PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Study protocol for the Melbourne Infant Study: BCG for Allergy and Infection Reduction (MIS BAIR), a randomised controlled trial to determine the non-specific effects of neonatal BCG vaccination in a low-mortality setting
AUTHORS	Messina, Nicole; Gardiner, Kaya; Donath, Susan; Flanagan, Katie; Ponsonby, Anne-Louise; Shann, Frank; RobinsBrowne, Roy; Freyne, Bridget; Abruzzo, Veronica; Morison, Clare; Cox, Lianne; Germano, Susie; Zufferey, Christel; Zimmermann, Petra; Allen, Katie; Vuillermin, P; South, Mike; Casalaz, Dan; Curtis, Nigel

VERSION 1 – REVIEW

REVIEWER	Paulo Camargos Federal University of Minas Gerais, Brazil
REVIEW RETURNED	31-Jul-2019

GENERAL COMMENTS	Comments/suggestions to authors: 1) as the decline in mortality/morbidity rates from LRI could be related to improvements in socioeconomic conditions, allow me to suggest you to include isocioeconomic, cultural and educational variables into the protocol, and statistical analysis; 2) according to ISAAC, there are countries, like Brazil, where high prevalence of asthma symptoms coexists with high BCG coverage; that findings were not in-depth assessed, but one could speculate on the role of non-atopic asthma; 3) again, allow me to suggest you to read and/or take in account in your References section (among others) the following papers: 3.1. Pereira MU et al. Nonatopic asthma is associated with helminth infections and bronchiolitis in poor children. Eur Respir J. 2007;29(6):1154-60 3.2. de Andrade CR et al. Does BCG revaccination protect against the development of asthma? Respir Med. 2013;107(2):317-9 4) finally, for more robust results, it would be interesting to include proper lab tests for the etiological diagnosis of viral and bacterial lower respiratory infections

REVIEWER	Rashmi Ranjan Das AIIMS Bhubaneswar India
REVIEW RETURNED	10-Aug-2019

GENERAL COMMENTS	First of all I would like to thank the authors for designing a very good study of global interest. There is no doubt that BCG vaccine protects against childhood infections and allergies in high mortality setting. Regarding the low mortality setting, the findings may be the same too (though the effect may be of lesser magnitude). But, this

	hypothesis needs to be tested so that a generalised recommendation can be made. I have few concerns that need to be addressed by the authors before I would recommend to accept it for publication. General comments 1. Premature infants have an inappropriate response to antigenic stimulation, so it would be better if the authors could stratify by gestational age also (32 to 37 weeks and >37 weeks) 2. Studies have shown that delaying BCG immunisation has better immune response. Can the time limit of including infants be increased from 10 days of life to 6 weeks of age (this may be good for infants born at 32 weeks as more number infants can be included because of risk of prolonged hospitalisation along with better immune response)

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Paulo Camargos
Institution and Country: Federal University of Minas Gerais, Brazil
Please state any competing interests or state 'None declared':None declared.

Please leave your comments for the authors below
Comments/suggestions to authors:
1) as the decline in mortality/morbidity rates from LRI could be related to improvements in socioeconomic conditions, allow me to suggest you to include socioeconomic, cultural and educational variables into the protocol, and statistical analysis;
As detailed in table 2, our study collects data on cultural and parent educational factors at baseline. We also collected postcode data at baseline which can be used to infer socioeconomic status using the Australian Bureau of Statistics Socio-Economic Indexes for Areas (SEIFA). To clarify this, we have included "region (postcode)" in Table 2 (pg 6)
However, as MIS BAIR is a randomised controlled trial (RCT), it is expected that these factors will be similarly distributed between the groups. The distribution of these factors will be reported with study findings. In addition, if multiple imputation is required for missing data and these factors are predictive of missingness or outcomes, they will be included in imputation models as described on page 9.

2) according to ISAAC, there are countries, like Brazil, where high prevalence of asthma symptoms coexists with high BCG coverage; that findings were not in-depth assessed, but one could speculate on the role of non-atopic asthma;
3) again, allow me to suggest you to read and/or take in account in your References section (among others) the following papers:
3.1. Pereira MU et al. Nonatopic asthma is associated with helminth infections and bronchiolitis in poor children. Eur Respir J. 2007;29(6):1154-60
3.2. de Andrade CR et al. Does BCG revaccination protect against the development of asthma? Respir Med. 2013;107(2):317-9
These publications, along with reviewer comment 2, address the issue of asthma in the absence of other atopic disease. In Australia, asthma is significantly associated with patient or family history of atopy, although there are cases of isolated asthma (i.e. asthma in children without patient or family history of atopy) in younger children (Owens L *et al*. Prevalence of allergic sensitization, hay fever, eczema, and asthma in a longitudinal birth cohort. *J Asthma Allergy*. 2018 Aug 13;11:173-180. doi: 10.2147/JAA.S170285).Our study collects information on family history of atopic and allergic disease, and this factor will be included as a subgroup analysis for asthma (as well as allergy and eczema), as stated on page 9. Also, if multiple imputation is required for asthma data, infant history of atopic sensitisation and eczema at 1 year of age will be included in imputations models (as described in page 9) of asthma at 5 years of age if they are found to be predictive of missingness or outcomes.

4) finally, for more robust results, it would be interesting to include proper lab tests for the etiological diagnosis of viral and bacterial lower respiratory infections
This would be of interest, however it is unfeasible and out of scope of the current study given the high participant numbers and length of the study. This may be assessed indirectly as part of the immunological analyses, e.g. assessment of anti-pathogen antibodies but such a sub-analysis is not an objective of the RCT and we have therefore not included this in the RCT study protocol.

Reviewer: 2

Reviewer Name: Rashmi Ranjan Das
Institution and Country: AIIMS Bhubaneswar
India
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below
First of all I would like to thank the authors for designing a very good study of global interest. There is no doubt that BCG vaccine protects against childhood infections and allergies in high mortality setting. Regarding the low mortality setting, the findings may be the same too (though the effect may be of lesser magnitude). But, this hypothesis needs to be tested so that a generalised recommendation can be made.
I have few concerns that need to be addressed by the authors before I would recommend to accept it for publication.

General comments
1. Premature infants have an inappropriate response to antigenic stimulation, so it would be better if the authors could stratify by gestational age also (32 to 37 weeks and >37 weeks)
As this is a RCT, it is expected that gestational age will be evenly distributed between the groups. However, gestational age of participants will be reported with study findings. In addition, if multiple imputation is required for missing data and these factors are predictive of missingness or outcomes, they will be included in imputations models as described in page 9.

2. Studies have shown that delaying BCG immunisation has better immune response. Can the time limit of including infants be increased from 10 days of life to 6 weeks of age (this may be good for infants born at 32 weeks as more number infants can be included because of risk of prolonged hospitalisation along with better immune response)
Studies (including our own) have not consistently found differences between early and late administration in relation to the immune response to BCG vaccine. Our study is designed to be consistent with WHO guidelines which recommends BCG vaccination as soon as possible after birth. The use of neonatal BCG vaccination in our RCT is also consistent with studies that have shown reduced all-cause infant mortality in neonates (ref 4 in manuscript) and a potential for greater beneficial effects of BCG when given earlier in life (WHO commissioned systematic review, ref 2 in manuscript).

VERSION 2 – REVIEW

REVIEWER	Prof Paulo Camargos, MD, PhD Federal University of Minas Gerais, Brazil
REVIEW RETURNED	01-Nov-2019

GENERAL COMMENTS	I've no further comments.