Reviewer’s report

Title: The impact of different doses of vitamin A supplementation on male and female mortality. A randomised trial from Guinea-Bissau.

Version: 2 Date: 19 June 2011

Reviewer: Siddhartha Gogia

Reviewer’s report:

Major Compulsory revisions

1. Abstract

“Children who had received the low dose tended to have higher mortality, the MRR being 1.20 (0.58 to 2.47) after 6 months and 1.15 (0.72 to 1.84) after 12 months. This tendency was similar in boys and girls. As hypothesised the low dose tended to be associated with lower mortality in girls if the most recent vaccine was DTP (MRR=0.56 (0.13 to 2.35) after 6 months).”

Change to

“There was no significant difference in mortality at 6 months and 12 months of follow up between the high dose VAS group and the low dose VAS group. The MRRs were 1.20 (0.58 to 2.47) after 6 months and 1.15 (0.72 to 1.84) after 12 months. This tendency was similar in boys and girls. There was no evidence of low dose VAS being associated with lower mortality in girls if the most recent vaccine was DTP, MRR=0.56 (0.13 to 2.35) after 6 months.”

2. “We found that the low dose was associated with a significant reduction in mortality at 6 and 9 months of follow-up[10].”

The abstract of the concerned paper reads as “(mortality rate ratio 0.69, 95% confidence interval 0.36 to 1.35) and nine months (0.62, 0.36 to 1.06) of follow-up. There was a significant interaction between sex and dose, the lower dose being associated with significantly reduced mortality in girls (0.19, 0.06 to 0.66) but not in boys (1.98, 0.74 to 5.29). The lower dose of vitamin A was consistently associated with lower hospital case fatality in girls (0.19, 0.02 to 1.45). Paradoxically, in children aged 6-18 months, the low dose was associated with slightly higher morbidity.”

Apart from mortality in girls, all other effects are not significant.

3.
Main analyses of mortality

“Mortality tended to be slightly higher for those who received the low dose, the MRR being 1.20 (0.58-2.47) after 6 months and 1.15 (0.71-1.84) after 12 months.”

Change to

“There was no significant difference in mortality at 6 months and 12 months of follow up between the high dose VAS group and the low dose VAS group; the MRR being 1.20 (0.58-2.47) after 6 months and 1.15 (0.71-1.84) after 12 months.”

4.

“We found a tendency for girls to benefit more from the low dose if the most recent vaccine before the campaign was DTP, the MRR being 0.56 (0.13-2.35) after 6 months of follow-up and 0.72 (0.27-1.94) after 12 months. There was no difference for boys.”

Change to

“There was no evidence of low dose VAS being associated with lower mortality in girls if the most recent vaccine was DTP, MRR=0.56 (0.13 to 2.35) after 6 months.”

5.

Post hoc analyses

This section should be deleted as statistically the data is not robust at all.

“If a child received VAS for the first time in this trial the low dose tended to be more beneficial, the MRR comparing the low dose versus the high dose being 0.61 (0.24-1.58) after 6 months of follow-up.”

There is actually no significant difference between the high and low dose groups.

“However, if a child had received VAS before, the high dose tended to be more beneficial (4.46 (0.97-20) (p for interaction=0.09)).”

Again, the difference is not statistically significant.

6.

Comparison of participants and non-participants

It’s desirable to compare the population characteristics of these 2 groups but there is no need to compare mortality rates between these 2 groups as a) this is not among the mentioned objectives. b) the results are speculative at best in the presence of a strong selection bias.

7.
Discussion

Please delete

‘Though none of our findings were significant we found the predicted pattern of a low dose being relatively more beneficial for girls with DTP as their most recent vaccination before enrolment. A post hoc analysis showed that girls who had received VAS previously tended to benefit more from receiving a high dose. Compared with non-participants, it was only boys and children who had received VAS previously, who benefited from participating in the campaign.”

8.
A priming effect of VAS?

As this section is completely based on the above mentioned non-robust post hoc analysis, it should be deleted.

Please consider the following statements

1. from reference 10, the reference which is the basis for the present study and has been the most widely cited in this article

“There was a significant interaction between sex and dose, the lower dose being associated with significantly reduced mortality in girls (0.19, 0.06 to 0.66) but not in boys (1.98, 0.74 to 5.29). The lower dose of vitamin A was consistently associated with lower hospital case fatality in girls (0.19, 0.02 to 1.45).”

2. From present article

“former VAS makes children more likely to benefit from another high-dose supplementation, and that especially girls might benefit even more from a high dose of vitamin A during childhood if supplemented previously.” and

3. “If a child received VAS for the first time in this trial the low dose tended to be more beneficial, the MRR comparing the low dose versus the high dose being 0.61 (0.24-1.58) after 6 months of follow-up. However, if a child had received VAS before, the high dose tended to be more beneficial (4.46 (0.97-20) (p for interaction=0.09)).”

What I understand from this is that if a subject gets a low dose before, another low dose does not benefit. A higher subsequent dose is needed for benefit. Programmatically, this would mean that the girls get a low dose initially and a high dose subsequently. “Priming refers to a increased sensitivity to certain stimuli due to prior experience.” Although, there is negative priming as well, the one described in psychology. It is the negative priming that is working here i.e. increase in the required dose for subsequent benefit. As the authors themselves admit that “However, this pattern of a sex-differential response to repeated VAS is not consistent in all vitamin A trials.” and “We have no biological explanation for a possible priming effect of VAS on subsequent VAS.”; this portion is best omitted, especially when it is based on data which suggest otherwise. And the conclusion “Hence, it may be speculated that children with sufficient vitamin A levels benefit more from subsequent VAS.” is biologically implausible.
9.
Please delete
"We have no biological explanation for a possible priming effect of VAS on subsequent VAS. One small study reported a priming dose of vitamin A to be associated with a higher increase in vitamin A concentration after VAS[22]. Hence, it may be speculated that children with sufficient vitamin A levels benefit more from subsequent VAS."

Sex-differences in the response to VAS
The present trial confirmed previous observations of sex-differences in response to VAS[8,10,19,23-28]. First, as seen in the previous trial, girls tended to benefit from a lower dose of VAS if DTP was the most recent vaccine. Furthermore, boys seemed to benefit more than girls from participating in the campaign. This sex-difference may be due to a negative interaction between VAS and DTP in girls[26-28]."

10.
Conclusions
"The trial confirmed that the impact of VAS may differ by sex and routine vaccinations and adds the observation that it may further be primed by previous VAS."

Change to
"There was no evidence of low dose VAS being associated with lower mortality in girls if the most recent vaccine was DTP, MRR=0.56 (0.13 to 2.35) after 6 months."
2. “Routine vaccines during childhood have been shown to have non-specific effects on overall mortality[4-7]. Our group hypothesised that the effect of VAS on mortality may depend on an amplification of the non-specific effects on the vaccines[8].”
Change to
“Routine vaccines during childhood have been shown to have additional non-specific beneficial effects in reducing overall mortality[4-7]. Our group hypothesised that the effect of VAS on mortality may depend on an amplification of the non-specific effects of the vaccines[8].”

3. “Previous trials have indicated that a low dose might be more beneficial than a higher dose on mortality[9,10] and morbidity[11].”
Change to
“Previous trials have indicated that a lower dose of vitamin A might be more beneficial than a higher dose in reducing mortality[9,10] and morbidity[11].”

4. Samples size considerations

“With an expected mortality of 1.2 % at 6 months of follow-up it would be possible to detect a 55% reduction in female mortality among girls …”
Change to
“With an expected mortality of 1.2 % at 6 months of follow-up it would be possible to detect a 55% reduction in mortality among girls....”

5. “In the previous trial we had found the low dose to be associated with a 72% reduction in mortality after 9 months[10].”
Change to
“In the previous trial we had found the low dose to be associated with a 72% reduction in female mortality after 9 months[10].”

6. Data analysis and statistical methods

“Statistical analysis was conducted using Stata/SE 9.2.”
(please give reference)
Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests.