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Title:
Prevention of infant eczema by neonatal Bacillus Calmette-Guérin vaccination: The MIS BAIR randomized controlled trial

Date:
2022-03-01

Citation:
Pittet, L. F., Messina, N. L., Gardiner, K., Freyne, B., Abruzzo, V., Francis, K. L., Morrison, C., Zufferey, C., Vuillermin, P., Allen, K. J., Ponsonby, A. L., Robins-Browne, R., Shann, F., Flanagan, K. L., Phillips, R., Donath, S., Casalaz, D. & Curtis, N. (2022). Prevention of infant eczema by neonatal Bacillus Calmette-Guérin vaccination: The MIS BAIR randomized controlled trial. Allergy European Journal of Allergy and Clinical Immunology, 77 (3), pp.956-965. https://doi.org/10.1111/all.15022.

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Article type : Original article

Prevention of infant eczema by neonatal Bacillus Calmette–Guérin vaccination: the MIS BAIR randomised controlled trial

Short title: Neonatal BCG to prevent infant eczema (MIS BAIR trial)

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This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/ALL.15022

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Manuscript Acceptance Date: 13-Jul-2021

Acknowledgements

The authors would like to thank the MIS BAIR participants and their families for their involvement in the trial. We also thank our recruitment and follow-up teams, as well as the members of the MIS BAIR data and safety monitoring committee. The MIS BAIR trial is funded by research grants from the National Health and Medical Research Council of Australia (GNT1051228 and GNT1099676), The University of Melbourne, The Royal Children's Hospital Foundation and the Murdoch Children's Research Institute. Dr Laure Pittet is supported by the Swiss National Science Foundation (Early Postdoc Mobility Grant number P2GEP3_178155).

Conflict of Interest disclosure statement: The authors have no conflict of interest to declare.

ABSTRACT

Background: Bacille Calmette-Guérin (BCG) vaccine could play a role in counteracting the rising prevalence of atopic diseases, through its beneficial off-target effects. We aimed to determine whether neonatal BCG vaccination reduces the incidence of eczema in infants.

Methods: Randomised controlled trial with 1272 infants allocated to receive BCG-Denmark or no BCG at birth. The primary outcome was the 12-month incidence of eczema based on 3-monthly questionnaires. Eczema was also assessed at a 12-month clinic visit. ClinicalTrial.gov: NCT01906853.

Results: The 12-month eczema incidence was 32.2% in the BCG-group compared with 36.6% in the control group (risk difference (RD) -4.3%, 95%CI -9.9% to 1.3%, multiple imputation model). In addition, comparing infants in the BCG-group with the control group, 15.7% vs. 19.2% had eczema lesions at the 12-month visit (RD -3.5%, 95%CI -8.0% to 1.0%); 35.7% vs. 39.0% reported using topical steroids (RD -3.3, 95%CI -9.2 to 2.7); and 7.3% vs. 10.2% had severe eczema scores (RD -3.0%, 95%CI -8.8% to 2.7%). In 344 high-risk infants (two atopic parents), the 12-month eczema incidence was 35.3% in the BCG-group compared with 46.8% in the control group (RD -11.5%, 95%CI -21.9% to -1.2%; number-needed-to-treat 8.7, 95%CI 4.6 to 83.3).

Conclusion: There is insufficient evidence to recommend neonatal BCG vaccination in all infants for the prevention of eczema in the first year of life; however, a modest beneficial effect was observed among high-risk infants. A single dose of BCG-Denmark soon after birth could reduce the incidence of eczema in infants with two atopic parents.

Key words

Atopic dermatitis, William's UK diagnostic criteria; *Mycobacterium bovis*; patient oriented eczema measure, POEM; SCORing Atopic Dermatitis scoring system, SCORAD; prevention, vaccine non-specific effect.

Word count

2864 words, 58 ref, 2 tables, 2 figures, 2 supplementary appendix.

Abbreviations

BCG	bacille Calmette-Guérin
CI	confidence interval
MIS BAIR	Melbourne Infant Study: BCG for allergy and infection reduction
NNT	number needed to treat
POEM	Patient Oriented Eczema Measure
RCT	randomised controlled trial
RD	risk difference
RRR	relative risk reduction
SCORAD	SCORing Atopic Dermatitis scoring system
Th	T helper

Author contribution

NC was the lead investigator and responsible for study conception, design and funding acquisition. NC, BF, SD and CZ developed the final scientific protocol and ethics application and all other authors provided critical evaluation and revision. KG co-ordinated and NC, DC, CM and VA were involved in implementation. LFP developed and NC, RP, KG, NLM, VA, SD, FS, RR-B, KLFr, KLFl and MS contributed to the statistical analysis plan. LFP led and KLFr, SD, NLM and KG contributed to statistical analysis. LFP drafted the manuscript, coordinated manuscript preparation and revision. All authors provided critical evaluation and revision of the manuscript.

INTRODUCTION

The prevalence of atopic diseases has increased over recent decades,[1,2] and globally up to a fifth of 6-year-old children have eczema symptoms.[1] The impact on families' quality of life is high,[3,4] and no preventive measures are available.

There is strong evidence that BCG vaccine has many nonspecific or off-target effects on the immune system,[5-10] leading to reduced susceptibility to unrelated pathogens,[11-15] auto-immune disorders[16] and atopic disease.[17-20] Reduced early exposure to microorganisms might have contributed to the rise in atopic diseases (the 'hygiene' or 'old friends' hypothesis).[1,2,21] Neonatal bacille Calmette-Guérin (BCG) vaccination provides an early, controlled microbial exposure that

might reduce the incidence of eczema[22] by promoting T helper (Th)1 immunity and supressing atopy-mediating Th2 immunity.[23-26]

Previous clinical trials suggest that BCG-induced immunomodulation of the developing immune system might reduce the prevalence of allergic disease and asthma but the results have been inconsistent.[17-20,27-30] The aim of the *Melbourne Infant Study: BCG for allergy and infection reduction* (MIS BAIR) trial was to determine whether neonatal BCG vaccination reduces the incidence of eczema, allergy, asthma and infectious episodes in the first years of life.[31] This paper reports the eczema outcomes during the first year of life.

METHODS

Study design and participants

The protocol for the MIS BAIR trial has been published previously.[31] Briefly, in this phase 3, randomised controlled trial (RCT), 1272 infants were randomised at birth, and followed for at least 12 months using online questionnaires and clinic visits.

Neonates were eligible during the first ten days of life if they were born after 32 weeks gestation, were over 1500 grams at birth, were medically stable, had no significant skin abnormality, had no indication for or contraindication to BCG vaccination, and had no older sibling included in the trial.[31] In the case of twins, only twin 1 was randomised and included in the analysis.

Trial procedures

Neonates were randomly assigned in a 1:1 ratio to either the intervention group (BCG) or the control group (no BCG) using a web-based computerised system (REDCap®).[32] The randomisation schedule was developed by an independent statistician, and used random permuted blocks of varying size to ensure concealment of allocation. Randomisation was stratified by mode of delivery (vaginal vs. caesarean), plurality of birth (singleton vs. twin) and recruitment site.

In the intervention group, a single 0.05 ml intradermal dose of BCG-Denmark vaccine (Santens Serum Institute; *Mycobacterium bovis,* Danish strain 1331) was administered over the left deltoid, within 24 hours of randomisation and before 10 days of age. Because BCG causes a visible scar,

families were aware of the group allocation, but the statisticians and the research nurses doing the 12-month visit remained blinded. During the last four months of the recruitment period, as a result of a global shortage, one batch of vaccine was used beyond the expiration date after consultating with the ethics committee and informing parents, with monitoring of bacterial viability.[33]

Data on demographics, pregnancy, and the perinatal period were collected at baseline. Parents then completed online questionnaires at 3, 6, 9, and 12 months of follow up, including questions on eczema-related symptoms, severity, and management. At the 12-month visit, an allergy nurse did an eczema assessment and severity grading, during which blinding was achieved by covering the left upper arm of the participant with a bandage to obscure any scar. The parents were also instructed prior to the visit not to reveal the allocation group to the nurse.

Outcomes

Outcome definitions are detailed in the statistical analysis plan (supplementary material 1). The primary outcome was the presence of any eczema in the first 12 months of life measured using the UK diagnostic tool on the 3-monthly questionnaires.[34,35] This tool was adapted to fit the participants' age, as well as online data collection. Briefly, eczema was defined as an itchy skin condition (major criterion), accompanied by at least 3 of the following minor criteria: (i) generally dry skin, (ii) lesions in skin creases or cheeks, (iii) atopic disease in a first-degree relative, (iv) visible eczema involving the flexures, head or limbs. Parents are considered to be able to accurately report dermatitis in their infants.[36]

Secondary outcomes included research nurse-diagnosed eczema, parent-report of medically diagnosed eczema, extended definition of eczema (using UK diagnostic tool or parent report of medically diagnosed eczema), age of onset of eczema, use of topical steroids, and eczema severity. The latter was assessed using the Patient Oriented Eczema Measure (POEM) score,[37] included in each 3-monthly questionnaire, and the SCORing Atopic Dermatitis scoring system (SCORAD),[38] assessed by the research nurse at the 12-month clinic visit.

Statistical analysis

All participants were analysed based on their randomisation allocation (intention to treat).

Outcomes were compared between groups using binary regression adjusted for the stratification factor of birth mode and reported as adjusted risk difference (aRD) with 95% confidence intervals (CI). The two other stratification factors (site and plurality) were not included as adjustments because 98.3% of infants were singleton and 95.2% were from the same site.

Additional adjusted models explored the potential heterogeneity of the effect by estimating the interaction between BCG and predefined subgroup variables (e.g. born to two atopic parents). Exploratory subgroup estimates were reported when there was evidence of an interaction.

Multiple imputation of 50 complete datasets by chained equations was included in the analysis of the primary outcome; auxiliary variables predictive of missingness or primary outcome were identified using univariate analysis (supplementary material 2). Secondary outcomes were analysed in complete case analyses. Severity outcomes were compared using the POEM and SCORAD score categories in infants with eczema using chi-square tests.[39,40]

Sample size was calculated using a local estimated incidence of eczema of 27%.[41] With 575 infants per group, there would be an 80% power with a two-sided α of 0.05 to detect a 20% reduction in eczema (i.e., from 27% to 20%), which was deemed to be a clinically relevant difference. Assuming that complete 12-month data would be available for 80% of the infants, it was planned to recruit 1428 participants.

Stata v.16.1 (StataCorp, College Station, Texas) was used for all analyses. All tests were two tailed.

Ethics and registration

This trial was performed in accordance with the NHMRC National Statement on Ethical Conduct in Human Research (2007) and the Note for Guidance on Good Clinical Practice (CPMP/ICH-135/95), and was approved by the Mercy Health Human Research Ethics Committee (12-28) and all participating hospitals. A multidisciplinary and independent data and safety monitoring committee overviewed patient safety and data collection. ClinicalTrial.gov: NCT01906853.

RESULTS

Baseline characteristics and follow-up

Between August 2013 and September 2016, 8552 women were approached at antenatal clinics of participating hospitals in Victoria, Australia, and 1396 provided informed consent (Figure 1). Enrolment had to stop prematurely due to a worldwide shortage of BCG. A total of 1272 neonates were randomised, with 637 allocated to the BCG group and 635 to the no-BCG group. Their characteristics are presented in Tables 1 and S1 (supplementary material 2); most families reported a history of atopic disease (eczema, asthma, and/or hay fever) in at least one person (82.5%, 1103/1272).

BCG was given at a median of 1.5 days of life (IQR 0.9 to 2.5) to 630 infants (including 56 beyond the expiration date). The parents of 5 infants refused the intervention, one infant failed to receive the intervention within 24 hours of randomisation, and one infant withdrew just after randomisation. Five infants allocated to the control group received BCG outside the trial at a median age of 6.1 months (range 4.6 to 11.7).

All four 3-monthly questionnaires were completed for 85.8% (1091/1272) of participants, and 86.0% (1094/1272) attended the 12-month visit at a median age of 1.1 years (IQR 1.1 to 1.2). Primary outcome data were available for 1103 (86.7%) infants; there were more missing data in the control group (14.8%, 94/635) than in the BCG group (11.8%, 75/637). There was an overall 6.4% rate (82/1272) of withdrawal or loss to follow-up, higher in the control group (8.0%, 51/635) than in the BCG group (4.9%, 31/637). There were minor differences in the characteristics of infants withdrawn or lost to follow-up compared with those who remained in the trial, and between the two groups (Table S1, supplementary material 2).

Eczema in the first year of life

In the complete case analysis, 32.0% of infants in the BCG group compared with 35.1% in the control group fulfilled the UK diagnostic criteria for eczema in the first year of life (Table 2, Figure 2). In the multiple imputation model, the proportions were 32.2% in the BCG group, compared with 36.6% in the control group (aRD -4.3%, 95%CI -9.9% to 1.3%).

At the 12-month visit, 15.7% of infants in the BCG group had active eczema compared with 19.2% in the control group (aRD -3.5%, 95%CI -8.0% to 1.0%). The incidence of parent-reported

medically diagnosed eczema was similar between groups, as well as the incidence of infants fulfilling the combined definition of eczema (Table 2; Table S2 and Figure S1, supplementary material 2). Use of topical steroids was 35.7% in the BCG group compared with 39.0% in the control group (aRD -3.3%, 95%CI -9.2% to 2.7%, multiple imputation model, Figure 2).

Among infants with eczema, the age of onset of eczema and severity scores are shown in Table S3, and Figures S2 and S3 (supplementary material 2). 7.3% of infants in the BCG group had severe eczema in the first 12 months of life compared with 10.2% in the control group (severe POEM or SCORAD score; aRD -3.0%, 95%CI -8.8% to 2.7%). In the first 3 months of life, 4.9% of infants with eczema in the BCG group compared with 15.9% in the control group had severe eczema (severe POEM score; aRD -11.0%, 95%CI -23.7% to 1.6%); and 62.2% compared with 64.2% reported eczema symptoms before 3 months of age (aRD -1.9%, 95%CI -11.7% to 7.9%), as shown in Figure 2, Table S3 and Figure S4 (supplementary material 2).

Subgroup analysis

The effect of BCG differed depending on the parents' history of atopic disease (p for interaction 0.04) and maternal BCG status (p=0.04).

When both parents reported a history of atopic disease, 35.3% of infants in the BCG group compared with 46.8% in the control group developed eczema in the first year of life (aRD -11.5%, 95%CI -21.9% to -1.2%; number needed to treat (NNT) of 8.7, 95%CI 4.6 to 83.3; Table 2 and Figure 2). In infants born to BCG-naïve mothers, 28.7% of infants in the BCG group compared with 34.6% in the control group developed eczema in the first year (aRD -6.0%, 95%CI -12.6% to 0.6%).

The incidence of eczema was higher in boys than girls (39.7% vs. 30.3% in the control group), and boys benefitted more from BCG vaccination, with only 32.7% of boys reporting eczema in the BCG group, but the interaction test was p=0.16. None of the other pre-specified potential effect modifiers influenced the outcome, including delivery mode, season of birth, timing of BCG and hepatitis B vaccination, BCG scarring and use of expired BCG (Table S4, Figures S5 and S6, supplementary material 2).

DISCUSSION

In this RCT, we found a 4.3% aRD (12% relative risk reduction (RRR), 95%CI -0.4% to 26%) in the overall 12-month incidence of eczema in infants who received neonatal BCG-Denmark vaccination compared with those who did not, with a statistically significant difference in infants born to atopic parents (aRD 11.5%; RRR 25%, 95%CI 3% to 42%).

Our results are consistent with those from two previous RCTs. In a Dutch trial involving 121 infants with an atopic predisposition, parent-reported eczema at 18 months of age was less frequent in the BCG group following vaccination at 6 weeks of age, with a second dose at 4 months in 19 (31%) non-responders (44.3% vs. 61.1%; aRD 16.8%; RRR 27.5%; NNT 6.0).[27] In an RCT in 4262 Danish infants, an overall RRR of 10% (95%CI 0% to 20%) in the incidence of eczema at 13 months of life was reported following neonatal BCG vaccination, with a 16% RRR (95%CI 5% to 26%) among children with atopic predisposition (NNT 21, 95%CI 12 to 76).[28]

In our trial, boys had a higher rate of eczema compared to girls (40% vs. 30% in the control group) as has been previously reported.[41-43] Interestingly, the observed reduction in eczema in BCG-vaccinated infants was greater in boys than girls. The interaction test gave p=0.16, but this finding is consistent with evidence suggesting a sex differential effect of both the specific and off-target effects of vaccines.[44]

The off-target effects of live-attenuated vaccines on survival seem to be influenced by pre-existing immunity.[45,46] In the Danish RCT, infants in the BCG group born to BCG-vaccinated mother had a lower risk of hospitalisation for infection.[47,48] A similar phenomenon was reported following re-vaccination with BCG, measles, smallpox and oral polio vaccines, as well as when measles vaccination was given after natural measles infection.[45] In the present trial, infants born to BCG-naïve mothers appeared to benefit more from BCG vaccination. As most mothers with a history of BCG vaccination were born overseas, a confounding factor might be an increased risk of eczema in second-generation East Asian immigrants in Australia.[41] Our results contrast with the results of a systematic review that suggests that BCG could be more beneficial in preventing eczema in children of non-western origin (odds ratio 0.78, 95%CI 0.62 to 0.97).[19]

The off-target effects of vaccines are influenced by concomitant administration of non-live vaccines.[49] It is therefore relevant that most of our participants (86.7%) received hepatitis B vaccination up to 24 hours after randomisation, as this vaccine is recommended at birth for all infants in Australia. Receipt of this non-live vaccine could have reduced the off-target effects of BCG. Moreover, participants received further non-live vaccines at 6 weeks, 4 months and 6 months of age according to the routine schedule. This might explain why the biggest differences in the POEM severity score was observed in the first three months of life: a single dose of BCG at birth reduced the incidence of severe eczema from 16% to 5% at 3 months of age.

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 non-live vaccines.[50] The administration of a second BCG dose at 4 months of age in 31% of the participants in the Dutch RCT may partly explain why the reduction in infant eczema was greater in that trial.[27] There is also increasing interest in the use of multiple doses of BCG, for example in the management of type 1 diabetes mellitis[51] and recurrent herpes simplex.[15]

Because of a worldwide shortage of BCG, the final sample size of our trial was smaller than planned, compromising the power of the trial. Our decision not to use a placebo might explain the higher drop-out rate in the control group, as observed in a previous BCG trial.[28] Participant blinding is virtually impossible in BCG trials, given the characteristic local reaction following vaccination. A disproportionate number of participants with a familial atopic predisposition withdrew or were lost to follow up in the control group, which may have led to an underestimate of the effect of the intervention; this limitation was partly addressed by the use of a multiple imputation model for the primary outcome.

The use of an expired BCG batch with verified bacterial viability in 56 participants is unlikely to have influenced the outcome. There was a similar rate of scar formation following BCG vaccination before and after the manufacturer-assigned expiration date.[33] The slightly lower rate of eczema reported among infants receiving an expired dose of BCG needs to be cautiously interpreted: it involved few participants, all were recruited in the last four months of the trial and all were born in the same season.

Our study population included a variety of ethnic backgrounds and family characteristics. However, the level of maternal education (67.1% with a university degree), and the rate of family history of atopic diseases (82.5%) were higher than the general Australian population. Most of the trial outcomes rely on parent-completed questionnaires. There is no established definition to assess the incidence of eczema in infants, and discrepancies between measures,[28,41] as well as between observers, are frequent.[52] The UK diagnostic criteria are widely used,[34,35,52,53] but they may not accurately reflect infant eczema, as flexural involvement is less common at that age.[54] A robust measure of eczema is clinical assessment by a blinded research nurse: in our trial, severe eczema was 2-fold less frequent in the BCG group. However, this measure is influenced by management, and even severe eczema can have a low SCORAD score if it has been well treated.

Eczema is usually the first manifestation of atopic disease, with a peak incidence in the first year of life and decreasing thereafter.[54] At one year of age, it is difficult to predict which participants will have mild transient eczema, and which will have severe life-long eczema. The main aim of any early intervention is to prevent the latter. Over 80% of MIS BAIR participants consented to an extension of the trial to re-evaluate the incidence of eczema and other atopic manifestations at 5-years of age.

In conclusion, our results suggest that BCG-Denmark reduces the development of eczema in infants with parental atopy with a NNT of 9. However, there is insufficient evidence to recommend BCG vaccination to all families for the general prevention of eczema. We did not find any significant impact of BCG vaccination on the age of onset of eczema, eczema severity or eczema medication use.

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Table 1: Participants characteristics and exposures during first year of life

	N	All participants n=1272	No BCG n=635	BCG n=637
Infant factors				
Age at randomisation, hours	1272	46.9 (43.3)	47.8 (45.2)	46.0 (41.3)
Sex, female	1272	630 (49.5%)	312 (49.1%)	318 (49.9%)
Birth weight, kg	1272	3.4 (0.5)	3.4 (0.5)	3.4 (0.5)
Gestational age at birth, weeks	1272	39.3 (1.4)	39.2 (1.4)	39.4 (1.41)
Twin pregnancy	1272	21 (1.7%)	10 (1.6%)	11 (1.7%)
Vaginal delivery	1272	812 (63.8%)	406 (63.9%)	406 (63.7%)
Hepatitis B vaccination ≤24 h post randomisation	1271	1103 (86.8%)	562 (88.5%)	541 (85.1%)
Infant ethnicity	1272			
Caucasian (3 to 4 grandparents are Caucasians)		949 (74.6%)	475 (74.8%)	474 (74.4%)
Asian (3 to 4 grandparents are Asians)		82 (6.4%)	39 (6.1%)	43 (6.8%)
Mixed Caucasian and Asian		62 (4.9%)	30 (4.7%)	32 (5.0%)
Other		179 (14.1%)	91 (14.3%)	88 (13.8%)
Season of birth	1272			
Summer		286 (22.5%)	137 (21.6%)	149 (23.4%)
Autumn		362 (28.5%)	185 (29.1%)	177 (27.8%)
Winter		314 (24.7%)	156 (24.6%)	158 (24.8%)
Spring		310 (24.4%)	157 (24.7%)	153 (24.0%)
Maternal factors				

Age at delivery, years	1271	32.6 (4.8)	32.7 (4.7)	32.6 (4.8)
History of BCG vaccination	1206	318 (26.4%)	159 (26.5%)	159 (26.3%)
Maternal education	1269			
No education / up to year 10		75 (5.9%)	34 (5.4%)	41 (6.5%)
Year 12 / trade		340 (26.8%)	175 (27.6%)	165 (26.0%)
University		854 (67.3%)	426 (67.1%)	428 (67.5%)
Familial and environmental factors at birth				
Number of household habitants	1272	2.9 (1.1)	2.9 (1.1)	2.9 (1.2)
Family history of eczema	1270	514 (40.5%)	263 (41.5%)	251 (39.5%)
Family history of any atopic disease [a]	1271	1049 (82.5%)	520 (81.9%)	529 (83.2%)
Both parents have an atopic disease [a]	1269	386 (30.4%)	194 (30.6%)	192 (30.2%)
Smoker living in the house during pregnancy	1269	222 (17.5%)	117 (18.5%)	105 (16.5%)
Exposure during first year of life				
Age at first DTP-containing vaccine, days	1240	50.0 (34.4)	50.4 (46.2)	49.6 (15.9)
Daycare attendance	1242	457 (36.8%)	238 (38.8%)	219 (34.9%)
Smoker living in the house in 1st year of life	1147	153 (13.3%)	82 (14.5%)	71 (12.2%)

[a] Any of eczema, hayfever, asthma.

BCG: bacille Calmette-Guérin; DTP: diphtheria-tetanus-pertussis; h: hours; y: years.

Categorical variables are reported as number (%), continuous variables are reported as mean (interquartile range).

Table 2: Eczema in the first year of life: incidence, age of onset and severity

	N	No BCG	BCG	Measure of effect	Adjusted estimate of effect (95% CI)[a]	p-value
Primary outcome (UK diagnostic tool)						
Multiple Imputation (50 imputations)	1272	36.6%	32.2%	aRD	-4.3 (-9.9 to 1.3)	0.1
Complete case analysis	1103	35.1% (190/541)	32.0% (180/562)	aRD	-3.1 (-8.6 to 2.5)	0.3
Secondary outcomes (eczema outcome)						
Active lesion of eczema at the 12-months visit	1096	19.2% (100/521)	15.7 (90/575)	aRD	-3.5 (-8.0 to 1.0)	0.1
Parent report of medically diagnosed eczema	1164	28.7% (164/571)	29.2% (173/593)	aRD	0.5 (-4.7 to 5.7)	0.9
Extended definition of eczema (primary outcome or parent-report)	1113	43.2% (235/544)	41.6% (237/569)	aRD	-1.5 (-7.3 to 4.3)	0.6
Use of topical steroid [b] (multiple imputation)	1272	39.0%	35.7%	aRD	-3.3 (-9.2 to 2.7)	0.3
Use of topical steroid (complete case analysis)	991	38.5% (186/483)	37.6% (191/508)	aRD	-0.9 (-6.9 to 5.2)	0.8
Subgroup analysis (for primary outcome)						
None or one parent with atopic disease	756	109/369 (29.5%)	119/387 (30.8%)	aRD	1.2 (-5.3 to 7.8)	0.7
Both parents with atopic disease	344	80/171 (46.8%)	61/173 (35.3%)	aRD	-11.5 (-21.9 to -1.2)	0.03
Born to mother BCG-naïve	763	130/376 (34.6%)	111/387 (28.7%)	aRD	-6.0 (-12.6 to 0.60)	0.07
Born to mother previously vaccinated with BCG	279	47/134 (35.1%)	62/145 (42.8%)	aRD	7.0 (-4.4 to 18.4)	0.3
Secondary outcomes (eczema onset and severity) [c]						
Age at first symptom of eczema						
Eczema onset before 3 months of age	370	122/190 (64.2%)	112/180 (62.2%)	aRD	-1.9 (-11.7 to 7.9)	0.7
Maximum POEM score category during follow up						
Clear	332	18/171 (10.5%)	18/161 (11.2%)	aRD	0.5 (-6.2 to 7.1)	0.9
Clear to mild	332	80/171 (46.8%)	78/161 (48.4%)	aRD	1.7 (-9.0 to 12.5)	0.8
Severe or very severe	332	13/171 (7.6%)	10/161 (6.2%)	aRD	-1.7 (-7.1 to 3.7)	0.5
Persistently high POEM scores (≥2 scores during follow up)						
Median score ≥ moderate	253	37/130 (28.5%)	45/123 (36.6%)	aRD	8.6 (-2.9 to 20.0)	0.1
SCORAD category at 12-month follow-up visit						

Clear	340	102/170 (60.0%)	109/170 (64.1%)	aRD	4.1 (-6.2 to 14.4)	0.4
Clear to mild	340	152/170 (89.4%)	155/170 (91.2%)	aRD	1.8 (-4.5 to 8.0)	0.6
Severe	340	8/170 (4.7%)	4/170 (2.4%)	aRD	-2.4 (-6.3 to 1.5)	0.2
Combination of POEM and SCORAD scores category						
Both scores clear	308	10/154 (6.5%)	15/154 (9.7%)	aRD	3.2 (-2.9 to 9.3)	0.3
Both scores clear to mild	308	67/154 (43.5%)	73/154 (47.4%)	aRD	3.7 (-7.4 to 14.8)	0.5
Any score severe or very severe [d]	364	19/187 (10.2%)	13/177 (7.3%)	aRD	-3.0 (-8.8 to 2.7)	0.3

[a] adjusted for stratification mode of delivery; [b] predictor included in the multiple imputation model; [c] among participants with eczema (as defined by primary outcome definition) and available data; [d] n=364 as it includes participants with either scores available.

aRD: adjusted risk difference; BCG: bacille Calmette-Guérin; CI: confidence interval; POEM: Patient Oriented Eczema Measure score[37]; SCORAD: SCORing Atopic Dermatitis scoring system.[38] Categories used as previously defined.[39,40]

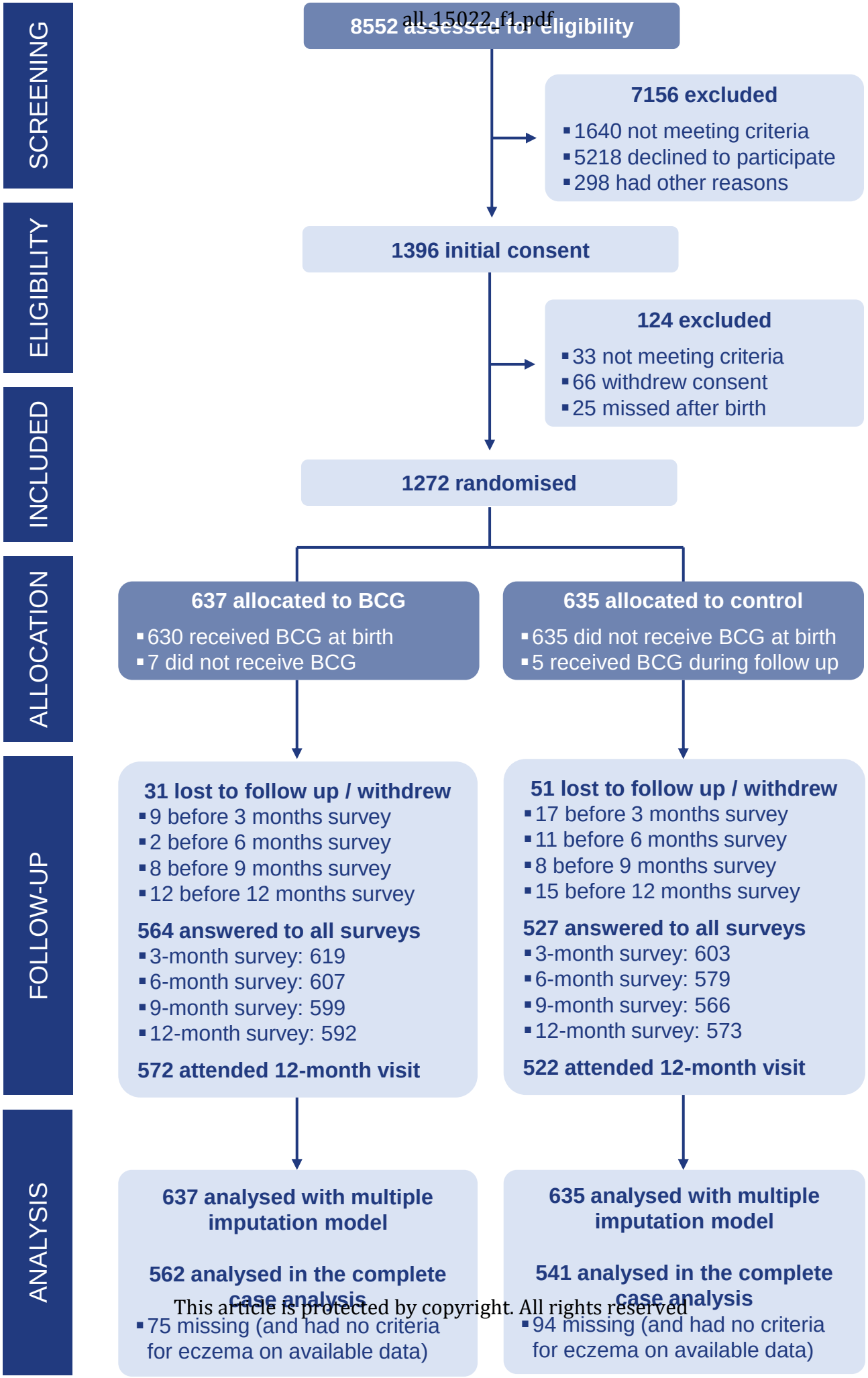
Figure legend

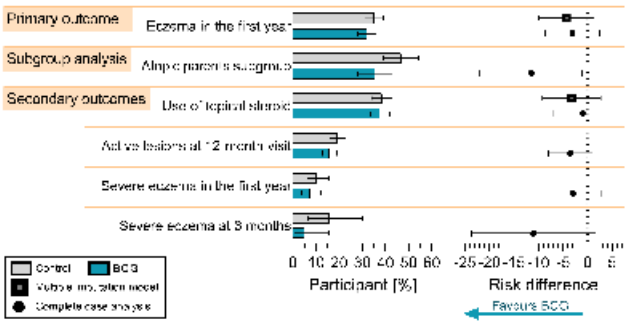
Figure 1: CONSORT diagram

BCG: bacille Calmette-Guérin.

Figure 2: Difference in incidence and severity of eczema between BCG and control groups

Left: Bars represent the proportion of participants fulfilling the criteria for the primary and secondary outcomes with error bars depicting 95% confidence intervals (CI). Right: Squares and dots represent adjusted risk differences for the multiple imputation models and complete case analysis respectively, with error bars depicting 95% CI.





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