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Systematic Review of the Non-Specific Effects of Bacillus Calmette-Guérin Vaccine on Child Mortality

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Abstract

Background: Until a different vaccine is given, BCG provides non-specific protection against diseases other than tuberculosis, mainly respiratory infections and sepsis.

Methods: A systematic review was made using the databases Medline, Lilacs, Cochrane Library, Scopus and the WHO review of BCG, using the terms BCG, non-specific effects, heterologous immunity, and child mortality. The objective was to quantify the effect of BCG on all-cause mortality until a different vaccine was given in children up to 5 years of age in low-income countries. Randomized trials and observational studies performed in low-income populations where all-cause mortality was reported were selected.

Results: Fifty-nine articles were found. Nine studies had a low to moderate risk of bias; they consisted of two randomized trials, six cohort studies and one case-control study; they were performed in Guinea-Bissau, India, Benin, Malawi and Senegal. The effect estimates were homogeneous, with I2=0.0% (p=0.71). Meta-analysis of all nine studies using a random effects model yielded an effect estimate of 0.56 (95% CI 0.46-0.69). The combined estimate for the two randomized trials of BCG-Denmark that had a low risk of bias was 0. 52 (95% CI 0.33- 0.82).

Conclusions: The two randomized trials and the seven observational studies suggests that, until a different vaccine is given, administration of the strains of BCG used in these studies approximately halved all-cause mortality in children under five years of age in these low-income countries.

Keywords: Vaccine; Tuberculosis; Mortality rate

Abbreviations: BCG: Bacillus Calmette-Guérin vaccine; DTP: Diphtheria-Tetanus-Pertussis Vaccine; WHO: World Health Organization.

Introduction

Worldwide between 1990 and 2015, the under 5 years of age (under 5) mortality rate decreased from 90 to 43 deaths per 1000 live births, and the annual number of under 5 deaths halved from 12.7 million to 5.9 million [1]. However, 5.9 million deaths per year is still far too many. If the whole world had the under 5 mortality rate of 3 per 1000 live births seen in Japan, Norway, Singapore and Sweden, there would have been only 0.4 million under 5 deaths worldwide in 2015 rather than 5.9 million. So, there were the possibility of avoiding 5. 5 million deaths of children under 5 years in 2015, a very impacting number for the families well being and for the nations. According to the World Health Organization (WHO), most of the 5.5 million excess deaths were caused by infections [2].

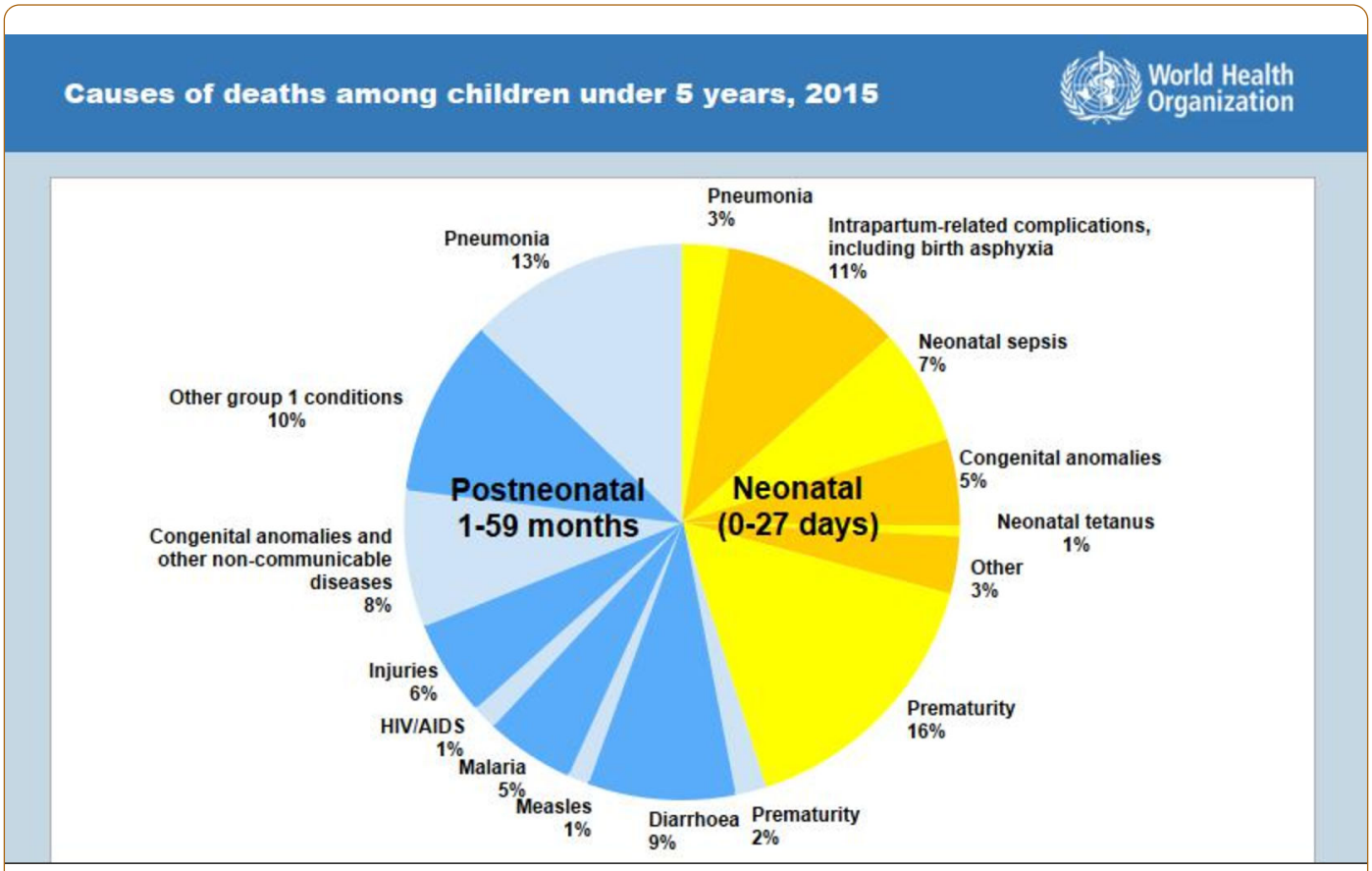

Figure 1 Causes of child mortality in 2015, from World Health Organization database.

In studies in the United States and the United Kingdom in the years 1940 to 1950, Bacillus Calmette-Guérin (BCG) vaccine was associated with a 25% reduction in all-cause child mortality from diseases other than tuberculosis [3]. Subsequently, observational studies in countries with high infant mortality rates supported these findings [4]. In 2014, a cohort study in 18 countries reported a reduction of 17% to 37% in the risk of acquiring lower airways respiratory disease in children under 5 years old vaccinated with BCG [5]. In 2014, a review of the non-specific effects of BCG performed for the World Health Organization (WHO) concluded that "the estimated effects are in the region of a halving of mortality risk", and pointed out that deaths from tuberculosis are infrequent in the first five years of life, "so any effect of BCG vaccine on all-cause mortality is not likely to be attributable to any great extent to fewer deaths from tuberculosis" [6].

WHO recommends BCG vaccination as soon as possible after birth in countries with a high incidence of tuberculosis [7]. For preterm infants with gestational age below 36 weeks, vaccination is recommended just after the child reaches one month of age. However, many children in high-mortality regions are not vaccinated with BCG at birth [8] **(Figure 1).**

Because of the potential importance of the finding that, until a different vaccine is given, BCG may be associated with substantial reductions in mortality in children less than 5 years of age, we performed a systematic review of studies of the effect of giving BCG on all-cause mortality in children in low-income countries.

Methods

A systematic review was made using the databases Medline, Lilacs, Cochrane Library, Scopus and the WHO review of BCG, using the terms BCG, non-specific effects, heterologous immunity, and child mortality. Articles published up to January 2015 were included. The search strategy was individualized for each database and the bibliography of articles searched for further studies. The inclusion criteria were randomized trails, cohort studies and case-control studies performed in low-income populations with high under 5 mortality rates where all-cause mortality was reported and the article was written in English, Portuguese or Spanish. The titles and abstracts were reviewed by two authors; articles that did not fulfill the inclusion criteria for population and intervention were excluded. The selected articles had their full text read and critically appraised. Where available, the effect of BCG on mortality from both tuberculosis and other causes of death was noted. The exclusion criteria were BCG vaccination after five years of age, articles about the non-specific effects of BCG that did not report under 5 mortality, and studies that did not report subsequent mortality separately for BCG alone when a substantial proportion of children received whole-cell diphtheria-tetanus pertussis vaccine (DTP) or measles vaccine with or after BCG. Because of the evidence that BCG made by

different manufacturers may have very different clinical properties [9], the strain of BCG used was noted where possible. Statistical analysis was performed using Stata version 14.1 (Statacorp, College Station, Texas).

Results

Fifty-nine articles were found, 15 were eligible for detailed analysis, and nine were included in the final analysis **(Figures 2 and 3; Table 1)** [10-18]. The nine studies with a low to moderate risk of bias consisted of two randomized trials, six cohort studies and one case-control study. The studies were performed in Guinea-Bissau (four studies), India (two studies), Benin, Malawi and Senegal.

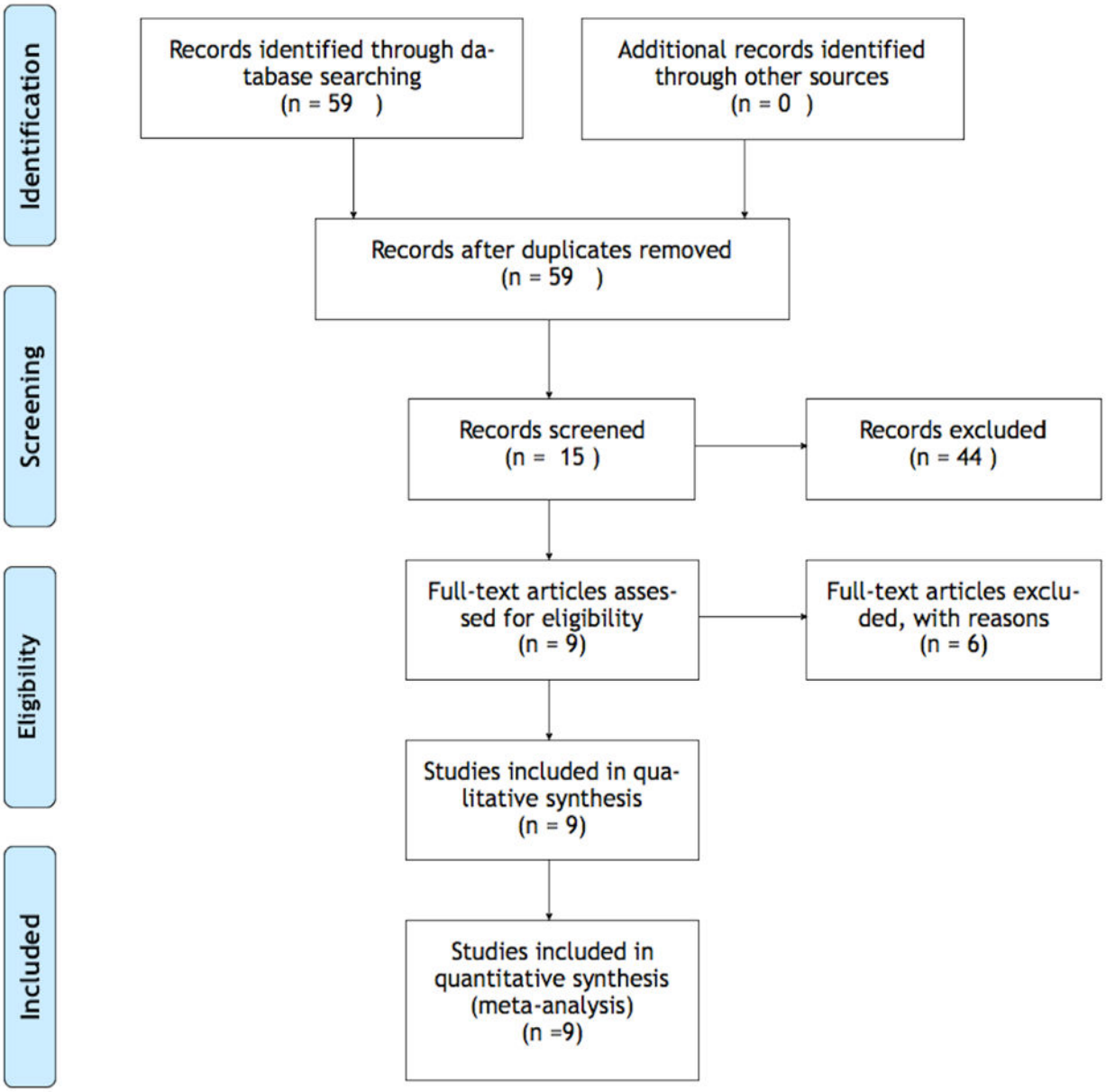

Figure 2 Flow diagram.

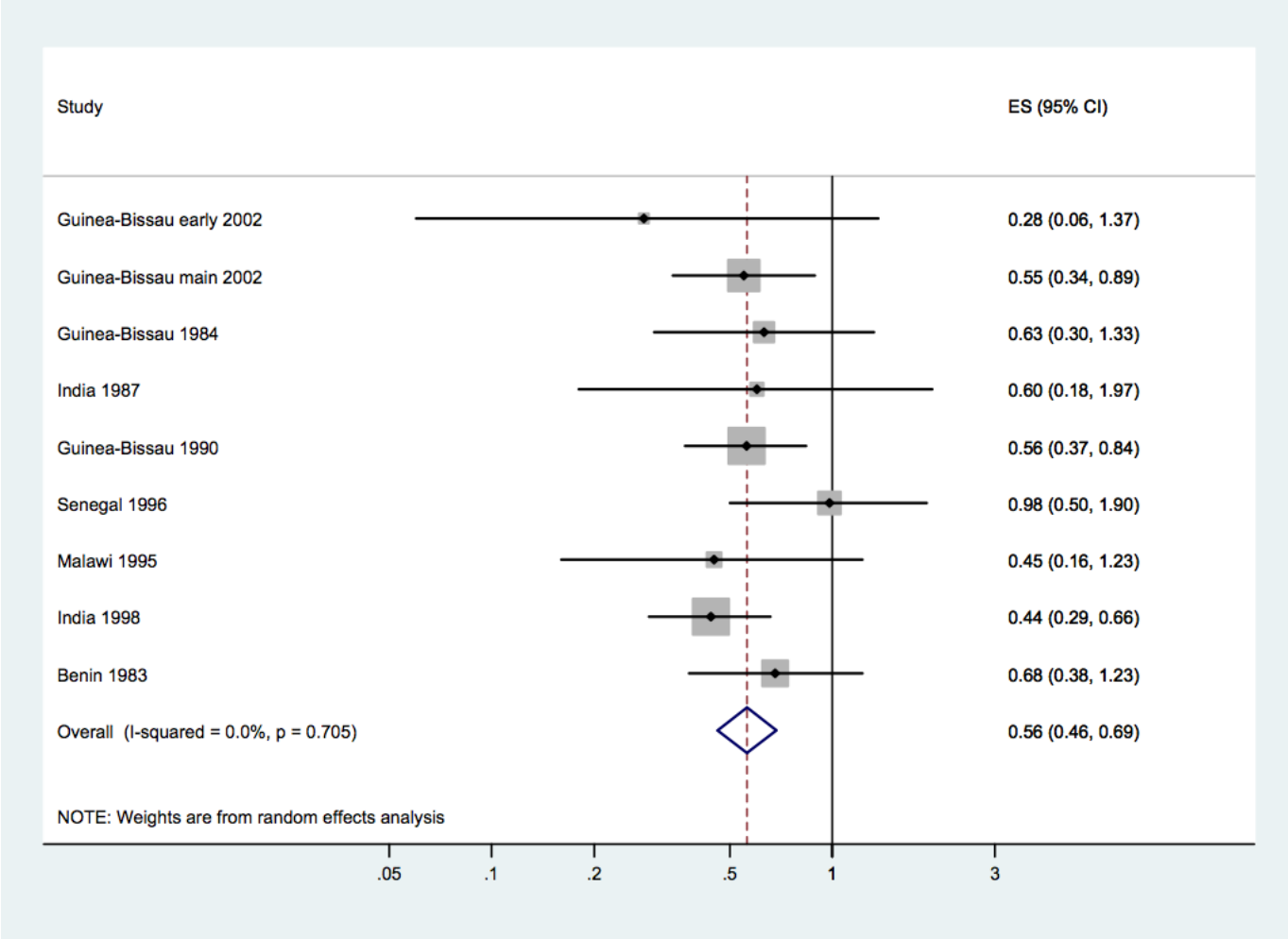

Figure 3 Forest plot of studies of the effect of BCG on all-cause mortality in children under 5 years of age in high-mortality countries (ES=effect size).

Table 1 Studies of the effect of BCG on all-cause mortality in children under 5 years of age in high-4-mortality countries.

Studies included in this analysis		Number of children	Age	Assessment of unvaccinated status	Confounding	Subsequent DTP	Adjustment	Effect
Guinea-Bissau 2002-3003	Blenng-Saann. P1DJ 2012; 31:306-8	105	0-4 w	Randaomized trial	Low	None	Age	0.28 (0.06-1.37)
Guinea-Bissau 2002-2008	Aaby, JID 2011; 204: 245-52	2320	0-4 w	Randaomized trial	Low	None	Age	0.55 (0.34-0.89)
Guinea-Bissau 1984-1985	Aaby, IJE 2004; 33: 374-80	1657	2-8 m	BCG given by researchers	Moderate	Many	Age, Sex, DTP, other	0.63 (0.30-1.33)
India 1987-1989	Hirve, Vaccine 2012; 30: 7300-8	3072	0-12 m	Vaccination card, 34% not seen	Moderate	None	None	0.60 (0.18-1.97)
Guinea-Bissau 1990-1996	Aaby, BMJ 2002 online; 2011/10/29	5274	1-6 m follow up	Vaccination card, 7% not seen	Moderate	Many	Age, other	0.56 (0.37-0.84)

Senegal 1996-1999	Aaby, TRSTMH 2015; 109: 77-84	4120	44% by 12 m to 24 m	no card assumed unvaccinated	Moderate	Many censored	Age, Sex, other	0.98 (0.50-1.23)
Malawi 1995-1997	Aaby, PIDJ 2006; 25: 721-7	751	0-6 m	clinic register, 29% dead card unseen	Moderate	Many censored	Age, other	0.45 (0.16-1.23)
India 1998-2002	Moulton, TMIH 2005; 10: 947-55	10274	0-6 m	Home interview	Moderate	Many censored	Age	0.44 (0.29-0.66)
Benin 1983-1987	Velema, IJE 1991; 20: 474-9	294	Observed 4-36 m	Clinic register, Case-control study	Moderate	Many	Age, Sex, other	0.68 (0.38-1.23)
Studies included in the WHO analysis but excluded from this analysis								
PNG 1989-94	Lehmann, IJE 2005;34: 138-48	3937	0-6 m	no card assumed unvaccinated	High: Unvaccinated 233/1000 died	Many	Age, DTP, other	0.17 (0.09-0.34)
Guinea-Bissau 1989-1999	Roth, PIDJ 2004; 23: 544-50	695	0-6 m	Vaccination card		Many	Age, Sex, other	0.05 (0.01-0.46)
Studies excluded from both the WHO analysis and this analysis								
Burkina Faso 1985-1993	Vaugelade, BMJ 2004; 329: 1309-11	9085	Mean 4.8 m, 6 m follow up	No card assumed unvaccinated	High	Some with DTP	Age, other	0.5 (0.34-0.75)
Bangladesh 1986-2001	Breiman, Lancet 2004; 364: 2204-11	37894	0-60 m	No card assumed unvaccinated	High	Many with DTP	Age	0.2 (0.07-0.54)
Ghana 1998-2004	Bawah, ScjPubHlth 2010; 38: 95-103	17967	57% by 12 m to 60 m	No card assumed unvaccinated	High	Many	Age, other	0.18 (0.17-0.20)
India 2006-2011	Krishnan, TMIH 2013; 18: 1329-37	11390	0-5 w	Clinic Record, else assumed unvaccinated	High: Age Cofounding	Few	None	0.12 (0.09-0.16)

Two studies that were included in the WHO analysis of the non-specific effects of BCG were excluded from this analysis because they had a very high risk of bias **(Table 1)**. The study in Papua New Guinea had a very high mortality rate of 233 per 1000 person years among unvaccinated children aged 1-5 months compared to only 31 per 1000 person years in vaccinated children, in a region with a 0-12 month mortality of 68 per 1000 live births at the time. Frailty bias occurred because government policy was that children should not be immunized if they were unwell, so unvaccinated children were a high-risk group. In the cohort study of low-birth-weight infants in Guinea-Bissau, babies were vaccinated as they reached 2.5 kg weight, so unvaccinated time was greater in low-weight high-risk infants and vaccinated time was greater in heavier lower-risk children, introducing frailty bias. Four cohort studies were excluded from both this analysis and the WHO analysis because of high risk of bias **(Table 1)**. Most studies did not state the strain of BCG used.

In the nine studies included in this analysis, meta-analysis showed that the effect estimates were homogeneous, with I2=0.0%, with p=0.71 **(Figure 2)**. A fixed effects model yielded an effect estimate of 0.56 (95% confidence interval 0.46-0.67) and a random effects model yielded 0.56 (95% CI 0.46-0.69). The combined estimate for the two randomized trials of BCG-Denmark in Guinea-Bissau that had a low risk of bias was 0.52 (95% CI 0.33-0.82).

The WHO analysis included three pseudo-randomized trials performed in North America in the 1930s and 1940s, as well as the two cohort studies from Papua New Guinea and Guinea-Bissau that were excluded from this analysis because of bias [19,20]. Meta-analysis showed substantial heterogeneity in the 14 WHO studies with I2=62% (p=0.001), but the random effects estimate of 0.53 (95% CI 0.40-0.72) was very similar to the random effects estimate of 0.52 (95% CI 0.33-0.82) from the nine studies in our analysis [21-24].

Discussion

Cohort studies overestimate the beneficial effects of BCG if they are subject to frailty bias (when ill children are not vaccinated), ascertainment bias (children with no vaccination record who die are assumed to be unvaccinated when some are vaccinated), and survival bias (if vaccination status is determined retrospectively and vaccination cards are destroyed when a child dies) [25-27]. On the other hand, cohort studies will underestimate the beneficial effects of BCG if they are subject to age bias (when younger unvaccinated children at high risk of dying are compared to older vaccinated

children), if no allowance is made for administration during follow-up of beneficial vaccines such as BCG or measles vaccine or oral polio vaccine, or if no allowance is made for DTP given with or after BCG (as DTP reduces the benefit from BCG) [28,29].

Our selection of cohort studies was designed to minimize the risk of major bias. We excluded Papua New Guinea 1989-1994 and Guinea-Bissau 1989-1999 because there was evidence of substantial frailty bias in these studies [19,20]. Three other cohort studies were excluded because of co-administration of DTP, and the assumption that children were unvaccinated if there was no record of their having a vaccination card (especially if no children were censored for lack of information) [21-23]. Another study was excluded because the analysis was not adjusted for age, and the BCG-unvaccinated children were younger than BCG-vaccinated children [30]. Evidence that we eliminated major sources of bias is provided by the finding that the combined estimate for the seven observational studies of 0.57 (95% CI 0.46-0.71) was similar to the combined estimate for the two randomized trials of 0.52 (95% CI 0.33-0.82); the randomized trials had a low risk of bias. This large reduction in all-cause mortality, largely because of fewer deaths from pneumonia and sepsis [10-11], was not due to a specific effect of BCG on mycobacterial infection because tuberculosis is an uncommon cause of death in the first five years of life [6].

BCG is likely to be more effective when child mortality is very high and most deaths are caused by infection; as mortality falls, a higher proportion of deaths are due to non-infectious causes that are unlikely to be prevented by BCG.

The most likely mechanism for the beneficial effect of BCG is an alteration in innate immune function, which would explain why an effect is seen early in the first 1-3 days after vaccination. 30 In adults, immunization with the BCG vaccine leads to elevated production of the pro-inflammatory cytokines tumor-necrosis factor and interleukin 1b in response to non- BCG–related stimuli that is maintained for up to 3 months after vaccination. Furthermore, monocytes recovered 1 year after such vaccination still display increased expression of the co-receptor CD14, pattern-recognition receptors (for example, Toll-like receptor 4) and the receptor for mannose. The underlying molecular mechanisms that lead this sustained alteration in function of the innate immune system following immunization with the BCG vaccine appear to relate to changes in the epigenetic regulation of gene expression following innate stimulation. The effect on innate immunity is at least in part due to an epigenetic mechanism mediated by methylation of histone. 31 In other words, exposure to BCG changes both the phenotype as the circulation status of mononuclear cells, increasing CD14+ number of monocytes and their receptors expression. In addition, it is known that modification of histones (acetylation or methylation) is crucial in regulating the inflammatory response in the body and it was observed that vaccination with BCG increases the trimethylation of histone H3 in lysine K4 (H3K4). In a combination of studies *In vivo* and *In vitro*, it has been demonstrated that an epigenetic change NOD2 mediated at the level of histone methylation is the mechanism by which BCG acts in the immune system. So, it was concluded that monocytes can be reprogrammed and "trained" to a new phenotype acquired after vaccination with BCG and it can cause two types of immune responses: 1. classical and induces a specific immune response involving antigen specificity by T cells and immunological memory leading to protection against tuberculosis, 2. induces adaptive response based on reprogramming the mononuclear phagocyte system, which results in protection against other infections other than tuberculosis. It is possible that changes in innate immunity following such immunization differ according to age and sex of the recipients; age-dependent differences between infants and adults have been noted in their innate immunity in general and in their response to the BCG vaccine in particular [30-32].

There is evidence that BCG vaccine produced by different manufacturers has very different clinical effects. Unfortunately, most investigators did not record the strain of BCG that was used in the studies reported here. We know that BCG-Denmark was used in the two randomized trials in low-birth-weight babies in Guinea-Bissau [9,10], but it cannot be assumed that other strains of BCG will have the same effect. BCG-Denmark and BCG-Japan both contain at least two different genomes, which may explain the considerable variation in clinical effects between batches from individual manufacturers. We need to determine what genomes are in all the BCG products made by the major manufacturers, determine the most effective genome, and standardize production using that genome.

The evidence that BCG has beneficial non-specific effects has important implications for policy [32]. In addition to developing a vaccine based on the most effective genome, we need to ensure that as many children as possible are given BCG at birth in high-mortality countries. Although it is policy for BCG to give at the time of birth, the vaccine is usually supplied in 20-dose vials and many clinics do not open a vial until they have 8-12 infants to immunize, so most neonates do not currently get BCG at birth. In addition, if a new vaccine is developed that provides better protection than BCG against tuberculosis in older children and adults, there will be a strong case for continuing to give BCG to neonates to provide the beneficial non-specific effects.

The evidence that BCG approximately halves all-cause mortality suggests that substantial further reductions in child mortality could be achieved by giving BCG at birth to all babies in high-mortality countries, and by identifying the BCG genome that provides the most effective protection against tuberculosis and infections other than tuberculosis. We urgently need randomized trials of other BCG strains in addition to the two trials of BCG-Denmark that have been performed in Guinea-Bissau.

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Conflict of Interest

The authors have no conflicts of interest to disclose.

Clinical Trial Registration

Not registered.

Contributors' Statements

Cintia Cruz: Dra Cruz conceptualized and designed the study, designed the data collection instruments, reviewed the selected articles, carried out the initial analyses, reviewed and revised the manuscript and approved the final manuscript as submitted.

Bruna Almeida: Dra Almeida conceptualized and designed the study, designed the data collection instruments, reviewed the selected articles, carried out the initial analyses, reviewed and revised the manuscript and approved the final manuscript as submitted.

Eduardo Troster: Dr Troster conceptualized and designed the study, designed the data collection instruments and coordinated and supervised data collection, critically reviewed the manuscript, and approved the final manuscript as submitted.

Cardim Oliveira: Dr Cardim conceptualized and designed the study, designed the data collection instruments, worked on the statistical analyses, critically reviewed the manuscript, and approved the final manuscript as submitted.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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