PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	The optimal age of measles immunization in low-income countries: A secondary analysis of the assumptions underlying the current policy
AUTHORS	Aaby, Peter ; Martins, Cesario; Garly, May-Lill; Rodrigues, Amabelia; Benn, Christine; Whittle, Hilton

VERSION 1 - REVIEW

REVIEWER	Samuel L. Katz, M.D. W.C. Davison Professor & Chair emeritus Department of Pediatrics Duke University School of Medicine Durham, N.C. 25510, U.S.A. I have no competing interests other than consultation with the members of the Measles Initiative.
REVIEW RETURNED	03-Jan-2012

GENERAL COMMENTS	This is an heroic effort to present all the relevant background and appropriate studies that relate to the designation of the age at which a single dose or two doses of measles vaccine should be given to infants in resource-poor nations. With current deliberations regarding the possible revision of the present recommendations and the eventual addition of rubella vaccine to the schedule (ref. Global Measles and Rubella Strategic Plan 2011-2020, Draft: 7 November 2011, WHO/IVB/10.xx), this is especially timely.

REVIEWER	Jim Goodson Epidemiologist Disease Elimination and Eradication Branch Global Immunization Division Centers for Disease Control and Prevention 1600 Clifton Road, NE; Mailstop A-04 Atlanta, GA 30333 I declare that I have no competing interests.
REVIEW RETURNED	14-Feb-2012

THE STUDY	The research question for this study is not clearly defined. In the Introduction, the authors state that “the current policy of vaccination children against measles at 9 months of age in low-income countries is based on assumptions…” and cite references from 1979, 1981, and 1982. However, the authors do not acknowledge more current policy statements including the WHO measles vaccine position paper that was revised and published in 2009. This current position paper includes pertinent references citing more recent evidence that

	was available at that time of revisions. It is not clear that the example of Machakos in 1974 is as helpful today. In addition, any discussion regarding the rates of death from measles with or without vaccination and at various ages of vaccination depends hugely on the epidemiology of the disease.
RESULTS & CONCLUSIONS	The article is something between a commentary and a review of the literature. It is a bit long for the former and for the latter needs a better description of the literature search strategy used and a more careful review of studies. The authors state the scope is low-income countries but limit their review to Africa. A large study in Latin America provided similar results to the Kenyan study (see Bull PAHO 1982;16(3):272). The authors' clear desire to argue their thesis may have led them to ignore relevant studies contradicting their various theses. They also do not include relevant field studies of vaccine effectiveness that may be relevant.
GENERAL COMMENTS	The review of the history of the policy setting process does not seem complete. For example, there is no discussion as to the need for balancing logistical and financial considerations in resource-limited settings. Historically, in Africa, support for even one dose of measles vaccine was not clear and arguments were put forward by donors that measles vaccination was too expensive. It took time and experience to realize that measles vaccination was a worthy investment even if eventually a 2-dose schedule would be necessary to control the disease. The authors do not consider the benefits of achieving herd immunity. Control programs might better work to achieve high coverage with 2 doses rather than focusing on individual protection. The claim that 2 doses given before 12 months of age will eliminate all measles deaths would require a fuller examination of vaccination coverage, vaccine effectiveness, and expected disease epidemiology than the authors present if policy changes were to be considered. In the Conclusions, the authors state “However, the most important problem is that measles vaccine has major non-specific beneficial effects and the earlier it is given, the earlier the children will benefit from this advantage”. As evidence for this statement, the authors reference the sutdy by Aaby P. et al (Aaby P, Martins CL, Garly ML, Bale C, Andersen A, Rodrigues A, Ravn H, Lisse IM, Benn CS, Whittle H. Non-specific effects of standard measles vaccine at 4.5 and 9 months of age on childhood mortality: Randomized controlled trial. BMJ 2010;341:c6495.) The findings from that study do not fully support the concluding statement. In that Aaby et al. randomized, control trial, no significant difference was found in all-cause child mortality among children who received early measles vaccination compared with children who received measles vaccination at nine months. Although, when the analysis was stratified by sex, there appeared to be a significant non-specific benefit among girls with early measles vaccination. However, the overall difference in mortality by the Kaplan-Meier curves was negligible, 1-2%, and the authors did not provide data on the causes of death among that group. Many of the points that the authors make against the assumptions in the late 1970’s are valid and are substantiated by more recent evidence available in the published literature. For example, it is widely known that vaccinated children have less severe disease, and that children can still get measles even after seroconverting. However, little evidence exists to support the authors’ claim that

	vaccination causes “substantial non-specific benefits” independently of its prevention of measles disease, and therefore earlier vaccination is better. Most of the studies looking at non-specific effects of vaccine have been done in Guinea Bissau, and before jumping to conclusions, it is important to replicate these studies in other environments where measles has been well-controlled and overall child mortality is lower.

VERSION 1 – AUTHOR RESPONSE

Reviewer: Samuel L. Katz, M.D.
W.C. Davison Professor & Chair emeritus
Department of Pediatrics
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Durham, N.C. 25510, U.S.A.

I have no competing interests other than consultation with the members of the Measles Initiative.

This is an heroic effort to present all the relevant background and appropriate studies that relate to the designation of the age at which a single dose or two doses of measles vaccine should be given to infants in resource-poor nations. With current deliberations regarding the possible revision of the present recommendations and the eventual addition of rubella vaccine to the schedule (ref. Global Measles and Rubella Strategic Plan 2011-2020, Draft: 7 November 2011, WHO/IVB/10.xx), this is especially timely.

PA: The timeliness has been mentioned in the introduction.

Reviewer: Jim Goodson
Epidemiologist
Disease Elimination and Eradication Branch Global Immunization Division Centers for Disease Control and Prevention

I declare that I have no competing interests.

The research question for this study is not clearly defined. In the Introduction, the authors state that “the current policy of vaccination children against measles at 9 months of age in low-income countries is based on assumptions…” and cite references from 1979, 1981, and 1982. However, the authors do not acknowledge more current policy statements including the WHO measles vaccine position paper that was revised and published in 2009. This current position paper includes pertinent references citing more recent evidence that was available at that time of revisions. It is not clear that the example of Machakos in 1974 is as helpful today. In addition, any discussion regarding the rates of death from measles with or without vaccination and at various ages of vaccination depends hugely on the epidemiology of the disease.

PA: The introduction has been rewritten to set the issues of the 9-months of age vaccination policy in its historical as well as the current context (timeliness as mentioned by professor Katz). Though other elements (including general vaccination campaigns, a second dose of MV) have been added in the current drive to eliminate/eradicate measles infection, the MV at 9 months of age policy has remained the key element in the measles vaccination strategies. The evidence for the 9 month strategy is therefore still important for current and future policies. The introduction clearly states that the empirical basis for this policy is the research question.

The article is something between a commentary and a review of the literature. It is a bit long for the former and for the latter needs a better description of the literature search strategy used and a more careful review of studies. The authors state the scope is low-income countries but limit their review to Africa. A large study in Latin America provided similar results to the Kenyan study (see Bull PAHO 1982;16(3):272).

PA: The search strategy was spelt out in the supplementary material and has now been further explained in the introduction and methods as also requested by the editorial board.

No example of where a “more careful review of studies” was needed is provided by the reviewer.

We can change the title to Africa if the reference to “low-income countries” is considered inconsistent. However, the current 9-month policy was based on the discussion in Africa and to limit the length of the paper and the number of references we restricted the examination of the empirical evidence to the African studies. This background has been emphasised in the methods section. Reference is made to the fact that several similar studies can be found from Asia and Latin America, including the one mentioned by the reviewer.

The authors' clear desire to argue their thesis may have led them to ignore relevant studies contradicting their various theses. They also do not include relevant field studies of vaccine effectiveness that may be relevant.

PA: The reviewer presents no example of relevant studies contradicting our “various theses” which we have ignored. We do present those we have found – for example, we have discussed in the paper that all studies have been included even though vaccine efficacy was not high in some of the studies and the vaccine may have been less than optimal.

The reviewer presents no example of omitted “relevant field studies of vaccine effectiveness that may be relevant”. To our knowledge we have not omitted any study with relevance for the case fatality by vaccination status or by age (Tables 2-4). The possibility that there may be other studies we have not found was discussed under “Strength and weaknesses” and it was concluded that given the consistency of the study already found a few more studies would be unlikely to change the trends.

The review of the history of the policy setting process does not seem complete. For example, there is no discussion as to the need for balancing logistical and financial considerations in resource-limited settings. Historically, in Africa, support for even one dose of measles vaccine was not clear and arguments were put forward by donors that measles vaccination was too expensive. It took time and experience to realize that measles vaccination was a worthy investment even if eventually a 2-dose schedule would be necessary to control the disease.

PA: In the discussion of a two-dose strategy we are making reference to the fact that economic considerations may have been important for chosing a one-dose strategy but the stated and repeated argument against a two-dose strategy in the medical literature is that coverage would be too low.

As suggested by the reviewer we have expanded on the opposition to measles vaccination and the initial lack of belief in its effect on survival among donors. This has been mentioned in the introduction as a background information setting the policy decision in context.

The authors do not consider the benefits of achieving herd immunity. Control programs might better work to achieve high coverage with 2 doses rather than focusing on individual protection. The claim

that 2 doses given before 12 months of age will eliminate all measles deaths would require a fuller examination of vaccination coverage, vaccine effectiveness, and expected disease epidemiology than the authors present if policy changes were to be considered.

PA: We do not understand the critique which is raised here. We are clearly advocating a two-dose strategy, though an early one. The reviewer is presumably thinking about these sentences on page 9: "The studies of two doses of MV suggest that both the first and the second dose of measles vaccine are effective and that an early two-dose strategy would be associated with a major reduction in measles and overall mortality (7,65-70). Hence, an early dose at 6 months of age and a second dose at 9 months of age would have eliminated virtually all measles mortality." Is the reviewer saying that an early two dose strategy would have less effect on herd immunity than the strategy currently promoted by WHO to give MV at 9 mo and 18 months of age? If so some documentation for that statement would be needed.

We may add that within our recent trial of MV at 4½ months of age the youngest children vaccinated at 18-20 weeks of age had 100% (95% CI 73-100%) protection against verified measles infection whereas children vaccinated at 5-6 months of else had a vaccine efficacy of 87%(44-97%) (unpublished data). Hence, it is by no means certain that children vaccinated very early and therefore having lower antibody responses will have lower protection against clinical disease. They may well have more cellular immunity.

In the Conclusions, the authors state "However, the most important problem is that measles vaccine has major non-specific beneficial effects and the earlier it is given, the earlier the children will benefit from this advantage". As evidence for this statement, the authors reference the sutdy by Aaby P. et al (Aaby P, Martins CL, Garly ML, Bale C, Andersen A, Rodrigues A, Ravn H, Lisse IM, Benn CS, Whittle H. Non-specific effects of standard measles vaccine at 4.5 and 9 months of age on childhood mortality: Randomized controlled trial. BMJ 2010;341:c6495.) The findings from that study do not fully support the concluding statement. In that Aaby et al. randomized, control trial, no significant difference was found in all-cause child mortality among children who received early measles vaccination compared with children who received measles vaccination at nine months. Although, when the analysis was stratified by sex, there appeared to be a significant non-specific benefit among girls with early measles vaccination. However, the overall difference in mortality by the Kaplan-Meier curves was negligible, 1-2%, and the authors did not provide data on the causes of death among that group.

PA: The paper refers in several places to the evidence for the statement "measles vaccine has major non-specific beneficial effects" - pages 10-11 are about "The non-specific beneficial effects of MV". Reference is made to many studies here: ref 11, 30,32,33,38 ,77-88,90-92. Hence there are clearly a lot of studies supporting this statement. To prevent any misunderstanding we have added further references to the statement in the conclusion in the revised paper.

Furthermore, the comments made about the BMJ 2010;341:c6495 study are somewhat misleading. As hypothesised there was significant beneficial effects for girls in the ITT analysis of an early two-dose strategy compared with the currently recommended strategy of one dose at 9 months. We are surprised by the statement that the difference in mortality was negligible, 1-2%. If overall mortality between 4 and 36 months of age has been reduced by more than 20% it can't be negligible. As far as we know that is the largest reduction in overall mortality claimed for any vaccine except for BCG which we have shown to reduce neonatal mortality by more than 40% (1,2). We do present the measles deaths in the study by conducting an analysis by censoring for measles infection to estimate the effect of measles vaccination on non-measles related mortality. Furthermore, the reviewer is not mentioning that there was a major interaction in the study related to reception of neonatal vitamin A supplementation (VAS). Among the children who did not receive neonatal VAS (it is current WHO

policy not to receive neonatal VAS) the reduction in all-cause mortality between 4 and 36 months of age was more than 40%.

Since the BMJ2010:c6495 paper has already been explained in detail in the text and reference has been made to the other data available about the beneficial non-specific beneficial effects of measles vaccine we do not think it is necessary to further enlarge on this issue in the revised version.

Many of the points that the authors make against the assumptions in the late 1970's are valid and are substantiated by more recent evidence available in the published literature. For example, it is widely known that vaccinated children have less severe disease, and that children can still get measles even after seroconverting. However, little evidence exists to support the authors' claim that vaccination causes "substantial non-specific benefits" independently of its prevention of measles disease, and therefore earlier vaccination is better. Most of the studies looking at non-specific effects of vaccine have been done in Guinea Bissau, and before jumping to conclusions, it is important to replicate these studies in other environments where measles has been well-controlled and overall child mortality is lower.

PA: We appreciate that the reviewer accepts several of the points made in relation to the assumptions. Since our group was the first to point out that vaccinated children had less severe disease in Africa (Vaccinated children get milder measles infection: a community study from Guinea Bissau. J Infect Dis 1986;154:858 63) we are pleased that this has now become common knowledge. However, the reviewer´s main objection is that "little evidence exists to support the authors' claim that vaccination causes "substantial non-specific benefits" independently of its prevention of measles disease, and therefore earlier vaccination is better. Most of the studies looking at non-specific effects of vaccine have been done in Guinea Bissau, and before jumping to conclusions, it is important to replicate these studies in other environments where measles has been well-controlled and overall child mortality is lower". As mentioned above the present paper deals extensively with this topic – however, mostly in relation to the evidence for the effect of measles vaccination before 9 months of age. We have now also mentioned the studies of the effect of measles vaccination after 9 months of age (references 30,32,33). There are reasons to emphasise that the finding from Guinea-Bissau are likely to apply to other countries with high childhood mortality from infectious diseases. Studies from Congo (11) and Bangladesh (90) randomising different areas to vaccination or no vaccination has shown much larger effect on survival than can be explained by prevention of measles infection. An individualised randomised study in Sudan (75) comparing measles vaccine versus meningococcal vaccine between 5 and 9 months of age showed a major significant effect on survival (91%) unrelated to protection against measles infection. Furthermore, Frank Shann has summarised five randomised trials of measles vaccination from (Bissau, Gambia, Senegal, and Sudan) showing that MV at 9 month reduced female mortality by 47% (23-63%) (Arch Dis Childh 2010;95:662-7) compared with children who had previously received early MV (and therefore did not get measles) but at 9 months received an inactivated vaccine (DTP, IPV) as cross-over vaccine. In these randomised trials MV was compared with inactivated vaccines and showed a major reduction in mortality unrelated to protection against measles infection. This can only be described as a beneficial non-specific effect – and most of these randomised trials were conducted outside Guinea-Bissau.

These points have been added to the section on The non-specific beneficial effects of MV or in the discussion.

Hence this final critique of the reviewer is not correct. There are many studies showing non-specific beneficial effects of MV and they are not all from Guinea-Bissau.

1. Aaby P, et al. Randomised trial of BCG vaccination at birth to low-birth-weight children: Beneficial non-specific effects in the neonatal period? JID 2011:204:245-51

2. Biering-Sørensen S, et al. Small randomised among low-birth-weight children of Bacillus Calmette-Guérin vaccination at first health center contact. Pediatr Inf Dis J 2012;31:306-8