PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Does the effect of vitamin A supplements depend on vaccination status? An observational study from Guinea Bissau
AUTHORS	Ane B Fisker, Peter Aaby, Carlito Bale, Ibraima Balde, Sofie Biering-Sørensen, Jane Agergaard, Cesario Martins, Bo M Bibby, Christine S Benn

VERSION 1 - REVIEW

REVIEWER	David I Thurnham NICHE, University of Ulster. Coleraine, UK No conflicts of interest
REVIEW RETURNED	10/11/2011

THE STUDY	No information is given on the VA status of the subjects. Giving a high dose of VAis of questionalble benefit if status is already good. References are OK but it would be useful to have a reference to the VA status of the community or subjects.
RESULTS & CONCLUSIONS	The question of vitamin A status is ignored and believe it to be good from some evidence I have seen elsewhere. Hence how doses VA provide a benefit against mortality of status is already good?
REPORTING & ETHICS	Authors are just presenting an analysis of collected date. No ethical issues need addressing.
GENERAL COMMENTS	Referee Comments: The effect of VA provided in campaign may depend on vaccination status ..... General comments: An interesting report suggesting that VA supplements (VAS) given following measles vaccination is associated with lower mortality but if the VAS follows DPT vaccination, then there is a higher mortality in the VAS group. Most of my comments are minor but there is one big omission from the paper which will obviously influence the way the results are interpreted. The authors fail to give any background information on the VA status of the community. They suggest at one point that those children in lower socio-economic groups will have poorer VA status but no evidence is provided. Minor comments 1. Page 2 line 10: the punctuation comer is not needed 2. Page 4 line 13: I think it should be made clear to the reader that reference 2 is a very brief (non-refereed) report of a very large study. You assume page 16 line 43 that WHO recommendations for DPT at 18 mo would have been applied to the children in the study but what evidence is there that this was so? I think you should supply the evidence to support your point. There is a lot of evidence that WHO recommendation for VA supplements are very poorly met in many states. 3. Page 6 line 43: You mention that the expiry date on the VA

	capsules was overrun by one month. In fact I think you should say how old the capsules were as well. The two capsules you had analysed were approximately 75-85% of the stated amount but fresh capsules would probably have contained 10-20% more than 200,000 IU so the amount of deterioration may have been considerable. 4. Page 7 para 2: It would help the reader if you would provide another figure to illustrate the activities in the three trials. 5. Page 10 line 55: The sentence beginning on this line would read better if you add the words “When the data were adjusted for etc etc.....” 6. Page 12 line 36: Would it be better to start the sentence “The epidemic could explain....”? I assume you are referring to the cholera outbreak? Or did you mean ‘any outbreak of illnesses’.? 7. Page 13 para 1: Your study was done in what you describe as 6 suburban districts. Did all districts have equal access to VAS? Were there any differences in the proportions of supplemented and non-supplemented children between the districts? Were any districts more rural than any other? In other words do you have any evidence from your study area to support your suggestion that deaths were more likely in non-supplemented children in more rural areas? If you have it might support para 3 on page 14, which seems a little speculative? 8. Page 16 line 43: see para 2 above

REVIEWER	Frank Wieringa Senior Researcher UMR204 NutriPass IRD- Centre de Montpellier France no conflict of interest
REVIEW RETURNED	14/11/2011

GENERAL COMMENTS	The manuscript 'The effect of vitamin A provided in campaign may depend on vaccination status: Observational study from Guinea-Bissau' by Ane Fisker and colleagues aids new, important data to a far too little selection of papers on the interaction between vitamin A supplementation and vaccination in children. The authors followed the effect on mortality of 2 vitamin A campaigns in 2007 and 2008 in vaccinated children, and compared this with the mortality in children not receiving vitamin A. Of course, these types of research are bound to sensitive for bias, as children not receiving vitamin A are also more likely to be further away from health care, or less likely to seek health care. However, the authors have tried to keep potential bias to the minimum by careful selection of e.g. observation time. 1. What I miss in the manuscript however is the mean observation periods for both groups, that is, the time over which the supplemented and non-supplemented children were observed. In Table 2 and 3, the authors mention deaths / person yrs, but it is unclear to me how many months on average children contributed to this. As always, things never go the way to planned. So, the authors report 2 major events which occurred during the study. The first being that some of the vitamin A capsules being distributed in 2007 were out of date. The authors had the capsules analysed, and

	provide convincing evidence that although the capsules contained less vitamin A than needed, this is not likely to have affected the study outcomes. Furthermore, I would like to commend the authors for including this information in the manuscript, as far too often, authors tend to leave out information which might not look nice, and sometimes when reading a manuscript it seems to me that research is only a bed of roses (and I wonder why I am struggling so hard). But by including this type of information, the study and the results reported are becoming far more trustworthy to me. The other event is an epidemic of cholera, starting just before the VAS campaign in 2008, en lasting for the whole period up to the next VAS campaign in december 2008. The authors have assessed, using verbal autopsies, that up to 10 deaths in their cohort of children could have died from cholera in 2008. There appears to be a higher mortality due to diarrheal diseases in the VAS group than in the non-VAS group (9 VAS vs 2 non-VAS; 2007+2008 data). 2. I miss p-values for this comparison. Even if it is not statistical significant, I find these findings very relevant. Instead, the authors give p-values for malaria deaths in the VAS supplemented children vs children with non-VAS or no information. Although this might be statistical significant, I find this less relevant, as this is probably reflecting a bias in subject population, as the authors themselves also state, whereas this is not the case for the effect of VAS on diarrhea/cholera. 2b. When looking at several recent meta-analysis, vitamin A appears to protect against diarrheal disease, whereas there appears to be a tendency towards more respiratory infections. The current manuscripts reports the opposite. Although maybe not reaching statistical significance, there is a negative effect on diarrheal disease (see above) and no effect on respiratory infection (9 VAS vs 6 non-VAS). The authors should mention this more clearly in the discussion. 3. page 9. If I understand correctly, the 772 children who received only OPV as their last vaccination (203+ 569, Table 3). However, in addition many more received e.g. DTP+OPV or MV+OPV as their last vaccination, but these were classified as DTP or MV. The authors need to give a better argumentation on why these children were classified as DTP or MV, and not for example a child with DTP+OPV classified as OPV, or classified under both DTP and OPV. Given the apparently strong interaction between VAS and OPV in this study (8/569 deaths vs 0/203!) warrants this. 4. In earlier studies by this group, strong differences between boys and girls emerged. In the present study, these differences are not apparent. Can the authors discuss this a bit more in the discussion 5. The authors mention that mortality and morbidity is normally higher in the rainy season than in the dry season. There appears to be no effect of vitamin A in the rainy season, but a large effect in the dry season. But the authors fail to explore this in the discussion. One reason why these differences could arise is that different types of pathogens are emerging during the the dry and rainy season (viral vs extracellular bacterial infections) and that vitamin A helps against some types of pathogens, but not against others (or even has harmful effects). This could explain the difference between the 2007

	and 2008 campaign. Another possibility is that vitamin A when supplemented to a subject with an acute phase response it not absorbed. There are some reports from Zambia (C Clewes, Micronutrient forum 2007) that the increase in plasma retinol in children with an APR was zero just weeks after a high dose of vitamin A, and that there were much more children with an APR in december (rainy season) than in july (dry season). Minor issues. 6. Page 7. It is unclear whether the booster DTP was given after august 2008 or not. Please rewrite 7. page 9. The paragraph 'We examined ... compared' is a bit unclear, and lacks connection with the statistical analysis description below. Please rewrite 8. page 10. Why were the 8% (459/6026) of the children in 2007 and the 7% of the children in 2008 not followed? In total, the authors were able to follow 85% and 83% of the total available children, still a very decent figure. 9. page 11, first line. 'Effect was similar'. What do you mean with 'similar'? I find a MMR of 0.69 and 1.14 not similar! Even though both fail to reach statistical significance. Rephrase 10. page 11. Please provide real numbers for deaths cases in 2007 and 2008, in addition to the MMR 11. page 11. The paragragh : 'The difference between .... data not shown'. should be incorporated in the paragraph on page 10 on background factors. 12. Page 13. Discussion, first paragraph. I would not refer to the 22% lower adjusted mortality in VAS but to the 7% lower crude mortality in this study, as this corresponds more closely to the reported 24% reduction after VAS in the most recent meta-analysis, which is a crude mortality rate also. 13. page 16. .... tested and approved. Do you mean 'approved' (allowed) or do you mean 'proved' (proven effect). Table 1. Add # of deaths below age and above vaccine information Table 2. add 'The effect on mortality' to the title Table 3. add 'The effect on mortality..' to the title Table 3. What are the p=0.05 and p=0.19 in the line of OPV (no VAS)? Table 3. Add 'supplemented to the titles for boys and girls Table 3. Why MV as reference. Would it have been different if DTP was taken as reference (that is, would there have been a difference between OPV and DTP)

VERSION 1 – AUTHOR RESPONSE

Reviewer: David I Thurnham
NICHE, University of Ulster.
Coleraine, UK
No conflicts of interest

No information is given on the VA status of the subjects. Giving a high dose of VAis of questionalble benefit if status is already good.
References are OK but it would be useful to have a reference to the VA status of the community or subjects.

The question of vitamin A status is ignored and believe it to be good from some evidence I have seen

elsewhere. Hence how doses VA provide a benefit against mortality of status is already good?

Authors are just presenting an analysis of collected date. No ethical issues need addressing.

Referee Comments:
The effect of VA provided in campaign may depend on vaccination status .....
General comments:
An interesting report suggesting that VA supplements (VAS) given following measles vaccination is associated with lower mortality but if the VAS follows DPT vaccination, then there is a higher mortality in the VAS group. Most of my comments are minor but there is one big omission from the paper which will obviously influence the way the results are interpreted.
The authors fail to give any background information on the VA status of the community. They suggest at one point that those children in lower socio-economic groups will have poorer VA status but no evidence is provided.
ABF: Information on local vitamin A status has been added: “WHO classifies Guinea-Bissau as having a public health problem of VAD(12). We have previously found that 16% of 4-month-old children were vitamin A deficient (retinol binding protein (RBP) concentration equivalent to plasma retinol less than 0.70 µmol/L)(13). During 2007-2008 we assessed vitamin A status in 181 children aged 9-17 months presenting for vaccinations and found that 70% of the children had a RBP concentration equivalent to plasma retinol less than 0.70µM (unpublished data)” (page 6).

Minor comments
1. Page 2 line 10: the punctuation comer is not needed
ABF: The comma has been deleted.

2. Page 4 line 13: I think it should be made clear to the reader that reference 2 is a very brief (non-refereed) report of a very large study.
ABF: It has been specified that the information is a preliminary report: “However, according to a preliminary report(2) of a recent cluster randomised trial involving more than 1 million Indian children VAS as compared to no VAS was not associated with any survival benefit.” (page 4).

You assume page 16 line 43 that WHO recommendations for DPT at 18 mo would have been applied to the children in the study but what evidence is there that this was so? I think you should supply the evidence to support your point. There is a lot of evidence that WHO recommendation for VA supplements are very poorly met in many states.
ABF: We have found no report of DTP booster coverage. The sentence has been changed to: “From this perspective it may be no coincidence that the recent huge trial of one million children in India, a booster dose of DTP is recommended at 18 months of age(42), showed no beneficial effect of biannual VAS(2).” (page 18).

3. Page 6 line 43: You mention that the expiry date on the VA capsules was overrun by one month. In fact I think you should say how old the capsules were as well. The two capsules you had analysed were approximately 75-85% of the stated amount but fresh capsules would probably have contained 10-20% more than 200,000 IU so the amount of deterioration may have been considerable.
ABF: The Vitamin A capsules were manufactured in November 2004 – this information has been added on page 7. A dose of 85% of the stated amount would still be a high dose supplement.

4. Page 7 para 2: It would help the reader if you would provide another figure to illustrate the activities in the three trials.
ABF: I have prepared a figure as supplementary figure.

5. Page 10 line 55: The sentence beginning on this line would read better if you add the words “When

the data were adjusted for etc etc....."
ABF: Changed as suggested.

6. Page 12 line 36: Would it be better to start the sentence "The epidemic could explain...."? I assume you are referring to the cholera outbreak? Or did you mean 'any outbreak of illnesses'.?
ABF: Yes, we mean to refer to the cholera epidemic. The sentence has been changed from "An epidemic could potentially explain the higher mortality after the 2008-campaign." to "This epidemic could potentially explain the higher mortality after the 2008-campaign.".

7. Page 13 para 1: Your study was done in what you describe as 6 suburban districts. Did all districts have equal access to VAS? Were there any differences in the proportions of supplemented and non-supplemented children between the districts? Were any districts more rural than any other? In other words do you have any evidence from your study area to support your suggestion that deaths were more likely in non-supplemented children in more rural areas? If you have it might support para 3 on page 14, which seems a little speculative?
ABF: All six suburban districts had the similar access to campaign supplementation since the number of posts in the district is based on the size of the target population. The coverage outside the capital area was higher. We have changed: "According to national data VAS coverage was considerably higher in the rural areas" to: "According to national data VAS coverage was considerably higher outside the capital and hence outside the urban study area" (page 15).

8. Page 16 line 43: see para 2 above
ABF: We have added the following sentences to the discussion: "Since the trial has not yet been formally published, limited information is available." (page 14).

Reviewer: Frank Wieringa
Senior Researcher
UMR204 NutriPass
IRD- Centre de Montpellier
France

no conflict of interest

The manuscript 'The effect of vitamin A provided in campaign may depend on vaccination status: Observational study from Guinea-Bissau' by Ane Fisker and colleagues aids new, important data to a far too little selection of papers on the interaction between vitamin A supplementation and vaccination in children.

The authors followed the effect on mortality of 2 vitamin A campaigns in 2007 and 2008 in vaccinated children, and compared this with the mortality in children not receiving vitamin A.
Of course, these types of research are bound to sensitive for bias, as children not receiving vitamin A are also more likely to be further away from health care, or less likely to seek health care. However, the authors have tried to keep potential bias to the minimum by careful selection of e.g. observation time.

1. What I miss in the manuscript however is the mean observation periods for both groups, that is, the time over which the supplemented and non-supplemented children were observed. In Table 2 and 3, the authors mention deaths / person yrs, but it is unclear to me how many months on average children contributed to this.
ABF: The sentence: "Median length of follow-up and inter-quartile range was 6.2 (4.4-6.4) months for supplemented, 4.2 (3.2-5.1) months for non-supplemented and 2.9 (1.8-3.4) months for children for whom we did not obtain information." has been added on page 10.

As always, things never go the way to planned. So, the authors report 2 major events which occurred during the study. The first being that some of the vitamin A capsules being distributed in 2007 were out of date. The authors had the capsules analysed, and provide convincing evidence that although the capsules contained less vitamin A than needed, this is not likely to have affected the study outcomes.
Furthermore, I would like to commend the authors for including this information in the manuscript, as far too often, authors tend to leave out information which might not look nice, and sometimes when reading a manuscript it seems to me that research is only a bed of roses (and I wonder why I am struggling so hard). But by including this type of information, the study and the results reported are becoming far more trustworthy to me.

The other event is an epidemic of cholera, starting just before the VAS campaign in 2008, en lasting for the whole period up to the next VAS campaign in december 2008.
The authors have assessed, using verbal autopsies, that up to 10 deaths in their cohort of children could have died from cholera in 2008. There appears to be a higher mortality due to diarrheal diseases in the VAS group than in the non-VAS group (9 VAS vs 2 non-VAS; 2007+2008 data). 2. I miss p-values for this comparison. Even if it is not statistical significant, I find these findings very relevant.
Instead, the authors give p-values for malaria deaths in the VAS supplemented children vs children with non-VAS or no information. Although this might be statistical significant, I find this less relevant, as this is probably reflecting a bias in subject population, as the authors themselves also state, whereas this is not the case for the effect of VAS on diarrhea/cholera.
ABF: The effect of VAS on death due to diarrhoeal disease is 1.87(0.40;8.71), p=0.43. The MRR has been added, page 14: “Campaign participation had no significant effect on the risk of death due to diarrhoea the MRR being 1.87 (0.40;8.71)”

2b. When looking at several recent meta-analysis, vitamin A appears to protect against diarrheal disease, whereas there appears to be a tendency towards more respiratory infections. The current manuscripts reports the opposite. Although maybe not reaching statistical significance, there is a negative effect on diarrheal disease (see above) and no effect on respiratory infection (9 VAS vs 6 non-VAS). The authors should mention this more clearly in the discussion.
ABF: Due to the uncertainty connected with verbal autopsies and the small number of deaths, we would not put too much emphasis on causes of death. However, the sentence: “This contrasts with a recent meta-analysis which estimates 28% (9%;43%) reduction in diarrhoea related mortality(1).” has been added (page 17).

3. page 9. If I understand correctly, the 772 children who received only OPV as their last vaccination (203+ 569, Table 3). However, in addition many more received e.g. DTP+OPV or MV+OPV as their last vaccination, but these were classified as DTP or MV. The authors need to give a better argumentation on why these children were classified as DTP or MV, and not for example a child with DTP+OPV classified as OPV, or classified under both DTP and OPV. Given the apparently strong interaction between VAS and OPV in this study (8/569 deaths vs 0/203!) warrants this.
ABF: We pursued the hypothesis that the effect of VAS after DTP was different from the effect of VAS after MV. According to the schedule, DTP is supposed to be given with OPV. This was the case for 96% (3519/3680) of the children who had received DTP as the most recent vaccine prior to the campaign (1 death (VAS) occurred among the 161 children who received only DTP). Also according to the schedule, MV is not supposed to be given with OPV, however this did happen in some cases (mainly due to Trial C) and 7% (205/2814) of the children had received OPV with MV (3 deaths 1 VAS, 2 no-VAS occurred among the 205 children who received MV+OPV).

We have added the number of children receiving DTP +/- OPV and MV +/- OPV as well as references

to previous studies where the vaccine groups have been combined. The paragraph now reads: “In line with previous studies(11;16), children who received OPV along with another vaccine were classified according to the co-administered vaccine, i.e. DTP alone (161 children) and DTP+OPV (3519 children) were classified as DTP and children who received MV+OPV (205 children) and MV alone (2609) were classified as MV.” (Page 8).

4. In earlier studies by this group, strong differences between boys and girls emerged. In the present study, these differences are not apparent. Can the authors discuss this a bit more in the discussion
ABF: In an attempt to explain the lack of differential effect between the sexes, we have pursued the previous observation of a priming effect of VAS in girls. This post hoc analysis revealed some evidence that reception of VAS in 2007 has an effect on survival after the 2008 campaign.

To the methods section we have added: “Finally, previous studies have indicated that the effect of VAS in girls depend on whether or not girls have received VAS on a previous occasion(20;21). We therefore investigated whether survival after the 2008 campaign varied with reception of VAS in the 2007 campaign.” (page 10).

The analyses have been presented in the added paragraph in “Results” (page 13):

“Effect of supplementation in 2007 on survival after the 2008-campaign
Survival after the 2008-campaign was better for children who had also been supplemented in the 2007 campaign. Among 3520 children supplemented in 2008, 69% (2441) had been eligible for supplementation in 2007; 1435 (59%) had received VAS, 917 (38%) had not and 89 (4%) had no information on participation. Children supplemented in both campaigns had lower mortality (8 deaths / 623 PYRS) than children who had not received VAS in 2007 but received VAS in 2008 (15 deaths / 394 PYRS), the adjusted MRR being 0.34 (0.14;0.80). This beneficial effect of prior VAS was more pronounced for girls (MRR=0.14 (0.03;0.68)) than for boys (MRR=0.59 (0.20;1.77)) (test of interaction between sex and VAS, p=0.14).”

This result may explain the lack of a sex-differential effect in the present study, and this has been added in the “Discussion” (Page 16):

“We had expected that a negative effect of VAS with DTP would be most pronounced for girls. This was not the case in the present study. However, we have in recent studies shown that mortality after VAS is lowered in girls who have received VAS on a previous occasion(20;21) and this was also the case in the present study. Thus, if repeated dosing alleviates the negative effects of VAS seen in girls in previous studies, it may explain why the sex-differential effects of VAS in the DTP time window become less pronounced than after the first dose of VAS(25;26).”

5. The authors mention that mortality and morbidity is normally higher in the rainy season than in the dry season. There appears to be no effect of vitamin A in the rainy season, but a large effect in the dry season. But the authors fail to explore this in the discussion. One reason why these differences could arise is that different types of pathogens are emerging during the the dry and rainy season (viral vs extracellular bacterial infections) and that vitamin A helps against some types of pathogens, but not against others (or even has harmful effects). This could explain the difference between the 2007 and 2008 campaign.

Another possibility is that vitamin A when supplemented to a subject with an acute phase response it not absorbed. There are some reports from Zambia (C Clewes, Micronutrient forum 2007) that the increase in plasma retinol in children with an APR was zero just weeks after a high dose of vitamin A, and that there were much more children with an APR in december (rainy season) than in july (dry season).

ABF: We agree that seasonal differences could be either due to varying pathogen prevalences over season or an effect of generally increased pathogen prevalence in the rainy season. We do not have data to analyse this, but we have now mentioned different explanations.
The paragraph now reads:
“We do not know what may have caused the observed tendency for a differential effect of VAS on mortality between the two campaigns. Previous studies have demonstrated seasonal variance in pathogen prevalences with distinct season-related epidemics of rota-virus (30), cryptosporidium(31), respiratory syncytial virus(32) as well as a malaria(33). The effect of VAS has been show to differ depending on the pathogen(34) and varying pathogen prevalences may therefore contribute to the seasonal differences. Based on the verbal autopsy data, VAS may have been associated with a higher risk of dying from cholera/diarrhoea during the cholera epidemic in 2008. An alternative explanation is the generally increased prevalence of infectious diseases in the rainy season, which may lead to impaired uptake and increased excretion of vitamin A(35). This could explain the lack of effect during the rainy season, but would not explain the vaccine differential effect. Regardless of the mechanism, the potential differential seasonal effects of VAS deserve further investigation.”

Minor issues.
6. Page 7. It is unclear whether the booster DTP was given after august 2008 or not. Please rewrite
ABF: Booster DTP was given in the routine program until March 2007. It was provided in a trial until October 2009. This has been clarified (page 7)

7. page 9. The paragraph 'We examined ... compared' is a bit unclear, and lacks connection with the statistical analysis description below. Please rewrite
ABF: The paragraph now reads: “We examined whether background factors were evenly distributed between children in the VAS, no VAS and no information group, as well between the two main groups (VAS and no VAS) using chi2 tests for categorical variables and ranksum test for age at the time of the campaign.”

8. page 10. Why were the 8% (459/6026) of the children in 2007 and the 7% of the children in 2008 not followed? In total, the authors were able to follow 85% and 83% of the total available children, still a very decent figure.
ABF: We censored follow-up for children who had moved, died, turned 3 years or received VAS in a randomised trial of VAS. We have stated this in Figure 1. The reference to Figure 1 has been has been made clearer: “Reasons for losses to follow-up are given in Figure 1” (page 10).

9. page 11, first line. 'Effect was similar'. What do you mean with 'similar'? I find a MMR of 0.69 and 1.14 not similar! Even though both fail to reach statistical significance. Rephrase
ABF: The sentence has been changed to: “The effect did not differ significantly for children aged 6-11 months who received 100,000 IU vitamin A (adjusted MRR=1.14 (0.41;3.19)) and children above 12 months who received 200,000 IU vitamin A and 250 mg mebendazole (adjusted MRR=0.69 (0.36;1.29)) (p=0.41, test of interaction) (Table 2).”

10. page 11. Please provide real numbers for deaths cases in 2007 and 2008, in addition to the MMR
ABF: Deaths and person years have been added, the sentence now reads: “Mortality was much higher in the rainy season after the 2008-campaign (57 deaths / 2208 PYRS) than in the dry season after the 2007-campaign (15 deaths / 2154 PYRS);”

11. page 11. The paragragh : 'The difference between .... data not shown'. should be incorporated in the paragraph on page 10 on background factors.
ABF: We find that since we are describing the effect of VAS stratified by background factors it belongs in the paragraph presenting the effect of VAS, rather than under background factors. It has therefore not been moved.

12. Page 13. Discussion, first paragraph. I would not refer to the 22% lower adjusted mortality in VAS but to the 7% lower crude mortality in this study, as this corresponds more closely to the reported 24% reduction after VAS in the most recent meta-analysis, which is a crude mortality rate also.
ABF: The meta-analysis is based on randomised trials – whereas our study is observational and therefore the adjusted effect is more likely to reflect the actual effect. However, we have now added the crude effect. The sentence now reads: “In our study, children receiving VAS in a campaign had 7% (-58%;45%) lower mortality compared with non-supplemented children in the crude analysis and 22% (-34%;54%) lower mortality in the adjusted analysis. “

13. page 16. .... tested and approved. Do you mean 'approved' (allowed) or do you mean 'proved' (proven effect).
ABF: We mean proved. The sentence has been shortened to “The circumstances under which the intervention is being implemented may differ from the circumstances under which it was originally tested.”

Table 1. Add # of deaths below age and above vaccine information
ABF: We fear that including follow-up information in the background table would confuse the reader. Since we are conducting prospective follow-up, we think the information should be provided in the tables describing the effect of VAS on mortality (Tables 2+3).

Table 2. add 'The effect on mortality' to the title
ABF: Done

Table 3. add 'The effect on mortality..' to the title
ABF: Done

Table 3. What are the p=0.05 and p=0.19 in the line of OPV (no VAS)?
ABF: The p-values refer to the test for a different mortality rate in the supplemented and non-supplemeted children. This has been added in a footnote. “&Test for different mortality rate in supplemented and non-supplemented children”

Table 3. Add 'supplemented to the titles for boys and girls
ABF: We fear that this may not represent the analysis adequately. The mortality rate ratio is provided for supplemented compared to non-supplemented in all the columns, for both the entire group, boys and girls.

Table 3. Why MV as reference. Would it have been different if DTP was taken as reference (that is, would there have been a difference between OPV and DTP)
ABF: The choice of MV as a reference is not well founded – and it could also have been DTP. In fact, since the DTP group is larger that may be a better choice. We have changed to the group as the reference, and as can be seen in Table 3, the effect of VAS with OPV does not differ significantly from the effect of VAS with DTP.

VERSION 2 – REVIEW

REVIEWER	David I Thurnham NICHE, University of Ulster. Coleraine, UK No conflicts of interest
REVIEW RETURNED	09/12/2011

The reviewer completed the checklist but made no further comments.

REVIEWER	Frank Wieringa Senior Researcher IRD - UMR204 - Montpellier, France
REVIEW RETURNED	06/12/2011

The reviewer completed the checklist but made no further comments.