Author's response to reviews

Title: Assessment of measles Immunity among Infants in Maputo City, Mozambique.

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Author's response to reviews: see over
Reply to the reviewers’ comments:

Reviewer 1: Tetsuo Nakayama

Comments from the Reviewer:
They concluded that these data indicate a need to revise immunization policy. Their conclusion seems to be overemphasized. The authors should perform comparative vaccine study to evaluate the immune response after vaccination at 6 months or at 9 months, in order to recommend the revised immune schedule. Depending upon the vaccine strain, serological response was different when measles vaccine was administered at 6 months of age. The word “a need to revise” is strong and “a need to re-evaluate”, “a need to perform further vaccine study”, or other mild expression would be better. There is no data supporting the last sentence in their experiments.

Reply from the Authors:
The conclusion has been re-written according to the Referee’s suggestion.

Reviewer 3: Claude P. Muller

Comments from the Reviewer:
1. On the one hand the authors claim that there were only few sporadic cases (41 and 53 in 2004 and 2005) in a city with 1.5 Million inhabitants and on the other hand they suggest that several infants (at least 14 (2.7%); IgM positive or IgG positive and mother IgG negative) had been in contact with wt virus. Is it possible that measles is underreported in Mozambique, because of limited sensitivity of surveillance?

2. If the specificities of the ELISAs were taken into account the number of possible “subclinical infections” would be significantly lower:
- Measles IgG test specificity = 86.7%; about 13% false positives can thus be expected, the percentage of IgG positive infants born from IgG negative mothers was 11.5 and 10% in the 6 and 9 months old cohorts respectively.
- Measles IgM test specificity = 96.6%; 3.8 and 6.3% of 6 and 9 months old infants were tested positive for measles IgM.

Reply from the Authors:
In a recent study (Ref. Jani, 2006), it has been described that the surveillance system in Mozambique under-reports measles but is sensitive enough to detect outbreaks. Text added in Discussion (page 11, paragraph 3).

We acknowledge that the specificity of the assays, especially of the IgG test, is an issue. However, it should be noted that five out of the 12 IgG positive infants that were born to IgG negative mothers, were also IgM positive. It is very unlikely that these represent false-positive results. Additionally, it is also highly unlikely that the higher proportion of IgG positive infants at 9-months (30.5% vs 12.3% in 6-month-olds) is due to more false-positive results in this age group.

To reflect this, the following text has been
3. How do the authors explain that there seemed to be only subclinical infections and that none of the infants had clinical symptoms? Which observations or reports was the absence of clinical symptoms based on? Is it possible that these reports had limited reliability? If mothers report that the child did not have measles or was not sick, what does this mean in a setting where fever is not usually measured, rash is difficult to make out on dark skin and many children are multimorbid.

4. Why would the authors want to vaccinate infants at 6 months of age already, if none of them had clinical measles despite the fact that some had supposedly been exposed to wt virus? Although vaccination against measles at 6 months of age may be of advantage (in some situations) the results from this study do not necessarily suggest this. In the conclusion the authors state that: “Our results show that, in Maputo City, six-month-old children seem to be better suited for immunization than nine-month old children. This evidence is further compounded by the fact that a relatively high proportion of nine-month-old infants develop an immune response after vaccination.” This conclusion is not backed-up by the results of added to the Discussion (page 13, paragraph 3):

“The main limitations of these tests are posed by difficulties in obtaining sufficient volumes of oral fluid from infants and by the relatively low sensitivity and specificity of the IgG assay. Indeed, it may be possible that the 12 IgG positive infants born to IgG negative mothers represent false-positive results. However, this is unlikely as five of these children were also IgM positive, further supporting our hypothesis that children are exposed to wild-type measles virus. It is also not likely that the higher prevalence of measles IgG in nine months old children is due to a higher rate of false-positive results in this age group.”

A past history of measles disease was collected verbally using the World Health Organization case definition (described under Methods; Ref. Hutchins, 2004). While the reliability of verbal reports is variable, it tends to be higher in settings where the disease occurs in periodic outbreaks. Moreover, rash-and-fever diseases are known to Mozambican populations (called Xitsanhana in Xichangana and Xironga, the two African languages spoken in Maputo city) and mothers regard it as an important disease. Thus, it is probable that mothers would recall classical cases of measles. However, this would not necessarily apply to atypical or mild cases of measles.

The conclusion has been re-written.
this study, since vaccination at 6 months of age has not been tested.

Reviewer 4: Julie Cliff

Comments from the Reviewer

Major revisions:
Possible influence of measles mass vaccination campaigns in 1979 on the age cut-off.

Reply from the Authors:
The 1979 campaign targeted children from 9 months to 5 years of age and had coverage of 95% (text added in Background, first paragraph, page 3). Based on this data, we changed the cut-off age to 30 years and re-analysed the data. There was no difference in the IgG prevalence among the two groups of mothers as there was no association between the mothers’ age and presence of IgG among their offspring (Table 2).

They need to state consistently through the paper how they defined seroconversion, what was the rate, and whether they believe it is low or high.

Minor Essential Revisions:
Background: ?fourth annual national vaccination campaigns.
Weight to age, height to age etc. not corrected

Changed to “fourth yearly national vaccination campaigns”.
Corrected as suggested by the reviewer.

REFERENCES:
