Neonatal Bacillus Calmette-Guérin Vaccination to Prevent Early-Life Eczema: A Systematic Review and Meta-analysis

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Abstract: Increasing evidence suggests that early-life bacillus Calmette-Guérin (BCG) vaccine could prevent atopic eczema through its beneficial off-target effects. In this meta-analysis, 3 randomized control trials with similar methods were included and enabled robust estimations with low heterogeneity, involving a total of 5655 children randomized to early-life BCG Denmark (n = 2832) or no BCG (n = 2823). Meta-analyses suggest a beneficial effect of BCG to prevent eczema (risk ratio [RR], 0.89; 95% confidence interval [CI], 0.82–0.98). In subgroup analyses, BCG was more beneficial in boys (RR, 0.84; 95% CI, 0.74–0.95) and in children born to 2 atopic parents (RR, 0.81; 95% CI, 0.68–0.97). The NNT to prevent one case of eczema among children of 1 or 2 atopic parent was 20 (95% CI, 12–50). Bacillus Calmette-Guérin Denmark leads to an 11% reduction in the risk of eczema in early life. A greater effect was observed with increasing predisposition. Given its well-established safety profile, neonatal BCG vaccination should be considered for children of atopic parents.

A topic dermatitis, also named atopic eczema, is a common skin disorder among infants and toddlers. Its prevalence has increased over the last decades,1,2 and it is now estimated that up to a fifth of 6-year-old children have symptoms of eczema.1 Improving hygiene standard is believed to have played a major role in the global increase in atopic diseases (the “hygiene” or “old friends” hypothesis).1,2 An allergic response to common allergens occurs less frequently in environments in which the immune system is focused on microbes, whereas in “sterile” environments, in the absence of microbial challenge, allergic responses develop via T helper 2 cell pathways.3,4 The latter results in atopic diseases, such as asthma, food allergy, allergic rhinoconjunctivitis, and atopic dermatitis.

The 100-year-old bacillus Calmette-Guérin (BCG) vaccine promotes T helper 1 cell responses5,6 and has been associated with lower responses to allergens in some studies.7–11 BCG vaccination has many non-specific or off-target effects on the immune system,12–17 leading to reduced susceptibility to unrelated pathogens and subsequent decrease all-cause mortality,18–24 as well as reduced autoimmune disorders25,26 and some atopic diseases.8–11,27–29
The aims of this systematic review and meta-analysis were to determine whether neonatal BCG vaccination, compared with no BCG vaccination, reduces the incidence of eczema in the first years of life in studies with a randomized controlled trial (RCT) design, and to identify whether any benefit is greater in certain subgroups.

METHODS

Search Strategy and Selection Process

In this systematic review, PubMed, Embase, Cochrane, and Medline were searched with no language restriction in April 2022 using the search strategies detailed in Appendix 1. References of relevant publications were reviewed and did not identify additional studies. Two authors (L.F.P., L.M.T.) independently screened the titles, abstracts, or full texts of potentially eligible articles. All RCTs evaluating the effectiveness of early-life BCG vaccination on the development of eczema were included in the meta-analysis. There were no exclusion criteria. Findings are reported according to the PRISMA statement.30

Data Extraction

Standardized data extraction forms were used to collect information, including first author; publication year; study period; country; setting; inclusion/exclusion criteria; type of participants (eg, predisposed children); dose, strain, and timing of BCG vaccination; intervention to the control group; blinding method; definition of eczema diagnosis; age at eczema assessment; and eczema outcome (overall and in subgroup analyses).

Authors of eligible articles were contacted by email to contribute to the prespecified subgroup analyses. The studies’ quality was assessed using the Risk of Bias 2 tool from the Cochrane collaboration.31

Outcomes and Subgroups

The prespecified primary analysis was the cumulative incidence of eczema in the first years of life, using the authors’ individual definition of the primary outcome. The prespecified secondary analyses were alternative definitions of eczema, including clinician-diagnosed eczema at the last clinic visit, parent-reported medically diagnosed eczema, and parent-reported use of topical steroids.

Prespecified subgroup analyses were done using the trials’ primary outcome definition of eczema and included sex (male, female), atopic predisposition (no atopic parents, 1 atopic parent, 2 atopic parents), ethnicity (100% Caucasian, not 100% Caucasian), maternal vaccination (BCG vaccination, with a pooled RR of 0.89 (95% CI, 0.82 to 0.98; Fig. 2A). The pooled risk difference of −3% (95% CI, −5% to −1%) represented a number needed to treat (NNT) of 33 (95% CI, 20 to 100).

Meta-analysis of the Trials’ Primary Outcomes

The methodology of the 3 RCTs included is detailed in Table 1, and the risk of bias in Supplementary Figure 1, http://links.lww.com/DER/A128. Briefly, the trials were all assessed as low risk of bias and included a total of 5655 children living in high-income countries, namely, the Netherlands,33 Denmark (Calmette trial),34,38 and Australia (MIS BAIR trial).35,39 Children in all 3 trials were randomized 1:1 to the intervention BCG-Denmark vaccination: at birth (within 7 or 10 days of life)34,35 or at 6 weeks of age33 (n = 2832 participants), or to a control group: placebo (saline) injection33 or a no intervention (n = 2823 participants).34,35 In the Dutch trial, inclusion was restricted to predisposed children, defined as having a mother or both a father and at least 1 sibling diagnosed with an allergic disease (asthma, allergic rhinitis, eczema, or food allergy).33 In addition, in the Dutch trial, 20 of 62 participants randomized to BCG were revaccinated at 4 months of age, as they had no scar and had a negative tuberculin skin test.33

Eczema was assessed at 12, 13, or 18 months of age, and the primary outcome was defined as parent-reported eczema,33 doctor-diagnosed eczema (parent-reported and/or during study visit),34 or using the UK diagnostic tool.35,40,41 In all 3 trials, blinding was achieved by instructing the parents not to reveal the vaccination status of their child at the telephone interviews or at the clinical visits and to cover the upper arm of their child with a bandage during the study visits to obscure any BCG scar, regardless of the group their child had been allocated to.

RESULTS

Study Selection

Of 302 unique potentially relevant published studies, 3 met the inclusion criteria (Fig. 1).33–35 One study was excluded from most of the subgroup analyses as individual level data were not available in the article, and the authors were not able to provide further information.33

Study Characteristics

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Meta-analysis of the Trials’ Primary Outcomes

The meta-analysis of the trials’ primary outcomes showed an 11% reduction in the cumulative incidence of eczema after early-life BCG vaccination, with a pooled RR of 0.89 (95% CI, 0.82 to 0.98; Fig. 2A). The pooled risk difference of −3% (95% CI, −5% to −1%) represented a number needed to treat (NNT) of 33 (95% CI, 20 to 100).

Meta-analysis of the Trials’ Secondary Outcomes

Prevalence of clinician-diagnosed eczema at the last clinic visit (at 13 or 18 months of age) showed a reduction of 20%, with a pooled RR of 0.80 (95% CI, 0.70 to 0.92; Fig. 2C). The pooled risk difference of −3% (95% CI, −5% to −1%) represented an NNT of 33 (95% CI, 20 to 100). There was no difference in the parent-reported use of topical steroids (pooled RR of 0.80; 95% CI, 0.57 to 1.12; pooled risk difference of −8%; 95% CI, −19% to 3%; Fig. 2D) or in the cumulative incidence of parent-reported medically diagnosed eczema (pooled RR of 1.05; 95% CI, 0.93 to 1.19; pooled risk difference of +1%; 95% CI, −1% to +3%; Fig. 2B).
Subgroup Analyses

In sex subgroup analyses, there was a 16% reduction of eczema among BCG-vaccinated boys (RR, 0.84; 95% CI, 0.74 to 0.95; risk difference, −5%; 95% CI, −8% to −2%; NNT 20; 95% CI, 12 to 50; Fig. 3A) that was not observed in BCG-vaccinated girls (RR, 0.90; 95% CI, 0.86 to 1.14; risk difference, 0%; 95% CI, −4% to +3%; Fig. 3A; P for subgroup differences = 0.08). In predisposition subgroup analyses, there was a 15% reduction among BCG-vaccinated children born to 1 or 2 atopic parents (RR, 0.85; 95% CI, 0.77–0.95; risk difference, −5%, 95% CI, −8% to −2%; NNT, 20; 95% CI, 12 to 50; Fig. 3B) that was not observed in those without any predisposition (RR, 1.03; 95% CI, 0.86 to 1.25; risk difference, +1%; 95% CI, −3% to +4%; Fig. 3B; P for subgroup differences = 0.08). The reduction was greatest (19%) among BCG-vaccinated children born to 2 atopic parents (RR, 0.81; 95% CI, 0.68 to 0.97; risk difference, −7%; 95% CI, −14% to −1%; NNT 14; 95% CI, 7 to 100; Supplementary Fig. 2, http://links.lww.com/DER/A128).

None of the other subgroup analyses influenced the outcome, including ethnicity subgroup, maternal vaccination subgroup, and BCG scar subgroup analyses (Fig. 4A and Supplementary Fig. 3, http://links.lww.com/DER/A128). However, supplementary post hoc subgroup analysis suggested that among BCG-vaccinated children born to BCG-vaccinated mothers, the reduction in the risk of eczema might be greater in those who developed a scar, compared with those who did not develop a scar (RR, 0.69; 95% CI, 0.46 to 1.03; risk difference, −11%; 95% CI, −24% to +2%; Fig. 4B).

Another supplementary post hoc subgroup analysis showed that the reduction of eczema was primarily driven by BCG-vaccinated boys with atopic predisposition, in whom a 19% risk reduction was observed (RR, 0.81; 95% CI, 0.70 to 0.93; risk difference, −7%, 95% CI, −12% to −3%; NNT, 14; 95% CI, 8 to 33; Fig. 5).

All the funnel plots are available in Supplementary Figure 4 (http://links.lww.com/DER/A128).

DISCUSSION

In this meta-analysis including more than 5600 children, we found an overall 11% (95% CI, 2% to 18%) decrease in the cumulative incidence of eczema in the first 13 to 18 months of life after early-life BCG vaccination in Denmark. Using the robust measure of clinical assessment by blinded trained staff, an even greater (20%; 95% CI, 8% to 30%) decrease in the prevalence of eczema was observed at the last follow-up visit. A difference in parent-reported use of topical steroids and in parent-reported medically diagnosed eczema was not apparent, but these are less robust outcome measures for infant eczema. The results were consistent across all 3 included studies, which are, to our knowledge, the only published RCTs to date on this topic. None of the trial raised any safety issue.
| Setting | The Dutch Study, Steenhuis et al<sup>33</sup> (2007) | Calmette, Thøstesen et al<sup>34</sup> (2018) | MIS BAIR, Pittet et al<sup>35</sup> (2022) |
| --- | --- | --- | --- |
| **Country** | The Netherlands; Recruitment: June 1999 to December 2001 | Denmark; Recruitment: October 2012 to November 2013 | Australia; Recruitment: August 2013 to September 2016 |
| **Participants** | 121 (initial plan 200): High-risk newborns, having either a mother, or both a father and at least 1 sibling with past or present allergic disease (defined as any of self-reported asthma, allergic rhinitis, eczema or food allergy) | 4262 (initial plan 4300): Healthy newborns (gestational age at least 32 wk) with no contraindication to receive BCG | 1272 (initial plan 1438): Healthy newborns (gestational age at least 32 wk) with no indication or contraindication to receive BCG |
| **Intervention** | BCG Denmark at 6 wk of age, second dose at 4 mo in 19 participants with no scar and negative tuberculin skin test (<3 mm) | BCG Denmark within 7 d of birth | BCG Denmark within 10 d of birth |
| **Control group** | Placebo injection | No intervention | No intervention |
| **Blinding** | Single blind (examiner blinded, parents not entirely blinded as local reaction are likely to happen in the intervention group, and some received a second dose) | Single blinded (examiner blinded, parents not blinded) | Single blinded (examiner blinded, statistician blinded, parents not blinded) |
| **Participants’ characteristics** | | | |
| Sex, female | 44% (54/121) | 47.4% (2021/4262) | 49.5% (630/1272) |
| Family history of atopic disease | 100% (121/121) | 63.3% (2661/4185) | 82.5% (1049/1271) |
| Both parents atopic | NA | 14.2% (574/4035) | 30.4% (386/1269) |
| Mother BCG vaccinated | NA | 17.8% (740/4192) | 26.4% (318/1206) |
| Ethnicity, 100% Caucasian | NA | 79.9% (3381/4233) | 63.1% (803/1272) |
| Country’s routine immunization schedule in the first 18 mo of life | NA, expected to be: DTP-IPV at 3, 5, and 12 mo; MMR at 15 mo | DTP-IPV-Hib at 3, 5, and 12 mo; PCV at 3, 5, and 12 mo; MMR at 15 mo | HBV vaccine at birth, 6-8 wk, 4 mo, and 6 mo; DTP-IPV-Hib at 6-8 wk, 4, 6, and 18 mo; Rotavirus at 6-8 wk and 4 mo; PCV at 6-8 wk, 4 mo, and 12 mo; MMR at 12 and 18 mo; MCV at 12 mo |
| **Outcomes (BCG vs no BCG group)** | | | |
| Primary outcome | Definition: parent-reported eczema at 18 mo: 44% (27/61) vs 61% (33/54) | Definition: Doctor-diagnosed eczema (telephone questionnaire and/or clinical examination) in the first 13 mo of life: 22.7% (466/2052) vs 25.4% (495/1952) | Definition: UK diagnostic tool in the first 12 mo of life; MI model: 32.2% vs 36.6%; CCA: 32.0% (180/562) vs 35.1% (190/541) |
| Parent report of medically diagnosed eczema | NA | Definition: Parent report of doctor-diagnosed eczema in the first 13 mo of life: 12.3% (250/2030) vs 11.5% (221/1928) | Definition: Parent report of doctor- or nurse-diagnosed eczema in the first 12 mo of life; CCA: 29.2% (173/593) vs 28.7% (164/571) |
| **Eczema diagnosed at last clinic visit** | At 18 mo: 23% (14/61) vs 30% (16/53) | 3 and/or 13 mo: 18.7% (385/2056) vs 21.8% (427/1959); 13 mo: 13.9% (285/2051) vs 16.4% (321/1951); SCORAD ≥10: 10.5% (215/2052) vs 13.1% (256/1952) | Definition: Defined as a SCORAD ≥10 (=mild to severe) at 13 mo; CCA: 15.7 (90/575) vs 19.2% (100/521) |
| **Use of topical steroids for treatment of eczema** | In the first 18 mo of life: 25% (15/61) vs 61% (33/54) | Definition: Parent-reported use of topical steroids for treatment of eczema; 13 mo: 7.8% (163/2059) vs 7.9% (193/2064); Cumulated 0–13 mo: 9.0% (189/2059) vs 9.2% (190/2064) | Definition: Parent-reported use of topical steroids for treatment of eczema in the first 12 mo of life; MI model: 35.7% vs 39.0%; CCA: 37.6% (191/508) vs 38.5% (186/483) |

**Subgroup analysis of the PO***

| **Female** | NA | 21.1% (207/983) vs 21.6% (197/912) | CCA: 31.3% (87/278) vs 30.3% (80/264) |
| **Male** | NA | 24.2% (259/1069) vs 28.7% (298/1040) | CCA: 32.7% (93/284) vs 39.7% (110/277) |
| **No atopic parent** | NA | Definition: Atopy defined as doctor-diagnosed eczema, hay fever, or asthma; 18.9% (157/830) vs 18.6% (149/800) | Definition: Atopy defined as self-reported eczema, hay fever, or asthma; CCA: 25.0% (25/100) vs 21.5% (23/107) |
| **1 atopic parent** | NA | 26.5% (199/812) vs 28.6% (220/770) | CCA: 32.8% (94/287) vs 32.8% (86/262) |
| **2 atopic parents** | NA | 29.6% (83/280) vs 34.3% (87/254) | CCA: 35.3% (61/173) vs 46.8% (80/171) |
| **1 or 2 atopic parents** | 44% (27/61) vs 61% (33/54) | 25.8% (305/1181) vs 30.1% (337/1119) | CCA: 33.6% (155/461) vs 38.5% (167/434) |
| **Mother BCG naive** | NA | 23.3% (390/1672) vs 25.2% (401/1589) | CCA: 28.7% (111/387) vs 34.6% (130/376) |
| **Mother BCG vaccinated** | NA | 20.1% (72/358) vs 26.2% (88/336) | CCA: 42.8% (62/145) vs 35.1% (47/134) |
| **BCG scar (in the BCG group)** | NA | 22.2% (412/1854) | CCA: 32.0% (156/490) |
| **No scar (in the BCG group)** | NA | 27.2% (53/195) | CCA: 34.5% (10/31) |
| **BCG scar (in the BCG group, born to BCG-naive mother)** | NA | 23.0% (349/1518) | CCA: 29.3% (99/338) |
| **No scar (in the BCG group, born to BCG-naive mother)** | NA | 26.5% (40/151) | CCA: 26.3% (5/19) |
| **BCG scar (in the BCG group, born to BCG-vaccinated mother)** | NA | 18.9% (60/317) | CCA: 41.5% (51/123) |
| **No scar (in the BCG group, born to BCG-vaccinated mother)** | NA | 29.3% (12/41) | CCA: 55.6% (5/9) |
| **Ethnicity: 100% Caucasian** | NA | Both parents Danish: 22.6% (377/1681) vs 24.8% (377/1523) | CCA: 27.3% (98/359) vs 29.2% (100/343) |
| **Ethnicity: not 100% Caucasian** | NA | At least 1 grandparent not Danish: 23.9% (86/360) vs 27.5% (115/418) | A least 1 grandparent not Caucasian; CCA: 40.4% (82/203) vs 45.5% (90/198) |

*Demographic data or primary outcome data are missing for some participants, reason why numbers do not round up.

BCG indicates bacillus Calmette-Guérin; CCA, complete case analysis; DTP-IPV-Hib, diphtheria, tetanus, pertussis, polio, Haemophilus influenzae type B vaccine; HBV, hepatitis B virus; MCV, meningococcal conjugate vaccine; MI, multiple imputation; MMR, measles, mumps, rubella vaccine; NA, not available; PCV, pneumococcal conjugate vaccine; PO, primary outcome; SCORAD, SCORing Atopic Dermatitis scoring system.37
Subgroup Analysis

A sex-differential effect was observed, with the effect of BCG vaccination being independently significant in boys, but not in girls. This is in line with studies reporting greater reduction in morbidity and all-cause mortality in boys after early BCG vaccination.42 Sex-based differences in immune responses are well described, and there is a sex-differential predisposition in autoimmune disorders,43–45 including eczema.46–48 In line with the literature,46–48 boys had a 1.3 higher incidence of eczema compared with girls in both trials included in the sex subgroup meta-analysis (29% vs 22%, and 40% vs 30%, in the control groups of the Calmette and the MIS BAIR studies, respectively). In addition, it is now well recognized that sex influences the immune response to infections and vaccines,43,49,50 and sex-differential effects have been observed for off-target effects of vaccination.12,51–53 These include
reduced all-cause mortality after the oral poliovirus vaccine in boys,
and increased all-cause mortality in girls after diphtheria-tetanus-pertussis vaccine and the RTS,S malaria vaccine. The potential mechanism underlying these differences remains uncertain; sex chromosomes and sex hormones could both play a role. 

A consistent finding across the included trials was that the off-target effect of BCG vaccination might only be clinically important when the individual risk of eczema is high. Bacillus Calmette-Guérin vaccination decreased the risk of eczema predominantly in children with an atopic predisposition. A greater effect was observed with increasing predisposition: the effect of early BCG vaccination on the development of eczema was the greatest among boys with atopic predisposition.

### Sex subgroup analysis of the cumulative incidence of eczema in the first 13 months of life

| Study or Subgroup | BCG | no BCG | Weight | M-H, Fixed, 95% CI | Year |
|-------------------|-----|--------|--------|---------------------|------|
| **Boys**          |     |        |        |                     |      |
| Thøæsen 2018      | 259 | 1089   | 344    | 0.72 [0.51, 1.03]   | 2002 |
| Pittet 2022       | 54  | 248    | 111    | 0.45 [0.28, 0.70]   | 2022 |
| **Subtotal (95% CI)** | 313 | 1337   | 554    | 0.85 [0.70, 1.04]   | 2022 |
| Total events      | 441 | 1637   | 2963   | 0.75 [0.65, 0.86]   |      |

**Girls**

| Study or Subgroup | BCG | no BCG | Weight | M-H, Fixed, 95% CI | Year |
|-------------------|-----|--------|--------|---------------------|------|
| Thøæsen 2018      | 207 | 983    | 259    | 0.70 [0.50, 1.00]   | 2007 |
| Pittet 2022       | 87  | 278    | 80     | 0.41 [0.26, 0.64]   | 2022 |
| **Subtotal (95% CI)** | 294 | 1261   | 1557   | 0.85 [0.74, 0.97]   | 2022 |
| Total events      | 490 | 1557   | 2047   | 0.75 [0.65, 0.86]   |      |

**Predisposition subgroup analysis of the cumulative incidence of eczema in the first 13 or 18 months of life**

| Study or Subgroup | BCG | no BCG | Weight | M-H, Fixed, 95% CI | Year |
|-------------------|-----|--------|--------|---------------------|------|
| **No atopic parent**
| Steenhuis 2007    | 27  | 61     | 80     | 0.78 [0.50, 1.20]   | 2007 |
| Thøæsen 2018      | 157 | 830    | 149    | 0.70 [0.30, 1.64]   | 2018 |
| Pittet 2022       | 25  | 100    | 23     | 0.73 [0.43, 1.25]   | 2022 |
| **Subtotal (95% CI)** | 208 | 930    | 1138   | 0.85 [0.70, 1.03]   | 2022 |
| Total events      | 228 | 1038   | 1266   | 0.75 [0.65, 0.86]   |      |

**1 or 2 atopic parents**

| Study or Subgroup | BCG | no BCG | Weight | M-H, Fixed, 95% CI | Year |
|-------------------|-----|--------|--------|---------------------|------|
| Steenhuis 2007    | 27  | 61     | 80     | 0.78 [0.50, 1.20]   | 2007 |
| Thøæsen 2018      | 305 | 1181   | 337    | 0.86 [0.75, 0.98]   | 2018 |
| Pittet 2022       | 155 | 461    | 167    | 0.87 [0.73, 1.04]   | 2022 |
| **Subtotal (95% CI)** | 487 | 1678   | 2165   | 0.85 [0.70, 0.95]   | 2022 |
| Total events      | 514 | 1678   | 2192   | 0.75 [0.65, 0.86]   |      |

**Figure 3.** Sex and predisposition subgroup meta-analysis. BCG, Bacille Calmette-Guérin; M-H, Mantel-Haenszel.
predisposition, with a risk reduction of nearly 20%. This is in line with a previous observation that clinically relevant off-target effects of vaccine may be more easily identified in predisposed individuals.\textsuperscript{19,53,69}

We found conflicting results in relation to the influence of maternal BCG status on the influence of BCG on eczema prevention. Maternal BCG vaccination has been reported to enhance the off-target effects of BCG in infants living in both high-\textsuperscript{70,71} and low-mortality settings\textsuperscript{72} as well as in immunological studies.\textsuperscript{73} In the 2 included trials collecting this information, only a low proportion of mothers were BCG vaccinated, and the population differed between the 2 trials. In the Danish Calmette Study, BCG-vaccinated mothers were primarily older mothers, in whom BCG had been administered at school, a program that stopped in the early 1980s. Most of the younger mothers were hence BCG naive. The Danish Calmette Study did not collect detailed information about ethnicity (only Danish vs not Danish), but most included participants were Danish, and almost two thirds of the BCG-vaccinated mothers were Caucasian. In contrast, in the Australian MIS BAIR study, many BCG-vaccinated mothers were from Asia, whereas BCG-naive mothers were mostly Caucasian; the results might therefore be confounded by the disproportionally high risk of eczema reported in second-generation East Asian immigrants in Australia.\textsuperscript{46} The predominance of Caucasian participants across the trials precludes the generalization of the results of the meta-analysis to non-Caucasian children.

Bacillus Calmette-Guérin vaccination induces a scar in a variable proportion of vaccinees, and BCG scar formation has been reported to be associated with greater off-target effects in children in several studies assessing all-cause mortality.\textsuperscript{74,75} In the 2 included trials collecting this information, only a low proportion of the BCG-vaccinated children did not develop a scar. In our meta-analysis, there was some suggestion that the presence of a BCG scar after vaccination is associated with a lower risk of eczema, particularly in children born to BCG-vaccinated mothers. This analysis, likely underpowered by the low number of children who did not develop a scar, is in line with recent reports on the synergic effect of BCG scarring and parental vaccination on BCG-induced off-target effects.\textsuperscript{70,76}

The BCG vaccine is among the most widely administered vaccines in the world, with a well-established safety profile. Local
reaction with redness, swelling, and tenderness usually appears at the injection site within 1 to 2 weeks after vaccination and evolves into a small ulcer that heals over several weeks to months to leave a generally acceptable small flat scar. Other adverse reactions to BCG vaccination include injection site abscess, regional lymphadenitis, and, very rarely, osteitis, or disseminated BCG infection.\textsuperscript{77–81}

Table 2. BCG to Prevent Eczema: A Meta-analysis

| Study or Subgroup | BCG | no BCG | Risk Ratio | Year |
|-------------------|-----|--------|------------|------|
|                   | Events | Total | Events | Total | Weight | M-H, Fixed, 95% CI | |
| 1.9.1 Boys, no atopic parent | | | | | | |
| Thøstesen 2018    | 87   | 434   | 81     | 414   | 13.3%  | 1.02 [0.78, 1.34] | 2018 |
| Pittet 2022       | 11   | 55    | 14     | 53    | 2.3%   | 0.76 [0.38, 1.52] | 2022 |
| Subtotal (95% CI) | 489  | 467   | 498    | 459   | 15.5%  | 0.99 [0.77, 1.27] | |
| Total events      | 98   | 95    |         |        |        |                    |   |
| Heterogeneity: Chi$^2$ = 0.63, df = 1 (P = 0.43), P = 0% Test for overall effect: Z = 0.11 (P = 0.91) |

| 1.9.2 Boys, 1 or 2 atopic parents | | | | | | |
| Thøstesen 2018    | 168  | 610   | 210    | 605   | 33.7%  | 0.79 [0.67, 0.94] | 2018 |
| Pittet 2022       | 82   | 228   | 96     | 224   | 15.5%  | 0.84 [0.67, 1.06] | 2022 |
| Subtotal (95% CI) | 838  | 829   | 894    | 830   | 49.2%  | 0.81 [0.70, 0.93] | |
| Total events      | 250  | 306   |         |        |        |                    |   |
| Heterogeneity: Chi$^2$ = 0.15, df = 1 (P = 0.70), P = 0% Test for overall effect: Z = 3.07 (P = 0.002) |

| 1.9.3 Girls, no atopic parent | | | | | | |
| Thøstesen 2018    | 70   | 396   | 68     | 386   | 11.0%  | 1.00 [0.74, 1.36] | 2018 |
| Pittet 2022       | 14   | 45    | 9      | 54    | 1.3%   | 1.87 [0.89, 3.90] | 2022 |
| Subtotal (95% CI) | 441  | 440   | 494    | 444   | 12.3%  | 1.10 [0.83, 1.45] | |
| Total events      | 84   | 77    |         |        |        |                    |   |
| Heterogeneity: Chi$^2$ = 2.33, df = 1 (P = 0.13), P = 57% Test for overall effect: Z = 0.64 (P = 0.52) |

| 1.9.4 Girls, 1 or 2 atopic parents | | | | | | |
| Thøstesen 2018    | 70   | 396   | 68     | 386   | 11.0%  | 1.00 [0.74, 1.36] | 2018 |
| Pittet 2022       | 73   | 233   | 71     | 210   | 11.9%  | 0.93 [0.71, 1.21] | 2022 |
| Subtotal (95% CI) | 629  | 596   | 680    | 596   | 23.0%  | 0.96 [0.79, 1.18] | |
| Total events      | 143  | 139   |         |        |        |                    |   |
| Heterogeneity: Chi$^2$ = 0.15, df = 1 (P = 0.70), P = 0% Test for overall effect: Z = 0.36 (P = 0.72) |

| Total (95% CI) | 2397 | 2332 | 100.0% | 0.91 [0.82, 1.00] |
| Total events   | 575  | 617  |         |        |        |                    | |
| Heterogeneity: Chi$^2$ = 8.44, df = 7 (P = 0.30), P = 17% Test for overall effect: Z = 1.99 (P = 0.05) Test for subgroup differences: Chi$^2$ = 5.25, df = 3 (P = 0.15), P = 42.9% |

Figure 5. Sex and predisposition combined subgroup meta-analysis. BCG, Bacille Calmette-Guérin; M-H, Mantel-Haenszel.

Strengths and Limitations

Strengths of our systematic review and meta-analysis include strict compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses and the Cochrane guidelines, and the high total number of included children. The risk of bias is minimal as we included only RCTs; as their methods are quite similar, the heterogeneity is low, resulting in robust estimations.

The trials used different eczema definitions for their primary outcome that were assessed between 12 and 18 months of age. Because there are no agreed easy-to-use tool to reliably define eczema, various definitions are used, each of them having limitations, particularly in the first years of life.\textsuperscript{36,82,83} Moreover, discordance between different measures of eczema have been reported within the same trial.\textsuperscript{34,36,46,84} However, this limitation was mitigated by doing supplementary meta-analysis using the trials’ secondary outcomes that were less heterogeneous in their definitions.

Another limitation is that most subgroup analyses included data from only 2 of the 3 trials, as the third study did not report results stratified by the subgroups of interest. The authors from the Dutch study were contacted but unable to provide supplementary information. However, the Dutch study participants represent only approximately 2% of the total number of included children and are unlikely to significantly change the results.

Finally, we were unable to evaluate the potential interaction from other vaccines on the ability of early-life BCG vaccination to prevent eczema. The off-target effects of vaccines are influenced by concomitant or subsequent administration of nonlive vaccines.\textsuperscript{55} Most participants included in the MIS BAIR trial received hepatitis B vaccination in the first week of life, as recommended locally, and this
nonlive vaccine could have reduced the off-target effects of BCG.\(^3\) Moreover, participants from the 3 included trials received further nonlive vaccines as of 6 weeks or 3 months of age according to their national vaccination schedule (Table 1). The adoption of a “live-vaccine-last schedule,” including a repeat dose of BCG, has been proposed as a way to counteract any off-target effects of nonlive vaccines.\(^8\) The administration of a second BCG dose at 4 months of age in 31% of the participants in the Dutch trial might partly explain why the greatest reduction in eczema was observed in that trial.\(^3\)

There is also increasing interest in the use of multiple doses of BCG, for example, in the management of type 1 diabetes mellitus\(^36\) and recurrent herpes simplex.\(^23\) To the best of our knowledge, multiple doses of BCG have never been tested for eczema.

**CONCLUSIONS**

The present meta-analysis documents an 11% reduction in the risk of developing eczema in the first year of life after early BCG vaccination in Denmark. The subgroup analyses found a greater effect among boys (16% reduction), BCG-vaccinated children with atopic predisposition (15% reduction), and the greatest effect among BCG-vaccinated boys with atopic predisposition (19% reduction) and among children born to 2 atopic parents (19% reduction). Although the absolute reductions are modest, given the high rate of predisposed parents and the well-established safety profile of BCG vaccine, neonatal BCG vaccination should be considered for predisposed children, in particular if the 2 parents are atopic, given an NNT of only 14.

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Appendix 1: Search Strategy

PubMed search
1. bCG vaccine [MeSH terms]
2. tuberculosis vaccines [MeSH terms]
3. BCG
4. Bacillus Calmette-Guerin
5. bacille calmette-guerin
6. mycobacterium bovis
7. tuberculosis vaccin*
8. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
9. dermatitis, atopic [MeSH terms]
10. pruritus [MeSH terms]
11. prurigo [MeSH terms]
12. atopic dermatitis
13. allergic dermatitis
14. allergic eczema
15. besnier's prurigo
16. prurigo besnier
17. dermatiti* OR eczema* OR pruritus OR pruritis OR itching OR neurodermatiti*
18. #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19
19. infant, newborn [MeSH Terms]
20. #21 OR #22 OR #23
21. randomized controlled trial [pt]
22. controlled clinical trial [pt]
23. placebo [tiab]
24. drug therapy [sh]
25. randomly [tiab]
26. trial [tiab]
27. groups [tiab]
28. NOT (animals [mh] NOT humans [mh])
29. #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33
30. #8 AND #20 AND #24 AND #34

Cochrane search
1. MeSH descriptor: [BCG vaccine] explode all trees
2. MeSH descriptor: [tuberculosis vaccines] explode all trees
3. BCG
4. Bacillus Calmette-Guerin
5. bacille calmette-guerin
6. mycobacterium bovis
7. tuberculosis vaccin*
8. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
9. MeSH descriptor: [dermatitis, atopic] explode all trees
10. atopic dermatitis
11. atopic eczema
12. allergic dermatitis
13. allergic eczema
14. besnier's prurigo
15. prurigo besnier
16. dermatiti* OR eczema* OR pruritus OR itching OR neurodermatiti*
17. #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16
18. MeSH descriptor: [infant, newborn] explode all trees
19. MeSH descriptor: [infant] explode all trees
20. child* OR infan* OR neonat* OR newborn OR new-born OR toddler
21. #18 OR #19 OR #20
22. randomized controlled trial
23. controlled clinical trial
24. randomi*
25. #22 OR #23 OR #24
26. #8 AND #17 AND #21 AND #25

MEDLINE search
1. tuberculosis vaccines/ or bcg vaccine/
2. Mycobacterium bovis/
3. [(bcg or ((Bacille or bacili or bacilli or bacillus) and (Calmette or calmet) and Guerin)).tw,kf.] [including related terms]
4. exp child/ or exp infant/
5. (neonate or neonatal or neo-natal or newborn or new-born or birth or baby or babies or infant or child).tw,kf.
6. dermatitis, atopic/ or exp eczema/ or skin diseases, eczematous/ or eczema/ or prurigo/ or pruritus/ or Neurodermatitis/
7. (((atopic or allergic) and (eczema or dermatitis)) or eczema or dermatitis or neurodermatitis or prurigo or pruritus or (skin and disease) or (Besnier and prurigo)).tw,kf.
8. clinical trials as topic/ or exp randomized controlled trials as topic/
9. (randomiz* or randomis* or RCT).tw,kf.
10. exp animals/ not human*.sh.
11. ((1 or 2 or 3) and (4 or 5) and (6 or 7) and (8 or 9)) not 10

Embase search
1. mycobacterium bovis/ or exp mycobacterium bovis bcg/
2. (bcg or ((Bacille or bacili or bacilli or bacillus) and (Calmette or calmet) and Guerin)).tw,kw,dq.
3. child/ or juvenile/ or exp infant/ or school child/ or toddler/
4. (neonate or neonatal or neo-natal or newborn or new-born or birth or baby or babies or infant or child).tw,kw,dq.
5. exp eczema/ or exp neurodermatitis/ or exp atopic dermatitis/ or exp pruritus/
6. ((atopic or allergic) and (eczema or dermatitis)) or eczema or dermatitis or neurodermatitis or prurigo or pruritus or (skin and disease) or (Besnier and prurigo)).tw,kw,dq.
7. exp randomized controlled trial/
8. (randomiz* or randomis* or RCT).tw,kw,dq.
9. (1 or 2) and (3 or 4) and (5 or 6) and (7 or 8)