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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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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, KLFI 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 disorders¹⁶ 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 eczema²² by promoting T helper (Th)1 immunity and suppressing 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 consulting 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 mellitus⁵¹ 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 1 st year of life	1147	153 (13.3%)	82 (14.5%)	71 (12.2%)
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^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 $\geq$ 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 score³⁷; 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.

SCREENING

ELIGIBILITY

INCLUDED

ALLOCATION

FOLLOW-UP

ANALYSIS

8552 assessed for eligibility

7156 excluded

- 1640 not meeting criteria
- 5218 declined to participate
- 298 had other reasons

1396 initial consent

124 excluded

- 33 not meeting criteria
- 66 withdrew consent
- 25 missed after birth

1272 randomised

637 allocated to BCG

- 630 received BCG at birth
- 7 did not receive BCG

635 allocated to control

- 635 did not receive BCG at birth
- 5 received BCG during follow up

31 lost to follow up / withdrew

- 9 before 3 months survey
- 2 before 6 months survey
- 8 before 9 months survey
- 12 before 12 months survey

564 answered to all surveys

- 3-month survey: 619
- 6-month survey: 607
- 9-month survey: 599
- 12-month survey: 592

572 attended 12-month visit

51 lost to follow up / withdrew

- 17 before 3 months survey
- 11 before 6 months survey
- 8 before 9 months survey
- 15 before 12 months survey

527 answered to all surveys

- 3-month survey: 603
- 6-month survey: 579
- 9-month survey: 566
- 12-month survey: 573

522 attended 12-month visit

637 analysed with multiple imputation model

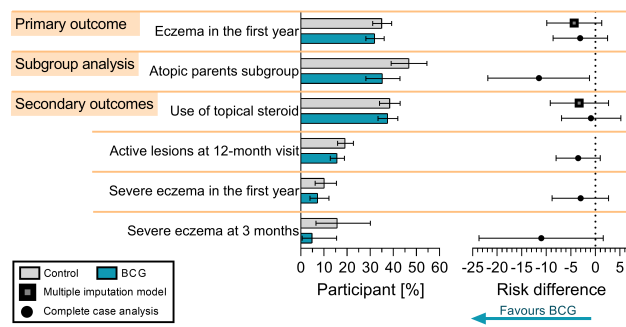
562 analysed in the complete case analysis

- 75 missing (and had no criteria for eczema on available data)

635 analysed with multiple imputation model

541 analysed in the complete case analysis

- 94 missing (and had no criteria for eczema on available data)



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FORM-STAT-04A-01	Statistical Analysis Plan
Version 1.1	

BCG12/01

**The Melbourne Infant Study
BCG for Allergy & Infection Reduction
(MIS BAIR)
Eczema outcome**

Document Version History

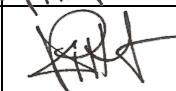
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LIST OF ABBREVIATIONS

AE	Adverse Event
BCG	Bacille Calmette Guerin
CRF	Case Report Form
FC	Food Challenge
GCP	Good Clinical Practice
ITT	Intent-To-Treat
POEM	Patient Oriented Eczema Measure
SAE	Serious Adverse Event
SCORAD	SCOring Atopic Dermatitis
SD	Standard Deviation
SE	Standard Error
MedDRA	Medical Dictionary for Regulatory Activities
WHO DD	World Health Organization Drug Dictionary

1. STUDY OBJECTIVES

1.1. PRIMARY OBJECTIVE

To determine if BCG immunisation at birth, compared to no BCG immunisation, leads to a reduction in measures of eczema in the first 12 months of life.

Note that the MIS BAIR study has three primary outcomes (allergy, infection, eczema). This Statistical Analysis Plan relates only to the eczema primary outcome.

2. BACKGROUND/INTRODUCTION

2.1. STUDY DESIGN

This is a phase III, randomised, controlled trial of infants recruited at Mercy Hospital for Women, Werribee Mercy, Geelong Hospital, St John of God and Murdoch Children's Research Institute in Melbourne over a 3-year period from August 2013 September 2016. The projected sample size was 1,438 infants, however randomisation to the study had to be stopped before this number was reached as study drug became unavailable due to a worldwide shortage. The actual number randomised was 1272. Infants were randomised within ten days after birth. The eczema primary outcome was measured at 1-year of age.

2.2. TREATMENT GROUPS

Randomisation was stratified by (i) site (hospital), (ii) method of delivery (Caesarean vs non-Caesarean) and (iii) plurality of birth (i.e. twins vs singletons). Infants were randomised within 10 days of birth to BCG vaccine or no BCG vaccine. Those randomised to BCG vaccine were to receive the vaccine within 24hrs of randomisation (and still within 10 days of birth). The member of the research team conducting the eczema severity assessment at 1-year of age was blinded to treatment group allocation, they had no access to the randomisation allocation data and a bandage was applied to the upper left arm to hide any potential scar.

2.3. STUDY POPULATION

1,272 healthy newborns were randomised, within 10 days of birth, in a 1:1 ratio, to study group 1 (BCG, n=637) or study group 2 (no BCG, n=635). A total of 21 sets of twins were included in the trial. Twin pairs were randomised to the same group but only one twin from each pair was included as a study participant, regardless of birth order.

Inclusion criteria to determine eligibility for randomisation according to protocol:

- Less than 10 days old;
- English speaking mother;
- An informed consent form must be signed and dated by their parent(s) or legally acceptable representative after the nature of the study has been explained and prior to any study assessments/procedures;
- The infant's mother has screened negative for HIV during this pregnancy;
- To ensure this is accurate, before randomisation staff will check the mother's pathology results to confirm the date of her HIV test is post conception for the current pregnancy (this date is recorded on the eligibility check form)
- Born no earlier than eight weeks before estimated date of delivery;
- Birth weight >1500g;

- The parent or guardian must expect to be able to complete four online/phone questionnaires over the infant's first 12 months of life and for the infant to be available for skin prick testing at a study site at 1-year of age

An infant meeting any of the following criteria will be excluded from study participation (as per the NH&MRC Immunisation Handbook (10th edition, 2013)):

- Any indication for BCG immunisation in the first 12 months of life including:
 - Likely travel to a high TB incidence country in the first year of life;
 - Aboriginal and Torres Strait Islander babies living in parts of Australia where the incidence of TB is higher;
 - Newborn babies, if either parent has leprosy or a family history of leprosy;
 - Newborn in contact with a patient with TB.
- Known or suspected HIV infection;
- Treatment with corticosteroids or other immunosuppressive therapy, including monoclonal antibodies against tumour necrosis factor-alpha (TNF-alpha) (e.g. infliximab, etanercept, adalimumab);
- Born to a mother treated with bDMARDs (e.g. TNF-alpha blocking monoclonal antibodies) in the 3rd trimester;
- Congenital cellular immunodeficiencies including specific deficiencies of the interferon gamma pathway;
- Malignancies involving bone marrow or lymphoid systems;
- Serious underlying illness including severe malnutrition;
- Medically unstable;
- Generalised septic skin disease and skin conditions such as eczema, dermatitis and psoriasis;
- Significant febrile illness;
- Sibling in the study (other than a twin)
- Multiple births more than twins.
- Born to mother who has tested Hep B antigen positive in current pregnancy and whose baby is likely to be given hepatitis B immunoglobulin.
- Mother has received celestone/betamethasone 48 hours before randomisation

Also excluded are infants with:

- A mother who is immunosuppressed;
- A family history of immunodeficiency;
- Consanguineous parents.

Vaccination may be deferred where the infant is medically unstable, until the infant is in good medical condition.

2.4. INTERVENTION

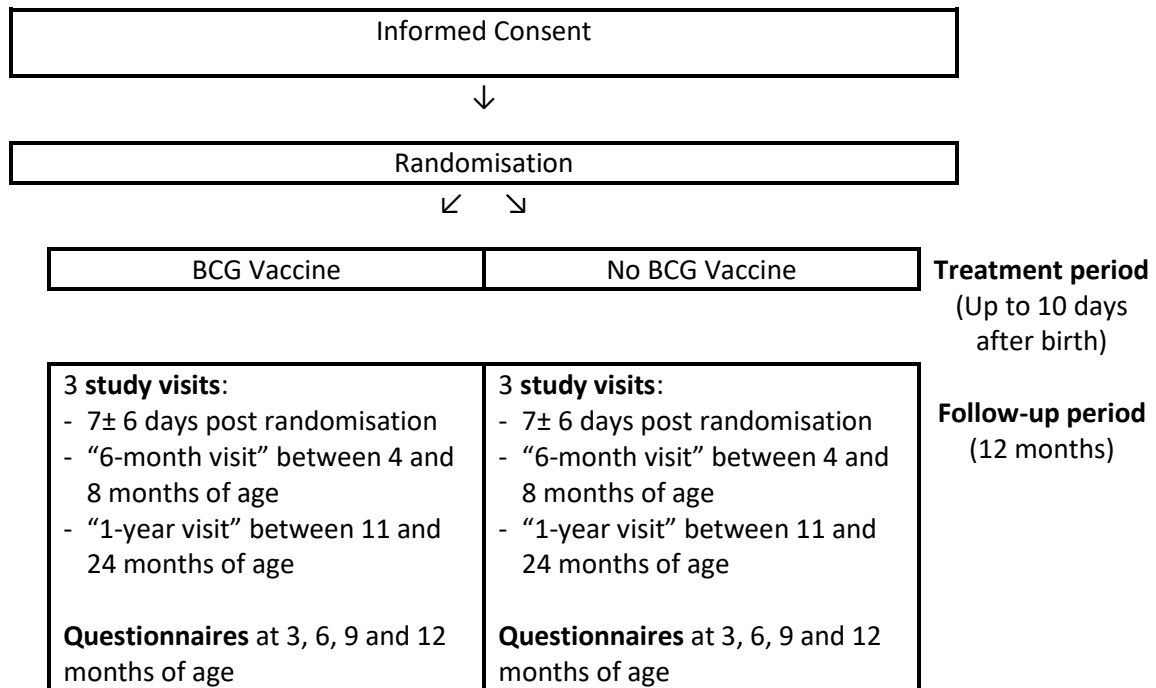
Study participants randomised to group 1 received a single 0.05 mL intradermal dose of BCG vaccine within 10 days of birth. The BCG vaccine used was BCG Vaccine SSI (a.k.a. BCG Denmark or BCG 10 Vaccine), a freeze-dried live vaccine prepared from an attenuated strain of *Mycobacterium bovis*. BCG vaccine was administered as a single, 0.05 mL intradermal dose over the left deltoid. A total of 57 participants were vaccinated with BCG vaccine batch 114010C (expiry 06/2016) after the original used-by-date within 3 months of expiration (use past the expiry date for the study was approved by the governing HRECs).

2.5. SAMPLE SIZE

Prevalence of eczema was estimated to be around 27%. A sample size of 575 in each arm would therefore have 80% power to detect a reduction of 20% (ie, from 27% to 20%). Assuming that complete 1-year data would be available for 80% of the participants we aimed to recruit 1428 participants.

2.6. STUDY PROCEDURE

Initial plan presented in a flow chart in Protocol version 11.



Data relevant to this outcome include: symptoms of eczema, medical diagnosis of eczema, age at eczema onset, use of steroids to treat eczema. Data was collected from parental-report via the 3-monthly questionnaires, and from the clinical assessment at the 1-year visit.

Details on measurement for primary outcome:**1. Eczema prevalence, self-report**

Measured by a modified version of **Williams' UK diagnostic criteria**^{1,2} during the infant's first year of life, collected at each of the 3-monthly surveys.

Data collected as follows:

- In the last three months, has *[child's-name]* had generally itchy skin?
- In the last three months, has *[child's-name]* had generally dry skin?
- Where has *[child's-name]* had dry skin?
 - Face
 - Around eyes
 - Neck
 - Under arms
 - Front of elbows
 - Behind knees
 - Groin area
 - Scalp
 - Napkin area
 - Tummy / Chest / Back
 - Other, please specify
- Have either *[mother's name]*, the biological father, or any of the full- or half- (not step-) siblings of the unborn child ever suffered from asthma?
- Have either *[mother's name]*, the biological father, or any of the full- or half- (not step-) siblings of the unborn child ever suffered from hayfever?
- Have either *[mother's name]*, the biological father, or any of the full- or half- (not step-) siblings of the unborn child ever suffered from eczema?

Details on measurement for secondary outcomes:**1. Medical diagnosis of eczema**

Parent report of eczema diagnosis, by a doctor or a nurse, in the first year of life. Data was collected via the 3-monthly surveys.

Data collected as follows:

- Has *[child's-name]* ever been diagnosed with eczema?
- Who diagnosed *[child's-name]* with eczema?

For doctor diagnosis:

- GP
- Paediatrician
- Hospital emergency doctor
- Dermatologist

For nurse diagnosis:

- Maternal and child health care nurse
- Other nurse

2. Eczema severity, self-report

On each questionnaire, the Patient Oriented Eczema Measure (POEM)³ tool questions were asked to every participant that either met the criteria for eczema using our modified version of the UK diagnostic criteria or had reported a diagnosis of eczema on that survey (or a previous survey). Data collected as follows:

The following questions relate to how much of [child's name]'s last week has been affected by itchy skin or eczema. Please answer the following questions in relation to the last week

- How many days has [child's-name]'s skin been itchy because of eczema/dry itchy skin?
- How many nights has [child's-name]'s sleep been disturbed because of eczema/dry itchy skin?
- How many days has [child's-name]'s skin been bleeding because of eczema/dry itchy skin?
- How many days has [child's-name]'s skin been weeping or oozing clear fluid because of eczema/dry itchy skin?
- How many days has [child's-name]'s skin been cracked because of eczema/dry itchy skin?
- How many days has [child's-name]'s skin been flaking off because of eczema/dry itchy skin?
- How many days has [child's-name]'s skin felt dry or rough because of eczema/dry itchy skin?

Details of modification	
POEM tool ³	MIS BAIR Database
Each question commences with "Over the last week,"	Not included in each question. A note was added at the beginning of the section providing the time frame
Each question uses the wording "your child's"	Child's name was used instead
Questions only include the word "because of their <u>eczema</u> "	Each question included the wording " <u>eczema/dry itchy skin</u> "
Option for answer "No days"	Option for answer "0 days"
"Don't know" not provided as a possible answer	"Don't know" included as an option for answering

3. Eczema severity, clinical assessment

Measured by an allergy nurse at the “1-year visit” using the SCORing Atopic Dermatitis (SCORAD) scale. ⁴

Area (A): To determine extent, the sites affected by eczema are added up in order to obtain the percentage of the whole body. To do so, each eczematous area was given a score (percentage of affected area), then these areas were added up, using the rule of 9 (see below), providing the percentage of whole body affected. Maximum score possible for value A is 100%.

Rule of 9 for calculation of percentage of whole body area

- Head and neck = 9%
- Upper limbs = 9% (each)
- Lower limbs = 18% (each)
- Anterior trunk = 18%
- Back = 18%
- Genitals = 1%

Intensity (B): To determine the severity, a representative area of eczema was selected. This was evaluated providing an intensity value to each of the following signs:

- erythema (redness)
- oedema/papulation (swelling)
- oozing/crusting
- excoriation (scratching)
- lichenification (skin thickening)
- xerosis (dry skin, assessed in another area where there is no inflammation).

Each item was scored from none (0), mild (1), moderate (2) to severe (3).

The maximum value provided to B is 18.

Subjective symptoms (C): two questions were asked in relation to itching and sleeping in the last week of the participant’s life.

Each question was given a value from unaffected (0) to worst possible (10).

A maximum of 20 is allocated to C.

The *final score* is calculated by adding the values of A, B and C with the following formulation: $A/5 + 7B/2 + C$.

The *interpretation* is as follows ⁷:

- 0 to 9.9 = clear
- 10.0 to 28.9 = mild
- 29.0 to 48.9 = moderate
- 49.0 to 103 = severe

4. Medication (topical steroid) used for eczema

Families were asked at each survey if topical steroids had been used in the preceding 3 months.

Data collected included:

- Have you used any topical steroids on *[child's-name]*'s skin in the last 3 months?
- How many different types or brands of topical steroids (e.g. cortisone cream) have you used to treat or manage a flare up of eczema or dry skin?
 - 1
 - 2
 - 3
 - 4
 - 5 or more
- What is the name of the first steroid cream you have used?
- How many separate flare-ups of eczema/dry skin have you used *[name-of-cream]* to treat?
- For the first time you used *[name-of-cream]*, how many days in a row did you use it for?
 - Less than 4 days in a row
 - Between 4 and 10 days in a row
 - More than 10 days in a row
 - Don't know

The first question was asked to all participants, including those without a positive answer to eczema. The following ones were only asked if topical steroids have been used.

5. Age of onset of eczema

Onset of eczema determined by eczema symptoms. Obtained from the 3-monthly surveys and from the clinical assessment at the 1-year visit.

3. POPULATIONS OF ANALYSIS

Inclusion criteria to determine eligibility for analysis:

- Randomised
- Did not withdraw consent for their data to be used.

Description of outcome	Raw or generated	Variable(s) name and type	Do file
Randomised	generated	ba_randomised_b	cr_clean_randomisation
Use of information not withdrew	raw	ba_wd_information_end	cr_consort_randomisation

4. OUTCOME VARIABLES

4.1. PRIMARY OUTCOME

Description of outcome	Raw or generated	Variable(s) name and type	Do file
Prevalence of eczema using William's UK diagnostic criteria	generated	po_eczemaUK_1yr (binary)	cr_3_PO_eczemaUK

Prevalence of eczema, defined by Williams' UK diagnostic criteria

- **Positive** if presence of eczema is determined using a modified version of Williams' UK diagnostic criteria, based on the data collected in the 3-monthly surveys during the first year of life. Eczema presence is defined by fulfilling the major criteria and at least three minor criteria.

MAJOR CRITERIA (mandatory)

1. Presence of **itchy skin**, defined as:

- Positive response to the question "In the last three months, has *[child's-name]* had generally itchy skin?" (at any 3-monthly survey)

OR

- Answered >1 days to the question "How many days has *[child's-name]*'s skin been itchy because of eczema/dry itchy skin?" (at any 3-monthly survey)

MINOR CRITERIA (3 or more of the following)

2. **MINOR n°1:** History of involvement of the **skin creases** or **cheeks**, defined as (at any 3-monthly survey):

- Checking the following areas:

- For skin creases:

- Neck
- Front of elbows
- Behind knees

- For cheeks:

- Face

OR

- Reporting in “other” that the following area were affected by using wording corresponding to the following areas:

- For skin creases:

- Ankle
- Behind ears
- Neck
- Crease

- For cheeks:

- Cheeks
- Face

3. **MINOR n°2:** History of **atopic disease** in a first-degree relative, defined as a positive answer to any of the following (baseline data):

- Have either [mother's name], the biological father, or any of the full- or half- (not step-) siblings of the unborn child ever suffered from asthma?
- Have either [mother's name], the biological father, or any of the full- or half- (not step-) siblings of the unborn child ever suffered from hayfever?
- Have either [mother's name], the biological father, or any of the full- or half- (not step-) siblings of the unborn child ever suffered from eczema?

4. **MINOR n°3:** History of a general **dry skin** in the last year, defined as a positive answer to the following question (at any 3-monthly survey):

- In the last three months, has [child's-name] had generally dry skin?

5. **MINOR n°4:** Visible **flexural eczema** or eczema involving the **head** or **limbs**, defined as (at any 3-monthly survey):

▪ Checking the following areas:

○For flexural eczema:

- Neck
- Front of elbows
- Behind knees

○For head:

- Face
- Around eyes

OR

▪ Reporting in “other” that the following area were affected by using the wording:

○For flexural eczema:

- Ankle
- Neck
- Crease

○For head:

- Face
- Cheeks
- Around eyes
- Behind ears

○For limbs:

- Ankle
- Leg
- Arm
- Hand
- Feet

Note: As previously published, parents are considered to be able to accurately report visible flexural dermatitis in their infants. A previous study has indeed observed that the accuracy of parents’ assessment of flexural involvement was comparable to the formal evaluation by a trained investigator.⁵

- **Negative** if a participant does not fulfil the criteria to be positive and has completed all 4 surveys.
- **Missing** if participant did not complete all 4 surveys and from data available participant does not fulfil the criteria to be positive.

4.2. SECONDARY PARAMETERS OUTCOMES

Description of outcome	Raw or generated	Variable(s) name and type	Do file
Medically-diagnosed eczema (parent-report)	generated	so_eczema_dx_1yr (binary)	cr_4_SO_med_diagnosed
Medically-diagnosed eczema (research nurse, 1 year visit)	generated	so_eczema_rn_1yr (binary)	cr_4_SO_med_diagnosed
Combined definition of eczema (UK diagnostic criteria or medically-diagnosed)	generated	so_eczema_1yr (binary)	cr_8_SO_eczema
Steroid use for eczema	generated	so_eczema_ster_1yr (binary)	cr_5_SO_medication
Age of onset	generated	so_eczema_onset_age (categorical)	cr_7_SO_age_onset
Early onset	generated	so_eczema_onset_3m (binary)	cr_7_SO_age_onset
Severity at 3 months (POEM score category)	generated	so_eczema_sev_3m (categorical)	cr_6_SO_severity
Severity at 6 months (POEM score category)	generated	so_eczema_sev_6m (categorical)	cr_6_SO_severity
Severity at 9 months (POEM score category)	generated	so_eczema_sev_9m (categorical)	cr_6_SO_severity
Severity at 12 months (POEM score category)	generated	so_eczema_sev_12m (categorical)	cr_6_SO_severity
No eczema (maximal POEM score low)	generated	so_eczema_sev_poem_no (binary)	cr_6_SO_severity
Mild eczema (maximal POEM score mild)	generated	so_eczema_sev_poem_mild (binary)	cr_6_SO_severity
Severe eczema (maximal POEM score high)	generated	so_eczema_sev_poem_sev (binary)	cr_6_SO_severity
Persisting moderate to severe (multiple POEM score)	generated	so_eczema_sev_poem_persist (binary)	cr_6_SO_severity
Clinical assessment of eczema (SCORAD)	generated	so_eczema_sev_scorad_1yr (categorical)	cr_6_SO_severity
No eczema (SCORAD score)	generated	so_eczema_sev_scorad_no (binary)	cr_6_SO_severity
Mild eczema (SCORAD score)	generated	so_eczema_sev_scorad_mild (binary)	cr_6_SO_severity
Severe eczema (SCORAD score)	generated	so_eczema_sev_scorad_sev (binary)	cr_6_SO_severity
No eczema (POEM + SCORAD scores low)	generated	so_eczema_sev_both_no (binary)	cr_6_SO_severity
Mild eczema (POEM + SCORAD scores mild)	generated	so_eczema_sev_both_mild (binary)	cr_6_SO_severity
Severe eczema (POEM + SCORAD scores high)	generated	so_eczema_sev_both_sev (binary)	cr_6_SO_severity

Secondary outcome definition

1. Medically-diagnosed eczema, parent-report:

- **Positive** if Participant has answered yes to the question “Has [child’s-name] ever been diagnosed with eczema?”
AND Participant has checked the following health professionals after the question “Who diagnosed [child’s-name] with eczema?”:
 - GP
 - Paediatrician
 - Hospital emergency doctor
 - Dermatologist
 - Maternal and child health care nurse
 - Other nurse.
- **Negative** if the participant does not fulfil the criteria to be positive and has answered no to the question “Has [child’s-name] ever been diagnosed with eczema?” at the 12-month survey.
- **Missing** if participant does not fulfil the criteria to be positive and did not complete the 12-month survey.

2. Medically-diagnosed eczema, by research nurse at the 1 year visit:

- **Positive** if participant has been diagnosed with eczema by the study nurse at the one year study visit, defined as a SCORAD score of 10 or more (mild to severe).
- **Negative** if the participant does not fulfil the criteria to be positive.
- **Missing** if participant did not attend the 1 year visit.

3. Eczema, extended definition (Williams’ UK diagnostic criteria or medically diagnosed)

- **Positive** if participant fulfils the criteria to be positive using a modified version of Williams’ UK diagnostic criteria or eczema was confirmed by a medical professional.
- **Negative** if the participant does not fulfil the criteria to be positive and fulfils the criteria to be negative for both definitions.
- **Missing** if participant does not fulfil the criteria to be positive or negative.

4. Medication and/or steroid used for eczema

Participant were asked at each survey “Have you used any topical steroids on [child’s-name]’s skin in the last 3 months?” followed by “What is the name of the steroid cream you have used?”

- **Positive** if a participant has answered “yes” to the use of topical steroids in any of the 4 surveys.

- **Negative** if answers provided do not fulfil the criteria to be positive and all 4 surveys have been completed.
- **Missing** if participant did not complete all 4 surveys, answered at least once “declined” or “don’t know” at any of the survey, and from data available participant does not fulfil the criteria to be positive.

Note: Where participants have only listed creams that do not contain steroids (e.g. emollient, antibacterial cream), or steroid-containing creams that is not typically used in isolation to treat eczema lesions (e.g. steroid-containing cream for diaper rash), these will NOT be cleaned as positive.

5. Age of onset of eczema

In participants with eczema (according to Williams’ UK diagnostic criteria or eczema medically diagnosed), the age of onset will be defined according to the first time point (either 3, 6, 9, or 12 months) the participant reported a symptom of eczema or was medically diagnosed with eczema, whichever arrives first.

- **Onset by 3 months** if
 1. Participant fulfils the major or any minor UK diagnostic criteria (excluding familial history of atopic disease) of the primary outcome at the 3-month survey.
OR
 2. Participant fulfils the criteria for “medically-diagnosed eczema” at the 3-month survey.
- **Onset by 6 months** if
 1. Participant fulfils for the first time the major or any minor UK diagnostic criteria (excluding familial history of atopic disease) at the 6-month survey.
OR
 2. Participant fulfils for the first time the criteria for “medically-diagnosed eczema” at the 6-month survey.
- **Onset by 9 months** if
 1. Participant fulfils for the first time the major or any minor UK diagnostic criteria (excluding familial history of atopic disease) at the 9-month survey.
OR
 2. Participant fulfils for the first time the criteria for “medically-diagnosed eczema” at the 9-month survey.
- **Onset by 12 months** if
 1. Participant fulfils for the first time the major or any minor UK diagnostic criteria (excluding familial history of atopic disease) at the 6-month survey.
OR
 2. Participant fulfils for the first time the criteria for “medically-diagnosed eczema” at the 6-month survey.

6. Eczema severity, self-report (POEM score)

POEM consists of seven quality-of-life related questions related to eczema that parents completed on behalf of the participant. The aim of these questions was to provide the parent's perception of severity and to describe how many days of 'last week' was the participant affected by eczema.

Each of the POEM question is allocated a score between 0-4 adding up to a maximum of 28 points.

For example: "How many days has [child's name]'s skin been itchy because of eczema/dry itchy skin? "

Scoring:

- No days = 0
- 1-2 days = 1
- 3-4 days = 2
- 5-6 days = 3
- Every day = 4

Interpretation of total score ⁶:

- 0 – 2 = Clear or almost clear
- 3 – 7 = Mild eczema
- 8 – 16 = Moderate eczema
- 17 – 24 = Severe eczema
- 25 – 28 = Very severe eczema

In the case of a missing answer or the option "Don't know" being selected, the scoring allocated will be 0. The questionnaire will not be scored if two or more questions are left unanswered or 2 or more "Don't know" options being selected.

Definitions used:

No eczema is defined as not having any POEM score more than 2 points (corresponding to "clear" eczema).

Mild eczema is defined as not having any POEM score more than 7 points (corresponding to "clear" and "mild" eczema).

Severe eczema is defined as at least one POEM score of 17 to 28 points (corresponding to "severe" and "very severe" eczema).

Persisting moderate to severe eczema is defined as a median POEM score of 8 to 28 points (corresponding to "moderate", "severe" and "very severe" eczema) in patients that have at least 2 POEM scores.

7. Eczema severity, clinical assessment (SCORAD)

The *final score* is calculated by adding the values of A, B and C with the following formulation: $A/5 + 7B/2 + C$. The interpretation is as follows {Chopra, 2017 #10}:

- 0 to 9.9 = clear
- 10.0 to 28.9 = mild
- 29.0 to 48.9 = moderate
- 49.0 to 103 = severe

Definitions used:

No eczema is defined as a SCORAD score less than 10 (corresponding to “clear”).

Mild eczema is defined as a SCORAD score less than 29 (corresponding to “clear” and “mild” eczema).

Severe eczema is defined as a SCORAD score of 49 or more (corresponding to “severe” eczema).

8. Eczema severity, combination of both scores (POEM & SCORAD)

Definitions used:

No eczema is defined as not having any POEM score more than 2 points (corresponding to “clear” eczema) AND a SCORAD score less than 10 (corresponding to “clear”).

Mild eczema is defined as not having any POEM score more than 7 points (corresponding to “clear” and “mild” eczema) AND a SCORAD score less than 29 (corresponding to “clear” and “mild” eczema).

Severe eczema is defined as at least one POEM score of 17 to 28 points (corresponding to “severe” and “very severe” eczema) OR a SCORAD score of 49 or more (corresponding to “severe” eczema).

4.3. OTHER PARAMETERS

DEMOGRAPHY AND BASELINE

Description of outcome	Raw or generated	Variable(s) name and type	Do file
Maternal factors			
Maternal age at the time of participant's birth	generated	mo_agebirth_bi (continuous)	cr_1age_at_x_inf
Highest level of education completed by the time participant's birth	raw	mo_education_t1_bi (categorical)	cr_4table1_maternal
Place of birth, categorical variable: East and South East Asia, South Asia, Australia, UK and Ireland, Continental Europe, Mid East, Africa, North America, South America, Oceania (excl. Australia)	generated	mo_birthplace_pr (categorical)	cr_4table1_maternal
Maternal smoking during pregnancy	raw	mo_smoke_pr (binary)	cr_4table1_maternal
Maternal BCG vaccine received at any time in the past	generated	mo_bcg_pr (categorical)	cr_4table1_maternal
Vaccines received during the pregnancy	raw	mo_vaccinations_pr (categorical)	cr_4table1_maternal
Probiotics taken during the pregnancy, any type	raw	mo_probiotic_pr (binary)	cr_4table1_maternal
Low vitamin D at any stage during the pregnancy, by laboratory report	generated	mo_lowvitd_pr (binary)	cr_4table1_maternal
Vitamin D supplement taken at any point during pregnancy	raw	mo_vitdsup_pr (binary)	cr_4table1_maternal
Paternal factors			
Paternal age at the time of participant's birth	generated	fa_agebirth_bi (continuous)	cr_5table1_paternal
Paternal birth place	generate	fa_birthplace_bi (categorical)	cr_5table1_paternal
Infant factors			
Sex	raw	ba_sex_bi (binary)	cr_7table1_infant
Age at randomisation	generated	ba_age_rand_ra (continuous)	cr_1age_at_x_inf
Infant birth weight, in grams (mean, SD)	raw	ba_weight_bi (continuous)	cr_7table1_infant
Low birth weight (<2500grams)	generated	ba_lowbweight_bi (binary)	cr_7table1_infant
Gestation at birth, number of weeks including 1 decimal (mean, SD)	raw	ba_gestationdec_bi (continuous)	cr_7table1_infant
Gestation at birth, categorical variable: <37 weeks, 37-42 weeks, >42 weeks.	generated	ba_gestationcat_bi (categorical)	cr_7table1_infant
Ethnicity	generated	ba_ethnicity_bi (categorical)	cr_7table1_infant

Twin/Singleton	raw	ba_plurality_bi (binary)	cr_7table1_infant
SCN/NICU admission >24 hours	generated	ba_scn_24hour_bi (binary)	cr_7table1_infant
Hepatitis B vaccine prior to or up to 24hrs post randomisation	raw	ba_hepbvacc24_bi (binary)	cr_7table1_infant
Antibiotics in first week of life	generated	ba_anti_firstweek_bi (binary)	cr_7table1_infant
Birth factors			
Mode of delivery (% vaginal)	generated	ba_delivery_bi (binary)	cr_6table1_birth
Intrapartum antibiotic use	raw	mo_anti_lab_bi (binary)	cr_6table1_birth
Season of birth	generated	ba_season_birth_bi (categorical)	cr_1age_at_x_inf
Familial or environmental factors			
Total number of household habitants during the pregnancy	generated	env_household_hab_pr (categorical)	cr_8table1_enviro
Total number of children under school age (< 5 years) during the pregnancy	raw	env_child_u5_pr (categorical)	cr_8table1_enviro
Total number of school age children (5 to 18 years) during the pregnancy	raw	env_child_5to18_pr (categorical)	cr_8table1_enviro
Daycare attendance (≥ 3 days/week) for sibling of participant during pregnancy	raw	env_childcare_pr (binary)	cr_8table1_enviro
Smokers living in the house during pregnancy	generated	env_household_smo ke_pr (binary)	cr_8table1_enviro
Pet dog exposure during pregnancy	raw	env_dog_pr (binary)	cr_8table1_enviro
Pet cat exposure during pregnancy	raw	env_cat_pr (binary)	cr_8table1_enviro
Livestock exposure during pregnancy	raw	env_livestock_pr (binary)	cr_8table1_enviro
Family history of any allergic disease: present or past history of allergy on at least one first degree relative of the participant (mother, father, full or half sibling).	generated	env_famhx_allergy_p r (binary)	cr_8table1_enviro
Family history of atopic disease: present or past history of atopic disease on at least one first degree relative of the participant (mother, father, full or half sibling).	generated	env_famhx_atopia_p r (binary)	cr_8table1_enviro
Both parents with present or past history of atopic disease	generated	env_2parhx_atopia_ pr (binary)	cr_8table1_enviro
Family history of eczema: present or past history of eczema on at least one first degree relative of the participant (mother, father, full or half sibling).	generated	env_famhx_eczema_ pr (binary)	cr_8table1_enviro

Both parents with present or past history of eczema	generated	env_2parhx_eczema_pr (binary)	cr_8table1_enviro
Family history of food allergy: present or past history of food allergy on at least one first degree relative of the participant (mother, father, full or half sibling).	generated	env_famhx_asthma_pr (binary)	cr_8table1_enviro
Family history of asthma: present or past history of asthma on at least one first degree relative of the participant (mother, father, full or half sibling).	generated	env_famhx_asthma_pr (binary)	cr_8table1_enviro
Family history of hay fever: present or past history of hay fever on at least one first degree relative of the participant (mother, father, full or half sibling).	generated	env_famhx_hayfever_pr (binary)	cr_8table1_enviro

Exposure during first year of life			
Cessation of breastfeeding (≤3m, >3-6m, >6-9m, >9m-12m, >12m)	generated	env_bf_cese_cat (cat)	cr_15table1_supp
Smokers living in the house during first year of life	generated	env_household_smo ke_1yr (binary)	cr_15table1_supp
Daycare attendance for participant during first year of life	raw	env_childcare_1yr (binary)	cr_15table1_supp
Daycare attendance for sibling/s of participant during first year of life	raw	env_sibcare_1yr (binary)	cr_15table1_supp
Livestock exposure	raw	fu12_livestock_yn (binary)	-
Pet dog exposure during first year of life	raw	env_dog_1y (binary)	cr_15table1_supp
Pet cat exposure during first year of life	raw	env_cat_1y (binary)	cr_15table1_supp
Travel	generate	env_travel_1yr (binary)	cr_15table1_supp
Age at first DTP vaccination	generate	ageat_dtp1st (binary)	cr_1age_at_x_inf

Supplementary Table: baseline factors or exposure during first year of life			
Maternal gravidity: primipara at the time of participant's birth	generated	mo_primipara_bi (binary)	cr_4table1_maternal
Antibiotic used in 3rd trimester, excluding labour.	raw	mo_antib_lasttrim_pr (binary)	cr_4table1_maternal
Pre-pregnancy BMI (mean, SD)	generated	mo_prepregbmi_pr (continuous)	cr_4table1_maternal
Weight gain during pregnancy	generated	mo_wtgain_pr (continuous)	cr_4table1_maternal
Birth order	raw	ba_birth_order_bi (categorical)	cr_7table1_infant
Vitamin D supplement	generated	ba_vitd_hospital_bi (binary)	cr_7table1_infant
Emergency caesarean birth (%)	generated	ba_cem_bi (binary)	cr_6table1_birth
Prolonged spontaneous rupture of membranes (>24hours)	generated	mo_prom_24hours_bi (binary)	cr_6table1_birth
Maternal GBS	raw	mo_gbs_pr (binary)	cr_4table1_maternal
Intrapartum antibiotic use, i.e antibiotics given once labour has been declared as commenced as per participating site.	raw	mo_anti_lab_bi (binary)	cr_6table1_birth
Family history of secondary allergies: present or past history of secondary allergy on at least one first degree relative of the participant (mother, father, full or half sibling). Contact allergies will be excluded.	generated	env_famhx_sec_pr (binary)	cr_8table1_enviro

SAFETY

We will report on any severe adverse events related to the intervention. This includes BCG-osis and suppuratives lymphadenitis.

5. STATISTICAL METHODOLOGY

5.1. GENERAL METHODOLOGY

Details of the randomisation will be unblinded only once the sections of the database containing the baseline variables and primary and secondary outcome variables for this component of the MIS BAIR RCT has been locked and the Statistical Analysis Plan has been finalized and approved by the trial team.

Statistical analyses will follow standard methods for randomised controlled trials and the primary analysis will be by intention to treat (ITT), including all randomised participants where outcome data are available.

5.2. BASELINE DATA

The baseline characteristics of the participants will be summarized by group. Binary and categorical variables will be presented as the number and proportion in each category. Continuous variables will be presented as means and standard deviations (SDs), or medians and interquartile ranges (IQR) for skewed data.

5.3. HANDLING OF MISSING DATA

The primary analysis will be a complete case analysis. If the proportion of missing data on the primary outcome is more than 5%, the rate and patterns of missing data will be examined and, if appropriate, a sensitivity analysis will be performed to compare the results of analyses restricted to infants with complete data and analyses where those with missing data are included using multiple imputation. Multiple imputation models will be conducted for the outcome variables and 50 completed data sets will be imputed by chained equations including all the children initially randomised. The primary outcome, strata variable (mode of birth: vaginal/caesarean), and the variables predictive of missingness and infection listed below will be included in the imputation model. Although there are 2 other randomisation strata (study site and singleton/twin), the number of participants recruited at study sites other than the Mercy, and the number of twins, is so small that it is unlikely that it will be possible to multiply impute separately for these strata. Where possible, secondary outcomes will be included in the multiple imputation of the primary analysis, otherwise secondary outcomes will be analysed as a complete case analysis.

Additional variables to be included in multiple imputation

Variable description	Raw or generated	Variable name and type	Do file (variable created)
Infant ethnicity	generated	ba_ethnicity_bi (categorical)	cr7_table1_infant
Asian background	generated	ba_ethnicity_asian_bi (binary)	cr_20_ecz_multip_PO
Mother born in country with high TB prevalence	generated	mo_hightbcountry_pr (binary)	cr_20_ecz_multip_PO
Maternal BCG vaccination	raw	mo_bcg_pr (binary)	cr_4table1_maternal
Maternal education	generated	mo_education_t1_bi (categorical)	cr_4table1_maternal
Probiotics taken during the pregnancy, any type	raw	mo_probiotic_pr (binary)	cr_4table1_maternal
Smokers living in the house during pregnancy	raw	env_household_smoke_pr (binary)	cr_8table1_enviro
Maternal age at the birth of participant	generated	mo_agebirth_bi (continuous)	cr_1age_at_x_inf
Paternal age at the birth of participant	generated	fa_agebirth_bi (continuous)	cr_5table1_paternal
Only child at randomisation	generated	only_child (binary)	cr_20_ecz_multip_PO
Birth in autumn	generated	ba_season_birth_autumn (binary)	cr_20_ecz_multip_PO
Infant birth weight	raw	ba_weight_bi (continuous)	cr_7table1_infant
Daycare attendance for participant during first year of life	raw	env_childcare_1yr (binary)	cr_9table1_supps
Breastfeeding duration	generated	ba_bf_at_cat (cat)	cr_15table1_supp
Family history of eczema	generated	env_famhx_eczema_pr (binary)	cr_8table1_enviro
Family history of food allergy	generated	env_famhx_asthma_pr (binary)	cr_8table1_enviro

Family history of hay fever	generated	env_famhx_hayfever_pr (binary)	cr_8table1_enviro
Family history of food allergy	generated	env_famhx_food_pr (binary)	cr_8table1_enviro
Use of steroid cream during follow-up	generated	so_eczema_ster_1yr (binary)	cr_5_SO_medication

5.4. SUBGROUP ANALYSIS

Nine additional adjusted models will be estimated to explore potential heterogeneity of the effect of the intervention. Each model will include as covariates the stratification factors used in randomisation, and an interaction term estimating the interaction between the intervention and the subgroup variable (listed below). Should any of these interaction terms suggest evidence that the intervention varies between subgroups, specific subgroup estimates and confidence intervals will be presented obtained from the adjusted model. As the study is not powered for subgroup analysis, these analyses are considered exploratory.

Variable description	Raw or generated	Variable name and type	Do file (variable created)
Gender	raw	ba_sex_bi (binary)	cr_7table1_infant
Maternal BCG (parental report)	generated	mo_bcg_pr (binary)	cr_4table1_maternal
Both parents with atopic disease	generated	env_2parhx_atopia_pr (binary)	cr_8table1_enviro
Mode of delivery	generated	ba_delivery_bi (binary)	cr_7table1_infant
Season of birth	generated	ba_season_bi (categorical)	cr_1age_at_x_inf
Hepatitis B vaccination at birth	raw	ba_hepbvacc24_bi (binary)	cr_7table1_infant
Presence or absence BCG scar	raw	ba_scar_present_bi (binary)	cr100_bcg
Timing of BCG administration <48 hours of life	generated	ba_bcg_48hours_bi (binary)	cr100_bcg
Expired BCG	generated	ba_bcg_expired_bi (binary)	cr100_bcg

5.5. CLASSIFICATION OF PROTOCOL VIOLATION

All deviations / violations to the protocol will be summarized separately by group using absolute and relative frequencies.

5.6. ANALYSIS OF THE PRIMARY OUTCOME

The percentage of eczema prevalence at 12 months will be presented separately for children in the treatment and non-treatment groups. Comparison between the treatment arms will be estimated using binary regression adjusted for the stratification factors used during randomisation. Results will be presented as risk difference and its 95% confidence interval (CI).

As a sensitivity analysis, the same binary regression model will be re-run adjusting for any baseline variables where an imbalance between groups is found.

5.7. ANALYSIS OF THE SECONDARY OUTCOMES

For each secondary outcome, the percentage of study participants with the outcome will be presented separately for children in the treatment and non-treatment groups. Comparison between the treatment arms will be estimated using multinomial or binomial regression adjusted for the stratification factors used during randomisation. Results will be presented as risk difference and its 95% confidence interval (CI).

As a sensitivity analysis, the same regression model will be re-run adjusting for sex as well as any baseline variables where an imbalance between groups is found.

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7. CHIEF INVESTIGATOR AGREEMENT

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Supplementary material 2

This was provided as supplementary material to the publication by Pittet LF *et al.*

Neonatal BCG vaccination to prevent eczema in infants the MIS BAIR randomised controlled trial

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Table S1: Participant characteristics, categorised by retention in trial

		All participants	Overall		Not lost to follow up		Lost to follow up	
	n	n=1272	No BCG n=635	BCG n=637	No BCG n=584	BCG n=606	No BCG n=51	BCG n=31
Infant factors								
Age at randomisation, hours	1272	46.9 (43.3)	47.8 (45.2)	46.0 (41.3)	48.4 (45.7)	45.9 (41.3)	40.3 (37.9)	47.5 (43.4)
Sex, female	1272	630 (49.5%)	312 (49.1%)	318 (49.9%)	288 (49.3%)	302 (49.8%)	24 (47.1%)	16 (51.6%)
Birth weight, kg	1272	3.4 (0.5)	3.4 (0.5)	3.4 (0.5)	3.4 (0.5)	3.4 (0.5)	3.5 (0.5)	3.2 (0.5)
Birth weight <2.5kg	1272	45 (3.5%)	29 (4.6%)	16 (2.5%)	26 (4.5%)	13 (2.1%)	3 (5.9%)	3 (9.7%)
Gestational age at birth, week	1272	39.3 (1.4)	39.2 (1.4)	39.4 (1.41)	39.2 (1.5)	39.4 (1.4)	39.0 (1.4)	39.1 (1.3)
Gestational age <37 week	1272	35 (2.8%)	19 (3.0%)	16 (2.5%)	16 (2.7%)	15 (2.5%)	3 (5.9%)	1 (3.2%)
Twin pregnancy	1272	21 (1.7%)	10 (1.6%)	11 (1.7%)	9 (1.5%)	11 (1.8%)	1 (2.0%)	0 (0.0%)
Vaginal delivery	1272	812 (63.8%)	406 (63.9%)	406 (63.7%)	371 (63.5%)	386 (63.7%)	35 (68.6%)	20 (64.5%)
Admission (>24h) to critical care prior inclusion	1268	94 (7.4%)	52 (8.2%)	42 (6.6%)	46 (7.9%)	39 (6.4%)	6 (11.8%)	3 (10.0%)
Hepatitis B vaccination ≤24h post randomisation	1271	1103 (86.8%)	562 (88.5%)	541 (85.1%)	517 (88.5%)	512 (84.6%)	45 (88.2%)	29 (93.5%)
Infant ethnicity								
Caucasian (≥75% grandparents are Caucasians)	1272	949 (74.6%)	475 (74.8%)	474 (74.4%)	442 (75.7%)	453 (74.8%)	33 (64.7%)	21 (67.7%)
Asian (≥75% grandparents are Asians)		82 (6.4%)	39 (6.1%)	43 (6.8%)	36 (6.2%)	41 (6.8%)	3 (5.9%)	2 (6.5%)
Mix Caucasian and Asian		62 (4.9%)	30 (4.7%)	32 (5.0%)	27 (4.6%)	32 (5.3%)	3 (5.9%)	0 (0.0%)
Other		179 (14.1%)	91 (14.3%)	88 (13.8%)	79 (13.5%)	80 (13.2%)	12 (23.5%)	8 (25.8%)
Season of birth								
Summer	1272	286 (22.5%)	137 (21.6%)	149 (23.4%)	129 (22.1%)	139 (22.9%)	8 (15.7%)	10 (32.3%)
Autumn		362 (28.5%)	185 (29.1%)	177 (27.8%)	165 (28.3%)	167 (27.6%)	20 (39.2%)	10 (32.3%)
Winter		314 (24.7%)	156 (24.6%)	158 (24.8%)	146 (25.0%)	152 (25.1%)	10 (19.6%)	6 (19.4%)
Spring		310 (24.4%)	157 (24.7%)	153 (24.0%)	144 (24.7%)	148 (24.4%)	13 (25.5%)	5 (16.1%)
Birth order of participant								
1 st child	1272	686 (53.9%)	331 (52.1%)	355 (55.7%)	312 (53.4%)	342 (56.4%)	19 (37.3%)	13 (41.9%)
2 nd child		396 (31.1%)	208 (32.8%)	188 (29.5%)	191 (32.7%)	177 (29.2%)	17 (33.3%)	11 (35.5%)
3 rd child		149 (11.7%)	76 (12.0%)	73 (11.5%)	65 (11.1%)	68 (11.2%)	11 (21.6%)	5 (16.1%)
4 th child		31 (2.4%)	14 (2.2%)	17 (2.7%)	10 (1.7%)	15 (2.5%)	4 (7.8%)	2 (6.5%)
5 th child		10 (0.8%)	6 (0.9%)	4 (0.6%)	6 (1.0%)	4 (0.7%)	0 (0.0%)	0 (0.0%)
Antibiotic exposure								
During 3 rd trimester (excluding labour)	1266	169 (13.3%)	83 (13.1%)	86 (13.6%)	73 (12.5%)	81 (13.4%)	10 (20.0%)	5 (16.7%)
During labour	1253	277 (22.1%)	141 (22.5%)	136 (21.7%)	134 (23.3%)	132 (22.1%)	7 (13.7%)	4 (12.9%)
Prior discharge from birth hospital	1272	80 (6.3%)	47 (7.4%)	33 (5.2%)	42 (7.2%)	31 (5.1%)	5 (9.8%)	2 (6.5%)
Maternal factors								
Age at delivery, year	1271	32.6 (4.8)	32.7 (4.7)	32.6 (4.8)	32.9 (4.7)	32.8 (4.7)	30.7 (5.2)	28.7 (5.1)
Maternal BMI pre-pregnancy, kg/m ²	737	25.2 (5.3)	25.2 (5.5)	25.1 (5.2)	25.2 (5.5)	25.2 (5.2)	25.6 (5.3)	22.3 (4.1)
Maternal weight gain in pregnancy, kg	742	12.3 (7.3)	12.0 (7.3)	12.6 (7.2)	11.9 (7.3)	12.6 (7.2)	12.7 (7.6)	11.5 (8.2)
Primipara	1272	686 (53.9%)	331 (52.1%)	355 (55.7%)	312 (53.4%)	342 (56.4%)	19 (37.3%)	13 (41.9%)
History of BCG vaccination	1206	318 (26.4%)	159 (26.5%)	159 (26.3%)	145 (26.3%)	153 (26.6%)	14 (28.0%)	6 (20.0%)

	All participants		Overall		Not lost to follow up		Lost to follow up	
	n	n=1272	No BCG n=635	BCG n=637	No BCG n=584	BCG n=606	No BCG n=51	BCG n=31
Smoking during pregnancy	1269	43 (3.4%)	20 (3.1%)	23 (3.6%)	18 (3.1%)	18 (3.0%)	2 (3.9%)	5 (16.1%)
Probiotic use during pregnancy	1262	208 (16.5%)	110 (17.5%)	98 (15.5%)	107 (18.5%)	96 (15.9%)	3 (6.0%)	2 (6.7%)
Vitamin D deficiency during pregnancy ^a	1118	366 (32.7%)	182 (32.3%)	184 (33.2%)	163 (31.4%)	172 (32.3%)	19 (43.2%)	12 (52.2%)
Vitamin D supplementation during pregnancy	1267	859 (67.8%)	426 (67.1%)	433 (68.5%)	393 (67.3%)	418 (69.4%)	33 (64.7%)	15 (50.0%)
Mother GBS positive during pregnancy	1272	198 (15.6%)	108 (17.0%)	90 (14.1%)	104 (17.8%)	87 (14.4%)	4 (7.8%)	3 (9.7%)
Emergency C-section	1272	230 (18.1%)	110 (17.3%)	120 (18.8%)	102 (17.5%)	114 (18.8%)	8 (15.7%)	6 (19.4%)
Rupture of membrane > 24h	1233	91 (7.4%)	39 (6.3%)	52 (8.4%)	37 (6.5%)	51 (8.7%)	2 (4.1%)	1 (3.4%)
Maternal vaccination during pregnancy	1272							
Neither DTP nor influenza vaccine		374 (29.4%)	191 (30.1%)	183 (28.7%)	170 (29.1%)	171 (28.2%)	21 (41.2%)	12 (38.7%)
DTP vaccine only		210 (16.5%)	107 (16.9%)	103 (16.2%)	101 (17.3%)	94 (15.5%)	6 (11.8%)	9 (29.0%)
Influenza vaccine only		268 (21.1%)	134 (21.1%)	134 (21.0%)	127 (21.7%)	131 (21.6%)	7 (13.7%)	3 (9.7%)
Both DTP and influenza vaccine		420 (33.0%)	203 (32.0%)	217 (34.1%)	186 (31.8%)	210 (34.7%)	17 (33.3%)	7 (22.6%)
Maternal country of birth	1272							
Australia		923 (72.6%)	456 (71.8%)	467 (73.3%)	420 (71.9%)	443 (73.1%)	36 (70.6%)	24 (77.4%)
East & South East Asia		85 (6.7%)	48 (7.6%)	37 (5.8%)	45 (7.7%)	37 (6.1%)	3 (5.9%)	0 (0.0%)
United Kingdom or Ireland		70 (5.5%)	36 (5.7%)	34 (5.3%)	33 (5.7%)	34 (5.6%)	3 (5.9%)	0 (0.0%)
Continental Europe		42 (3.3%)	20 (3.1%)	22 (3.5%)	19 (3.3%)	22 (3.6%)	1 (2.0%)	0 (0.0%)
Middle East		20 (1.6%)	10 (1.6%)	10 (1.6%)	9 (1.5%)	9 (1.5%)	1 (2.0%)	1 (3.2%)
Africa		21 (1.7%)	8 (1.3%)	13 (2.0%)	5 (0.9%)	10 (1.7%)	3 (5.9%)	3 (9.7%)
South Asia		38 (3.0%)	21 (3.3%)	17 (2.7%)	19 (3.3%)	15 (2.5%)	2 (3.9%)	2 (6.5%)
South America		14 (1.1%)	7 (1.1%)	7 (1.1%)	6 (1.0%)	7 (1.2%)	1 (2.0%)	0 (0.0%)
North America		18 (1.4%)	7 (1.1%)	11 (1.7%)	7 (1.2%)	10 (1.7%)	0 (0.0%)	1 (3.2%)
Oceania, excluding Australia		41 (3.2%)	22 (3.5%)	19 (3.0%)	21 (3.6%)	19 (3.1%)	1 (2.0%)	0 (0.0%)
Maternal education	1269							
No education / up to year 10		75 (5.9%)	34 (5.4%)	41 (6.5%)	26 (4.5%)	30 (5.0%)	8 (15.7%)	11 (35.5%)
Year 12 / trade		340 (26.8%)	175 (27.6%)	165 (26.0%)	155 (26.5%)	152 (25.2%)	20 (39.2%)	13 (41.9%)
University		854 (67.3%)	426 (67.1%)	428 (67.5%)	403 (69.0%)	421 (69.8%)	23 (45.1%)	7 (22.6%)
Paternal factors								
Age at delivery, years	1239	34.5 (5.5)	34.5 (5.5)	34.5 (5.6)	34.7 (5.4)	34.7 (5.5)	31.7 (6.0)	30.9 (6.2)
Paternal country of birth	1255							
Australia		925 (73.7%)	462 (73.9%)	463 (73.5%)	420 (73.2%)	443 (73.8%)	42 (82.4%)	20 (66.7%)
East & South East Asia		52 (4.1%)	21 (3.4%)	31 (4.9%)	20 (3.5%)	31 (5.2%)	1 (2.0%)	0 (0.0%)
United Kingdom or Ireland		83 (6.6%)	40 (6.4%)	43 (6.8%)	39 (6.8%)	42 (7.0%)	1 (2.0%)	1 (3.3%)
Continental Europe		38 (3.0%)	15 (2.4%)	23 (3.7%)	15 (2.6%)	21 (3.5%)	0 (0.0%)	2 (6.7%)
Middle East		23 (1.8%)	13 (2.1%)	10 (1.6%)	12 (2.1%)	9 (1.5%)	1 (2.0%)	1 (3.3%)
Africa		33 (2.6%)	13 (2.1%)	20 (3.2%)	11 (1.9%)	16 (2.7%)	2 (3.9%)	4 (13.3%)
South Asia		38 (3.0%)	20 (3.2%)	18 (2.9%)	18 (3.1%)	16 (2.7%)	2 (3.9%)	2 (6.7%)
South America		8 (0.6%)	6 (1.0%)	2 (0.3%)	5 (0.9%)	2 (0.3%)	1 (2.0%)	0 (0.0%)

	All participants		Overall		Not lost to follow up		Lost to follow up	
	n	n=1272	No BCG n=635	BCG n=637	No BCG n=584	BCG n=606	No BCG n=51	BCG n=31
North America		12 (1.0%)	9 (1.4%)	3 (0.5%)	9 (1.6%)	3 (0.5%)	0 (0.0%)	0 (0.0%)
Oceania, excluding Australia		43 (3.4%)	26 (4.2%)	17 (2.7%)	25 (4.4%)	17 (2.8%)	1 (2.0%)	0 (0.0%)
Familial and environmental factors at birth								
Vitamin D supplementation in hospital	1268	370 (29.2%)	185 (29.2%)	185 (29.2%)	174 (29.8%)	181 (30.0%)	11 (21.6%)	4 (13.3%)
Number of household habitants	1272	2.9 (1.1)	2.9 (1.1)	2.9 (1.2)	2.8 (1.0)	2.9 (1.2)	3.2 (1.1)	3.3 (1.2)
≥1 household habitants under school age	1271	515 (40.5%)	263 (41.4%)	252 (39.6%)	235 (40.2%)	235 (38.8%)	28 (54.9%)	17 (54.8%)
≥1 household habitants of school age (5 to 18 year)	1271	210 (16.5%)	105 (16.5%)	105 (16.5%)	93 (15.9%)	97 (16.0%)	12 (23.5%)	8 (25.8%)
Sibling attending daycare ≥3 days/week at birth	1259	189 (15.0%)	91 (14.5%)	98 (15.5%)	79 (13.7%)	94 (15.7%)	12 (23.5%)	4 (12.9%)
Pet dog during pregnancy	1272	503 (39.5%)	247 (38.9%)	256 (40.2%)	226 (38.7%)	244 (40.3%)	21 (41.2%)	12 (38.7%)
Pet cat during pregnancy	1272	317 (24.9%)	156 (24.6%)	161 (25.3%)	149 (25.5%)	152 (25.1%)	7 (13.7%)	9 (29.0%)
Livestock exposure during pregnancy	1271	48 (3.8%)	26 (4.1%)	22 (3.5%)	24 (4.1%)	22 (3.6%)	2 (3.9%)	0 (0.0%)
Family history of eczema	1270	514 (40.5%)	263 (41.5%)	251 (39.5%)	242 (41.5%)	242 (40.0%)	21 (41.2%)	9 (29.0%)
Both parents have eczema	1270	31 (2.4%)	19 (3.0%)	12 (1.9%)	16 (2.7%)	12 (2.0%)	3 (5.9%)	0 (0.0%)
Family history of hayfever	1270	836 (65.8%)	408 (64.3%)	428 (67.4%)	384 (65.8%)	413 (68.4%)	24 (47.1%)	15 (48.4%)
Family history of asthma	1269	615 (48.5%)	298 (47.0%)	317 (49.9%)	274 (47.0%)	308 (51.0%)	24 (47.1%)	9 (29.0%)
Family history of any atopic disease ^a	1271	1049 (82.5%)	520 (81.9%)	529 (83.2%)	483 (82.7%)	507 (83.8%)	37 (72.5%)	22 (71.0%)
Both parents are atopic	1269	386 (30.4%)	194 (30.6%)	192 (30.2%)	181 (31.0%)	188 (31.1%)	13 (25.5%)	4 (12.9%)
Family history of any allergy or atopic disease	1262	1070 (84.8%)	528 (83.5%)	542 (86.0%)	490 (84.3%)	519 (86.6%)	38 (74.5%)	23 (74.2%)
Family history of any non-food allergy	1231	306 (24.9%)	153 (24.9%)	153 (24.8%)	145 (25.7%)	145 (24.6%)	8 (16.0%)	8 (28.6%)
Smokers living in the house during pregnancy	1269	222 (17.5%)	117 (18.5%)	105 (16.5%)	99 (17.0%)	87 (14.4%)	18 (35.3%)	18 (58.1%)
Household composition at birth								
Total number of household habitants	1272							
1		16 (1.3%)	6 (0.9%)	10 (1.6%)	5 (0.9%)	9 (1.5%)	1 (2.0%)	1 (3.2%)
2		575 (45.2%)	284 (44.7%)	291 (45.7%)	268 (45.9%)	283 (46.7%)	16 (31.4%)	8 (25.8%)
3		391 (30.7%)	205 (32.3%)	186 (29.2%)	188 (32.2%)	178 (29.4%)	17 (33.3%)	8 (25.8%)
4		190 (14.9%)	94 (14.8%)	96 (15.1%)	85 (14.6%)	87 (14.4%)	9 (17.6%)	9 (29.0%)
5		62 (4.9%)	29 (4.6%)	33 (5.2%)	22 (3.8%)	29 (4.8%)	7 (13.7%)	4 (12.9%)
6		23 (1.8%)	12 (1.9%)	11 (1.7%)	11 (1.9%)	10 (1.7%)	1 (2.0%)	1 (3.2%)
7		11 (0.9%)	4 (0.6%)	7 (1.1%)	4 (0.7%)	7 (1.2%)	0 (0.0%)	0 (0.0%)
8		2 (0.2%)	1 (0.2%)	1 (0.2%)	1 (0.2%)	1 (0.2%)	0 (0.0%)	0 (0.0%)
9		1 (0.1%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	0 (0.0%)
11		1 (0.1%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	0 (0.0%)
Number of household habitants under school age	1271							
0		756 (59.5%)	372 (58.6%)	384 (60.4%)	349 (59.8%)	370 (61.2%)	23 (45.1%)	14 (45.2%)
1		417 (32.8%)	216 (34.0%)	201 (31.6%)	194 (33.2%)	189 (31.2%)	22 (43.1%)	12 (38.7%)
2		90 (7.1%)	43 (6.8%)	47 (7.4%)	37 (6.3%)	42 (6.9%)	6 (11.8%)	5 (16.1%)
3		7 (0.6%)	3 (0.5%)	4 (0.6%)	3 (0.5%)	4 (0.7%)	0 (0.0%)	0 (0.0%)
4		1 (0.1%)	1 (0.2%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

	All participants		Overall		Not lost to follow up		Lost to follow up	
	n	n=1272	No BCG n=635	BCG n=637	No BCG n=584	BCG n=606	No BCG n=51	BCG n=31
Number of household habitants of school age	1271							
0		1061 (83.5%)	530 (83.5%)	531 (83.5%)	491 (84.1%)	508 (84.0%)	39 (76.5%)	23 (74.2%)
1		127 (10.0%)	65 (10.2%)	62 (9.7%)	58 (9.9%)	56 (9.3%)	7 (13.7%)	6 (19.4%)
2		64 (5.0%)	31 (4.9%)	33 (5.2%)	27 (4.6%)	31 (5.1%)	4 (7.8%)	2 (6.5%)
3		17 (1.3%)	8 (1.3%)	9 (1.4%)	7 (1.2%)	9 (1.5%)	1 (2.0%)	0 (0.0%)
4		1 (0.1%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	0 (0.0%)
5		1 (0.1%)	1 (0.2%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Exposure during first year of life								
Age at first DTP-containing vaccine, day	1240	50.0 (34.4)	50.4 (46.2)	49.6 (15.9)	50.4 (47.5)	49.1 (13.1)		
Family own a pet dog	1147	434 (37.8%)	207 (36.6%)	227 (39.0%)	207 (36.6%)	227 (39.0%)		
Family own a pet cat	1147	265 (23.1%)	135 (23.9%)	130 (22.3%)	135 (23.9%)	130 (22.3%)		
Family own livestock or live in a farm	1149	43 (3.7%)	24 (4.2%)	19 (3.3%)	24 (4.2%)	19 (3.3%)		
Travel overseas during first year of life	1148	257 (22.4%)	117 (20.7%)	140 (24.0%)	117 (20.7%)	140 (24.0%)		
Daycare attendance for participant	1242	457 (36.8%)	238 (38.8%)	219 (34.9%)	231 (39.8%)	218 (36.0%)		
Daycare attendance for household member	1155	349 (30.2%)	176 (30.6%)	173 (29.9%)	163 (30.3%)	164 (29.5%)		
Smokers living in the house during 1 st year of life	1147	153 (13.3%)	82 (14.5%)	71 (12.2%)	82 (14.5%)	71 (12.2%)		
Breastfeeding, age at cessation	1175							
No breastfeeding		29 (2.5%)	16 (2.8%)	13 (2.2%)	13 (2.3%)	10 (1.7%)		
Less than 1 week		33 (2.8%)	16 (2.8%)	17 (2.8%)	15 (2.7%)	15 (2.6%)		
Between 1 week and 3 months		207 (17.6%)	100 (17.5%)	107 (17.8%)	87 (15.7%)	99 (16.9%)		
Between 3 to 6 months		126 (10.7%)	68 (11.9%)	58 (9.6%)	67 (12.1%)	55 (9.4%)		
Between 6 to 9 months		126 (10.7%)	60 (10.5%)	66 (11.0%)	60 (10.8%)	65 (11.1%)		
Between 9 to 12 months		169 (14.4%)	85 (14.8%)	84 (14.0%)	85 (15.3%)	84 (14.4%)		
After 12 months		485 (41.3%)	228 (39.8%)	257 (42.7%)	228 (41.1%)	257 (43.9%)		

^a Any of eczema, hayfever, asthma.

DTP: diphtheria-tetanus-pertussis; GBS: Group B streptococcus.

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

Table S2: Eczema in the first year of life, incidence, age of onset and severity; rate ratio (to facilitate comparison with other trials)

	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%	aRR	0.88 (0.74 to 1.04)	0.1
Complete case analysis	1103	35.1% (190/541)	32.0% (180/562)	aRR	0.91 (0.77 to 1.08)	0.3
Secondary outcomes (eczema outcome)						
Active lesion of eczema at the 12-months visit	1096	19.2% (100/521)	15.7 (90/575)	aRR	0.82 (0.63 to 1.06)	0.1
Parent report of medically diagnosed eczema	1164	28.7% (164/571)	29.2% (173/593)	aRR	1.02 (0.84 to 1.22)	0.9
Extended definition of eczema (primary outcome or parent-report)	1113	43.2% (235/544)	41.6% (237/569)	aRR	0.96 (0.84 to 1.10)	0.6
Use of topical steroid ^b (multiple imputation)	1272	39.0%	35.7%	aRR	0.92 (0.78 to 1.07)	0.3
Use of topical steroid (complete case analysis)	991	38.5% (186/483)	37.6% (191/508)	aRR	0.98 (0.83 to 1.14)	0.8
Subgroup analysis (for primary outcome)						
None or one parent with atopic disease	756	109/369 (29.5%)	119/387 (30.8%)	aRR	1.04 (0.84 to 1.29)	0.7
Both parents with atopic disease	344	80/171 (46.8%)	61/173 (35.3%)	aRR	0.75 (0.58 to 0.97)	0.03
Born to mother BCG-naïve	763	130/376 (34.6%)	111/387 (28.7%)	aRR	0.83 (0.67 to 1.02)	0.07
Born to mother previously vaccinated with BCG	279	47/134 (35.1%)	62/145 (42.8%)	aRR	1.22 (0.91 to 1.64)	0.2
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%)	aRR	0.97 (0.83 to 1.14)	0.7
Maximum POEM score category during follow up						
Clear	332	18/171 (10.5%)	18/161 (11.2%)	aRR	1.06 (0.57 to 1.97)	0.9
Clear to mild	332	80/171 (46.8%)	78/161 (48.4%)	aRR	1.04 (0.83 to 1.30)	0.7
Severe or very severe	332	13/171 (7.6%)	10/161 (6.2%)	aRR	0.82 (0.37 to 1.82)	0.6
Persistently high POEM scores (≥2 scores during follow up)						
Median score ≥ moderate	253	37/130 (28.5%)	45/123 (36.6%)	aRR	1.27 (0.89 to 1.81)	0.2
SCORAD category at 12-month follow-up visit						
Clear	340	102/170 (60.0%)	109/170 (64.1%)	aRR	1.07 (0.90 to 1.26)	0.4
Clear to mild	340	152/170 (89.4%)	155/170 (91.2%)	aRR	1.02 (0.95 to 1.09)	0.6
Severe	340	8/170 (4.7%)	4/170 (2.4%)	aRR	0.50 (0.15 to 1.63)	0.3
Combination of POEM and SCORAD scores category						
Both scores clear	308	10/154 (6.5%)	15/154 (9.7%)	aRR	1.50 (0.70 to 3.24)	0.3
Both scores clear to mild	308	67/154 (43.5%)	73/154 (47.4%)	aRR	1.10 (0.86 to 1.40)	0.5
Any score severe or very severe ^d	364	19/187 (10.2%)	13/177 (7.3%)	aRR	0.73 (0.37 to 1.43)	0.4

^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.

aRR: adjusted risk ratio; BCG: bacille Calmette-Guérin; CI: confidence interval; POEM: Patient Oriented Eczema Measure score¹; SCORAD: SCORing Atopic Dermatitis scoring system.² Categories used as previously defined.^{3,4}

Table S3a: Age of onset of eczema and severity scores during follow-up (UK diagnostic criteria)

	No BCG (n=190)			BCG (n=180)			
	n (%)	95% CI		n (%)	95% CI		p-value
		Lower	Upper		Lower	Upper	
Age at first symptom of eczema (n=370)							
Between birth and 3 months old	122 (64.2%)	57.1%	70.8%	112 (62.2%)	54.9%	69.1%	0.8
Between 3 and 6 months old	43 (22.6%)	17.2%	29.2%	48 (26.7%)	20.7%	33.7%	
Between 6 and 9 months old	20 (10.5%)	6.9%	15.8%	16 (8.9%)	5.5%	14.1%	
Between 9 and 12 months old	5 (2.6%)	1.1%	6.2%	4 (2.2%)	0.8%	5.8%	
POEM score category at 3-month questionnaire (n=85)							
Clear	7 (15.9%)	7.6%	30.3%	2 (4.9%)	1.2%	18.2%	0.07
Mild	15 (34.1%)	21.4%	49.6%	12 (29.3%)	17.1%	45.3%	
Moderate	15 (34.1%)	21.4%	49.6%	25 (61.0%)	45.0%	74.9%	
Severe	6 (13.6%)	6.1%	27.7%	2 (4.9%)	1.2%	18.2%	
Very severe	1 (2.3%)	0.3%	15.2%	0 (0.0%)	1.2%	18.2%	
POEM score category at 6-month questionnaire (n=220)							
Clear	23 (20.7%)	14.1%	29.4%	21 (19.3%)	12.9%	27.9%	0.7
Mild	44 (39.6%)	30.9%	49.1%	37 (33.9%)	25.6%	43.4%	
Moderate	40 (36.0%)	27.6%	45.5%	46 (42.2%)	33.2%	51.8%	
Severe	4 (3.6%)	1.3%	9.3%	4 (3.7%)	1.4%	9.5%	
Very severe	0 (0.0%)	-	-	1 (0.9%)	0.1%	6.4%	
POEM score category at 9-month questionnaire (n=222)							
Clear	27 (22.9%)	16.1%	31.4%	26 (25.0%)	17.5%	34.3%	0.9
Mild	61 (51.7%)	42.6%	60.7%	51 (49.0%)	39.5%	58.7%	
Moderate	27 (22.9%)	16.1%	31.4%	25 (24.0%)	16.7%	33.3%	
Severe	3 (2.5%)	0.8%	7.7%	2 (1.9%)	0.5%	7.5%	
Very severe	0 (0.0%)	-	-	0 (0.0%)	-	-	
POEM score category at 12-month questionnaire (n=231)							
Clear	27 (23.3%)	16.4%	31.9%	38 (33.0%)	25.0%	42.2%	0.4
Mild	51 (44.0%)	35.1%	53.2%	47 (40.9%)	32.2%	50.2%	
Moderate	36 (31.0%)	23.2%	40.1%	28 (24.3%)	17.3%	33.1%	
Severe	2 (1.7%)	0.4%	6.7%	2 (1.7%)	0.4%	6.8%	
Very severe	0 (0.0%)	-	-	0 (0.0%)	-	-	
SCORAD score category at 12-month visit (n=340)							
No eczema	71 (41.8%)	34.5%	49.4%	83 (48.8%)	41.3%	56.4%	0.6
Clear	31 (18.2%)	13.1%	24.8%	26 (15.3%)	10.6%	21.6%	
Mild	50 (29.4%)	23.0%	36.7%	46 (27.1%)	20.9%	34.3%	
Moderate	10 (5.9%)	3.2%	10.6%	11 (6.5%)	3.6%	11.4%	
Severe	8 (4.7%)	2.4%	9.2%	4 (2.4%)	0.9%	6.1%	

BCG: bacille Calmette-Guérin; CI: confidence interval; POEM: Patient Oriented Eczema Measure score¹; SCORAD: SCORing Atopic Dermatitis scoring system.² Categories used as previously defined.^{3,4}

Sensitivity analysis using the extended definition of eczema are shown in Tables S3b and S3c.

Table S3b: Age of onset of eczema and severity scores during follow-up (sensitivity analysis using the extended definition of eczema)

	No BCG (n=190)			BCG (n=180)			
	n (%)	95% CI		n (%)	95% CI		p-value
		Lower	Upper		Lower	Upper	
Age at first symptom of eczema (n=472)							
Between birth and 3 months old	141 (60.0%)	53.6%	66.1%	132 (55.7%)	49.3%	61.9%	0.7
Between 3 and 6 months old	56 (23.8%)	18.8%	29.7%	67 (28.3%)	22.9%	34.4%	
Between 6 and 9 months old	27 (11.5%)	8.0%	16.3%	27 (11.4%)	7.9%	16.1%	
Between 9 and 12 months old	11 (4.7%)	2.6%	8.3%	11 (4.6%)	2.6%	8.2%	
POEM score category at 3-month questionnaire (n=102)							
Clear	9 (18.0%)	9.5%	31.5%	3 (5.8%)	1.8%	16.8%	0.04
Mild	19 (38.0%)	25.4%	52.4%	19 (36.5%)	24.4%	50.7%	
Moderate	15 (30.0%)	18.7%	44.4%	28 (53.8%)	40.0%	67.1%	
Severe	6 (12.0%)	5.4%	24.6%	2 (3.8%)	0.9%	14.5%	
Very severe	1 (2.0%)	0.3%	13.5%	0 (0.0%)	-	-	
POEM score category at 6-month questionnaire (n=264)							
Clear	33 (25.4%)	18.6%	33.6%	34 (25.4%)	18.7%	33.5%	0.8
Mild	52 (40.0%)	31.9%	48.7%	48 (35.8%)	28.1%	44.4%	
Moderate	41 (31.5%)	24.1%	40.1%	47 (35.1%)	27.4%	43.6%	
Severe	4 (3.1%)	1.2%	8.0%	4 (3.0%)	1.1%	7.8%	
Very severe	0 (0.0%)	-	-	1 (0.7%)	0.1%	5.2%	
POEM score category at 9-month questionnaire (n=254)							
Clear	33 (25.2%)	18.4%	33.4%	35 (28.5%)	21.1%	37.1%	0.9
Mild	67 (51.1%)	42.6%	59.7%	59 (48.0%)	39.2%	56.9%	
Moderate	28 (21.4%)	15.1%	29.3%	27 (22.0%)	15.5%	30.2%	
Severe	3 (2.3%)	0.7%	6.9%	2 (1.6%)	0.4%	6.4%	
Very severe	0 (0.0%)	-	-	0 (0.0%)	-	-	
POEM score category at 12-month questionnaire (n=276)							
Clear	37 (26.8%)	20.0%	34.9%	45 (32.6%)	25.3%	40.9%	0.5
Mild	58 (42.0%)	34.0%	50.5%	61 (44.2%)	36.1%	52.7%	
Moderate	41 (29.7%)	22.6%	37.9%	30 (21.7%)	15.6%	29.5%	
Severe	2 (1.4%)	0.4%	5.7%	2 (1.4%)	0.4%	5.7%	
Very severe	0 (0.0%)	-	-	0 (0.0%)	-	-	
SCORAD score category at 12-month visit (n=434)							
No eczema	87 (42.0%)	35.5%	48.9%	119 (52.4%)	45.9%	58.9%	0.2
Clear	37 (17.9%)	13.2%	23.7%	33 (14.5%)	10.5%	19.8%	
Mild	63 (30.4%)	24.5%	37.1%	57 (25.1%)	19.9%	31.2%	
Moderate	12 (5.8%)	3.3%	10.0%	14 (6.2%)	3.7%	10.2%	
Severe	8 (3.9%)	1.9%	7.6%	4 (1.8%)	0.7%	4.6%	

BCG: bacille Calmette-Guérin; CI: confidence interval; POEM: Patient Oriented Eczema Measure score¹; SCORAD: SCORing Atopic Dermatitis scoring system.² Categories used as previously defined.^{3,4}

Table S3c: Difference in age of onset of eczema and severity scores
(sensitivity analysis using the extended definition of eczema)

Secondary outcomes	No BCG	BCG	Measure of effect	Adjusted estimate of effect (95% CI) ^a	p-value
Age at first symptom of eczema (n=472)					
Before 3 months of age	141 (60.0%)	132 (55.7%)	aRD	-4.3 (-13.2 to 4.6)	0.3
After 3 months of age	94 (40.0%)	105 (44.3%)	Reference		
Maximum POEM score category during follow up (n=431)					
Clear	33 (15.4%)	35 (16.1%)	aRD	0.5 (-6.3 to 7.4)	0.9
Clear to mild	116 (54.2%)	126 (58.1%)	aRD	3.9 (-5.5 to 13.2)	0.4
Severe or very severe	13 (6.1%)	10 (4.6%)	aRD	-1.7 (-5.9 to 2.5)	0.4
Persistently high POEM scores (n=285, with ≥2 scores during follow up)					
Median score ≥ moderate	37 (25.7%)	45 (31.9%)	aRD	6.6 (-3.9 to 17.0)	0.2
SCORAD category at 12-month follow-up visit (n=434)					
Clear	124 (59.9%)	152 (67.0%)	aRD	7.1 (-2.0 to 16.1)	0.1
Clear to mild	187 (90.3%)	209 (92.1%)	aRD	1.7 (-3.7 to 7.0)	0.5
Severe	8 (3.9%)	4 (1.8%)	aRD	-2.2 (-5.3 to 1.0)	0.2
Combination of POEM and SCORAD scores category (n=401)					
Both scores clear	21 (11.0%)	27 (12.9%)	aRD	1.7 (-4.7 to 8.0)	0.6
Both scores clear to mild	96 (50.3%)	118 (56.2%)	aRD	5.9 (-3.9 to 15.6)	0.2
Any score severe or very severe ^b	19 (8.3%)	13 (5.6%)	aRD	-2.9 (-7.5 to 1.7)	0.2

^a adjusted for stratification mode of delivery.^b n=364 as include participants with either scores available.

aRD: adjusted risk difference; BCG: bacille Calmette-Guérin; CI: confidence interval; POEM: Patient Oriented Eczema Measure score¹; SCORAD: SCORing Atopic Dermatitis scoring system². Categories used as previously defined^{3,4}.

Table S4a: Subgroup analysis, test of interaction

	No BCG	BCG	p-value ^a
All participants			
Sex of child			0.2
Female (n=542)	80 (30.3%)	87 (31.3%)	
Male (n=561)	110 (39.7%)	93 (32.7%)	
Parental atopic disease			0.04
None or one parent (n=756)	109 (29.5%)	119 (30.7%)	
Both parents (n=344)	80 (46.8%)	61 (35.3%)	
Mother BCG status			0.04
BCG-naïve (n=763)	130 (34.6%)	111 (28.7%)	
Previous BCG (n=279)	47 (35.1%)	62 (42.8%)	
Delivery mode			0.3
Caesarean delivery (n=403)	64 (32.0%)	67 (33.0%)	
Vaginal delivery (n=700)	126 (37.0%)	113 (31.5%)	
Season of birth			
Summer (n=250)	38 (32.2%)	45 (34.1%)	Reference
Autumn (n=304)	65 (42.8%)	53 (34.9%)	0.2
Winter (n=280)	45 (33.1%)	40 (27.8%)	0.4
Spring (n=269)	42 (31.1%)	42 (31.3%)	0.8
Hepatitis B vaccination			0.9
≤24 h post randomisation (n=956)	171 (35.6%)	154 (32.4%)	
No or >24 h post randomisation (n=146)	19 (31.7%)	25 (29.1%)	

^a p-value for the interaction term (BCG status by variable).

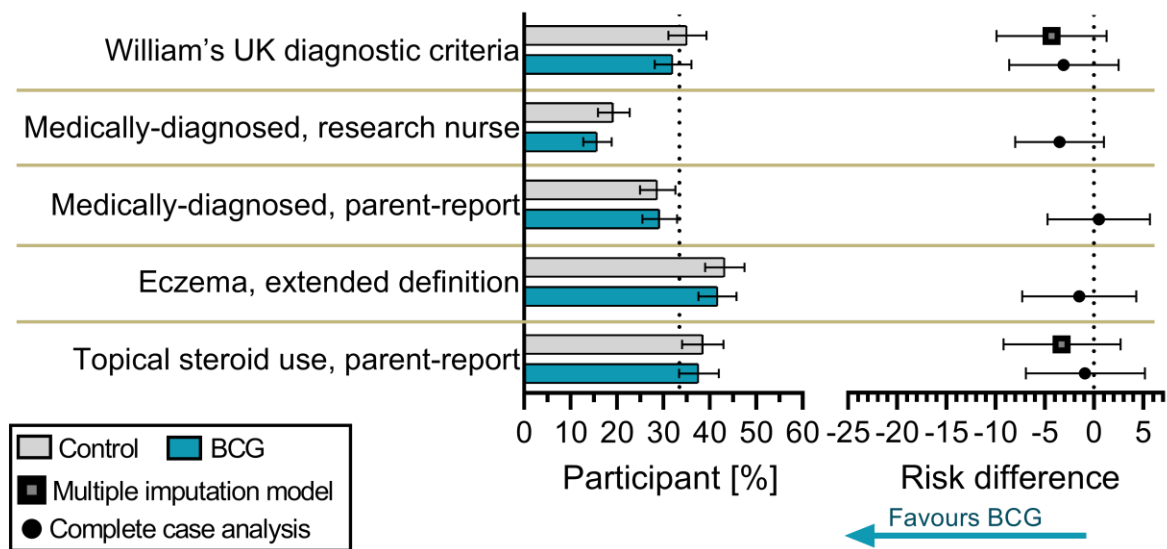
BCG: bacille Calmette-Guérin; h: hours.

Table S4b: BCG-subgroup analysis, test of interaction

	BCG	RD (95% CI)	p-value
BCG subgroups			
Presence of BCG scar		-2.6 (-20 to 15)	0.8
No scar visible (n=31)	10 (34.5%)		
Presence of scar (n=490)	156 (32.0%)		
Timing of BCG vaccination		0.03 (-9 to 8)	0.9
Before 48h of life (n=197)	116 (31.8%)		
After 48h of life (n=365)	64 (32.5%)		
Received expired BCG		-8.8 (-21 to 4)	0.2
No (n=510)	168 (32.9%)		
Yes (n=50)	12 (24.0%)		

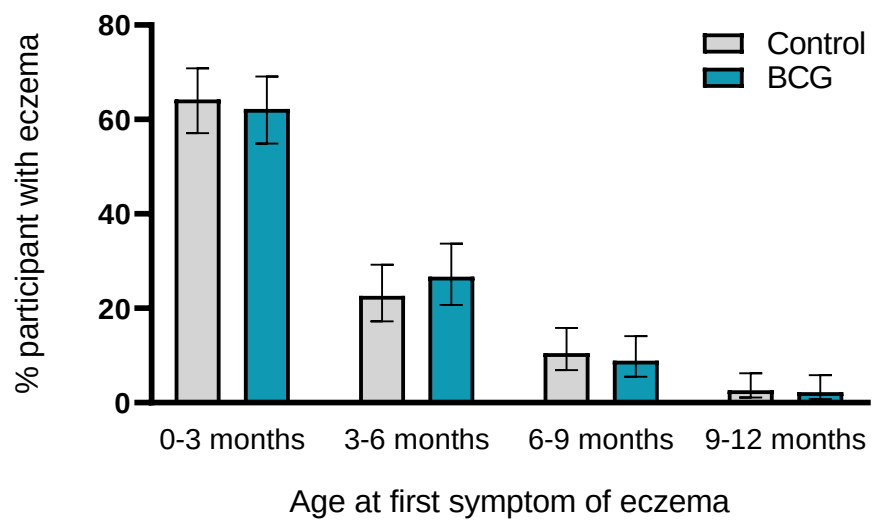
^a p-value afor the interaction term (BCG status by variable).

BCG: bacille Calmette-Guérin; CI: confidence interval; h: hours; RD: risk difference.

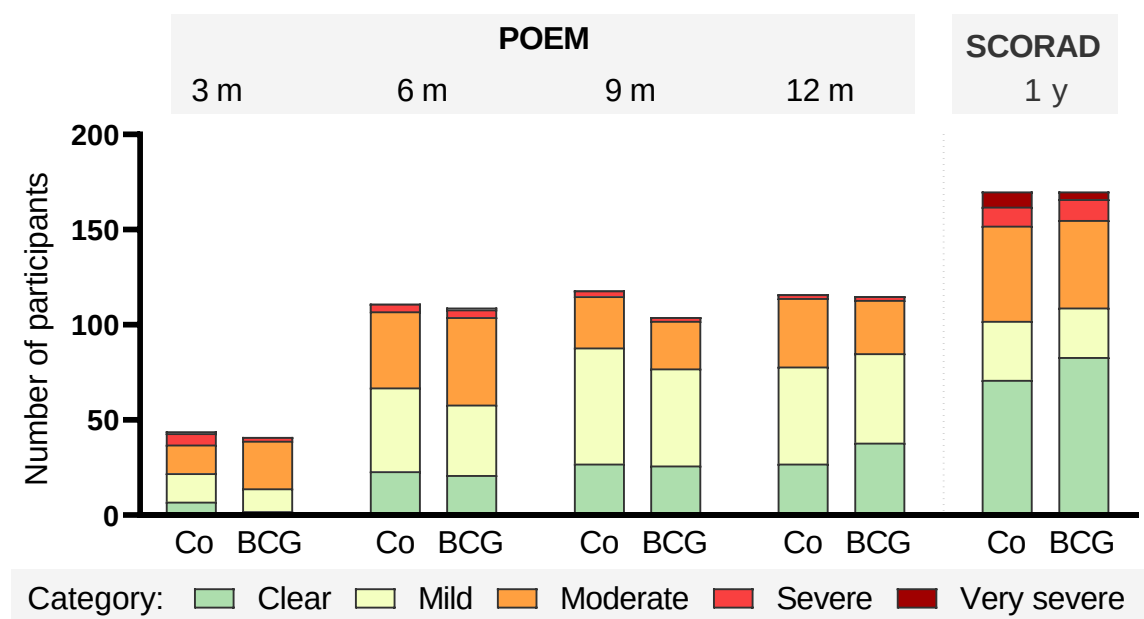
Figure S1: Difference in incidence of eczema between BCG and control groups

Left: Bars represent the proportion of participants fulfilling the criteria for the primary and secondary outcomes with error bars depicting 95% confidence intervals (CI).

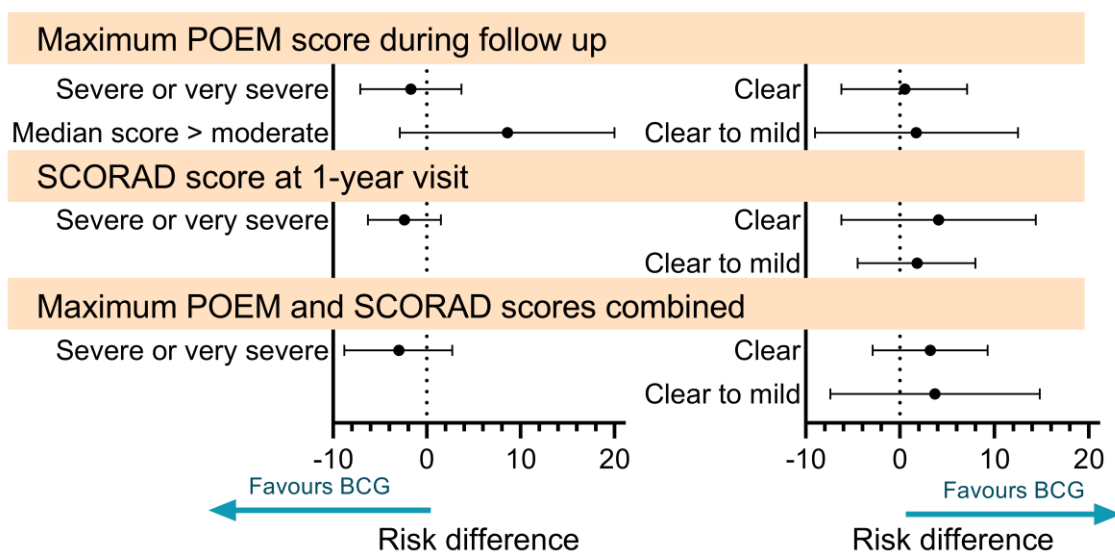
Right: Squares and dots represent adjusted risk differences for the multiple imputation model and complete case analysis respectively, with error bars depicting 95% CI.

Figure S2: Age of onset of eczema

The proportion of participants are indicated with 95% confidence intervals.

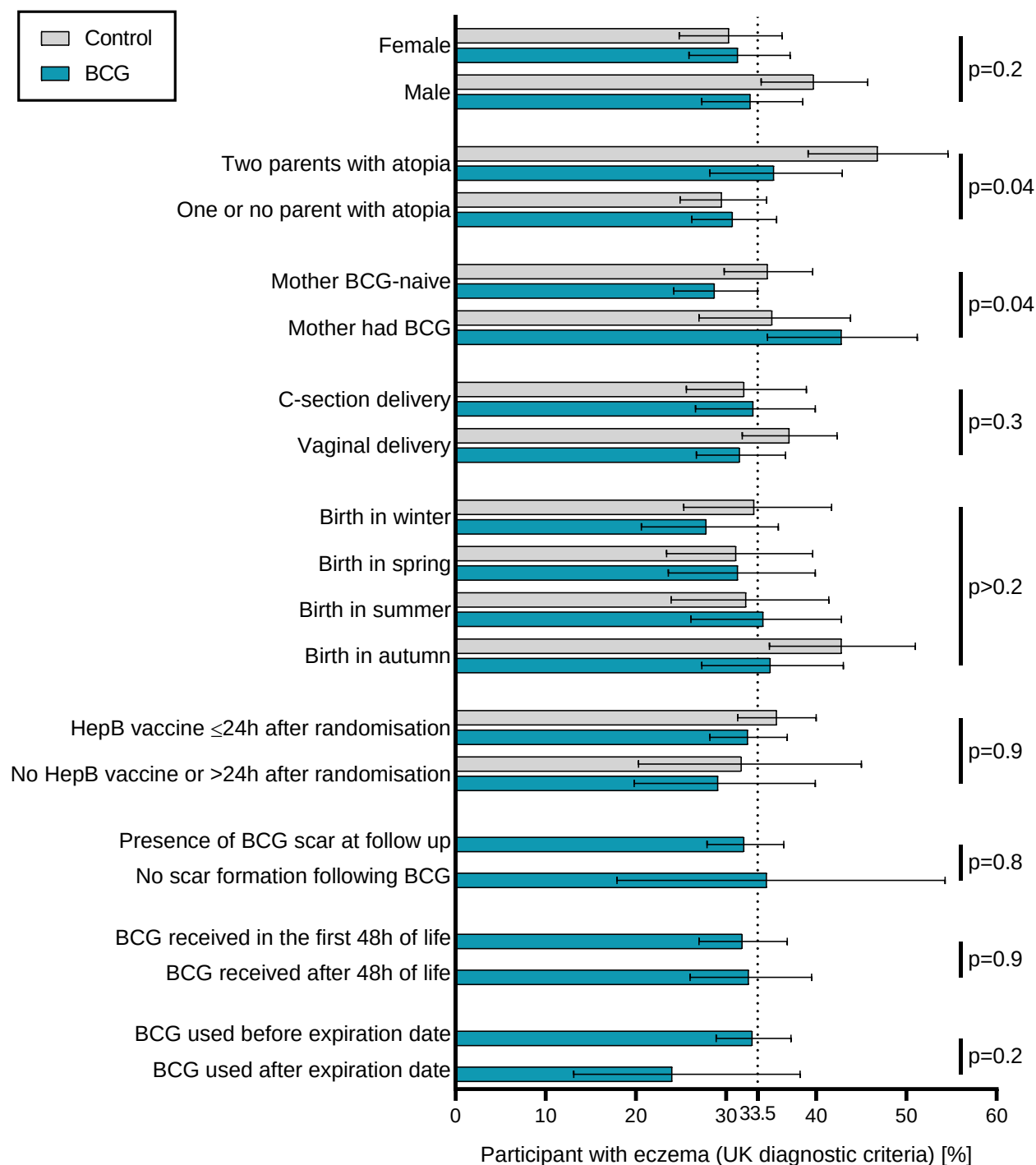
Figure S3: Severity of eczema symptoms

BCG: bacille Calmette-Guérin; Co: control group; POEM: Patient Oriented Eczema Measure score¹; SCORAD: SCORing Atopic Dermatitis scoring system.² Categories used as previously defined.^{3,4}

Figure S4: Difference in eczema severity scores between BCG and control groups

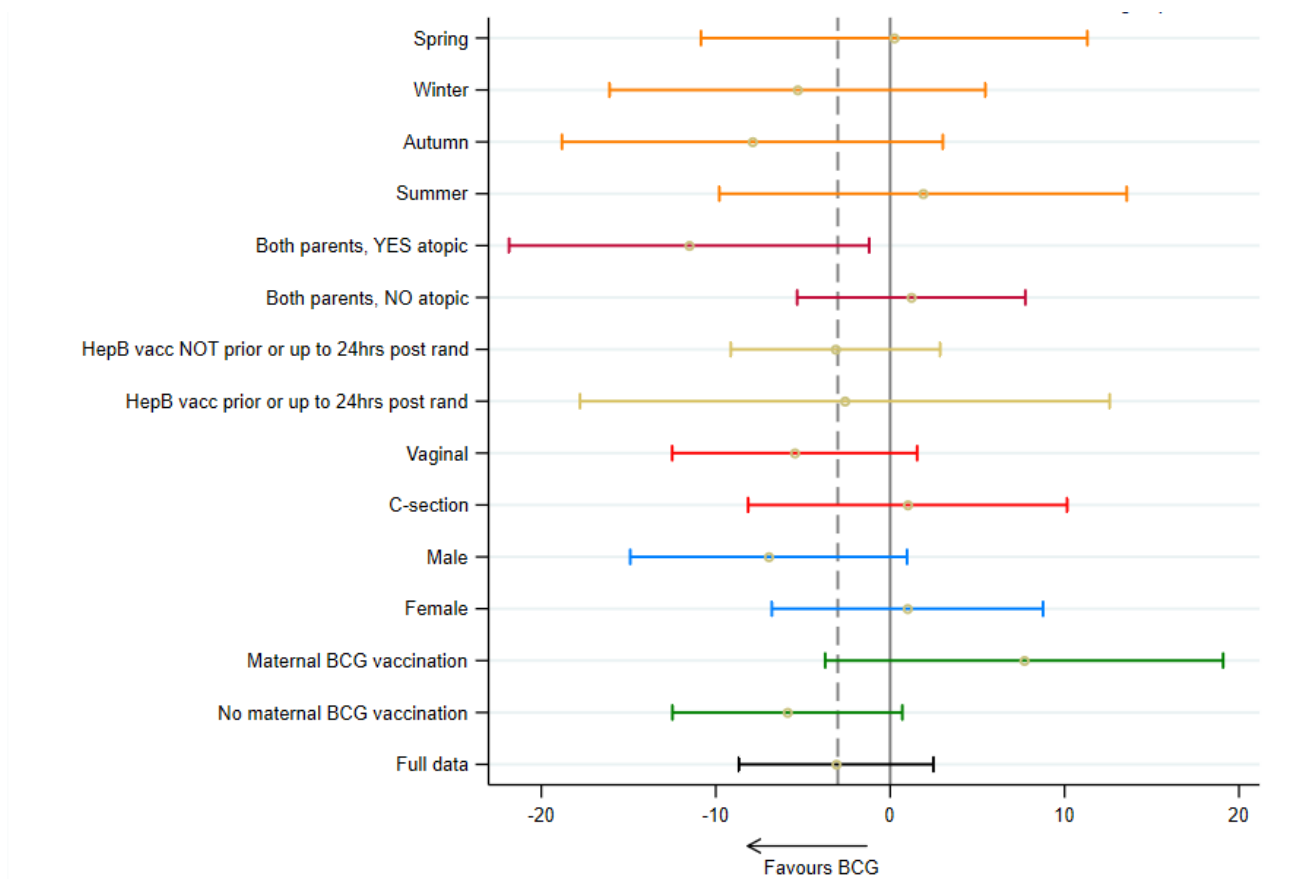
Adjusted risk differences with error bars depicting 95% confidence intervals (CI).

POEM: Patient Oriented Eczema Measure score¹; SCORAD: SCORing Atopic Dermatitis scoring system.²
 Categories as previously defined.^{3,4}

Figure S5: Incidence of eczema (subgroup analysis, interaction tests)

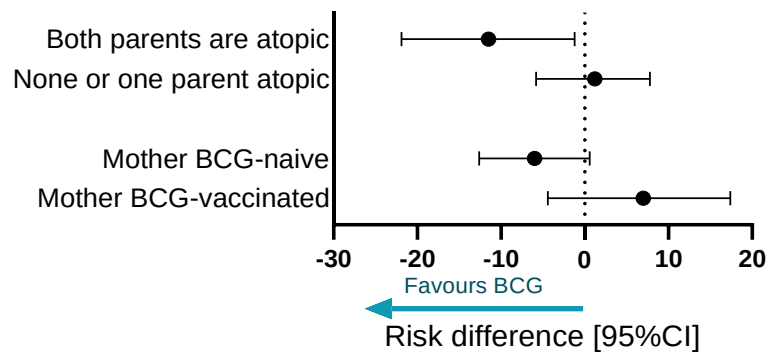
Bars represent the proportion of participants fulfilling the criteria for the primary outcome with 95% confidence intervals, within pre-specified subgroups. The dotted line indicates the overall incidence of eczema in the complete case analysis. P-values are for the interaction term (BCG status by variable).

Figure S6a: Difference in incidence of eczema between BCG and control groups (subgroup analysis)



The risk differences are represented with 95% confidential intervals. The dotted line at -3.1% represents the risk difference between the control group and the BCG group in the complete case analysis.

Figure S6b: Difference in incidence of eczema between BCG and control groups in subgroup analysis (variables with significant test of interaction)



The adjusted risk differences are represented with 95% confidence intervals.

Supplementary details for Multiple Imputation

The information provided here extends on the information provided in the manuscript with regard to the auxiliary variables included in the imputation.⁵

As there are over 1000 variables in the MIS BAIR data set, expert knowledge from the project's investigators was used to identify the variables correlated with the primary outcome of eczema (Table S7.1). The variables that were considered predictors of missingness are reported in Table S7.2. The auxiliary variables included in the model were: Infant ethnicity, Asian background, mother born in country with high tuberculosis prevalence, maternal BCG vaccination, maternal education, probiotics taken during the pregnancy, smokers living in the house during pregnancy, maternal age at the birth of participant, paternal age at the birth of participant, only child at randomisation, birth in autumn, infant birth weight, daycare attendance during first year of life, breastfeeding duration, family history of eczema, family history of food allergy, family history of hay fever, family history of food allergy, and use of steroid cream during follow-up.

Given we cannot confirm the assumption of missing at random which underpins the multiple imputation approach, auxiliary variables that are associated with missingness were included in the model to make this assumption more plausible.

Multiple imputation of 50 datasets was done by chained equations including all the randomised participants in Stata version 16.1. Given the imputation was for a binary variable the model diagnostics are limited to checking that the proportions in the imputed data set are reasonable and make sense. Hence the proportion of eczema in 10 of the 50 imputations was checked to see how much it varied from the complete case analysis (reported in main manuscript). There was very little difference between the proportions of eczema in the observed data set compared to the imputed data sets.

Table S7.1: Variables associated with the primary outcome included in the multiple imputation.

	No eczema n=733	Eczema n=370	Total n=1103
Infant factors			
Birth weight, kg	3391 (492)	3457 (484)	3413 (490)
Infant ethnicity			
Caucasian (≥75% grandparents are Caucasians)	584 (79.7%)	244 (65.9%)	828 (75.1%)
Asian (≥75% grandparents are Asians)	24 (3.3%)	46 (12.4%)	70 (6.3%)
Mix Caucasian and Asian	30 (4.1%)	29 (7.8%)	59 (5.3%)
Other	95 (13.0%)	51 (13.8%)	146 (13.2%)
Asian ethnicity			
No (max 25% grandparents are Asians)	674 (92.0%)	291 (78.6%)	965 (87.5%)
Yes (≥50% grandparents are Asians)	59 (8.0%)	79 (21.4%)	138 (12.5%)
Season of birth			
Winter, spring or summer	547 (74.6%)	252 (68.1%)	799 (72.4%)
Autumn	186 (25.4%)	118 (31.9%)	304 (27.6%)
Maternal factors			
Age at delivery, year	33.2 (4.6)	32.5 (4.6)	32.9 (4.6)
Missing	1 observation	0 observation	1 observation
Birth in high tuberculosis burden country			
No	672 (91.7%)	303 (81.9%)	975 (88.4%)
Yes	61 (8.3%)	67 (18.1%)	128 (11.6%)
History of BCG vaccination			
No	522 (75.4%)	241 (68.9%)	763 (73.2%)
Yes	170 (24.6%)	109 (31.1%)	279 (26.8%)
Missing	41 observations	20 observation	61 observations
Paternal factors			
Age at delivery, years	35.1 (5.2)	34.3 (5.5)	34.8 (5.4)
Missing	21 observations	7 observations	28 observations
Familial and environmental factors at birth			
Family history of eczema			
No	461 (63.0%)	182 (49.3%)	643 (58.4%)
Yes	271 (37.0%)	187 (50.7%)	458 (41.6%)
Missing	1 observation	1 observation	2 observations
Family history of hayfever			
No	262 (35.8%)	96 (25.9%)	358 (32.5%)
Yes	469 (64.2%)	274 (74.1%)	743 (67.5%)
Missing	2 observations	0 observation	2 observations
Family history of asthma			
No	382 (52.3%)	172 (46.5%)	554 (50.4%)
Yes	348 (47.7%)	198 (53.5%)	546 (49.6%)
Missing	3 observations	0 observation	3 observations
Family history of any food allergy			
No	624 (86.8%)	286 (78.4%)	910 (83.9%)
Yes	95 (13.2%)	79 (21.6%)	174 (16.1%)
Missing	14 observations	5 observations	19 observations
Exposure during first year of life			
Breastfeeding, age at cessation			
Less than 1 week	37 (5.0%)	23 (6.2%)	60 (5.4%)
Between 1 week and 3 months	99 (13.5%)	65 (17.6%)	164 (14.9%)
Between 3 to 6 months	76 (10.4%)	48 (13.0%)	124 (11.2%)
Between 6 to 9 months	84 (11.5%)	47 (12.7%)	131 (11.9%)
Between 9 to 12 months	122 (16.6%)	40 (10.8%)	162 (14.7%)
After 12 months	315 (43.0%)	147 (39.7%)	462 (41.9%)
Steroid use for eczema at 1 yr			
No	510 (81.3%)	92 (27.1%)	602 (62.3%)
Yes	117 (18.7%)	248 (72.9%)	365 (37.7%)
Missing	106 observations	30 observations	136 observations

Table S7.2: Variables associated with missingness included in the multiple imputation

	No missing data n=1103	Missing data n=169	Total n=1272
Infant factors			
Infant ethnicity			
Caucasian ($\geq 75\%$ grandparents are Caucasians)	828 (75.1%)	121 (71.6%)	949 (74.6%)
Asian ($\geq 75\%$ grandparents are Asians)	70 (6.3%)	12 (7.1%)	82 (6.4%)
Mix Caucasian and Asian	59 (5.3%)	3 (1.8%)	62 (4.9%)
Other	146 (13.2%)	33 (19.5%)	179 (14.1%)
Season of birth			
Winter, spring or summer	799 (72.4%)	111 (65.7%)	910 (71.5%)
Autumn	304 (27.6%)	58 (34.3%)	362 (28.5%)
Maternal factors			
Age at delivery, year	32.9 (4.6)	30.6 (5.3)	32.6 (4.8)
Missing	1 observation	0 observation	1 observation
Maternal education			
No education / up to year 10	44 (4.0%)	31 (18.3%)	75 (5.9%)
Year 12 / trade	282 (25.6%)	58 (34.3%)	340 (26.8%)
University	774 (70.4%)	80 (47.3%)	854 (67.3%)
Missing	3 observations	0 observation	3 observations
Paternal factors			
Age at delivery, years	34.8 (5.4)	32.0 (6.1)	34.5 (5.5)
Missing	28 observations	5 observations	33 observations
Familial and environmental factors at birth			
Only child in household at randomisation			
No	574 (52.1%)	79 (46.7%)	653 (51.4%)
Yes	528 (47.9%)	90 (53.3%)	618 (48.6%)
Missing	1 observation	0 observation	1 observation
Family history of hayfever			
No	358 (32.5%)	76 (45.0%)	434 (34.2%)
Yes	743 (67.5%)	93 (55.0%)	836 (65.8%)
Missing	2 observations	0 observation	2 observations
Family history of asthma			
No	554 (50.4%)	100 (59.2%)	654 (51.5%)
Yes	546 (49.6%)	69 (40.8%)	615 (48.5%)
Missing	3 observations	0 observation	3 observations
Smokers living in the house during pregnancy			
No	936 (85.1%)	111 (65.7%)	1047 (82.5%)
Yes	164 (14.9%)	58 (34.3%)	222 (17.5%)
Missing	3 observations	0 observation	3 observations
Exposure during first year of life			
Daycare attendance for participant			
No	685 (62.1%)	100 (71.9%)	785 (63.2%)
Yes	418 (37.9%)	39 (28.1%)	457 (36.8%)
Missing	0 observation	30 observations	30 observations
Breastfeeding, age at cessation			
Less than 1 week	60 (5.4%)	56 (33.1%)	116 (9.1%)
Between 1 week and 3 months	164 (14.9%)	52 (30.8%)	216 (17.0%)
Between 3 to 6 months	124 (11.2%)	24 (14.2%)	148 (11.6%)
Between 6 to 9 months	131 (11.9%)	7 (4.1%)	138 (10.8%)
Between 9 to 12 months	162 (14.7%)	7 (4.1%)	169 (13.3%)
After 12 months	462 (41.9%)	23 (13.6%)	485 (38.1%)
Steroid use for eczema at 1 yr			
No	602 (62.3%)	12 (50.0%)	614 (62.0%)
Yes	365 (37.7%)	12 (50.0%)	377 (38.0%)
Missing	136 observations	145 observations	281 observations

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