Author's response to reviews

Title: The effect of neonatal vitamin A supplementation on growth in the first year of life among low-birth-weight infants in Guinea-Bissau: two by two factorial randomised controlled trial

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Author's response to reviews: see over
Dear Editor

We thank the reviewers for their comments.
Please find below our point-to-point response to the reviewers’ comments.

Kind regards on behalf of all authors,
Sofie Biering-Sørensen

**Reviewer 1**

**Discretionary Revisions**

I suggest the study’s setting could be reinforce in the abstract.

*SBS: The study setting has been mentioned in the abstract, adding the information “Methods: We conducted a randomised two-by-two factorial trial in Guinea-Bissau” (page 3).*

Considering the objective, maybe the authors could include (BCG adn DTP) after vaccination status, just to define what kind of vaccines was investigated (and which were in results topic - tables).

*SBS: This has been revised as suggested (page 6)*

Looking at the references, there are some articles about the Bandim Health Project which help the understanding. Are there other projects about VAS that could be mentioned?

*SBS: We have now mentioned in the discussion another paper on neonatal VAS and the interaction with DTP (page 13)*
Reviewer 2

Major Compulsory Revisions

Sentences suggested don’t need to be copied exactly as such but their ideas should be incorporated into the text.

Abstract

Results: As hypothesised, by 2 months of age, VAS tended to have a beneficial effect on weight and head circumference when given with BCG but not when given without BCG (interaction: weight-for-age p=0.07 and head circumference-for-age: p=0.06). But at the same time, girls with VAS and < 1.5kg showed reduction in head circumference-for-age when compared to placebo (please include p) irrespective of BCG status.

SBS: It is correctly observed by the reviewer that girls with weight<1.5kg have a negative of VAS on weight and head circumference. We have therefore included the information from additional file 3 in table 3 to emphasize these results for the reader. Furthermore, these results are now mentioned in the result section as well as the discussion. However, the group of girls with weight<1.5 kg is a very small group (N=52) and we do therefore not consider it relevant to emphasize these results to the extent of mentioning them in the abstract.

Conclusion: The results support other trials indicating that VAS at birth does not have strong (exclude) consistent effects on childhood growth and seem to be temporary. They also support (exclude) show that whatever temporary effect it may have it differs by vaccination status, being beneficial when given with BCG at birth and when DTP is delayed.

SBS: We have followed these recommendations except from writing that the temporary effects may differ by vaccination status, since the point is that the temporary effects may be explained by vaccination status. The wording is now “The results support other trials indicating that neonatal VAS does not have consistent effects on childhood growth and if anything the effects seem to be temporary. They also show that the effect may differ by vaccination status, being beneficial when given with BCG at birth and when DTP is delayed. (page 3).
**Results**

Include findings for girls < 1.5 kg according to additional file 3.

*SBS: As mentioned above, we have included the results from additional file 3 in table 3 and we have furthermore mentioned the results for girls <1.5kg in the result section. The section now reads as follows “Stratified on weight group at inclusion, there was no beneficial effect of VAS among the different weight groups on weight-for-age, length-for-age and head-circumference-for-age at 2 months (Table 3). Among the smallest girls (weight<1.5 kg) there was a negative effect of VAS on weight-for-age and head circumference-for-age” (page 10).**

**Discussion**

Adjust it including VLBW girls as mentioned above.

*SBS: The suggestions have been included in the paper. “There was no effect of neonatal VAS on growth in the first year of life among LBW children with a supposedly low vitamin A status; in particular there was no beneficial effect among the smallest children with a birth weight below 1.5 kg, who if anything had a negative effect of VAS on weight and head circumference” (page 11).**

**Consistency with previous studies**

As above if appropriate.

*SBS: No relevant literature for the effect of VAS on growth in VLBW infants has been found. To the best knowledge of the authors, the only literature investigating the effect on growth of neonatal VAS in low income countries have not included children with a birth weight less than 1.5 kg in their studies.*
Strengths and weaknesses

The main weakness is the fact that vit A was never measured. Weight at birth was used as a proxy initially and the fact that the infants had or had not received vit A as neonates became the dependent variable. Any findings from there on are related to VAS (and we are assuming that any deficiency was potentially corrected or minimized).

SBS: We have included a discussion in the section “strengths and weaknesses” about the fact that vitamin A status was never measured and instead birth weight was used an indicator. The discussion now reads as follows “The vitamin A status of the children included in the study was not measured and we used birth weight as an indicator for vitamin A status. Though it would have been optimal to have individual vitamin A status assessed, it has been shown consistently that birth weight is a valid indicator of vitamin A status [8, 9].” (page 12).

On the other hand but related to the statement above, could any vit A deficiency initially corrected make a comeback during the first year of life? Could it be an explanation for the effect disappearing later during the first year of life? You don’t present any information regarding breastfeeding or any other food intake during this period. Or rate of infections. Would any of it impact vit A levels? Perhaps that could be expanded either here or in Interpretation.

SBS: We do not have information on the rate of infections or food intake during the period and it is therefore not included in the discussion. The rate of breastfeeding was 98% at 2 months of age. This information has been added (page 7). Furthermore, we have expanded the discussion about the fact that we saw an effect of VAS given with BCG at 2 months of age and no effect VAS at 6 and 12 months of age. We do not agree that the lack of effect by 6 and 12 months of age is due to reoccurring vitamin A deficiency, since a lack of effect actually indicates a negative effect in the VAS children after 2 months of age. We find it more likely that this is due to negative interaction between VAS and later DTP vaccine, as also seen for mortality.

“The beneficial effect of neonatal VAS given with BCG was only seen 2 months after inclusion; 6 and 12 months after inclusion there was no effect of VAS. These results could indicate that the
children might have had short term benefits from neonatal VAS correcting a potential vitamin A deficiency at baseline. Later on during the child’s first year of life the vitamin A deficiency might return. However, this would not explain why an initial positive effect of neonatal VAS at 2 months had disappeared at 6 and 12 months. As argued previously it is more likely explained by a negative interaction between VAS and DTP[21]. This is supported by the present study which showed a beneficial effect on weight and head circumference at 6 months after inclusion only among children who had received DTP after 2 months suggesting that the overall no effect at 6 months after inclusion might be caused by the majority of the children receiving DTP before 2 months.” (page 13).

‘but it should be noted that there was no general tendency for a better effect in the smallest children (data not shown)

*SBS: The results for both weight, length and head circumference by birth weight groups have now been included in table 3.

**Interpretation**

‘suggesting that neonatal VAS might amplify a negative effect of DTP’ (I find more logic with ‘suggestin that recent DTP might hinder any possible benefit given by VAS)

*SBS: Since we do not know the biological mechanism behind the interactions of VAS and vaccines both explanations could be valid and have therefore both been included in the discussion. The text now reads as follows “Furthermore, the timing of the DTP vaccination might influence the effect of VAS on growth at 6 months suggesting that neonatal VAS might amplify a negative effect of DTP or the negative effect of DTP might hinder a beneficial effect of VAS given with BCG.” (page 13)
indicating that vitamin A deficiency does not influence the effect of VAS on growth,' (exclude) suggesting that even supposedly deficient newborns do not benefit from VAS.

*SBS: The suggestion has been included in the paper (page 14).*

**Conclusion**

indicating that vitamin A status at the time of supplementation did not influence the effect on growth' (exclude) suggesting that VAS does not impact growth even within this population.

*SBS: Revised as suggested, the conclusion now reads “Overall there was no effect of providing 25,000 IU VAS at birth on growth in the first year of life among LBW children with a presumed low vitamin A status suggesting that neonatal VAS does not impact growth even within this population” (page 14).*

**Minor Essential Revisions**

**Abstract**

Results: ‘...when given with BCG and a (exclude) but not when given...’

*SBS: Corrected*

**References**

Complete ref 19

*SBS: The reference has been completed*
Additional file 3
For all children, receiving placebo and whose weight at birth was 2.00 – 2.49 kg, z-score for length is probably – 2.10

*SBS: Corrected*

Discretionary Revision
Abstract
Results: *As hypothesized* (exclude)

*SBS: Revised*