Co-administration of Oral Polio Vaccine and Bacillus Calmette-Guerin in Infants: Systematic Review of Low and Middle-income Countries

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ABSTRACT

Background: Immunization decreases 2 to 3 million deaths annually; however, an additional 1.5 million deaths could be avoided if global vaccination coverage improves. Immunization is one of the cornerstone interventions to reach the Millennium Development Goals (MDGs), especially the goal to decrease deaths among children under five years old. Childhood vaccinations have been illustrated to be effective in protecting children against vaccine preventable diseases in low and middle-income countries. As one of the earliest vaccines of the World Health Organization’s (WHO) Expanded Program on Immunization established in 1974, Bacillus Calmette-Guérin (BCG) is the main stone of childhood vaccination. Administering OPV together with BCG might downregulate the response to BCG vaccine (Kaur 2002; Faridi 2015). Reviewing different studies, it has reported that this may downregulate response to BCG in the form of fewer numbers of scar formation, reduced scar size, reduced in vivo response to purified protein derivative (PPD) and significantly lower IL-13 and IFN-γ and a tendency to have lower IL-10 in response to PPD at 6 weeks following immunization.

Objectives:
- To investigate whether co-administration of BCG and oral polio vaccine increases infant mortality rate.
- To investigate whether co-administration of oral polio vaccine and BCG attenuate the immune response to BCG compared to the administration of BCG alone.

Search methods: We searched through the following databases: MEDLINE, Register of Controlled Trials (CENTRAL); Scopus; CINAHL (EBSCO); Google Scholar; Clinicaltrials.gov and WHO International Clinical Trials Registry Platform (ICTRP). Main results: We found 1777 studies were through systematic electronic search. Therefore 1356 studies remained after excluding duplicated studies. We assessed and screened 855 studies, and only 11 articles were fully assessed. Among them, 6 studies were included in data analysis. There is high evidence that infant mortality rate was reduced by 22 % in BCG group compared to BCG-OPV group with a p-value of 0.09. Therefore, the evidence was moderate and low in specific mortality rate respectively boys and girls. Then, the mortality rate was reduced by 28% and 15 % respectively in boys and girls (p-value of 0.09 and 0.31). Local immune reaction (scar) was 41 % less likely present in BCG-OPV group compared to BCG alone. ). Therefore, the 95% CI is very wide and including the null value. Authors' Conclusions: An increasing number of vaccines targeting some of the leading causes of morbidity and mortality are reaching the world’s children. Evidence suggests that receipt of BCG reduce overall infant mortality. This review has shown that co-administration BCG-OPV could increase infant mortality. Therefore, the results could be considered in a context of several limitations.

Keywords: BCG, Oral polio vaccine, Co-administration, Infants.
1. INTRODUCTION

Immunization decreases 2 to 3 million deaths annually; however, an additional 1.5 million deaths could be avoided if global vaccination coverage improves (WHO 2016). Immunization is one of the cornerstone interventions to reach the Millennium Development Goals (MDGs), especially the goal to decrease deaths among children under five years old (WHO 2009). Childhood vaccinations have been illustrated to be effective in protecting children against vaccine preventable diseases in low and middle-income countries (Danielson 2009; Lakew 2015).

As one of the earliest vaccines of the World Health Organization’s (WHO) Expanded Program on Immunization established in 1974, Bacillus Calmette-Guérin (BCG) is the main stone of childhood vaccination (Harris 2016). It is a safe vaccine, widely used for neonatal vaccination in 84 % of countries and provided to over 100 million neonates annually to protect against childhood tuberculosis (TB) (Harris 2016).

BCG vaccine has proved its efficacy in several trials and epidemiological studies conducted (Roy 2014). Reported rates of the protective efficacy of BCG vaccines might have been affected by the methods and routes of vaccine administration and by the environments and characteristics of the populations in which BCG vaccines have been studied (CDC 1996). These trials illustrate that BCG has 60-80% protective efficacy against severe forms of tuberculosis in infants, particularly meningitis (Trunz 2006; Rodrigues 2011; Roy 2014), and its efficacy against pulmonary tuberculosis varies geographically (Colditz 1995; Lienhardt 2005; Abubakar 2013; Roy 2014). Furthermore, BCG vaccination contributes to the prevention and control of TB in limited situations when other strategies are inadequate (CDC 1996). The severity of active TB disease during childhood warrants special efforts to protect children, particularly those <5 years of age (CDC 1996). BCG is routinely administered to all newborn infants under the Universal Immunization Program Faridi 2015. From 1985 to 2010, WHO urged that OPV should be given at birth or first contact with the health system in low-income countries (Global advisory group 1985) (Lund 2015). OPV given at birth (OPV0) remains the policy in countries at high risk for polio infection (Lund 2015).

Therefore, concomitant administration of BCG and oral polio vaccine has a controversial effect on BCG efficacy in infants as shown in different trials and cohort studies. In fact, administering OPV with BCG might downregulate BCG vaccine response (Kaur 2002; Faridi 2015). Reviewing different studies, it has reported that this may downregulate response to BCG in the form of fewer numbers of scar formation, reduced scar size, reduced in vivo response to purified protein derivative (PPD) and significantly lower IL-13 and IFN-γ and a tendency to have lower IL-10 in response to PPD at 6 weeks following immunization (Faridi 2008; Sartono 2010; Faridi 2015). Recently, studies have also shown that giving OPV and BCG together to neonates induced to a significantly lower concentration of IFN-γ and decrease the levels of interleukin-5 to PPD, implying that OPV affected both Th-1 and Th-2 cytokine responses (Jensen 2014; Faridi 2015). Most BCG efficacy studies were done before the introduction of OPV at birth. It may be speculated that the addition of OPV to BCG at birth has further compromised the protection induced by BCG (Sartono 2010; Faridi 2015). After BCG vaccination, a cascade of reaction takes place where IL-2, interferon-γ, and TNF-α are predominantly secreted. Inflammation and suppuration at the site of BCG vaccination are mediated through interleukins (Sallusto 1999; Faridi 2015). Demonstrating then mucosal administration of OPV simultaneously with intradermal BCG vaccination at birth may have profound immunological consequences (Sartono 2010; Faridi 2015).

Previously, it has been shown that BCG vaccination given at birth in either NBW or LBW infants enhanced the immune response to PPD, characterized by elevated IL-5, IL-13 and IFN-c levels (4, and unpublished data) Sartono 2010. In the present study, the administration of OPV at the time of BCG priming at birth, reduced Th1 and Th2 cytokine responses to mycobacterial antigens in LBW infants, suggesting that OPV down-regulated cellular immune responses to BCG vaccine when the vaccines were administrated at the same time (Sartono 2010). One possible mechanism whereby OPV co-administered with BCG leads to a reduced cellular response to PPD may be a competition of OPV and BCG-activated T cells for resources and space (Stockinger 2004; Sartono 2010). A second possible mechanism is that poliovirus may have specific immune modulatory molecules that down-regulate immune responses to antigens to which immune responses are being mounted simultaneously (Vekemans 2002; Sartono 2010).

In developing countries, TB infection still constitutes a major public health problem among children. Even if, great improvement has been done to improve TB
immunization, the challenge remains still the same (Moliva 2015). In fact, the protective efficacy of BCG and its duration varies significantly according to geography and population age (Moliva 2015). Many new vaccines seek to improve upon BCG using genetic modifications, and although new vaccines are in development there remain several challenges to implementing them worldwide (Moliva 2015).

Tremendous progress in improving vaccination coverage has been made over the past four decades in many African countries (WHO 2005; (Lakew 2015). Strengthening routine immunization services, especially in countries with the greatest number of under-vaccinated children, should be a global priority to help achieve the fourth Millennium Development Goal of reducing mortality among children aged <5 years by two-thirds from 1990 to 2015 (MMWR 2011). Therefore, some interaction between vaccines should be highlighted so that the efficacy and effectiveness could be estimated. The review is analyzing the effect of oral polio vaccine on BCG in children less than five years in low and middle-income countries.

**Objectives**

- To investigate whether co-administration of BCG and oral polio vaccine increased infant mortality rate.
- To investigate whether co-administration of oral polio vaccine and BCG attenuate the immune response to BCG compared to the administration of BCG alone.

**2. METHODS**

**Criteria for considering studies for this review**

**Types of studies**

We included randomized control trials, non-randomized control trials, quasi-randomized control trials and prospective cohort studies.

**Types of participants**

Infants less than 5 years old.

**Types of interventions**

Co-administration of oral polio vaccine and BCG.

**Types of outcome measures**

*Primary outcomes*

All cause of mortality

*Secondary outcomes*

Local immune reaction

**Search methods for identification of studies**

The search strategy was made according to the above Mesh and keywords. We adapted the search strategy based on different databases: Children, infants, Inactivated Poliovirus Vaccine, Salk Vaccine, Immunization, Vaccination, Co-administration, Vaccine, BCG, Bacillus Calmette-Guerin Vaccine, Calmette-Guerin Bacillus Vaccine, Calmette's Vaccine, Calmette Vaccine, Calmettes Vaccine.

We will search the following databases: MEDLINE, Register of Controlled Trials (CENTRAL); Scopus; CINAHL (EBSCO); Google Scholar, Clinicaltrials.gov; WHO International Clinical Trials Registry Platform (ICTRP).

**Searching other resources**

We searched the World Health Organization (WHO) International Clinical Trials Registry Platform (apps.who.int/trialsearch/) and ClinicalTrials.gov for completed and ongoing studies to 3 November 2015. We checked the reference lists of all primary studies and reviewed articles for additional references. We did not email experts in the field about other published and unpublished studies that may be eligible for inclusion.

**3. ANALYSIS**

**Selection of studies**

Titles and abstracts of studies were screened for inclusion by two authors. Two authors independently applied the inclusion criteria to retrieve the full text of the selected studies. Any disagreements about inclusion criteria were discussed among the two authors. In the case of divergence, further information from the authors where papers contained insufficient information to make a decision about eligibility. We listed the excluded studies and the reason for their exclusion.

**Data extraction and management**

We designed data extraction form. Data was extracted independently by the two reviewers using the designed form. The main information recorded for each study was:

- study details: citation, study population, population size, study design,
- types of intervention
- Comparison
- Outcome Details: primary and secondary.
- Follow-up duration
- Power calculation

In the case of disagreement between two authors, a third author will be consulted to find out the resolution. In the case of missing or unclear data, the study authors will be contacted.

**Assessment of risk of bias in included studies**

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Critical appraisal of trials was conducted independently by two reviewers using the criteria recommended in the Cochrane Handbook (Higgins 2011). The following domains for assessing risk of bias was used as well as for randomized control trials and observational studies: sequence generation and allocation concealment (selection bias), blinding of participants and providers (performance bias), blinding of outcome assessor (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias), and other sources of bias. The tool involved assigning a judgment relating to the risk of bias for that entry, in terms of low, high or unclear risk. Therefore, the risk of bias in prospective cohort studies was assessed by the Newcastle-Ottawa Scale. In the case of disagreement between two reviewers, a third author was involved for consensus.

**Measures of treatment effect**
As only dichotomous data were included, the results were presented as summary risk ratio as well as odds ratio with 95% confidence intervals.

**Unit of analysis issues**
As we found no cluster RCTs to include in the review, we did not have to contend with a unit of analysis problems.

**Dealing with missing data**
We did not find any missing data in all included studies

**Assessment of heterogeneity**
We assessed statistical heterogeneity in each meta-analysis using the $I^2$ and $Chi^2$ statistics. We considered heterogeneity as substantial when $I^2$ was more than 50% or low $P$ value (less than 0.10) in the $Chi^2$ test for heterogeneity.

**Assessment of reporting biases**
Less than ten studies were included in the meta-analysis. We did not investigate reporting biases using funnel plots.

**Data synthesis**
Meta-analysis was carried out based on the participants, intervention, and outcome. We summarized each binary outcome using a random-effects model in a meta-analysis that compares intervention and control arms. The meta-analysis was performed using RevMan.

**Subgroup analysis and investigation of heterogeneity**
We included six studies and then subgroup analyses was carried out based on:
- Intervention modality (functionality and setting): to capture potential differences caused by different delivery mechanisms and settings for the intervention outside of the actual content of the intervention;
- Timing of outcomes (intermediate versus delayed): to investigate possible delay over time;
- Key population subgroups: gender and age

**Sensitivity analysis**
In our protocol, we planned to conduct a sensitivity analysis to monitor the robustness of the results. However, our meta-analysis only includes two studies. Therefore, we did not conduct a sensitivity analysis.

### 4. RESULTS

**Results of the search**
1777 studies were found after electronic search, 1356 studies remained after excluding duplicated studies, 855 studies were screened, 11 articles were fully assessed, 5 studies (Alam 2015; Jensen 2014; Kuruvilla 2009; Prentice 2015; Ryder 1993) were excluded with reasons and 6 studies (Benn 2008; Faridi 2015; Jensen 2015; Lund 2012; Lund 2015; Sartono 2010) were included in meta-analysis(Figure1).

**Fig. 1 Study flow diagram**

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Included studies
Six studies were included in this systematic review: three randomized control trials Jensen 2015; Lund 2012; Lund 2015, two natural experimental Benn 2008; Sartono 2010 and one prospective cohort study Faridi 2015 (Tables 1 & 2).

Table 1 Characteristics of included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Methods</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benn 2008</td>
<td>A Natural Experiment</td>
<td>A total of 962 children (22.1%) of the 4345 enrolled children did not receive OPV at birth. Setting: six suburban districts of the capital of Guinea-Bissau.</td>
<td>All trial infants were vaccinated intradermally in the upper left deltoid region with 0.05 ml BCG vaccine (Statens Serum Institut Copenhagen, Denmark). Infants received OPV or not.</td>
<td>Birth on mortality up to 12 months of age ((Deaths/pyrs). No OPV at birth: 30/859, OPV at birth: 149/3031 Boys No OPV at birth: 9/451, OPV at birth: 82/1514 Girls No OPV at birth: 21/408, OPV at birth: 67/1517</td>
<td>In total, 611 newborns enrolled in the main trial were eligible for inclusion in the immunological substudy. Of these, 461 infants had a follow-up blood sample taken; valid in vitro cytokine analyses were performed on 378 infants, valid differential counts were available for 212 infants, and paired baseline and follow-up measurements of RBP and CRP were obtained from 404 infants. Newborns with no over illness or malformations, weighing ≥ 2.5 kg. Setting: a health and demographic surveillance system site covering six suburban districts of Bissau, the capital of Guinea-Bissau, West Africa.</td>
</tr>
<tr>
<td>Faridi 2015</td>
<td>Prospective observational study.</td>
<td>152 term neonates born in the hospital and given BCG and OPV 0-dose simultaneously before discharge, within 7 days of birth (Group 1), and 122 infants born at home or in private health facility, not given an OPV-0 dose, coming for vaccination within 7 days of age (Group 2). The present study was conducted in the Department of Pediatrics, Era’s Medical College and Hospital, Lucknow, India during March 2008 to December 2010</td>
<td>BCG and OPV 0-dose simultaneously before discharge. Not given OPV-0 dose Follow up done at 6 weeks, 10 weeks, 14 week and 9 months</td>
<td>Local Reaction scar 14 weeks Intervention group: 76/148), Control group: 109/122 9 months Intervention group: 139/148), Control group: 115/122)</td>
<td>Results In total, 611 newborns enrolled in the main trial were eligible for inclusion in the immunological substudy. Of these, 461 infants had a follow-up blood sample taken; valid in vitro cytokine analyses were performed on 378 infants, valid differential counts were available for 212 infants, and paired baseline and follow-up measurements of RBP and CRP were obtained from 404 infants. Newborns with no over illness or malformations, weighing ≥ 2.5 kg. Setting: a health and demographic surveillance system site covering six suburban districts of Bissau, the capital of Guinea-Bissau, West Africa.</td>
</tr>
<tr>
<td>Jensen 2015</td>
<td>Parallel randomized control trial</td>
<td>Results In total, 611 newborns enrolled in the main trial were eligible for inclusion in the immunological substudy. Of these, 461 infants had a follow-up blood sample taken; valid in vitro cytokine analyses were performed on 378 infants, valid differential counts were available for 212 infants, and paired baseline and follow-up measurements of RBP and CRP were obtained from 404 infants. Newborns with no over illness or malformations, weighing ≥ 2.5 kg. Setting: a health and demographic surveillance system site covering six suburban districts of Bissau, the capital of Guinea-Bissau, West Africa.</td>
<td>Infants received OPV0 together with the BCG (OPV0 + BCG) or BCG alone (BCG). The BCG (Danish strain 1331, Statens Serum Institut, Copenhagen, Denmark) was given intradermally in the upper left deltoid region while the trivalent OPV was administered as two drops orally. The follow-up visit at 2, 4 or 6 weeks</td>
<td>scar 2 to 6 weeks OPV + BCG group: 155/174, BCG group: 170/188 Boys OPV + BCG group: 74/84, BCG group: 88/100 Girls OPV + BCG group: 81/90, BCG group: 81/88</td>
<td>Results In total, 611 newborns enrolled in the main trial were eligible for inclusion in the immunological substudy. Of these, 461 infants had a follow-up blood sample taken; valid in vitro cytokine analyses were performed on 378 infants, valid differential counts were available for 212 infants, and paired baseline and follow-up measurements of RBP and CRP were obtained from 404 infants. Newborns with no over illness or malformations, weighing ≥ 2.5 kg. Setting: a health and demographic surveillance system site covering six suburban districts of Bissau, the capital of Guinea-Bissau, West Africa.</td>
</tr>
<tr>
<td>Lund 2015</td>
<td>Randomized control trial, factorial design</td>
<td>LBW children do not receive BCG at birth, but only when they have reached 2500 g.</td>
<td>Infants randomized to BCG at birth were vaccinated intradermally in the deltoid region with 0.05 ml BCG vaccine. All children were to receive OPV at birth according to the WHO recommendations, and we noted on the inclusion form whether the children received OPV0 or not.</td>
<td>Mortality after 12 months (MR per 100 person years.)</td>
<td>Results In total, 611 newborns enrolled in the main trial were eligible for inclusion in the immunological substudy. Of these, 461 infants had a follow-up blood sample taken; valid in vitro cytokine analyses were performed on 378 infants, valid differential counts were available for 212 infants, and paired baseline and follow-up measurements of RBP and CRP were obtained from 404 infants. Newborns with no over illness or malformations, weighing ≥ 2.5 kg. Setting: a health and demographic surveillance system site covering six suburban districts of Bissau, the capital of Guinea-Bissau, West Africa.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group 1 (not receiving OPV at birth):</th>
<th>Group 2 (OPV and BCG):</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boys</td>
<td>14/84</td>
</tr>
<tr>
<td>Girls</td>
<td>6/33</td>
</tr>
</tbody>
</table>

**Mortality after 12 months (MR per 100 person years.)**

<table>
<thead>
<tr>
<th>Group 1 (not receiving OPV at birth):</th>
<th>Group 2 (OPV and BCG):</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boys</td>
<td>8/51</td>
</tr>
<tr>
<td>Girls</td>
<td>5/51</td>
</tr>
</tbody>
</table>

**Scar reaction**

<table>
<thead>
<tr>
<th>Group 1 (not receiving OPV at birth):</th>
<th>Group 2 (OPV and BCG):</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boys</td>
<td>35/37</td>
</tr>
<tr>
<td>Girls</td>
<td>12/12</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group 1 (not receiving OPV at birth):</th>
<th>Group 2 (OPV and BCG):</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boys</td>
<td>3/25</td>
</tr>
<tr>
<td>Girls</td>
<td>2/25</td>
</tr>
</tbody>
</table>

**Notes**

A total of 226 children died within the first 12 months of life; 14 in the No OPV group, 22 in the OPV ±2 months group and 212 in the total OPV group.

**Methods**

Parallel randomized control trial

**Participants**

7012 healthy normal-birth-weight neonates

3467 neonates were vaccinated with BCG at birth and 3494 neonates BCG + OPV

**Interventions**

Infant mortality of OPV by randomizing neonates to OPV or no OPV with BCG at birth. All infants were vaccinated intradermally in the upper left deltoid region with 0.05 mL of BCG vaccine (Statens Serum Institut, Copenhagen, Denmark). Length of follow-up: 12 months

**Outcomes**

**Infant mortality (MR per 1000 person-years (Death/Person-days))**

- **BCG + OPV group:** 73/151485, BCG group: 87/133978
- **Boys**
  - BCG + OPV group: 37/610407, BCG group: 50/593164
- **Girls**
  - BCG + OPV group: 36/541078, BCG group: 37/540814

**Sartono 2010**

**Methods**

A Natural Experiment study design

**Participants**

Bandim Health Project (BHP) in Bissau, Guinea-Bissau.

**Interventions**

BCG (0.05 ml; Statens Serum Institut, Copenhagen, Denmark) was provided by the BHP and given intradermally in the upper left deltoid region. We noted at the inclusion form whether the children received OPV or not.

**Outcomes**

**Scar**

Low-birth-weight infants

- **2 months**
  - BCG only: 90/97, BCG+OPV: 124/134
  - **6 months**
  - BCG only: 74/78, BCG+OPV: 118/122

Normal-birth-weight infants

- **2 months**
  - BCG only: 203/227, BCG+OPV: 198/210
  - **6 months**
  - BCG only: 217/227, BCG+OPV: 193/198

**Table 2 Risk of Bias**

**Benn 2008**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgment</th>
<th>Support for judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>High Risk</td>
<td>Randomization is not used in natural experimental study design.</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>High Risk</td>
<td>Each envelope contained 100 lots, 50 marked “1”, and 50 marked “2”, indicating from which of two numbered bottles, “1” or “2”, the child should receive</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Low Risk</td>
<td>The code was only opened when all children had reached 12 months of age.</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Low Risk</td>
<td>Outcomes were assessed through medical records.</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low Risk</td>
<td>All analyses were conducted including all children...</td>
</tr>
</tbody>
</table>
## Selective reporting (reporting bias)
- **Faridi 2015**: Low Risk
  - All prespecified outcomes were assessed

## Other bias
- **Faridi 2015**: Low Risk
  - The study seems to be free of other bias.

### Faridi 2015

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgment</th>
<th>Support for judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>High Risk</td>
<td>Prospective cohort study, randomization was not used.</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>High Risk</td>
<td>Prospective cohort study, allocation concealment is not appropriate</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>High Risk</td>
<td>...no blinding of investigators.</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Low Risk</td>
<td>Outcomes were objectively assessed.</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low Risk</td>
<td>The loss to follow-up was minimized, and intention to treat was used in the analysis.</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low Risk</td>
<td>All prespecified outcomes were assessed.</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low Risk</td>
<td>The study seems to be free of other bias.</td>
</tr>
</tbody>
</table>

### Jensen 2015

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgment</th>
<th>Support for judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low Risk</td>
<td>Numbers in parentheses represent the randomization...</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear Risk</td>
<td>Information was not provided to judge 'Yes' or 'No.'</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Low Risk</td>
<td>The technicians processing the samples were blinded to the randomization.</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Low Risk</td>
<td>Laboratory records were used to assess the outcome</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low Risk</td>
<td>Lost to follow up ineligible for follow sample was minimized.</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low Risk</td>
<td>The trial has been described elsewhere (Lund, submitted; clinicaltrials.gov: NCT00710983).</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low Risk</td>
<td>The study appears to be free of other bias.</td>
</tr>
</tbody>
</table>

### Lund 2012

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgment</th>
<th>Support for judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low Risk</td>
<td>...the effect of providing 25,000 IU of vitamin A to LBW children in a two-by-two factorial design.</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>High Risk</td>
<td>the mother drew a lot from an envelope randomizing her child to one of the study groups</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Unclear Risk</td>
<td>We do not have enough information to judge 'Yes' or 'No.'</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Low Risk</td>
<td>Outcomes were assessed objectively through records.</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low Risk</td>
<td>The loss to follow-up was minimized in this study.</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low Risk</td>
<td>The trial was registered at <a href="http://clinicaltrials.gov">http://clinicaltrials.gov</a>, number NCT00168610</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low Risk</td>
<td>The study could be free of other bias or confounding</td>
</tr>
</tbody>
</table>

### Lund 2015

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgment</th>
<th>Support for judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low Risk</td>
<td>...24 stapled lots; 12 lots were marked “BCG,” 12 “BCG OPV.”</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>High Risk</td>
<td>The study supervisor prepared the envelopes; there were separate envelopes for boys and girls.</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>High Risk</td>
<td>There was no placebo or blinding.</td>
</tr>
</tbody>
</table>

### Blinding of outcome assessment (detection bias)

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgment</th>
<th>Support for judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>High Risk</td>
<td>She drew a randomization number indicating whether the children would be BCG vaccinated early or not.</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear Risk</td>
<td>Insufficient information to judge 'Yes' or 'No.'</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Unclear Risk</td>
<td>Insufficient information to judge 'Yes' or 'No.'</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Low Risk</td>
<td>Outcomes were objectively assessed through medical records.</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low Risk</td>
<td>These children were retained in the analysis of scar reaction since...</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low Risk</td>
<td>The trials were registered at <a href="http://www.clinicaltrials.gov">www.clinicaltrials.gov</a>, registration number, NCT00146302, and NCT00168597.</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low Risk</td>
<td>This study seems to be free of other bias.</td>
</tr>
</tbody>
</table>

### Excluded studies

Four studies were excluded among which Alam 2015; Jensen 2014; Kuruvilla 2009; Ryder 1993 (Table 3).

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alam 2015</td>
<td>This is a cross-sectional study. Furthermore, the outcome assessed is different than those included in this review.</td>
</tr>
<tr>
<td>Jensen 2014</td>
<td>The outcomes are different than those included in the review</td>
</tr>
<tr>
<td>Kuruvilla 2009</td>
<td>This is a cross-sectional study</td>
</tr>
<tr>
<td>Prentice 2015</td>
<td>This study assessed iron metabolism as an outcome</td>
</tr>
<tr>
<td>Ryder 1993</td>
<td>This study assessed other types of outcomes</td>
</tr>
</tbody>
</table>

### Effects of interventions

All cause of mortality: In infants less than 5 years old, the administration of BCG reduced infantile mortality compared to BCG-OPV co-administration (RR 0.93, 95% CI 0.60 to 1.45, participants: 2289651, 3 studies, p-value: 0.74, M-H, Random). Considering only RCT, infantile mortality was reduced by (OR 0.78, 95% CI 0.59 to 1.04, participants: 2285761, 2 studies, p-value: 0.09, M-H, Random). (Figure 2 & 3)

*Fig. 2 Forest plot of comparison: 1 All cause of mortality, outcome: 1.1 All cause of mortality.*
The specific cause of mortality (boys): In boys less than 5 years, the mortality rate was reduced in BCG alone compared to BCG-OPV co-administration (RR 0.72 95% CI 0.49 to 1.06, boys: 1203695, 2 studies, p-value: 0.09, M-H, Random). Figure 4

The specific cause of mortality (girls): The mortality rate was reduced by 15% in girls less than 5 years who received BCG alone compared to BCG-OPV co-administration (RR 0.85 RR0.63 to 1.16, girls: 1083991, 3 studies, p-value: 0.31, M-H, Random). Figure 5

Local immune reaction (scar): The scar was reduced in infants who received BCG-OPV co-administration compared to BCG alone (OR 0.59 95% CI 0.12 to 2.96, 1069 infants, 3 studies, p-value: 0.52, M-H Random. Therefore, the 95% CI is very wide and including the null value. Then, the result of local immune reaction is not statistically significant. Figure 6

Fig. 6 Forest plot of comparison: 1 All cause of mortality, outcome: 1.3 Local immune reaction (scar).

5. **DISCUSSION**

Considering RCT and experimental study Benn 2008; Lund 2012; Lund 2015, infant mortality rate was reduced by 7% in BCG group compared to BCG-OPV co-administration. This result is not statistically significant. Therefore, only RCT Lund 2012; Lund 2015 have shown that infant mortality rate was reduced by 22% in BCG group compared to BCG-OPV group. The mortality rate was reduced by 28% and 15% respectively in boys and girls. Those results included the null value then they are not statistically significant.

Local immune reaction (scar) was 41% less likely present in BCG-OPV group compared to BCG alone. Therefore, the 95% CI is very wide and including the null value. Then, the result of the local immune reaction is not statistically significant.

This review could influence public health policy in immunization calendar because the quality of evidence is high with all mortality outcomes when RCT only are considered. Therefore the specific cause of mortality in boys and girls were respectively graded low and moderate. Furthermore, overall results included the null value, and then further studies will be important to highlight BCG-OPV co-administration. Besides, this study should be considered with several limitations. In fact, only two randomized control trials from the same other showed statistically significant in infant mortality. In addition, three studies identified were observational in nature, downgrading then the level of evidence.

Reviewing the overall risk of bias, allocation concealment was adequate in randomized control trials Jensen 2015; Lund 2012; Lund 2015. Allocation concealment is not applicable for natural experimental and prospective studies. Performance bias was adequate in Benn 2008; Jensen 2015, and unclear in Sartono 2010, therefore, the risk of bias was high in Lund 2012; Lund 2015. All the studies reported low-risk attrition; reporting and other potential sources of bias (Figure 7 & 8).

Fig. 7 The risk of bias graph: review authors’ judgments about each risk of bias item presented as percentages across all included studies.

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6. CONCLUSION

An increasing number of vaccines targeting some of the leading causes of morbidity and mortality are reaching the world’s children. Several studies have illustrated that BCG immunization reduces overall infant mortality (Higgins 2016). Therefore, some factors could influence BCG efficacy and effectiveness. This systematic review has shown that co-administration BCG-OPV could increase infant mortality. Therefore, the results could be considered in a context of several limitations.

REFERENCES
