The Journal of Infectious Diseases

REVIEW ARTICLE

Does BCG Vaccination Protect Against Nontuberculous Mycobacterial Infection? A Systematic Review and Meta-Analysis

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Background. The incidence of nontuberculous mycobacterial (NTM) infections is increasing worldwide, particularly NTM lymphadenitis and skin infections (Buruli ulcer). This review summarizes the evidence for the protective effectiveness of BCG vaccination against NTM disease.

Methods. A systematic search using PRISMA guidelines was done for controlled studies investigating the protective effectiveness of BCG vaccination against NTM disease in immunocompetent individuals. This revealed 10 studies, including almost 12 million participants.

Results. Three cohort studies in industrialized countries suggest that the incidence of NTM lymphadenitis is greatly reduced among BCG-vaccinated children compared with BCG-unvaccinated children, with a risk ratio (RR) of 0.04 (95% confidence interval [CI], .01–.21). In two randomized trials in low-income countries, BCG protected against Buruli ulcer for the first 12 months following vaccination (RR, 0.50 [95% CI, .37–.69]). Four case-control studies had conflicting results. One cohort study found that individuals with Buruli ulcer are less likely to develop osteomyelitis if they have a BCG scar (RR, 0.36 [95% CI, .22–.58]). No studies have compared different BCG vaccine strains or the effect of revaccination in this setting.

Conclusions. The protective effect of BCG vaccination against NTM should be taken into consideration when deciding on recommendations for discontinuation of universal BCG vaccination programs and in assessing new vaccines designed to replace BCG.

Keywords. NTM; atypical; lymphadenitis; Buruli ulcer; *M. ulcerans*.

Nontuberculous mycobacteria (NTM) are ubiquitous, being found in water, soil, and animals. Although >170 species have been identified, the majority of human NTM disease is caused by <20 species [1]. In immunocompetent children, NTM most frequently cause cervicofacial lymphadenitis or skin and soft tissue infections. The commonest NTM skin infection worldwide is Buruli ulcer, a chronic, progressive skin lesion caused by *Mycobacterium ulcerans*. Untreated, the ulcer can progress to osteomyelitis and lead to permanent bone destruction.

Although not a notifiable disease, the incidence of NTM lymphadenitis in industrialized countries is reported to be between 0.6 and 2.2 cases per 100 000 children per year [2–4], with the highest incidence in children <4 years of age. Epidemiological studies in developing countries are lacking. Buruli ulcer has been reported in 33 countries, and 15 countries regularly provide data to the World Health Organization (WHO) [5]. The incidence in Africa is estimated to be between 21 and 320 cases per 100 000 per year [6, 7] in Australia, at 1 case per 100 000 per year [5, 8], and in Japan at 0.005 cases per 100 000 per year. In Africa, about half of the cases occur in children <15 years of age, whereas in Australia and Japan approximately 15% of cases occur in this age group [5].

Over the past few decades, the reported incidence of NTM lymphadenitis, as well as Buruli ulcer, has been increasing [6, 7, 9–12]. This might be attributable partly to improved awareness, enhanced reporting, and better diagnostic methods, but it is also possible that the apparent increase is related to the discontinuation of BCG vaccination programs in industrialized countries. As BCG vaccine is a live attenuated strain of *Mycobacterium bovis* that shares epitopes with NTM, it is plausible that it provides specific cross-protection against NTM disease. This review and meta-analysis summarizes studies that have investigated the protective effectiveness of BCG vaccination against NTM disease in immunocompetent children and adults.

Received 29 January 2018; editorial decision 4 April 2018; accepted 6 April 2018; published online April 7, 2018.

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The Journal of Infectious Diseases® 2018;218:679–87

DOI: 10.1093/infdis/jiy207

Table 1. Studies Reporting on the Protective Effect of BCG Vaccination Against Nontuberculous Mycobacterial Lymphadenitis in Industrialized Countries[a]

Study [Reference] Study Period, Location	Age of Participants	Study Type (Level of Evidence)	Outcome and Diagnostic Methods (Number of participants)	Vaccine Strain	No. of Cases: BCG-Vaccinated	No. of Cases: BCG-Unvaccinated	Risk Ratio (95% CI)	Key Findings and Comments Including NTM Species Cultured
Katila et al [18] 1977–1986, Finland	Children	Retrospective population-based cohort study (2c)	Lymphadenitis: clinical 31; histology 31; skin test 10; culture 11	1977 BCG Sweden; 1978–1986 BCG Glaxo	25[a]/8333333	6[a]/300 000	0.15 (.06–.37)	BCG vaccination reduced the risk of NTM infection • Highest protection at 1–4 y of age • 35% of cases were laboratory confirmed[b] • MAC 9, *M. malmoense* 2 • Vaccine status determined by vaccination record
Trnka et al [17] 1986–1993, Czech Republic	Children	Prospective population-based cohort study (2c)	Lymphadenitis: clinical 27; histology 27; skin test 15; culture 4	BCG Russia	0/746 087	27/190 874	0.00 (.00–.08)	BCG vaccination reduced the risk of MAC lymphadenitis • 15% of cases were laboratory confirmed[b] • Cervical 24, mediastinal 2, cervical plus mediastinal 1 • Vaccine status determined by vaccination record
Romanus et al [16] 1969–1990, Sweden	Children <15 y	Retrospective and prospective population-based cohort study (2c)	Extrapulmonary NTM infection: clinical 387; culture confirmed 387	1969–1978 BCG Sweden; 1978–1990 BCG Denmark	8/809 299	379/1 469 698	0.04 (.02–.08)	BCG vaccination reduced the risk of NTM infection • Lymphadenitis/soft tissue infection 379, skin infection 5, osteoarticular infection 2, otitis media 1 • 100% of cases were laboratory confirmed[b] • MAC 321, *M. malmoense* 43, *M. marinum* 4, *M. scrofulaceum* 4, Runyon III[c] 4, nontypeable 4, *M. chelonae* 3, *M. fortuitum* 2, *M. xenopi* 2, *M. avium* 1, *M. kansasii* 1, *M. terrae* 1 • Vaccine status determined by vaccination record

Abbreviations: CI, confidence interval; MAC, *Mycobacterium avium-intracellulare* complex; NTM, nontuberculous mycobacteria.

[a]Includes 2–6 possible infections with *Mycobacterium tuberculosis*.

[b]By culture or polymerase chain reaction.

[c]Nontyped, slow-growing, nonchromogenic mycobacteria.

Table 2. Randomized Controlled Trials Reporting on the Protective Effect of BCG Vaccination Against Buruli Ulcer

Study [Reference] Study Period, Location	Age of Participants	Study Type (Level of Evidence)	Outcome and Diagnostic Methods (Number of Participants)	Vaccine Strain	No. of Cases: BCG-Vaccinated	No. of Cases: BCG-Unvaccinated	Risk Ratio (95% CI)	Key Findings and Comments
Bradley et al [19] 1967–1968, Uganda	Children and adults (31% <15 y)	RCT (1b)	Buruli ulcer: clinical 65; histology 63; culture 31	BCG Glaxo	21/606 (3%)	44/624 (7%)	0.49 (.30–.82)	BCG vaccination reduced the risk of Buruli ulcer • Overall protection rate reported as 47% (P = .007) • Protection was only in the first year after vaccination (72% protective in first 6 mo) • Protection 18% in high-incidence settings, 74% in low-incidence areas (P = .03) • Onset of symptoms was delayed by 2–3 mo in those BCG vaccinated • 48% of cases were laboratory confirmed[a]
Smith et al [20] 1970–1974, Uganda	Children and adults (48% <15 y)	RCT (1b)	Buruli ulcer: clinical 100; histology 48	BCG Glaxo	34/2775 (1%)	66/2764 (2%)	0.51 (.34–.77)	BCG vaccination reduced the risk of Buruli ulcer • Overall protection rate reported as 47% (P < .01) • Protection was only in the first year after vaccination (63% protective in first 12 mo) • Protective only in participants with tuberculin reactions of <4 mm before vaccination (P < .05) • BCG-vaccinated individuals had smaller skin lesions (P < .01) • No cases were laboratory confirmed[a] • Retrospective case-control part of study: RR, 0.78 95% CI (.50–1.21)

Abbreviations: CI, confidence interval; RCT, randomized controlled trial; RR, risk ratio.

[a]By culture or polymerase chain reaction.

METHODS

A systematic search was done according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [13] for studies investigating the protective effectiveness of BCG vaccination against NTM disease. In April 2017, Medline (1946 to present) and Embase (1947 to present) were searched using the Ovid interface with the following search terms: (nontuberculous OR non-tuberculous OR NTM OR atypical mycobacteria OR environmental mycobacteria OR Buruli ulcer OR *Mycobacterium avium* OR *Mycobacterium ulcerans* OR *Mycobacterium avium-intracellulare*) AND (BCG vaccin* OR *Mycobacterium bovis*) without language limitations. The references of identified articles were hand-searched for further studies. The following variables were extracted from the included studies: year of study, country, study design, number of participants, age of participants, BCG vaccination status, BCG vaccine strain, NTM disease, diagnostic methods, and key findings. Review Manager (version 5.3) was used for calculation of risk ratios, odds ratios, and the meta-analyses. Diversity in study design and reporting, which might result in selection and reporting bias, precluded quality evaluation according to the PRISMA guidelines. The ROBINS-1 tool [14] was used to assess risk of bias.

RESULTS

The literature searches yielded 812 articles relating to NTM and 1543 articles relating to Buruli ulcer. Of these, 10 fulfilled the inclusion criteria of controlled studies investigating the protective effectiveness of BCG vaccination against NTM disease in immunocompetent individuals. One study was excluded because it included the same patients as one of the other identified studies [15].

NTM Lymphadenitis in Industrialized Countries

Three studies from industrialized countries, all population-based cohort studies, compared the incidence of NTM lymphadenitis in a total of 9 888 719 BCG-vaccinated children with 1 960 572 non-BCG-vaccinated children. Of these children, 445 were diagnosed with NTM disease. All three studies reported a greatly reduced incidence of NTM lymphadenitis in BCG-vaccinated compared to BCG-unvaccinated children; the overall risk ratio (RR) was 0.04 (95% confidence interval [CI], .01–.21]) (Table 1 and Figure 1). The number needed to treat (NNT) calculated from the three cohort studies was 4835 (95% CI, 4403–5362).

A nationwide surveillance study in Sweden, done after discontinuation of routine neonatal BCG vaccination, reported 387 children with confirmed extrapulmonary NTM disease (83% with *Mycobacterium avium-intracellulare* complex [MAC], 97% presenting with lymphadenitis) over a period of 22 years. Only nine of the 390 children had received BCG vaccine (0.02%). The cumulative incidence rate of NTM infection was 5.9 per 100 000 in BCG-vaccinated children aged <5 years and 26.8 per 100 000 in BCG-unvaccinated children [16]. Similarly, a study from the Czech Republic after discontinuation of routine BCG vaccination, in which children were screened for NTM disease by skin test, reported 27 cases of MAC lymphadenitis over a period of 6 years. All the cases occurred in BCG-unvaccinated children with an incidence of NTM lymphadenitis of 3.6 per year per 100 000 [17]. In Finland, during the period when BCG vaccine was routinely administered to newborns, the incidence of NTM lymphadenitis between 1 and 4 years of age was 0.3 per 100 000 per year in BCG-vaccinated children and 1.5–2.5 per year in BCG-unvaccinated children [18].

Buruli Ulcer

Six studies investigated the protective effectiveness of BCG vaccination against Buruli ulcer, comparing the incidence in 6475 BCG-vaccinated adults and children with 13 612 BCG-unvaccinated adults and children. The strongest evidence comes from two randomized controlled trials (RCTs) done in Uganda (Table 2 and Figure 2A). These reported a considerably lower incidence of Buruli ulcer in BCG-vaccinated compared with BCG-unvaccinated participants, with an RR of 0.50 (95% CI, .37–.69). The NNT calculated from the three cohort studies was 4835 (95% CI, 4403–5362). Protection following BCG vaccination was higher in low-incidence than in high-incidence settings (74% vs 18%; P = .03) [19] and was only short-term (within the first year after vaccination), with an overall reduction of Buruli ulcer of 47% (P < .01) [19, 20]. In one of these studies, BCG-vaccinated individuals had smaller skin lesions compared with unvaccinated individuals [20].

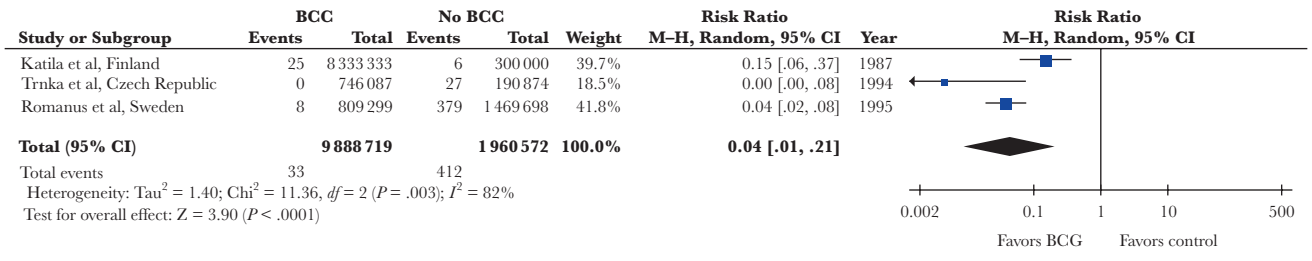

Figure 1. Comparison of incidence of nontuberculous lymphadenitis infection in BCG-vaccinated and BCG-unvaccinated children in industrialized countries. Abbreviations: CI, confidence interval; M–H, Mantel-Haenszel.

Four case-control studies (two from Benin, one from Ghana, and one from the Congo, Ghana, and Togo) investigated the protective effectiveness of BCG against Buruli ulcer (Table 3). Two studies suggest a reduced risk of Buruli ulcer in BCG-vaccinated individuals [21, 22], and two suggest no benefit [23, 24]; when the results of all four case-control studies are combined, there is no evidence of a protective effect of BCG (odds ratio, 1.34 [95% CI, .19–1.51]) (Figure 2B) [21, 22, 25–27].

Osteomyelitis

One cohort study from Benin compared the incidence of osteomyelitis in patients with Buruli ulcer in 304 BCG-vaccinated adults and children with the incidence in 68 BCG-unvaccinated adults and children (Table 4 and Figure 3). This showed that BCG vaccination protected against the development of osteomyelitis in patients with Buruli ulcer (RR, 0.36 [95% CI, .22–.58]) [23]. However, the study did not specify how many cases were laboratory confirmed; therefore, inclusion of osteomyelitis caused by pathogens other than NTM might have led to an overestimate of the rate of protection.

DISCUSSION

The protective effectiveness of BCG vaccination against *Mycobacterium tuberculosis* and *Mycobacterium leprae* is well recognized [24, 28]. There is also evidence that infection with NTM might confer protection against *M. tuberculosis* infection or interact with the effectiveness of BCG vaccination [29–31]. In contrast, whether BCG vaccination protects against NTM infections has been controversial.

Our review found strong evidence from large European surveillance studies that BCG vaccination protects against NTM lymphadenitis in children. The rate of NTM infections in Finland, when there was universal neonatal BCG vaccination, was 30 times lower than the rate in Sweden, which did not have universal neonatal BCG vaccination, despite both countries having similar environmental and epidemiological characteristics [18]. In addition, in the Czech Republic and in Sweden, a sharp increase in NTM infection in children was observed after stopping universal neonatal BCG vaccination [16, 17].

For Buruli ulcer, there is strong evidence from two RCTs for a protective effect of BCG vaccination in the first year after the vaccination [19, 20]. The results of the case-control studies are difficult to interpret given their disparate findings. Furthermore, it is important to consider that the RCTs estimated the effectiveness of BCG vaccine under the optimal storage, handling, and administration conditions of a clinical trial [19, 20], while this was not necessarily the case in the case-control studies [21, 22, 25, 27]. In addition to the study included in our review, which reports smaller skin lesions in patients with Buruli ulcer who have previously received a BCG vaccine [20], another study (not included in this review because the BCG vaccination status was not reported in the control group) reported a shorter duration to healing [26]. A further study (not included due to incomplete data) suggested that BCG vaccination protects against severe forms of Buruli ulcer with multiple skin lesions [32]. In addition to the evidence from the study included in our review [23], this study also indicates that BCG vaccination might protect patients with Buruli ulcer from progression to NTM osteomyelitis [32] .

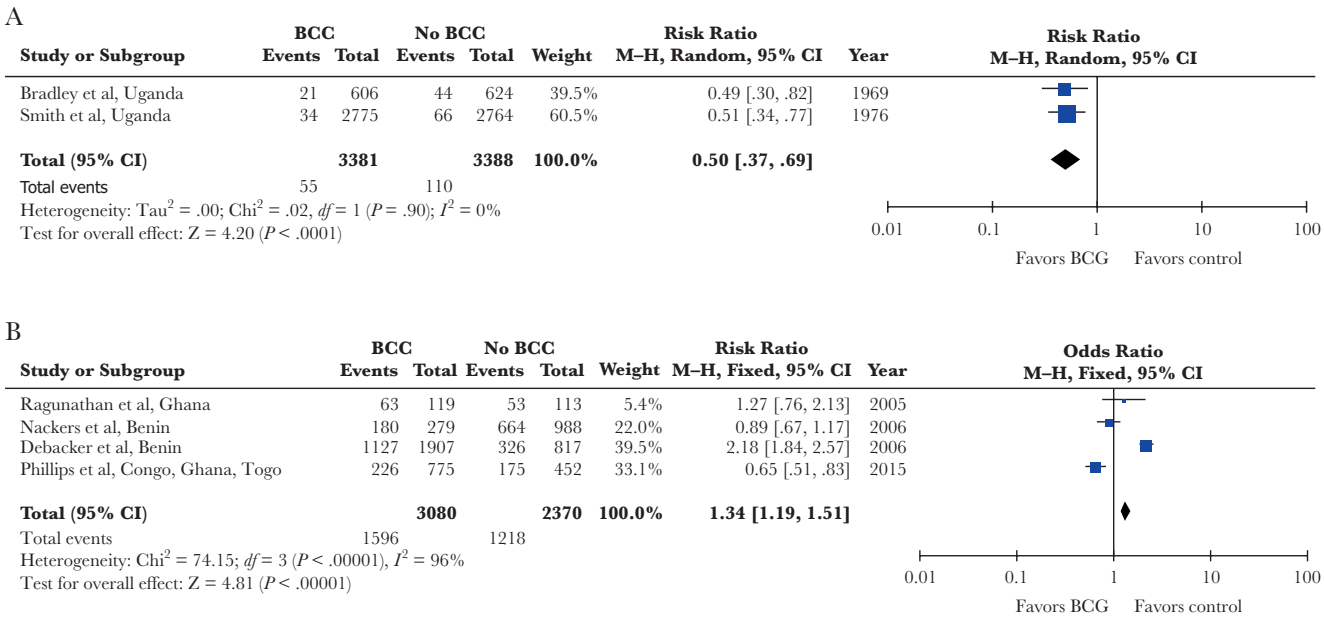

Figure 2. Comparison of incidence of Buruli ulcer in BCG-vaccinated and BCG-unvaccinated participants in randomized controlled trials (*A*) and case-control studies (*B*). Abbreviations: CI, confidence interval; M–H, Mantel-Haenszel.

Table 3. Case-Control Studies Reporting on the Protective Effect of BCG Vaccination Against Buruli Ulcer

Study [Reference] Study Period, Location	Age of Participants	No. of Participants		Study Type (Level of Evidence)	Outcome and Diagnostic Methods (Number of Participants)	Vaccine Strain	No. of Cases		Odds Ratio (95% CI)	Key Findings and Comments
		BCG-Vaccinated	BCG-unvaccinated				BCG-vaccinated/ Cases	BCG-vaccinated/ Controls		
Raghunathan et al [25] 2000, Ghana	Children and adults (62% <15 y)	119	113	Retrospective case-control study (3b)	Buruli ulcer: clinical 116; histology 79; stain 13; culture 54; PCR 106	Various	63/116 (54%)	56/116 (48%)	1.27 (.76–2.13)	BCG vaccination did not reduce the risk of Buruli ulcer • Approximately 95% of cases were laboratory confirmed[a] • Vaccine status determined by presence of scar
Debacker et al [27] 1997–2003, Benin	Children and adults (38% <15 y)	1907	817	Retrospective case-control study (3b)	Buruli ulcer: clinical 1453	Various	1127/1453 (78%)	780/1271 (61%)	2.18 (1.84–2.57)	BCG vaccination did not reduce the risk of Buruli ulcer • No cases were laboratory confirmed[a] • Vaccine status determined by presence of scar
Nackers et al [22] 2002–2003, Benin	Children and adults (48% <13 y)	279	988	Retrospective case-control study (3b)	Buruli ulcer: clinical 844; stain or histology or culture or PCR 134	Various	180/844 (21%)	99/423 (23%)	0.89 (.67–1.17)	BCG vaccination reduced the risk of Buruli ulcer • Protection (adjusted for socioeconomic status) 12% (95% CI, 24%–37%) • Most received BCG vaccination as neonates and were included >1 y after vaccination • <16% cases were laboratory confirmed[a] • Vaccine status determined by presence of scar or vaccination record
Phillips et al [21] 2010–2013, Congo, Ghana, Togo	Children and adults (54% <19 y)	775	452	Retrospective case-control study (3b)	Buruli ulcer: clinical 401; stain 277; culture 56; PCR 373	Congo: 2010–2011 BCG Japan, 2012 BCG Japan or Russia, 2013 BCG Russia; Ghana: BCG Japan; Togo: BCG Russia	226/401 (56%)	549/826 (66%)	0.65 (.51–.83)	BCG vaccination reduced the risk of Buruli ulcer (but authors stated not after stratifying by country and age) • BCG vaccination did not influence duration or time to healing of skin lesions • Approximately 95% of cases were laboratory confirmed[a] • Vaccine status determined by presence of scar

Abbreviations: CI, confidence interval; PCR, polymerase chain reaction.

[a]By culture or PCR.

Table 4. Studies Reporting on the Protective Effect of BCG Vaccination Against *Mycobacterium ulcerans* Osteomyelitis in Patients With Buruli Ulcer

Study [Reference] Study Period, Location	Age of Participants	Study Type (Level of Evidence)	Outcome and Diagnostic Methods	Vaccine Strain	No. of Cases		Risk Ratio (95% CI)	Key Findings and Comments
					BCG-Vaccinated	BCG-Unvaccinated		
Portaels et al [23] 2004, Benin	Children and adults (60% <15 y)	Cohort study (2b)	Osteomyelitis in patients with Buruli ulcer: clinical 55; stain or culture or PCR 55	Not specified	34/304 (11%)	21/68 (31%)	0.36 (.22–.58)	BCG vaccination protected against *Mycobacterium ulcerans* osteomyelitis in children and adults with Buruli ulcer • Vaccine status determined by presence of scar • Not specified how many cases were laboratory confirmed[a]

Abbreviations: CI, confidence interval; PCR, polymerase chain reaction.

[a]By culture or PCR.

Notably, all but one of the studies reporting on the protective effect of BCG vaccination against Buruli ulcer assessed BCG vaccinations status only by the presence of a scar. Determining BCG vaccination status by the presence of a scar has a sensitivity of between 55% and 97% [33–35] and therefore its use may underestimate BCG vaccine effectiveness in comparative studies. However, the presence of a scar does not predict protection against tuberculosis [36, 37], and failure to develop a BCG scar might be an indication of poor vaccination technique [38]. As this might also be the case for NTM disease, using the presence of a scar rather than administration of BCG could, on the contrary, also overestimate protection.

There is some evidence to suggest that vaccine strain and genotype influence the protective effectiveness of BCG against *M. tuberculosis* [39–41]. It is therefore plausible that there is variation between different BCG strains in their protective effectiveness against NTM disease. The vaccine strains used in the studies included in this review varied considerably, precluding meaningful analysis.

A trial that included 121 020 people in Malawi showed that revaccination with BCG approximately halved the risk of leprosy compared with a single BCG vaccination, even though it did not protect against pulmonary tuberculosis [42]. It would be of interest to determine whether revaccination with BCG increases the strength or duration of protection against NTM.

A number of animal studies support the notion that BCG vaccination protects against NTM infection. Mice, rabbits, and guinea pigs vaccinated intracutaneously with BCG Dubos II are protected against *M. avium* administered intravenously [43]. Mice vaccinated with BCG Pasteur or Glaxo subcutaneously, intravenously or through the aerogenic route are protected against aerogenic infection with *M. avium* and *Mycobacterium kansaii*, but not against *Mycobacterium simiae* or *Mycobacterium intracellulare* [44, 45]. One study in mice found that the effectiveness of BCG vaccination against NTM infection varies according to differences in host conditions and different strains of *M. ulcerans* [46].

Recent trials have investigated the possibility of developing vaccines with greater effectiveness against NTM. The mycobacterial antigen 85A has 85% amino acid sequence similarity in *M. ulcerans* and *M. bovis*. A DNA vaccine encoding this antigen protects mice against Buruli ulcer [47]. This vaccine has been further developed, combining antigen 85A from *Mycobacterium smegmatis* with BCG in a live-recombinant vaccine, and protects mice against Buruli ulcer [48]. A single immunization with a plasmid expressing the BCG antigen DNA-35 protects mice against infection with *M. avium* [49].

The strengths of this review are the comprehensive literature search, the clearly defined inclusion criteria, and the use of meta-analysis to assess results from multiple studies. The main limitations are the heterogeneity between studies in design, including the use of different BCG strains. Further limitations are potential differences between the groups who received and did not receive BCG vaccine, such as epidemiological factors, access to healthcare, and intensity of surveillance. Additionally, the use of BCG scar to assess vaccination status in retrospective studies and the inclusion of non-laboratory-confirmed cases of NTM infection probably introduces bias. The risk of bias in the studies is summarized in Table 5.

Overall, our review and meta-analysis indicates that BCG vaccination protects against NTM. It is likely that effectiveness of BCG vaccination varies between different NTM diseases, populations, age groups, and the BCG strain used to vaccinate. The increase in incidence of NTM lymphadenitis in industrialized countries that have discontinued universal BCG vaccination might therefore be related to the loss of protection afforded by this vaccine.

Our review suggests that the protective effect of BCG vaccination against NTM should be taken into consideration when deciding on recommendations for discontinuation of universal BCG vaccination programs and in assessing new vaccines designed to replace BCG. In deciding vaccine policy, the incidence and the severity of the disease, as well as the NNT, are important considerations. The NNT with BCG vaccine to prevent one case of NTM lymphadenitis is probably unjustifiably high when considered in isolation, as NTM lymphadenitis is relatively rare and usually has a favorable outcome despite a frequently long and troublesome course. In contrast, Buruli ulcer is a serious condition with crippling sequelae and has been identified by the WHO as an emerging public health problem. The potential importance of BCG vaccination for preventing Buruli ulcer has been recognized in a recent WHO position paper [50].

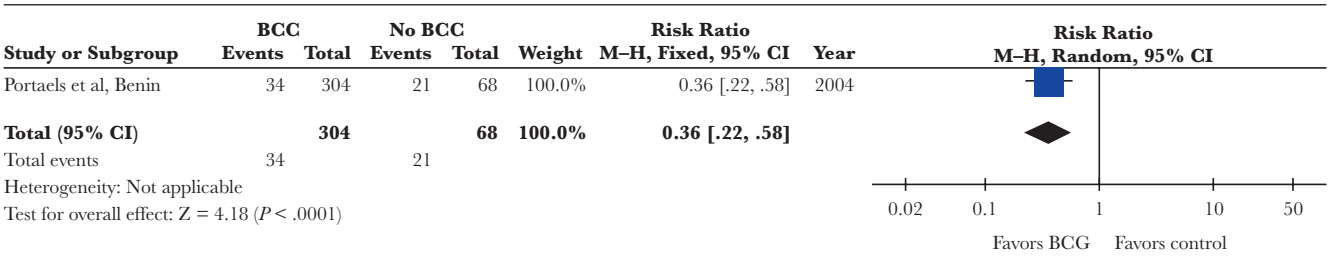

Figure 3. Comparison of incidence of osteomyelitis in BCG-vaccinated and BCG-unvaccinated participants with Buruli ulcer. Abbreviations: CI, confidence interval; M–H, Mantel-Haenszel.

Table 5. Summary of Risk of Bias in Studies Included in the Review

Study, First Author [Reference]	Publication Year	Study Type	Confounding	Selection Bias	Misclassification Bias	Performance Bias	Attrition Bias	Detection Bias	Reporting Bias
Lymphadenitis									
Katila [18]	1987	CS	5	3	3	3	4	2	2
Trnka [17]	1994	CS	4	1	2	4	3	5	2
Romanus [16]	1995	CS	4	1	2	3	3	5	2
Buruli ulcer									
Bradley [19]	1969	RCT		–		+	–	–	–
Smith [20]	1976	RCT		–		–	–	–	–
Raghunathan [25]	2005	CCS	4	3	5	3	4	3	4
Debacker [27]	2006	CCS	5	4	5	3	5	3	4
Nackers [22]	2006	CCS	4	4	5	3	4	3	5
Phillips [21]	2015	CCS	5	4	4	3	4	3	4
Mycobacterium ulcerans osteomyelitis									
Portaels [23]	2004	CS	3	4	5	3	4	3	4

Scale: 1 = very low; 2 = low; 3 = moderate; 4 = high; 5 = very high.

Abbreviations: CCS, case-control study; CS, cohort study; RCT, randomized controlled trial.

Notes

Author contributions. P. Z. drafted the initial manuscript and performed the systematic review and meta-analysis. N. C. and A. F. critically reviewed and revised the manuscript. All authors approved the final manuscript as submitted.

Financial support. P. Z. is supported by a Fellowship from the European Society of Paediatric Infectious Diseases and an International Research Scholarship from the University of Melbourne.

Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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