

BMJ RESPONSE 20 Nov 2011

Re: BMJ.2011.000387 entitled "Effect of vitamin A supplementation to women of reproductive age on cause specific early and late infant mortality in rural Ghana; ObaapaVitA double blind cluster randomised placebo controlled trial"

Editors comments

Our main problem with the paper was that we did not think it added enough, for general readers, to what is already known about supplementation with vitamin A. The committee was puzzled that the findings on the two prespecified secondary outcomes weren't included in the original paper published in the Lancet. You also present two post-hoc analyses done in response to the Guinea Bissau paper, showing no effects of sex or season on the findings. I'm afraid the committee decided this was not enough for a BMJ paper, and that we were under no obligation to keep pursuing your paper, since the Guinea Bissau paper tested a different intervention from that studied in your paper (ie infant dosing after birth vs maternal treatment during pregnancy). We did not have any specific criticism of the design or methods.

- We did not include the two prespecified secondary outcomes (cause and age specific infant mortality) in our initial publication due to space limitations. This information has now been included on Page 4 Paragraph 3 of the revised manuscript.
- We believe that the data from the prespecified secondary outcomes should be published as these data elucidate important elements in the causal pathway of vitamin A using a large sample of over 60,000 infants in rural Africa. Vitamin A reduces infection and improves epithelial integrity in older children thus it is of importance to assess whether the same causal pathway could be affected in younger infants; and to look specifically at effects on infection specific mortality and prematurity specific mortality. We have emphasised these points on Page 9 Paragraph 5 and Page 10 Paragraph 1 of the revised manuscript.
- We also believe that the data from the post hoc analyses provide important new evidence about the effects of vitamin A supplementation in male and female infants in Africa. Our findings contrast with the only other African study which has considered these factors (Guinea Bissau). In particular, we failed to demonstrate any harm from vitamin A supplementation to women of reproductive age in infant males or females in our study population in either early or late infancy. These findings add to the ongoing debate about the safety of vitamin A supplementation and add important information about whether vitamin A supplementation may have differential effects on infant mortality in boys and girls. Neither the Cochrane review nor our Lancet paper examined these issues. We have highlighted these issues on Page 11 Paragraph 2 of the revised manuscript.

Reviewer Comments:

Reviewer: 1 H.P.S. Sachdev

Comments:

For the authors

This manuscript presents important information on infant deaths from a well conducted Vitamin A supplementation trial in pregnancy in Africa. Although a very small proportion of the results were encapsulated in the earlier main publication in the Lancet and included in systematic reviews, the detailed results in this manuscript are relevant as: (i) causes of deaths are reported from a large sample in Africa to evaluate the impact on cause specific mortality; (ii) these provide evidence regarding the differential mortality effects in relation to gender and the season, which is important in relation to the ongoing controversy on this subject particularly in the media; and (iii) would be relevant to the ongoing WHO supported trials on neonatal Vitamin A supplementation.

I have only a few relatively minor comments:

The authors appear to be focusing disproportionately higher on the safety aspect in the box "We also failed to demonstrate any harm from vitamin A supplementation to women of reproductive age in infant males or females in our study population". In reality, there is no evidence of either benefit or harm and this should be stated accordingly only.

- We agree with the reviewer and we have changed the text in the last paragraph of the box to read "We also failed to demonstrate any benefit or harm from vitamin A supplementation to women of reproductive age in infant males or females in our study population. There was also no modification of the effect of vitamin A supplementation and mortality by season."

The number of Tables may need reduction.

- We are happy to reduce the number of tables if requested by the editors.

Reviewer: 2 Parul Christian

Comments:

This is a well written paper of a secondary outcome from a large RCT conducted in Ghana, which examined vitamin A (VA) supplementation effects on maternal mortality. As with the maternal mortality outcome, the findings are negative, i.e. there was no effect of the intervention on infant mortality by cause or age.

There are some issues that need to be addressed as follows:

- a. Include a brief explanation as to why this outcome, albeit secondary, was not included in the first paper, especially as both outcomes were linked, and were planned a priori.

- We did not include these outcomes in our initial publication due to space limitations. This information has now been included on Page 4 Paragraph 3 of the revised manuscript.

b. It would be important to explain how evaluating the effect of maternal VA supplementation during pregnancy on infant survival speaks to findings from the study providing a large dose of VA at birth? This is important because the stratified analyses are motivated by the findings in the newborn vitamin A supplementation study.

- We agree with the reviewer. The data from the post hoc analyses provide important new evidence about the effects of vitamin A supplementation in male and female infants in Africa. Our findings contrast with the only other African study which has considered these factors (Guinea Bissau). In particular, we failed to demonstrate any harm from vitamin A supplementation to women of reproductive age in infant males or females in our study population in either early or late infancy. These findings add to the ongoing debate about the safety of vitamin A supplementation and add important information about whether vitamin A supplementation may have differential effects on infant mortality in boys and girls. Neither the Cochrane review nor our Lancet paper examined these issues. We have highlighted these issues on Page 11 Paragraph 2 of the revised manuscript.

c. Add information about the minimum detectable HR given the sample size estimated for the rarer outcome of pregnancy-related mortality.

- We agree with the reviewer that this information is important. The sample size of 62,000 infants was sufficient to detect at least a 15% effect of vitamin A supplementation on neonatal, early infant and late infant mortality. We have added this information on Page 7 Paragraph 1 of the revised manuscript.

d. Which of the outcomes (neonatal, 1-5 mo, 5-11 mo) were hypothesized to be different between group. Is there value in providing total infant mortality rate as well, i.e. adding a panel for that in Table 3?

- We hypothesised that vitamin A supplementation would have significant effects on all three groups. We have included this information on Page 5 Paragraph 1 of the revised manuscript. The effect on total infant mortality is presented in the initial Lancet paper thus we do not feel we need to present this data again in this paper. However, we would be happy to do this if the editors wish this.

e. The main issue is that maternal weekly 25,000 IU of VA during pregnancy is not the same intervention as a direct dose of 50,000 IU given to a newborn soon after birth. The efficacy (and safety) of maternal vitamin A supplementation at the dosage used demonstrated previously in a trial Nepal in the mid 1990's and again in Bangladesh, recently, although not in Africa. However, it is unclear if any safety concern related to infant mortality with maternal supplementation has been raised. Rather the purported harm to infants in the Guinea Bissau study was related to newborn dosing. Thus, this needs some clarification in the discussion.

- We agree with the reviewer. This is a similar point to that raised in point 'b'. The data from the post hoc analyses provide important new evidence about the effects of vitamin A supplementation in male and female infants in Africa. Our findings contrast with the only other African study which has considered these factors (Guinea Bissau). In particular, we failed to demonstrate any harm from vitamin A supplementation to women of reproductive age in infant males or females in our study population in either early or late infancy. These findings add to the ongoing debate about the safety of vitamin A supplementation and add important information about whether vitamin A supplementation may have differential effects on infant mortality in boys and girls. Neither the Cochrane review nor our Lancet paper examined these issues. We have highlighted these issues on Page 11 Paragraph 2 of the revised manuscript.

Minor:

Not sure why "VPM - verbal post-mortems" is introduced as a term, when the reference (#17) refers to these as verbal autopsies.

- We are happy to refer to these questionnaires as either verbal post mortems or verbal autopsies. We are happy to change the name to verbal autopsies if the editors wish it.