Reviewer’s report

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

Version: 2 Date: 6 January 2015

Reviewer: Benjamin Arnold

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.

(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.

(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.

(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)


(5) I did not see a CONSORT checklist for the trial included in the supporting information materials -- that would be essential to confirm proper reporting.


=== Minor essential revisions ===

(6)
Page 9: replace “less deaths” with “fewer deaths”

Page 10: reference to “Table 2” should be to “Table 1”, I think.

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.

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.