *Studies were grouped into WHO global regions and World Bank country-level economies as of October, 2018. †Studies were designated as being located in a country with a high burden of tuberculosis, as classified by WHO.

Table 1: **Characteristics of participants in primary analyses**

version 16.0, for our analyses. This study is registered with PROSPERO, CRD42020180512.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

We identified 14 927 original records from our database searches, of which we screened 9753 through an exclusionary keyword algorithm (figure 1). We tested the exclusionary words approach for accuracy by implementing the exclusionary algorithm on a random list of 100 titles that were also manually screened for

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See Online for appendix

eligibility to our study. Our exclusionary algorithm eliminated all articles that were excluded by manual screening with 100% specificity. We reviewed 512 full-text articles published on or after Jan 1, 1998 (figure 1). 80 study groups were contacted for individual participant data and study groups from 48 studies agreed to share their data, which were collated into a single database of 461 285 contacts of tuberculosis cases. 16 studies without data on BCG vaccination and six studies that were done in countries (the Netherlands, Australia, Canada, Germany, Spain, and the USA) that do not recommend BCG vaccination at birth were excluded. 26 studies from 17 countries were included in our systematic review and meta-analysis (figure 1; appendix pp 12–13). Included cohorts measured different outcomes of interest: 26 cohorts had information on the BCG vaccination status of tuberculosis contacts and any tuberculosis (n=68 552); 14 studies had information on BCG vaccination and the development of pulmonary (n=57 279) or extrapulmonary (n=56 183) tuberculosis; and four studies had data on BCG vaccination and subsequent mortality (n=18 175; table 1). 20 (77%) studies had a prospective study design. Studies were from geographically diverse settings in 17 countries (appendix p 47). The majority of participants were recruited in the Western Pacific region (n=35 947), the region of the Americas (n=17 205), and the African region (n=12 800; table 1). Studies assessing mortality were located in South Africa, Taiwan, Uganda, and Viet Nam. Most studies were located in a latitude from 10° to less than 20° (n=47 834) or from 20° to less than 30° (n=13 959); one study was done in a latitude of 40° or more (n=150).

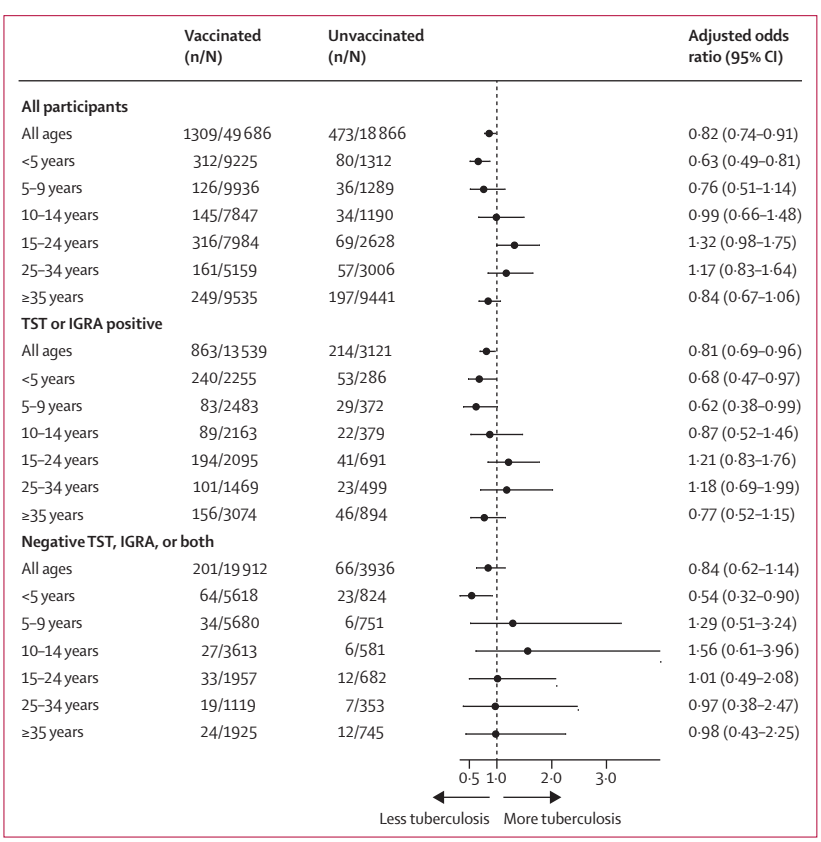

Figure 2: **BCG vaccination at birth and the risk of all tuberculosis, stratified by infection status and age**
Each stratified model used separate, mixed-effects, binary, multivariable logistic regression analyses with study-level random effects. We assumed a conditional Bernoulli distribution of the response given the random effects. Models were adjusted for the variable of interest, baseline age, sex, previous tuberculosis, and whether data were collected prospectively or retrospectively. Age was adjusted within each age stratum. Analysing raw numbers might not translate well into adjusted odds ratios due to the mixed-effects model. IGRA=IFNγ release assay. TST=tuberculin skin test.

Similar proportions of BCG-vaccinated versus unvaccinated participants were male (46·7% *vs* 40·2%; aOR 1·03, 95% CI 0·99–1·07), living with HIV (1·5% *vs* 2·4%; aOR 1·00, 0·77–1·30), or had a history of previous tuberculosis (3·8% *vs* 3·1%; aOR 1·05, 0·93–1·18). There was similar BCG vaccine coverage among the age groups younger than 15 years (9225 [87·5%] of 10 537 for ages <5 years, 9936 [88·5%] of 11 225 for ages 5–9 years, and 7847 [86·8%] of 9037 for ages 10–14 years), which was higher than the coverage in the older age groups (7984 [75·2%] of 10 612 for ages 15–24 years, 5159 [63·2%] of 8165 for ages 25–34 years, and 9535 [50·2%] of 18 976 for ages ≥35 years). Compared with unvaccinated participants, participants who were BCG-vaccinated had slightly higher rates of tuberculin skin test or IFNγ release assay positivity (aOR 1·09, 95% CI 1·01–1·17) and tuberculin skin test positivity (aOR 1·09, 1·01–1·17) but similar rates of IFNγ release assay positivity (aOR 0·97, 0·81–1·17).

Among 68 552 participants, 1782 (2·6%) developed tuberculosis (1309 [2·6%] of 49 686 BCG-vaccinated participants *vs* 473 [2·5%] of 18 866 unvaccinated participants). The overall effectiveness of BCG vaccination against all forms of tuberculosis was 18% (aOR 0·82, 95% CI 0·74–0·91). When stratified by age, BCG vaccination only significantly protected against all tuberculosis in children younger than 5 years (aOR 0·63, 95% CI 0·49–0·81; figure 2). Of participants aged 10 years or older, effectiveness was highest among those aged 35 years or older, but this increase did not reach statistical significance (figure 2).

Among participants with positive tuberculin skin tests or IFNγ release assays, BCG vaccination significantly protected against tuberculosis in all participants, participants younger than 5 years, and participants aged 5–9 years (figure 2). The vaccine was not protective among those without positive tests, unless they were younger than 5 years (0·54, 0·32–0·90; figure 2). The vaccine was significantly protective against tuberculosis among female participants (aOR 0·53, 0·36–0·79), but not among male participants (0·82, 0·55–1·23).

We did a range of secondary multivariable regression analyses of all tuberculosis, further adjusting for preventive therapy, index HIV status, index smear status, index cavitary status, WHO region, and country

	Number of cohorts	Participants	Events	Adjusted odds ratio (95% CI)
Pulmonary tuberculosis				
All participants				
All ages	14	57 279	1250	0·81 (0·70–0·94)
<5 years	14	7233	154	0·73 (0·48–1·11)
5–9 years	13	8630	82	0·79 (0·38–1·62)
10–14 years	13	7025	125	0·84 (0·50–1·40)
15–24 years	11	9217	311	1·20 (0·87–1·76)
25–34 years	8	7494	179	1·31 (0·86–1·99)
≥35 years	8	17 680	399	0·81 (0·63–1·05)
Positive TST or IGRA				
All ages	13	12 594	738	0·80 (0·65–0·99)
<5 years	13	1611	118	0·79 (0·46–1·34)
5–9 years	12	2046	59	0·96 (0·46–2·02)
10–14 years	12	1873	85	0·85 (0·44–1·63)
15–24 years	10	2105	192	1·16 (0·74–1·83)
25–34 years	7	1592	111	1·45 (0·73–2·91)
≥35 years	7	3367	173	0·80 (0·49–1·30)
Negative TST, IGRA, or both				
All ages	13	18 278	167	0·98 (0·65–1·46)
<5 years	13	4352	33	0·65 (0·28–1·50)
5–9 years	12	4978	23	4·94 (0·65–37·57)
10–14 years	12	3251	23	0·97 (0·38–2·50)
15–24 years	10	2296	39	1·28 (0·54–3·05)
25–34 years	7	1244	18	0·92 (0·27–3·18)
≥35 years	7	2157	31	0·84 (0·30–2·31)
Extrapulmonary tuberculosis				
All participants				
All ages	14	56 183	144	0·96 (0·65–1·41)
<5 years	14	7104	23	0·46 (0·19–1·12)
5–9 years	13	8571	18	0·54 (0·17–1·69)
10–14 years	13	6920	20	2·45 (0·54–11·08)
15–24 years	11	8941	35	1·43 (0·60–3·42)
25–34 years	8	7341	24	0·79 (0·35–1·79)
≥35 years	8	17 306	24	2·92 (0·98–8·00)

(Table 2 continues in next column)

(Continued from previous column)

	Number of cohorts	Participants	Events	Adjusted odds ratio (95% CI)
Positive TST or IGRA				
All ages	13	11 926	70	0·91 (0·48–1·73)
<5 years	13	1508	15	0·55 (0·18–1·73)
5–9 years	12	1997	10	0·43 (0·12–1·54)
10–14 years	12	1799	11	0·71 (0·13–3·94)
15–24 years	10	1932	19	1·35 (0·43–4·27)
25–34 years	7	1484	3	..
≥35 years	7	3206	12	2·58 (0·18–36·37)
Negative TST, IGRA, or both				
All ages	13	18 236	35	1·03 (0·46–2·34)
<5 years	13	4325	7	0·34 (0·07–1·51)
5–9 years	12	4961	7	1·05 (0·11–9·83)
10–14 years	12	3326	8	..
15–24 years	10	2266	7	0·91 (0·18–4·73)
25–34 years	7	1228	4	0·97 (0·08–11·23)
≥35 years	7	2130	2	..

Events were a composite of both prevalent tuberculosis (diagnosed at or within 90 days of baseline) and incident tuberculosis (diagnosed more than 90 days after baseline). If the odds ratio is not presented, there was not enough statistical power due to small sample sizes or too few events. Each stratified model used separate, mixed-effects, binary, multivariable logistic regression analyses with study-level random effects. We assumed a conditional Bernoulli distribution of the response given the random effects. Models were adjusted for the variable of interest, baseline age, sex, previous tuberculosis, and whether data were collected prospectively or retrospectively. Age was adjusted within each age stratum. The number of events for the vaccinated and unvaccinated groups in each stratification can be found in the appendix (appendix pp 24–25). Analysing raw numbers might not translate well into adjusted odds ratios due to the mixed-effects model. IGRA=IFNγ release assay. TST=tuberculin skin test.

Table 2: **BCG vaccination at birth and the occurrence of pulmonary and extrapulmonary tuberculosis, stratified by infection status and age**

For the **WHO databases** see https://www.who.int/teams/global-tuberculosis-programme/data

For the **study protocol** see https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=180512

income status. No secondary variables modified the relationship between BCG vaccination and tuberculosis risk (appendix p 49). Findings stratified by IFNγ release assay (appendix p 23) and tuberculin skin test (data not shown) results separately (and not as a composite variable) were generally consistent with the analysis using the composite variable, although age-specific results were limited in those with IFNγ release assay tests due to small numbers of participants and events.

14 cohorts reported on whether tuberculosis was pulmonary or extrapulmonary (n=57 421). Among 1394 tuberculosis cases in these cohorts, 1250 (89·7%) were pulmonary and 144 (10·3%) were extrapulmonary. BCG vaccination significantly protected against pulmonary tuberculosis events among all participants (916 [2·2%] in 41 119 vaccinated participants *vs* 334 [2·1%] in 16 161 unvaccinated participants; aOR 0·81, 95% CI 0·70–0·94) and among those with a positive tuberculin skin test or IFNγ release assay (0·80; 0·65–0·99; table 2; appendix pp 24–25). Protection against pulmonary tuberculosis was only present in children younger than 3 years (aOR 0·58, 95% CI 0·35–0·98; table 2). Vaccine effectiveness was higher among female participants (0·57, 0·32–1·03) than among male participants (0·92, 0·51–1·68). BCG vaccination was not protective against extrapulmonary tuberculosis events overall (106 [0·3%] in 40 318 vaccinated participants *vs* 38 [0·2%] in 15 865 unvaccinated participants; aOR 0·96, 95% CI 0·65–1·41). For extrapulmonary tuberculosis, BCG vaccination produced a suggestive but statistically non-significant protective effect in children younger than 5 years (table 2). BCG vaccination was not effective at preventing extrapulmonary tuberculosis among female participants (aOR 0·66, 95% CI 0·34–1·11) or male participants (1·33, 0·78–2·28).

A multivariable model adjusting for tuberculin skin test or IFNγ release assay positivity at baseline showed that BCG vaccination remained protective for pulmonary tuberculosis (aOR 0·80, 95% CI 0·66–0·97) and not

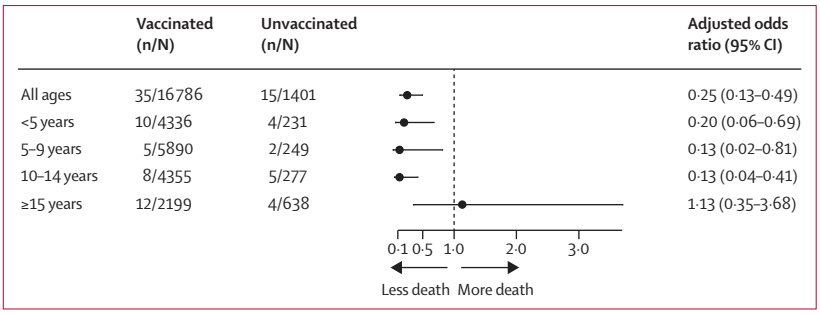

Figure 3: **BCG vaccination at birth and the risk of death, stratified by age**
Each stratified model used separate, mixed-effects, binary, multivariable logistic regression analyses with study-level random effects. We assumed a conditional Bernoulli distribution of the response given the random effects. Models were adjusted for the variable of interest, baseline age, sex, previous tuberculosis, and whether data were collected prospectively or retrospectively. Age was adjusted within each age stratum.

protective for extrapulmonary tuberculosis (0·73, 0·45–1·17; appendix p 48).

In four studies that followed up tuberculosis contacts for death, 18 175 participants were evaluated and 50 (0·3%) deaths occurred (35 [0·2%] of 16 780 vaccinated participants and 15 [1·1%] of 1395 unvaccinated participants). Among children younger than 15 years, increasing age was associated with a reduced risk of death (aOR 0·92 per year, 95% CI 0·86–0·98). Among participants aged 15 years or older, increasing age was strongly associated with death (aOR 1·08 per year, 1·08–1·09). BCG vaccination was significantly protective against death for all ages, for participants younger than 5 years, for participants aged 5–9 years, and for participants aged 10–14 years (figure 3). Among participants aged 15 years or older, there was no relationship between BCG vaccination and death (figure 3).

Heterogeneity was generally low (I^2<50%; appendix p 18) and the majority of studies were rated as high or moderate quality (appendix pp 28–33).

Discussion

The BCG vaccine is a crucial component of tuberculosis control and is given to more than 100 million newborn babies every year.[4,28] Nevertheless, there is continued debate concerning the ability of BCG vaccination to prevent tuberculosis and death.[3,5,9,10] Using individual-level data from 26 case-contact cohort studies comprising 68 552 exposed participants followed up for a median duration of 2·0 years, we found that infant BCG vaccination was effective in preventing all tuberculosis, pulmonary tuberculosis, and death, especially among younger children. When stratified by age, BCG vaccination at birth only significantly protected against all tuberculosis in children younger than 5 years. This effect was consistent in participants with either positive or negative tuberculin skin tests or IFNγ release assays. These results suggest that infant BCG vaccination, although important to young children who are at high risk of tuberculosis,[20,29–31] does not prevent adult-type cavitary tuberculosis and is therefore insufficient to impede the tuberculosis epidemic, providing further evidence that novel vaccines are urgently needed.

We found that infant BCG vaccination was protective against all forms of tuberculosis (18% effectiveness). Among the subset of 14 cohorts reporting specific forms of tuberculosis, we found evidence for a small, significant reduction in the rate of pulmonary tuberculosis with vaccination (19% effectiveness). For both of these outcomes, protection was concentrated in young children. Whether BCG vaccination protects young children from pulmonary tuberculosis is controversial and previous results have been heterogeneous.[1,3,4] Unfortunately, we were unable to investigate latitude as an important cause for this heterogeneity because the majority of studies included were done at latitudes of less than 30°. Among participants younger than 5 years who had recorded tuberculin skin test or IFNγ release assay results, children were slightly more protected from tuberculosis if they had negative (46% effectiveness) rather than positive (32% effectiveness) results, consistent with previous trials that have found a high BCG vaccine efficacy (59%) among tuberculin skin test-negative infants vaccinated at birth.[8] This effect seemed to wane faster among participants with negative tests than among participants with positive tests, either due to the small numbers of participants who tested negative or a combination of vaccine-induced and infection-induced immunity. BCG vaccination did not generally protect from all tuberculosis for participants aged 5 years or older or from pulmonary or extrapulmonary disease when stratified by age group, although statistical power for the outcome of extrapulmonary disease was limited after age stratification. Importantly, vaccine effectiveness in people exposed to tuberculosis contacts, as included in the cohorts in this analysis, might differ from effectiveness in people from the general population.

We found marked protection from death among BCG-vaccinated children in our study. Protection persisted until participants were aged 14 years. Sex-specific differences in BCG effectiveness have been variably observed in previous studies.[10,13,14] In a previously published prospective birth cohort study, girls were more likely to benefit from BCG vaccination than were boys.[13] However, a combined analysis of three randomised trials in Guinea-Bissau found that the efficacy of BCG vaccination was much greater in boys than in girls aged 0–1 month due to marked reduction in mortality among boys in the first month of life (largely driven by a reduction in sepsis).[14] Our results extend this finding across a larger age range into adolescence. We were not able to identify specific mechanisms by which BCG vaccination might have reduced mortality, as causes of death were not reported by each study. Previous experimental and observational studies have found that BCG vaccination might provide non-specific or off-target immune protection against an array of other pathogens.[1,3,10] Although our results should be cautiously

interpreted, they add to the sparse empirical evidence on the relationship between BCG vaccination and mortality in children. Furthermore, they affirm the value of BCG vaccination among children in tuberculosis-endemic settings and underscore the need to identify effective supplementary vaccines to protect against tuberculosis among adolescents and adults.[32,33]

Our study has numerous strengths. Importantly, most studies included in the analysis were done in the past 10 years in countries with a high tuberculosis burden, including India, South Africa, China, Viet Nam, Indonesia, Uganda, The Gambia, and Brazil. By contrast, several previously published studies examining the protective effect of BCG vaccination only considered low-burden settings and the historical literature before 1950.[1,6] Several studies done during the past two decades have also provided further input.[17,34] 77% of the cohorts examined in our analysis had a prospective design, thus decreasing potential recall biases and increasing confidence of proper case detection. In addition, many cohorts provided important secondary information, such as tuberculin skin test or IFNγ release assay results, HIV status, and histories of previous tuberculosis; these data were largely unavailable in previous studies.[1,3] The inclusion of these characteristics allowed us to investigate and explore variability across studies.

Our findings are subject to several limitations. First, the studies included were observational in nature and therefore exposure to BCG vaccination was not randomised. There is no longer clinical equipoise for a clinical trial on BCG vaccination. However, the availability of individual-level data on demographic and clinical information from contacts and index cases and cohort-level characteristics from each individual study allowed for adjustment. Despite adjustment, residual or unmeasured confounding is possible and might have biased our effectiveness values upwards. BCG vaccination might theoretically reflect health-care access and higher socioeconomic status, which could plausibly confound the risk of the outcomes we have measured. Our results showing a protective effect in young children and predominantly no effect among adolescents and adults, consistent with previous trials,[6] suggest that this bias might be minimal. Second, we utilised the classifications of BCG vaccination used in each study, which were based on a BCG vaccine scar and vaccination records. Exposure misclassification might occur if a scar does not form. However, BCG scar formation is a sensitive indicator of vaccination status, and few vaccinated children from various settings do not show a scar years after vaccine administration.[35–37] Third, although our results were largely consistent when analysing by QuantiFERON-TB and tuberculin skin test status, sample size and statistical power were low. Fourth, our mortality analysis must be interpreted with caution. Due to the observational nature of the studies we included, vaccinated children might have had higher socioeconomic status and greater access to health care and have been more likely to have received other vaccinations compared with BCG-unvaccinated children, leading to overestimation of mortality benefit. Furthermore, the studies with mortality data were from a small number of settings, potentially impacting our results and their generalisability. Finally, because diagnosing extrapulmonary tuberculosis is challenging in many of the included settings and the type of extrapulmonary disease (eg, tuberculous meningitis or miliary tuberculosis) was often not reported, it is probable that extrapulmonary tuberculosis was underdiagnosed and we were unable to evaluate BCG vaccine effectiveness against specific forms of extrapulmonary tuberculosis.

In conclusion, using a combined analysis of 26 cohort studies comprising 68 552 participants, we have shown that infant BCG vaccination is effective at preventing all tuberculosis and death in young children. The protective effect of BCG vaccination against tuberculosis waned in participants aged 5 years or older, consistent with historical studies.[6] These associations were not modified by evidence of *M tuberculosis* infection at baseline in these cohorts. These results suggest that protective immunity against *M tuberculosis* should be boosted after childhood.

Contributors

All authors contributed to data acquisition. LM and OC did the systematic search, screened and identified studies, and made final decisions regarding study inclusion. LM received and checked the data, did all analyses, and had full access to all materials and results. LM and OC accessed and verified the underlying data. LM wrote the first draft of the manuscript. All authors read and edited the drafted manuscript for important intellectual content and assisted in data interpretation. All authors approved the final version of the manuscript. All authors contributed data to the large, merged individual participant dataset, but some of the data were not accessible to all authors due to data sharing agreements and restrictions by each study group. All authors had final responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

The data used for this analysis can be made available upon reasonable request once all relevant substudies from the consortium are reported and completed. The data dictionary can be made available upon request to the corresponding author.

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