Author's response to reviews

Title: Early BCG vaccine to low-birth-weight infants and the effects on growth in the first year of life: A randomised controlled trial

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Author's response to reviews: see over
Dear Editor,

Many thanks for the opportunity to submit a revised version of this paper. We are sorry that it became delayed due to a maternity leave and vacation. Below, please find a point-to-point response to the reviewers’ comments. We hope the paper is now acceptable for publication.

Best wishes, on behalf of the authors,

Andreas Andersen (second author)

Reviewer's report:

The manuscript reports results from a trial on the early delivery of BCG vaccine to low birthweight infants compared to current standard practice, which is to deliver of BCG vaccine to low birthweight infants after they have gained weight or at age 6 weeks, when they begin they receive DTP vaccine. A subgroup of the trial cohort enrolled in the latter part of the study was further randomized to a factorial 2x2 design with BCG x vitamin A supplementation. The additional vitamin A intervention was ignored for the purpose of the present analysis after it was found to have no effect and no strong interaction with the BCG vaccine treatment. The authors further stratified the analysis by sex and by birth weight. Overall, the article is pretty well written and clear. I have made some suggestions where the authors could improve the reporting of their statistical methodology so that readers can completely understand how they analyzed the trial data. The high rates of attrition, most likely differential by treatment, unfortunately complicate the analysis and interpretation. However, the authors have done a fair job of qualifying their results in the Discussion section by pointing out this significant limitation.

I have been asked to focus on the statistical review of the manuscript, and so my
comments focus on that particular area.

=== Major Comments ===

(1)
Page 7. In the Statistical Analysis section, the authors describe their statistical modeling technique. However, “Longitudinal linear regression model” is not specific. The authors should specify the specific type of modeling approach that they used, such as Generalized Linear Models (GLM), Generalized Estimating Equations (GEE), Generalized Linear Mixed Models (GLMM) or some other approach – there are a number of different estimation approaches that they could have used and it is unclear what they actually did.

Answer: We have changed the sentence to “We used general/multivariate normal linear models estimated by maximum likelihood to examine ...” and added Mallinckrodt 2008 as a reference (now numbered as reference [15]).

(2)
Page 7. The authors describe the form of the linear model that they used in words, but it would be very helpful to readers if they provided the actual linear regression model equation so that it is clear what they actually did, since it seems they relied on a fairly complicated model. (Fortunately, Table 2 provides both the unadjusted means and the adjusted estimates – based on a comparison of the adjusted estimates to the differences in means, it seems like most of the interference is not through the modeling technique used and is instead driven by the study design). I don’t think that there is a strong justification for pooling the data over the different time points – I think a more straightforward approach would be to estimate the differences between groups at each time point separately (2, 6, 12 months), with each estimate conditional on the baseline value of the outcome – but if the authors used a fully saturated model (unclear based on the current description) then the approaches will give the same answer.

Answer: The model equation has now been provided. We furthermore added that
“interaction between early BCG and time (early BCG×time) allowing separate effects of early BCG to be estimated at 2, 6 and 12 months”. Thus, it should now be clear that the differences between groups are estimated at each time point separately (2, 6, 12 months) conditional on the baseline value.

The reviewer’s point that the two approaches will give the same answer if there is no dropout is also stated “In effect, this saturated simultaneous model of the measurements across time corresponds to three separate linear regression models with the 2, 6, or 12 months measurement as outcome and the baseline measurement as covariate. The main difference is that the correlation between the measurements at 2, 6, and 12 months is taken into account and all observed information is used.”

(3)

Page 7. “To model a realistic (decreasing) covariance structure between measurements across time…” Please provide details about how you modeled the covariance structure between measurements – this seems to imply that you assumed a correlation model, but it is unclear based on the current text.

Answer: The changes mentioned above, including the model equation, hopefully give a sufficiently detailed description of the applied modelling now.

(4)

Page 9. The attrition rates beyond the 2 month measurement are very high (31% by 6 months and 38% by 12 months) and so it would seem to me that the inference in the trial is fairly limited beyond 2 months, particularly since the children who dropped out tended to have worse anthropometry at enrollment. This underscores the potential for selection bias due to differential survival and attrition, and the high potential for the trial to underestimate the effect of early BCG vaccination on infant growth. Although the authors have attempted to reduce this bias by conditioning their effects on the baseline measurements of their outcomes, this is only a partial solution, as they note in their Discussion, and is a major limitation of the study. Given this high level of attrition, I
think 1) that claiming there was a “high follow-up rate” in the Discussion (page 11) is slightly at odds with the empirical losses to follow-up, and: 2) the authors should justify why they did not attempt to re-weight their study population to account for potentially selective attrition using either inverse probability weights or multiple imputation to correct for this bias. Hernan 2004 describes the basic problem and solution, and the authors’ software, Stata, implements the routines for inverse weighting (-te- routines) and multiple imputation (-mi- routines)


Answer:

1) “ensuring a high follow-up rate” has now been deleted.

2) The applied Mixed Model Repeated Measures MMRM model is unbiased under the missing at random (MAR) assumption (Mallinckrodt 2008). MMRM uses information from the observed outcomes via the within-patient correlation structure to provide information about the unobserved outcomes without explicitly imputing the missing data. Thus, MMRM uses all the observed data (randomization group, baseline values, and observed outcome values). Assuming MAR, the proposed inverse probability weighting (IPW) and multiple imputation (MI) will give very similar results to the likelihood based MMRM. If we had extra measured information that could predict the dropout, the IPW solution (Hernan 2004) could be helpful. However, we do not have such information. Therefore, we have not used IPW or MI to model the results under the MAR assumption.

Sensitivity analyses to assess the effect of missing not at random (MNAR) or informative dropout could potentially be conducted. However, such analyses are very complex to conduct and interpret and they would require a lot of attention and space in the paper. We attempted to make a joint longitudinal and survival model using the stjm package in Stata but encountered difficulties in estimating the models, an apparently quite frequent complication. We have therefore not presented results of such analyses.
I did not see a CONSORT checklist for the trial included in the supporting information materials -- that would be essential to confirm proper reporting.


Answer: The present study represents a growth study within a large randomised trial with mortality as the primary outcome, which was reported in J Inf Dis 2011. This main paper fulfilled all CONSORT criteria for reporting randomised trials. We believe it would be a bit too much to describe all trial details in the present paper, and therefore provide essential information and refer to the main papers for further detail.

(Methods section: “The present growth study was conducted within a randomised trial which had the primary objective to investigate the effect of early BCG on infant mortality. The trial has been described in detail elsewhere [9]”. Hence, the CONSORT checklist would not be applicable for the present paper.)

=== Minor essential revisions ===

(6)
Page 9: replace “less deaths” with “fewer deaths”
Answer: Changed as suggest

(7)
Page 10: reference to “Table 2” should be to “Table 1”, I think.
Answer: We thank the reviewer for noting and pointing out this error. Changed as
suggest

(8)

Page 10:
“The effect of early BCG on weight-for-age and MUAC was beneficial in the highest weight group but negative in both the medium and the low weight group.”
There is not a lot of support in the data for this statement unless you qualify that any benefits at all on these two outcomes are among girls.

Answer: We have modified the sentence, it now reads: “The effect of early BCG on weight-for-age and MUAC tended to be beneficial in the highest weight group but the tendency was opposite in both the medium and the low weight group (high vs. medium/low: $p=0.04$).”

=== Discretionary revisions ===

(9)
The authors may wish to also cite the following recent article on the non-specific effects of early childhood vaccines:

Answer: Cited as suggested, and we also included a more recent review, instead of two of the perhaps less important references.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.
Declaration of competing interests:
I declare that I have no competing interests.