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The optimal age of measles immunization in low-income countries: 35 years with a policy based on flawed assumptions

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Abstract

Background and objective The current policy of measles vaccination at 9 months of age in low-income countries was decided in the mid-1970s following a study of seroconversion at different ages in Kenya. The policy was not tested for its overall impact on child survival but was based on six assumptions. We examined the empirical evidence for these assumptions.

Data sources and methods Existing reviews and additional literature search of African community studies of measles infection.

Main outcome The predicted effect on measles and all-cause mortality.

Results All assumptions were flawed. Most notably, seronegative vaccinated children may have considerable protection against measles infection. Second, vaccinated measles cases ("vaccine failures") have around one-third the case fatality of unvaccinated measles cases. Third, infant measles cases have around 2-fold higher case fatality than older cases. Fourth, "vaccine failures" did not lead to lack of confidence because the children had milder measles infection. Fifth, in the randomised trials of early two-dose measles vaccination compared with one dose at 9 months of age, mortality was significantly reduced until 3 years of age. Had these factors been studied, the optimal age of measles vaccination had probably been at 6 or 7 months leading to more mild "vaccine failures" among older children but fewer severe unvaccinated cases among infants. Furthermore, the two-dose trials indicate that measles vaccine reduces mortality from other causes than measles infection.

Conclusions Many lives may have been lost by not finding the optimal age of measles vaccination. The measles vaccination policy is still based on assumptions about seroconversion and it is now recommended to increase the age of measles vaccination to 12 months in countries with limited measles transmission. As measles vaccination may have non-specific beneficial effects this policy is likely to increase child mortality.

Article summary

Article focus

- An empirical analysis of the six assumptions underlying the current measles vaccination policy for low-income countries.
- Determine the implications for child survival of not testing the optimal measles vaccination policy.

Key messages

- All six assumptions were flawed; most important were the assumptions that vaccinated children who did not seroconvert are fully susceptible to measles infection, that the severity of measles is the same in vaccinated cases ("vaccine failures") and in unvaccinated children, that the severity of measles infection is the same in infancy or later, and that it had to be a one-dose programme.
- The current evidence suggests that the optimal age of measles immunization in terms of reducing child mortality had probably been 6 or 7 months of age had the policy been tested.
- A two-dose policy would have been even better in terms of reducing child mortality.

Strength and limitations

- The current measles vaccination policy for low-income countries is not based on any evidence about the impact on overall survival.
- There are few studies testing some of the assumptions. However, there are many studies testing the two key assumptions about severity of measles in vaccinated children and in infancy and these studies provide a consistent answer.

Introduction

With the spectacular success in measles control in the last 10-15 years(1-3), few people realize that the current policy of vaccinating children against measles at 9 months of age in low-income countries is based on assumptions (4-6) and not on specific studies documenting the optimal age of measles vaccination to reduce overall child mortality (7). Even fewer people will realize that the assumptions were not substantiated. As current policies continue to be based on these assumptions, it is necessary to discuss their empirical basis. The present analysis suggests that all assumptions were flawed and had the policy been tested it is likely that the measles vaccination programme might have had a much larger effect on child survival in low-income countries.

The optimal age of measles immunization: Six assumptions

In the first measles vaccination campaigns in West and Central Africa in the 1960s children were targeted from 6 months of age (8-12). Initially it was thought that it would be sufficient to conduct campaigns every 2nd or 3rd year to control measles. However, the epidemiologists soon learned that intervals of 6 or 12 months between campaigns were necessary to control measles. In the 1970s, routine vaccination programmes were introduced and the optimal age of routine measles vaccination was debated (13-15). Following the experience with the campaigns, several African countries recommended measles vaccination at 6, 7 or 8 months of age when a routine programme was initially started. A study sponsored by the Ministry of Health in Kenya and WHO assessed the seroconversion rates at different ages between 5 and 12 months and recommended measles vaccination at 7½ months of age (16) and for several years measles vaccine was administered at 8 months of age in Kenya (17). Since some of those vaccinated at 6 months were not protected some countries and many researchers recommended a second dose at 9 months of age or later (16-18). However, there were fear that early vaccination would produce too many vaccine failures and a one-dose programme was considered necessary because mothers would not bring their children back for a second dose (10,19). Hence the Expanded Programme on Immunization (EPI) recommended a one-dose policy (4-6,13). In 1980, the Global Advisory Group of EPI endorsed this policy and recommended measles vaccination as early as possible after 9 months of age (5).

The recommendation was based on the belief that the expected reduction in mortality could be computed from seroconversion rates (13,20) and the policy was justified several times by analyses of the seroconversion data from Kenya (4,6). In these analyses it was assumed that seroconversion was associated with full protection against measles infection (*first assumption*) and that non-seroconversion was associated with full susceptibility to measles infection (*second assumption*). As shown in Table 1, the seroconversion following measles immunization at different ages had been determined in a study in Kenya (Column 2) (16). Not unexpectedly seroconversion increased with age for the calculation of this measure (a fourfold or more increase over baseline) is dependent on level of maternal antibody which wanes as the child ages. Based on cumulative measles incidence figures (Column 1), it was calculated how many measles cases had been prevented assuming everybody got vaccinated at a specific age (Column 3), how many "vaccine failures" would occur after the age of vaccination (Column 4) and how many

cases would occur before the specific age of vaccination (Column 5). In making these calculations it was assumed that "vaccine failures" and unvaccinated measles cases were equally severe (*third assumption*) and that it did not matter whether measles was acquired in infancy or later in childhood (*fourth assumption*). Vaccination at 8, 9, and 10 months of age prevented roughly the same proportion of cases, between 79% and 84% (Column 3) (4,6,13). Vaccination at 8 month resulted in considerably more vaccine failures (15%) than vaccination at 9 months (7%). Since vaccine failures were assumed to jeopardize the credibility of the measles immunization programme (*fifth assumption*) (4,6,13), it was concluded that the optimal age for administration of measles vaccine would be 9 months. At the time the EPI assumed that the case fatality in measles infection was 4% in Africa and it will be seen in Column 6 that the number of estimated measles deaths in a birth cohort of a 1000 children would indeed be lowest (between 6.4 and 8.4) for vaccination at 8-10 months of age. In making this analysis of the effect of only one dose of measles vaccine (4,6), the EPI assumed that a two-dose policy was infeasible or unjustified (*sixth assumption*).

Methods

Selection of studies. We looked for empirical evidence in African community studies to support or refute these assumptions. The original policy was mainly justified in relation to the epidemiology of measles infection in Africa where the case fatality was clearly higher than in other regions (21-25). Most community studies of measles infection are indeed from Africa.

Over the last 20-25 years, several reviews of community studies of the measles case fatality compiled studies of relevance for particularly assumption three and four (21-25). Furthermore, as specified in the supplementary material, we made PubMed searches for additional publications relevant for all assumptions. We included one unpublished report from a large epidemic in Bissau in 1991-1992 which has remained unpublished because the physician (Henning Andersen) handling the epidemic died tragically in an accident shortly after the epidemic.

We distinguished between prospective community studies and surveys retrospectively assessing events since the precision of information on vaccination status and age presumably is better in prospective community studies. Though hospital and health centre studies may have data on the severity of measles infection by vaccination status or age, we have not included these studies in the analysis since biased admission for some groups might have made the result non-representative.

Since the analysis of the assumptions suggested that standard-titre measles vaccination before 9 months of age could be beneficial, we assessed the empirical evidence from studies which assessed the effect of early and later measles vaccination on mortality. Again we used all reviews of community studies and trials assessing the impact of measles vaccination on child mortality (24,26,27). Additional PubMed searches for studies comparing the mortality of measles vaccinated and unvaccinated children did not identify further studies. Studies of medium and high-titre measles vaccines were not included in these analyses as they have been analysed elsewhere (28,29).

Statistical analyses. The Mantel-Haenszel weighted relative risk stratifying for study or age groups was used to estimate common trends.

Ethics. Since the study is based on review of existing data, approval from an ethical committee was not needed.

Results

Assumption 1: children who seroconvert to measles vaccine have absolute protection against measles infection. A number of smaller studies have documented that a few children do get measles after having seroconverted (30-33). Hence, seroconversion does not give absolute protection. However, there are no general epidemiological studies from Africa and it is therefore difficult to estimate the impact on protection. Since no large series have been reported it seems likely that the effect has been small.

Assumption 2: vaccinated children who do not seroconvert are fully susceptible to measles infection. In a study in Senegal, vaccinated children who were seronegative when exposed to measles infection at home had a 49% (95% CI 21-68%) protection against clinical disease compared with unvaccinated seronegative children exposed under similar conditions (30). It is possible that the children had acquired vaccine-induced measles antibodies earlier but subsequently lost them. Based on the literature search, no other study has tested the susceptibility of "seronegative" vaccinated children. If approximately half the seronegative children have clinical protection it would have major consequences for the calculation of the optimal age of measles vaccine. In animal studies cellular immunity may be obtained without having measurable antibodies (34). There is also good evidence from studies of hepatitis B vaccination that antibody concentration wane with time but the majority of older seronegative children if infected are protected from chronic carriage and its damaging consequences (35).

The concept of seroconversion to compare the effect of vaccination at different age is in itself problematic. Seroconversion is not the same as seroprotection and the use of the term inevitably disadvantages data from studies that have vaccinated at earlier ages when maternal antibodies are still present. Thus a child immunized at 6 months of age when the maternal antibody level is say 62.5 miU may fail the test for conversion (a four-fold increase) yet still have a protective level of 125 miU at 9 months of age.

Assumption 3: severity of measles infection in vaccinated children ("vaccine failures") and unvaccinated children is the same. The EPI perceived "vaccine failures" as due to the vaccine being inactivated by improper storage and handling or due to neutralization of the vaccine by maternal antibodies (11,14). Hence, it was assumed that these children were fully susceptible to measles infection. However, many epidemiological studies in the 1980s and 1990s suggested that measles vaccinated children who contracted measles infection had milder disease (36,37). This would suggest that the children had partial measles immunity, not enough to protect them but enough to modify the severity of the disease. In the community studies of the acute measles case fatality shown in Table 2, the measles case fatality was 2 to 5-fold lower for vaccinated cases ("vaccine failures") than

for unvaccinated children with measles infection. The effect was similar in the prospective community studies (case-fatality ratio=0.37 (0.27-0.52)) and the retrospective surveys (case-fatality ratio=0.41 (0.29-0.56)).

All studies with relevant data were included in Table 2 irrespective of whether vaccine efficacy (VE) against measles infection was high or substandard. In several studies, the VE was not high but nonetheless the vaccine appeared to have had an effect; for example, in Kenya VE was only 18% but measles-vaccinated children who developed measles had still 2-fold lower measles mortality than measles unvaccinated children (Table 2). Only one community survey from Niger reported that measles vaccine was not particularly effective against measles infection and that there was no effect of vaccination on the case fatality in measles infection (46).

A few studies followed the children for longer than the one month which is the normal time limit for acute measles deaths. The long-term trend was the same with considerable better survival among vaccinated than unvaccinated children after measles infection (Table 3). Combining the prospective community studies in Tables 2 and 3 would suggest a 3-fold reduction in acute and/or long-term mortality among vaccinated children even though some of the vaccine failures may have been due to inactivated measles vaccines. In the four studies (31,40,49, unpublished) having information on both acute and long-term mortality, mortality was nearly 5-fold lower for the vaccinated cases (mortality ratio= 0.21 (0.13-0.34)). Several hospital or health centre based studies have also compared vaccinated and unvaccinated children and reported that measles vaccinated children had less severe measles infection (50-53). A few community studies from India and PNG have also suggested lower case fatality for vaccinated measles cases (54,55).

In most of the epidemiological studies (Table 2), it was not possible to control for age given the way the data was reported. However, in 6 studies (17, 36, 38, 40, 42, unpublished data) age could be controlled and there was little difference in the case-fatality ratio in the unadjusted analysis (0.27 (0.17-0.42)) and the age-adjusted analysis (0.30 (0.18-0.49)). It could be speculated that vaccinated children had more health-system-compliant mothers and that they therefore had more care and milder infection. However, in many of the original studies, measles vaccine had been provided in community campaigns and not in routine service and vaccination status depended on whether the mother had been around at the time of the campaign and not on any compliance bias (36). In the studies which controlled for background factors, the differential effect of vaccination on the measles case fatality was increased (36,41). Furthermore, several studies have found that “vaccine failures” occur after high intensity of exposure, i.e. “vaccine failures” are more likely to be secondary cases exposed at home (36,37). Since secondary cases have a higher case fatality than index cases (36,37,56), the milder infection among vaccinated children is even more surprising. The possibility that measles vaccinated children have milder disease due to modified immune responses and not merely due to social confounding is strengthened by the many studies showing that measles vaccination is associated with beneficial effects on overall child survival (26,27). If the severity of measles is not the same in vaccinated and unvaccinated children it would strongly affect the estimated benefit of vaccinations at different ages.

Assumption 4: severity of measles is the same whether measles infection is acquired in infancy or later. In the hypothetical EPI model in which all children were vaccinated at a specific age, the unvaccinated measles cases would occur in infancy, before measles vaccination, whereas most "vaccine failures" would occur much later after the first year of life. The epidemiological evidence is consistent in suggesting that the case fatality is higher in infancy than among older children in African community studies (Table 4). These studies suggest around a two-fold higher measles case-fatality in infancy, the case fatality ratio being 1.87 (1.63-2.14). The effect was similar before measles vaccine was introduced in these communities (case fatality ratio=2.04 (1.58-2.63)) (see Studies before the introduction of MV, Table 4). If that was indeed the case, it would be more advantageous to have a few vaccine failures later in life rather than leave infants less than 9 months of age unprotected.

Assumption 5: vaccine failures lead to lack of credibility of the vaccination programme. Apparently it was assumed that African mothers would loose confidence if measles vaccine did not provide complete and life-long immunity. One study from Tanzania stated that acceptance of measles vaccination was low because of the many failures experienced by children vaccinated before 9 months of age but provided no specific information on how data had been collected (63). In contrast, many African mothers have experienced that vaccinated children have mild measles (36). In cultures where mothers have learnt that everybody has to get measles, the advantage of "mild measles" is easy to see whereas it is difficult to "see" complete "life-long protection" if you still expect your child will get measles some day. In the only community study which examined the credibility of the programme in relation to "vaccine failures", we showed that the younger siblings of thought to be "vaccine failures" had a significant higher coverage for measles vaccination (95% (33/35)) than siblings of children who had been successfully vaccinated and not had measles infection (78% (630/809)) (relative risk= 1.21 (1.11-1.32)) (36). Hence, it may have worked the other way around; seeing your child get mild measles after vaccination strengthened the credibility of the programme.

Assumption 6: it had to be a one-dose policy. The main argument advanced for a one-dose policy was that compliance with the second dose was too low (10,13,62,64). This is surprising since others have described that mothers sought vaccination so eagerly that it was impossible to maintain the age eligibility criteria for vaccinations during campaigns (11). It may have been poor information which meant that mothers did not seek the second dose of measles vaccine in some countries. In Guinea-Bissau, we had very good compliance and improved coverage with a two-dose schedule (65). The two-dose group had better protection against measles infection than the one-dose group (65). A two-dose schedule has also been shown to be effective in Niger (66), India (67) and Saudi Arabia (68). Hence, an early two-dose schedule is both feasible and effective.

Only two trials have compared child mortality following two doses of MV, the first being given before 9 months, with mortality after the standard dose of MV at 9 months of age (Table 5). In the small trial from Sudan (69), DTP vaccinations were not controlled and many children received DTP after measles vaccine. DTP administered with or after

measles vaccine has negative effects on female survival (28,71). We therefore conducted a large randomized trial including only children who had received DTP3 before enrolment and therefore would not receive DTP after MV (70). Among children who had not received neonatal vitamin A supplementation (VAS) which interacted negatively with early MV(70), two doses of MV at 4.5 and 9 months of age compared with the current policy of one dose at 9 months of age reduced mortality between 4.5 and 36 months of age with 50% (22-68%) in the per-protocol analysis (Table 5). There was a significant reduction in non-measles related mortality of 45% (14-65%) (70). The combined estimate for the two trials showed that the early two-dose measles vaccination strategy may reduce mortality by as much as 48% (23%-65%) compared with the currently recommended standard dose at 9 months of age. Even if the children receiving neonatal VAS were included, the combined estimate was 31% (9-48%) (Table 5).

The only other study to report mortality after two early doses of MV is a natural experiment from Guinea-Bissau in the early 1980s. Children were vaccinated in annual or biannual campaigns rather than through routine service. Hence, it was possible to compare in an unbiased way the survival of children who happened to be less than 9 months of age when vaccinated and those vaccinated at the recommended age of 9-11 for MV. MV at 4-8 months and a later dose after 9 months compared with one dose of MV at 9-11 months of age was associated with 59% (15-81%) lower mortality between 9 months and 5 years of age (72). Hence, the two-dose studies indicate that MV before 9 months of age is associated with major reductions in child mortality.

The implications of the assumptions for the estimated prevention of measles mortality. We calculated how variations in these six assumptions affect the optimal age of MV in terms of reducing measles mortality (Table 1, Columns 7-10). Using the best estimate that the case fatality rate is one-third lower for vaccinated measles cases than for unvaccinated cases (Tables 2 and 3), the number of estimated measles deaths would have been lowest with general vaccination at 8 months (Column 7). Assuming furthermore that infants have 2-fold higher case fatality than older children (Table 4) the estimated number of measles deaths would have been lowest after vaccination at age 7 months (Column 8). Hence, it might have been better to vaccinate at 7 months of age and have some more vaccine failures later in childhood than to have many unvaccinated cases with high mortality in infancy. Adjusting for the possibility that non-seroconverting vaccinated children have some protection (30), the optimal age for measles immunization in a one-dose strategy would have moved to 6 or 7 months of age (Columns 9 and 10).

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.

Discussion

The main justification for measles vaccination in low-income countries was to reduce child mortality from measles infection (13). However, the policy was never tested for its

effect on survival. The assumptions were believed to be true, and a small seroconversion study was considered sufficient evidence for the policy (4-6). Thirty-five years ago the six assumptions may have appeared self-evident and programmatic decision apparently had to be taken about the optimal age for measles vaccination. However, all assumptions have been contradicted for years but no change has been made in the policy.

Strength and weaknesses

The quality of the data and relative strength of these assumptions can be discussed. There are likely to be a few more studies which were not found with the literature search since several of the studies identified in previous reviews were not found by the search terms. However, many reviews over the last 25 years have covered the areas of community studies of measles infection and the impact of MV so it is unlikely that there would be many studies not included. Furthermore, the estimates from different studies were consistent and it is unlikely that the addition of further studies would have a major impact on the estimates.

The assumed case fatality of measles infection does not matter for the estimated impact of the optimal policy on measles mortality. With another case fatality level the epidemiological arguments about assumptions 2-4 would still have the same relative effects on the number of deaths prevented. However, as evidenced in Tables 2 and 4, most community studies from Africa suggest that the case fatality may have been higher than 4% and the impact of the optimal measles vaccination strategy on overall mortality may therefore have been even larger. Other assumptions may also have been important; for example, the incidence data were from a rural study rather than from an urban area (16). In an urban area the incidence would have been higher at younger ages and it might have been advantageous to vaccinate even earlier. As maternal measles antibody levels have declined in low-income countries (7), earlier vaccination would also have produced better seroconversion rates and it would have been even more advantageous to vaccinate early.

Consistency with previous studies: The non-specific beneficial effects of MV. The conclusion that earlier measles vaccination is likely to have been better for child survival is based on a reconsideration of the programme´s own assumptions about effect on measles mortality. However, what is the evidence for the impact on mortality of measles vaccine before 9 months of age?

Several studies have assessed the impact of measles vaccine before 12 months of age (26,82) but few studies have separately measured the effect on overall mortality of measles vaccination before 9 months of age in an unbiased way (Table 6). In the 1970s, researchers in Congo followed two districts which initially had similar overall mortality and then introduced measles vaccination at 7 months of age in one district (60). Measles vaccination administered at 7 months of age reduced overall mortality between 7 and 21 months of age by 71% (2-91%) compared with the neighbouring district which did not get measles vaccination (60). In the early 1980s in Guinea-Bissau, children were vaccinated in annual or biannual campaigns. Hence, it was possible to compare in a "natural experiment" manner the survival of children who had been measles vaccinated

before 9 months of age and those vaccinated at 9 months of age, the recommended age of measles vaccination. One dose of MV at 4-8 months compared with 9-11 months of age was associated with 31% (-8-54%) lower mortality between 9 months and 5 years of age (72). As mention above the effect was even stronger if they also received a second dose of MV after 9 months of age. During a civil war in Guinea-Bissau in 1998 (73), we followed children who had been randomised to measles vaccination at 6 months of age compared with children who had been randomised to IPV. Due to the war the children did not get the standard measles vaccination at 9 months of age. During the 3 months of intensive fighting when everybody had fled the study area and mortality was high, the measles vaccinated children had 70% (13-92%) lower mortality than the measles-unvaccinated group.

These studies of one dose of MV before 9 months of age as well as the studies of early two-dose MV suggest that the reduction in mortality from MV before 9 months of age is much larger than can be explained by the prevention of measles infection. WHO estimates that measles deaths caused 10% of under-five deaths (83). However all available studies of the mortality impact of MV (24,26,27,82) suggest that the effect of measles immunization on mortality is much greater than expected. There are several reasons that this beneficial effect is a consistent observation and that the effect can not be explained by the prevention of acute measles infection. First, all studies, in which measles vaccine was not administered with DTP, provided strong evidence of a beneficial effect of measles vaccine on overall mortality (26). Second, all studies censoring for measles infection in the survival analysis to estimate the impact on non-measles related mortality found that prevention of measles-specific deaths explained little and the beneficial effect was due to prevention of non-measles related mortality (26,70,82,84). For example, in the per-protocol analysis of the largest randomised trial (70), measles vaccine at 4.5 and 9 months compared with the standard dose at 9 months of age reduced non-measles related mortality significantly for all children and separately for girls. Third, the beneficial effect of measles vaccine is usually stronger for girls than for boys (70,85,86). Since measles mortality is not higher for girls than boys, this observation suggests sex-differential mechanisms related to immune stimulation. Hence, standard measles vaccine may protect against other infections and have a beneficial effect on child survival even when measles is eliminated.

The possible biological explanations for non-specific beneficial effects of MV have not been explored in humans. In animal studies of heterologous immunity, previous stimulation with infections may have a major effect on the capacity to handle a lethal dose of an unrelated infection (87). Two trials form Bissau suggest that the beneficial effect of MV is better for children vaccinated in the presence of maternal measles antibodies than for children having no measurable maternal antibodies at the time of MV (82,88). This may be the mechanism explaining why MV before 9 months of age is better than later.

The optimal age of measles vaccination: optimizing seroconversion or impact on overall child survival. The most unfortunate consequence of not testing the optimal age of measles immunization may have been that the beneficial non-specific effects of

measles vaccine were not detected (26). To the extent MV has non-specific beneficial effects the question of the optimal age of measles vaccination acquires a new meaning. By lowering the age of measles vaccination, children would benefit not only from earlier protection against measles infection but also from the beneficial non-specific effects against non-measles infections and overall child mortality would be reduced. On the other hand, if the age of vaccination is increased, children would benefit less from the non-specific beneficial effects and overall child mortality would increase. Hence, policies optimizing the non-specific effects clash with those designed to enhance seroconversion.

Conclusions: Old assumptions linger on

The supplementary immunization activities (SIA) with measles vaccine has eliminated measles infection in Latin America and reduced the incidence in major ways in the rest of the world (1-3). The world is now planning to eradicate measles infection. With the SIA success in measles control, the optimal age of measles immunization is likely to be considered an irrelevant issue. However, as discussed above, measles vaccine has also non-specific effects which need to be taken into consideration in the planning of vaccination programmes. The prevention of all-cause mortality rather than measles mortality should be the primary objective. The evidence for the current policy – or rather the lack thereof - should be properly reviewed and revised by the global and regional immunization programmes. Otherwise old assumptions about seroconversion rates being the basis for the optimal age of immunisation may linger on and continue to influence policy.

There are major consequences of focusing solely on specific measles mortality. First, as the current policy is mostly determined by our understanding that seroconversion gets better with increasing age, the tendency will be that with improved control of measles infection, age of vaccination will be increased. Following the elimination of measles in Latin America, the recommended age of primary measles immunization was raised to 12 months in 1996 (3). Again this decision was based on assumptions and not on studies documenting the overall effect on morbidity and mortality. Following the success of measles campaigns in other continents it has also been recommended by SAGE (the Strategic Advisory Group of Experts) to increase the age of measles vaccination to 12 months in areas with low levels of measles transmission (89). The underlying assumption about better seroconversion at higher ages may no longer be valid with the decline in maternal antibody levels (7,90). For example, we have obtained 100% seropositivity and 99% protective levels after measles vaccine at 9 months of age with both Schwarz and Edmonston-Zagreb measles vaccine strains in Guinea-Bissau (91).

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 (70,82). Increasing the age of measles vaccine from 9 to 12 months may reduce the beneficial effects in the age group between 9 and 12 months of age in which mortality is still high. The lives lost by not having the non-specific beneficial effects of measles vaccine in the 9-11 months age group could well be more than the lives saved by improved measles control. In a sense the studies of early two-dose MV have shown

precisely that by showing that adding an additional dose of measles vaccine at 4-6 months of age reduced overall mortality (70).

Second, in the current paradigm for control of infectious diseases, the ultimate success in public health is to eradicate the disease and then remove the vaccine to reduce economic costs as happened for smallpox and vaccinia in the 1970s (20). This may happen for measles infection and measles vaccine within the next 10-20 years (92). If measles vaccine has major beneficial non-specific effects (70), to remove measles vaccine or reduce its coverage would increase child mortality levels considerably in low-income countries unless we in the meantime find a vaccine which has all the same beneficial immune stimulating effects as measles vaccine.

After 35 years, it may be time to develop a policy for the optimal age of measles immunization – a policy which is based on evidence about the impact on overall health and child-survival and not only on assumptions about the impact of specific prevention against measles infection. A two-dose measles vaccination strategy, providing measles vaccine at 4.5 months of age, after the three DTP vaccines, and again at 9 months of age, may significantly improve child survival and provide a solid basis of immunity which if necessary can be enhanced by supplementary measles immunisation activities at a later age (7,70). Any future changes in the age of measles immunization due to elimination of measles infection, changes in the epidemiology of measles infection, decline in maternal antibody levels, introduction of new measles vaccines or in the timing of other vaccines should be tested in trials to determine their overall impact on child health.

Contributions*:* PA and HW have been involved in studies of measles vaccination for more than 30 years in West Africa; MLG, CM, CB and AR have been involved in measles vaccination trials since the early 1990s. The first draft was written by PA; all authors contributed to the final version of the paper. PA will act as guarantor of the study.

Conflict of interest: nothing to declare

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Table 1. Projected reduction in measles cases and measles deaths with measles immunization at ages four to ten months. Machakos, Kenya 1974-1981

Expanded Programme on Immunization model (6)						Estimated number of measles deaths in a cohort of 1000 children				
	Column1	Column 2	Column 3	Column 4	Column 5	Column 6	Column 7	Column 8	Column 9	Column 10
	Cumulative measles incidence (%)	Serocon-version from MV (%)	Prevented cases (%)	Vaccine Failures (%)	Cases prior to MV(%)	EPI assumption: Case fatality 4%	Adjusting vaccination status[1]	Adjusting vaccination status and age of infection[2]	Adjusting vaccination status, age of infection, and seronegative 50% protection[3]	Adjusting vaccination status, age of infection, and seronegative 25% protection[3]
Age 4 months	0.5	15	15	85	0	34	11.3	11.3	5.7	8.5
Age 5 months	1.0	35	35	65	0	26	8.6	8.6	4.3	6.5
Age 6 months	2.8	52	51	48	1	19.6	6.8	7.2	**4.0**	5.6
Age 7 months	6.1	72	69	28	3	12.4	4.9	***6.1***	4.3	**5.2**
Age 8 months	9.5	86	79	15	6	8.4	***4.4***	6.8	5.8	6.3
Age 9 months	14.4	95	84	7	9	***6.4***	4.5	8.1	7.7	7.9
Age 10 months	18.6	98	82	4	14	7.2	6.1	11.7	11.5	11.6

Notes: MV=measles vaccine; The estimated number of measles deaths was obtained by multiplying the number of vaccine failures (column 4) and cases prior to MV (column 5) in a cohort of 1000 children by the case fatality rates as indicated in the following notes: 1. Assumption: The relative case fatality ratio is 1/3 for vaccinated versus unvaccinated cases, i.e. 4% for unvaccinated cases and 1.33% for vaccinated cases. 2. Assumption: The relative case fatality ratio is 1/3 for vaccinated versus unvaccinated cases. The case fatality ratio is twice as high for unvaccinated cases occurring in infancy. Hence, the estimated case fatality ratios are 8% for unvaccinated cases occurring in infancy and 1.33% for vaccinated cases. 3. Assumption: Seronegative children had 50% or 25%

protection against measles. Hence, the estimated case fatality ratios are 8% for unvaccinated cases occurring in infancy and 1.33% for vaccinated cases but there were fewer vaccinated cases than indicated in column 4.

Table 2. Relative acute measles case fatality ratio for measles-vaccinated and measles-unvaccinated cases in African prospective community studies and community surveys

Country	Period	Study	Vaccinated cases (%) (deaths/cases)	Unvaccinated cases (%) (deaths/cases)	Measles case fatality ratio
Bissau (36)	1980-82	PCS; urban	9%(5/53)	17%(18/108)	0.58 (0.23-1.49)*
Bissau (36)[1]	*1980-82*	*PCS; urban (only secondary cases)*	*14%(3/21)*	*46%(11/24)*	*0.30 (0.10-0.86)**
Guinea-Bissau (38)	1983-1984	PCS; urban	4%(4/90)	9%(21/234)	0.41 (0.14-1.22)*
Guinea-Bissau (31)	1984-1987	PCS; 2 year follow-up	0% (0/4)	13% (2/16)	0 (0-23.10)
Bissau (39)	1985-1987	PCS; children < 2yrs; urban	5%(1/22)	11%(10/90)	0.41 (0.06-3.03)#
Bissau (unpublished&)	1991	PCS; children < 10 yrs; urban	2%(10/412)	13%(64/478)	0.24 (0.12-0.49)*
Senegal (40)	1987-1994	PCS; rural	0%(0/127)	2%(18/1085)	0 (0-1.94)*
Ghana (41)	1989-1991	PCS; rural; Vitamin A trial with measles surveillance	10%(15/153)	17%(136/808)	OR=0.42 (0.21-0.83) ##
Kenya (17)	1986	SUR; all ages; rural	2%(2/41)	11%(11/98)	0.51(0.08-3.08)*
Kenya (42)	1988	SUR; Children <5yrs; rural	0%(0/23)	10%(18/182)	0 (0-1.54)*
Chad (43)	1993	SUR; rural	0%(0/23)	8%(61/801)	0 (0-2.18)
Niger (44)	2003-2004	SUR**; urban	0.4%(1/286)	6%(29/481)	0.06 (0.01-0.42)
Chad (44)	2004-2005	SUR** ; urban	0.4%(2/494)	8%(18/212)	0.05 (0.01-0.20)
Nigeria (44)	2004-2005	SUR**; rural	9%(1/11)	7%(79/1131)	1.30 (0.20-8.54)
Sudan (45)	2004	SUR;	0.4%(2/556)	1%(7/568)	0.29 (0.06-1.40)
Niger (46)	1991-1992	SUR; rural	17%(20/118)	15%(61/410)	1.14 (0.72-1.81)
Zimbabwe (47)	1980-1989	SUR; urban	2%(8/335)	7%(20/302)	0.36 (0.16-0.81)
Total					0.39 (0.31-0.49)

Sources: Reviews of measles case fatality studies (21-25) and PubMed search for measles mortality/case fatality in vaccinated children (see Supplementary material); & compiled by Henning Andersen shortly before he died.

Notes: PCS= prospective community studies; SUR= community surveys or outbreak investigations; 1. Mortality is high because only secondary cases are included in the analysis. Since this analysis is a subgroup within the larger study, it has not been included in the combined estimate; *Adjusted for age; # adjusted for district; ## adjusted for age, sex, weight-for-age z-score, paternal education and season; ** Mortality was only reported for children with at least 30 days of follow-up whereas the proportion of

vaccinated was reported among all cases. It has been assumed that the proportion vaccinated cases was the same among those with follow-up as among all cases.

Table 3. Relative measles case-fatality ratio for measles-vaccinated and measles-unvaccinated cases in African prospective community studies and community surveys with long-term follow-up

Country	Period	Study; period of follow-up	Vaccinated cases (%) (deaths/persons)	Unvaccinated cases (%) (deaths/persons)	Mortality ratio
Guinea-Bissau (48)[1]	1988	PCS; 5 year follow-up;	4% (1/23)	16% (8/46)	0.25 (0.03-1.88)
Guinea-Bissau (31)	1984-1987	PCS; 2 year follow-up	0% (0/4)	14% (2/14)	0 (0-20.10)
Burundi (49) [2]	1988-1989	SUR; 7 month follow-up	3/1363 person-months	19/2629 person-months	0.30 (0.09-1.03)
Senegal (40)	1987-1994	PCS; 1 year follow-up	0% (0/127)	1% (15/1055)	0 (0-2.32)
Bissau (unpublished&)	1991-1994	PCS; 3 year follow-up	3% (8/319)	9% (29/338)	0.29 (0.14-0.63)
Total					0.27 (0.14-0.50)

Sources: Reviews of measles case fatality studies (21-25) and PubMed search for measles mortality/case fatality in vaccinated children (see Supplementary material); & compiled by Henning Andersen shortly before he died.
Notes: PCS= prospective community studies; SUR= community surveys or outbreak investigations; 1. There was no data on acute case fatality in the present study since the study only included children who had a convalescent sample collected; 2. This study did not report the acute case fatality but only overall mortality for the 7 months of follow-up.

Table 4. Relative measles case fatality ratio for infants and older children in African prospective community studies and community surveys

Country	Period	Type of study	Infants (%) (deaths/cases)	Children 1+ year (%) (deaths/cases)	Measles case-fatality ratio
Studies before the introduction of MV					
Gambia (56)#	1961	PCS; rural	31%(12/39)	13%(47/356)	2.33 (1.36-4.00)
Guinea-Bissau (38)	1979	PCS; Urban	28%(22/79)	14%(55/380)	1.92 (1.25-2.96)
Guinea-Bissau (57)	1980	PCS; Rural	47%(7/15)	21%(31/147)	2.21 (1.18-4.13)
Senegal (37)	1983-86	PCS; Rural	12%(19/165)	6%(79/1335)	1.95 (1.21-3.13)
Studies after introduction of MV					
Kenya (58)	1974-1976	PCS; rural	6%(4/63)	7%(24/361)	0.96 (0.34-2.66)
Kenya (58)	1976-1977	PCS; rural	4%(5/125)	1%(7/540)	3.09 (1.00-9.56)
Kenya (17)	1986	SUR; rural	17%(5/29)	7%(8/110)	2.37 (0.84-6.71)
Kenya (42)	1988	SUR; rural	22%(9/41)	5%(11/207)	4.13 (1.83-9.33)
Senegal (37)	1987-1990	PCS; rural	2%(1/43)	2%(9/598)	1.55 (0.20-11.9)
Senegal (40)	1991-1994	PCS; rural	6%(4/72)	1%(4/499)	6.93 (1.77-27.1)
Guinea-Bissau (59)	1980-1982	PCS; urban	30%(7/23)	9%(10/115)	3.50 (1.49-8.24)
Guinea-Bissau (38)	1983-1984	PCS; urban	9%(5/56)	7%(20/268)	1.20 (0.47-3.05)
Zaire (60)	1974-1977	PCS; urban	6%(12/194)	6%(53/844)	0.99 (0.54-1.81)
Ghana (41)	1989-1991	PCS; rural	21%(28/131)	15%(123/830)	1.44 (1.00-2.08)
Chad (43)	1993	SUR; urban	6%(9/156)	8%(52/668)	0.74 (0.37-1.47)
Niger (61)	2003	SUR; rural	16%(13/83)	9%(79/862)	1.71 (0.99-2.94)
Niger (46)	1991-1992	SUR; rural	40%(16/40)	13%(65/488)	3.00 (1.93-4.67)
Niger (44)	2003-2004	SUR; urban	7%(8/111)	3%(22/656)	2.15 (0.98-4.71)
Chad (44)	2004-2005	SUR; urban	5%(5/97)	2%(15/609)	2.09 (0.78-5.63)
Nigeria (44)	2004-2005	SUR; rural	11%(5/47)	7%(75/1095)	1.55 (0.66-3.66)
Zimbabwe (47)	1980-1989	SUR; rural	13%(13/103)	3%(15/534)	4.49 (2.20-9.16)
Sudan (45)	2004	SUR;	3%(1/36)	1%(9/1108)	3.42 (0.45-26.28)
Longer follow-up than 1 month					
Burundi (49)##	1989	SUR; rural; 7 months follow-up	14%(2/176 person-months)	6%(20/3816 person-months)	2.17 (0.51-9.20)
Gambia (62)	1981	SUR; rural; 9 months follow-up	64%(7/11)	10%(13/124)	6.07 (3.07-12.0)
Total					1.87 (1.63-2.14)

Sources: Reviews of measles case fatality studies (21-25) and PubMed search for community studies of measles mortality/case fatality in infants or by age in Africa (see Supplementary material).
Notes: MV=measles vaccine; PCS=prospective community study, i.e. the population was known before the epidemic and information is likely to have been obtained for all children; SUR= retrospective survey; # The age grouping is 7-12 months and 12-120 months. Measles deaths and total number of children in age group were reported in this study. It has been assumed that all children between 7 and 120 months contracted measles. In this period there were no measles vaccinations available. The last epidemic had occurred 12-13 years earlier; ## The age grouping is 0-8 and 9+ months; ¤ Numbers read from a graph

Table 5. Vaccine efficacy against overall mortality in randomised trials of an early two-dose measles vaccination schedule compared with the standard dose of measles vaccination at 9 months of age

Country and period	Age interval	Comparison (Vaccines)	Administration of DTP	Deaths/person-years or persons	Mortality rate ratio	Comments
Sudan (69) 1989-1992	5-9 months	MV vs Control (Meningococcal A+C)	DTP not given simultaneous with MV but could have been given after MV	1/60.5 vs 6/61.2	0.18 (0.02-1.54)	1st vaccine in 2-dose group was Connaught HTMV and 2nd dose was Schwarz standard MV
	9-36 months	2nd vs 1st MV		7/371.6 vs 7/355.9	0.96 (0.34-2.73)	
	5-36 months				0.60 (0.25-1.45)#	
Guinea-Bissau (70) 2003-2009	4.5-9 months	MV vs Control (no vaccine)	DTP not given simultaneous with MV and after MV; all had DTP3 one month before enrolment	5/398.8 vs 29/821.8	0.33 (0.13-0.86)	Vitamin A supplementation (VAS) at birth is not official policy. Hence, only results for children who did not receive VAS is presented.#
	9-36 months	2nd vs 1st MV		20/2054.4 vs 67/3881.1	0.56 (0.34-0.93)	
	4.5-36 months				0.50 (0.32-0.78)#	

Source: All studies reporting mortality in trials of two doses of measles vaccine (MV) (24,26,27). Only the per-protocol results have been used comparing children who received two doses of MV with those receiving one dose at 9 months. No additional studies of early two-dose measles vaccination reporting impact on mortality were found by PubMed searches (see Supplementary material).
Note: # The combined estimate (Stata) was 0.52 (0.35-0.77); if the children receiving vitamin A at birth were also included, the combined estimate was 0.69 (0.52-0.91).

Table 6. Vaccine efficacy against overall mortality for one dose of standard-titre measles vaccine before 9 months of age

Country	period	Comparison	Results
Early measles vaccination at 7 months of age compared with children unvaccinated community			
Congo (60)	1974-1977	MV administered at 7 months of age; children followed to 21 and 34 months of age. Mortality from 7 to 21 months of age for vaccinated children (3/230.5 pyrs) compared with unvaccinated children from control area (21/470.7 pyrs)	MRR for 7 to 21 months =0.29 (0.09-0.98) MRR for 7 to 34 months =0.52 (0.21-1.27)
Comparing MV at 4-8 months versus MV at 9-11 months of age			
Guinea-Bissau (72)	1980-1982	Natural experiment: MV at 4-8 versus MV at 9-11 mo compared from 9 to 60 months of age	MRR (MV-4-8mo/MV-9-11mo) 0.69 (0.46-1.08)
Comparing children randomsied to MV at 6 months versus IPV at 6 months during a war situation			
Guinea-Bissau (73)	1998	Children were randomised to MV (4/214) or inactivated polio vaccine (11/219) at 6 months of age. Due to a war they did not received the planned MV at 9 mo. Follow-up for 3 months in a war situation	70% (13 to 92)

Sources: All studies examining the general effect of standard measles vaccine (MV) on child survival (as compiled by all available reviews (24,26,27)) have been screened for information on measles vaccination before 9 months of age. There have been several other studies of the impact of MV before 12 months of age on child survival (74-81) but most of these studies could not distinguish the effect of MV before 9 months of age. However, all studies suggested that early MV had a better effect on child survival than later MV. No additional studies of one-dose measles vaccination/immunization before 9 months of age reporting impact on mortality were found by PubMed searches (see Supplementary material). Studies of medium and high-titre measles vaccines have not been included (28,29)

The optimal age of measles immunization in low-income countries: 35 years with a policy based on flawed assumptions

Search strategy: For each assumption we used existing reviews and in December 2011 we made a PubMed search for relevant papers as described below. The title and abstract of papers in English, French, Portuguese, Spanish, German and Scandinavian languages was assessed to ascertain whether the paper was potentially relevant. Potentially relevant papers were read. The large majority of papers were not from Africa, were reviews or case reports and not community based studies, had no information on mortality, or the vaccine was not single dose measles vaccine.

Assumption 1: children who seroconvert to measles vaccine have absolute protection against measles infection.
We searched for "measles infection seropositive vaccinated children" (N=12) and "measles vaccine failure" (N=318). There are many case reports that this is not true but no African community study.

Assumption 2: vaccinated children who do not seroconvert are fully susceptible to measles infection.
We searched for "measles infection seronegative vaccinated children" (N=13) and "measles vaccine failure" (N=318). This provided only one relevant reference (30).

Assumption 3: severity of measles infection in vaccinated children ("vaccine failures") and unvaccinated children is the same.
We searched for "measles mortality vaccinated children" (N=143), "measles vaccine mortality" (N=775), "measles case fatality" (N=161) and "measles vaccine failure" (N=318). Relevant studies included in Tables 2 and 3.

Assumption 4: severity of measles is the same whether measles infection is acquired in infancy or later.
We searched for "measles case fatality" (N=161) and "measles mortality/death Africa" (N=620). Relevant studies included in Table 4.

Assumption 5: vaccine failures lead to lack of credibility of the vaccination programme.
We searched "measles vaccine failure" (N=318) and "measles vaccine/vaccination/immunisation credibility" (N=2). This search produced one paper dealing with the relationship between "vaccine failure" and the acceptance or credibility of measles vaccination (63). One study was known from our own research (36).

Assumption 6: it had to be a one-dose policy.
We used the reviews of measles vaccination studies (24,26,27,82) and search papers on *Two/2 dose measles vaccine trial" (N=144), "Two/2 dose measles vaccination/immunization and mortality/death" (N=108) and "early measles vaccination/immunization mortality/death" (N=123). This produced only two African trials of the effect on child survival of a 2-dose measles vaccinations schedule compared with a 1-dose schedule (see Table 5).

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE : The optimal age of measles immunization in low-income countries: 35 years with a policy based on flawed assumptions			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Only in abstract, page 2
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4-5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5, supplementary annex
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary annex
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Supplementary annex
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Supplementary annex
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Supplementary annex
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6

PRISMA 2009 Checklist

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency ($e.g., I^2$) for each meta-analysis.	6

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Discussion page 10
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Supplementary annex
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Tables 2-6
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	5,7
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Tables 2-6
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Pages 6-9
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	7,10
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	3,10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	12-14
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	14

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The optimal age of measles immunization in low-income countries: 35 years with a policy based on flawed assumptions

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The optimal age of measles immunization in low-income countries: 35 years with a policy based on flawed assumptions

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Abstract

Background and objective The current policy of measles vaccination at 9 months of age in low-income countries was decided in the mid-1970s following a study of seroconversion at different ages in Kenya. The policy was not tested for its overall impact on child survival but was based on six assumptions. We examined the empirical evidence for these assumptions.

Data sources and methods Existing reviews and additional literature search of African community studies of measles infection.

Main outcome The predicted effect on measles and all-cause mortality.

Results All assumptions were flawed. Most notably, seronegative vaccinated children may have considerable protection against measles infection. Second, vaccinated measles cases ("vaccine failures") have around one-third the case fatality of unvaccinated measles cases. Third, infant measles cases have around 2-fold higher case fatality than older cases. Fourth, "vaccine failures" did not lead to lack of confidence because the children had milder measles infection. Fifth, in the randomised trials of early two-dose measles vaccination compared with one dose at 9 months of age, mortality was significantly reduced until 3 years of age. Had these factors been studied, the optimal age for a single dose of measles vaccine would probably have been 6 or 7 months, leading to more mild "vaccine failures" among older children, but fewer severe unvaccinated cases among infants. Furthermore, the two-dose trials indicate that measles vaccine reduces mortality from other causes than measles infection.

Conclusions Many lives may have been lost by not determining the optimal age of measles vaccination. The current measles vaccination policy is still based on assumptions about seroconversion and it is now recommended to increase the age of measles vaccination to 12 months in countries with limited measles transmission. Based on current evidence this policy is likely to increase child mortality.

Article summary

Article focus

- An empirical analysis of the six assumptions underlying the current measles vaccination policy for low-income countries.
- Determine the implications for child survival of not testing the optimal measles vaccination policy.

Key messages

- All six assumptions were flawed; most important were the assumptions that vaccinated children who did not seroconvert are fully susceptible to measles infection, that the severity of measles is the same in vaccinated cases ("vaccine failures") and in unvaccinated children, that the severity of measles infection is the same in infancy or later, and that it had to be a one-dose programme.
- The current evidence suggests that the optimal age for a single dose of measles vaccine would probably have been 6 or 7 months of age had the policy been tested.
- An early two-dose schedule at 4-5 months and 9 months of age would have been even better in terms of reducing child mortality.

Strength and limitations

- The current measles vaccination policy for low-income countries is not based on any evidence about the impact on overall child survival.
- There are few studies testing some of the assumptions. However, for the two key assumptions relating to severity of measles in vaccinated infants and children there is ample evidence which suggests that measles is less severe in vaccinated cases.

Introduction

With the spectacular success in measles control in the last 10-15 years(1-3) and the current policy to move ahead with elimination and eventually eradication of measles infection (4), there is now a discussion of when to introduce the second dose of measles vaccine (5). However, few people realize that the key policy of vaccinating against measles at 9 months of age in low-income countries is not based on evidence documenting the optimal age of measles vaccination to reduce overall child mortality.

In the 1970s policy makers found it necessary to formulate a common policy for low-income countries (6-8) since many donors and scientists at the time questioned the value of measles vaccination. Measles infection was believed to kill mainly malnourished children likely to die of other infections if not from measles and hence some people thought that measles vaccine would not reduce overall mortality, but merely change the cause of death (9-11). The policy makers' definition of the optimal age of measles vaccination of 9 months was based on a number of assumptions (6-8). Though these assumptions for vaccinating at age 9 months were not subsequently substantiated the policy has remained in effect. Recently, though, it has been recommended that primary measles vaccination should be at 12 months of age in countries where measles infection has been controlled (12).

Before the global policy is changed it is timely to examine the empirical basis for the assumptions underlying the current policy. Since these assumptions have not been research issues we have had to use a search strategy including review articles and case reports to assess the validity of the original assumptions (see supplementary material). The present analysis suggests that all these assumptions were flawed. Had the policy been tested in randomised trials measuring the impact on mortality of vaccination at different ages it is likely that the age of measles vaccination had been changed, with the result that the measles vaccination programme had had a much larger effect on child survival in low-income countries.

The optimal age of measles immunization: Six assumptions

In the first measles vaccination campaigns in West and Central Africa in the 1960s children were targeted from 6 months of age (13-17). Initially it was thought that it would be sufficient to conduct campaigns every 2nd or 3rd year to control measles. However, the epidemiologists soon learned that shorter intervals of 6 or 12 months between campaigns were necessary to control measles. In the 1970s, routine vaccination programmes were introduced and the optimal age of routine measles vaccination was debated (18-20). Following the experience with the campaigns, several African countries recommended measles vaccination at 6, 7 or 8 months of age. A study sponsored by the Ministry of Health in Kenya and WHO assessed the seroconversion rates at different ages between 5 and 12 months and recommended measles vaccination at 7½ months of age (21). For several years measles vaccine was administered at 8 months of age in Kenya (22). Similar studies were conducted in Latin America (23). Since some of those vaccinated at 6 months were not protected some countries and many researchers recommended a second dose at 9 months of age or later (20,24). However, there were fears that early vaccination

would produce too many vaccine failures and a one-dose programme was considered necessary because mothers would not bring their children back for a second dose (15,25). Therefore, the Expanded Programme on Immunization (EPI) recommended a one-dose policy (6-8,18). In 1980, the Global Advisory Group of EPI endorsed this policy and recommended measles vaccination as early as possible after 9 months of age (7).

The recommendation was based on the belief that the expected reduction in mortality could be computed from seroconversion rates (18,26) and the policy was justified several times by analyses of the seroconversion data from Kenya (6,8). In these analyses it was assumed that seroconversion was associated with full protection against measles infection (*assumption 1*) and that non-seroconversion was associated with full susceptibility to measles infection (*assumption 2*). As shown in Table 1 (Column 2), the data from Kenya (21) showed that seroconversion increased with age. This was not unexpected since the calculation of this measure (a fourfold or more increase over baseline) is dependent on level of maternal antibody which wanes as the child ages. Based on cumulative measles incidence figures (Column 1), it was calculated how many measles cases had been prevented assuming everybody was vaccinated at a specific age (Column 3), how many "vaccine failures" would occur after the age of vaccination (Column 4) and how many cases would occur before the specific age of vaccination (Column 5). In making these calculations it was assumed that "vaccine failures" and unvaccinated measles cases were equally severe (*assumption 3*) and that it did not matter whether measles was acquired in infancy or later in childhood (*assumption 4*). Vaccination at 8, 9, and 10 months of age prevented roughly the same proportion of cases, between 79% and 84% (Column 3) (6,8). Vaccination at 8 month resulted in considerably more vaccine failures (15%) than vaccination at 9 months (7%). Since vaccine failures were assumed to jeopardize the credibility of the measles immunization programme (*assumption 5*) (6,8,18), it was concluded that the optimal age for administration of measles vaccine would be 9 months. At the time the EPI assumed that the case fatality in measles infection was 4% in Africa and it will be seen in Column 6 that the number of estimated measles deaths in a birth cohort of a 1000 children would indeed be lowest (between 6.4 and 8.4) for vaccination at 8-10 months of age. In making this analysis of the effect of only one dose of measles vaccine (6,8), the EPI assumed that a two-dose policy was not feasible or unjustified (*assumption 6*).

Methods

Selection of studies. We looked for empirical evidence in community studies to support or refute these assumptions. The original policy was mainly justified in relation to the epidemiology of measles infection in Africa where the case fatality was clearly higher than in other regions (27-31). Most community studies of measles infection are indeed from Africa and we have therefore restricted the analyses and the tables 2-4 to the African studies. These tables are believed to be exhaustive for Africa and they are not contradicted by community studies from Latin America and Asia. For the analysis of the impact of measles vaccination on child mortality we included all studies from Asia and Latin America.

The search strategy has been defined in the supplementary material. Since there are few specific studies to test the six assumptions we have had to use case reports of measles outbreaks to assess their validity. Over the last 20-25 years, several reviews of community studies of the measles case fatality compiled studies of relevance for particularly assumption three and four (27-31). Furthermore, as specified in the supplementary material, we made PubMed searches for additional publications relevant for all assumptions. We included one unpublished report from a large epidemic in Bissau in 1991-1992 which has remained unpublished because the physician (Henning Andersen) handling the epidemic died tragically in an accident shortly after the epidemic.

We distinguished between prospective community studies and surveys retrospectively assessing events since the precision of information on vaccination status and age presumably is better in prospective studies. Though hospital and health centre studies may have data on the severity of measles infection by vaccination status or age, we have not included these studies in the analysis since biased admission for some groups might have made the result non-representative.

Since the analysis of the assumptions suggested that measles vaccination before 9 months of age could be beneficial, we assessed the empirical evidence from studies which assessed the effect of early measles vaccination on mortality. Again we used all reviews of community studies and trials assessing the impact of measles vaccination on child mortality (30,32-35). Additional PubMed searches for studies comparing the mortality of measles vaccinated and unvaccinated children did not identify further studies. As explained in the footnote to table 6, we have emphasised the studies in which inactivated vaccines were not administered simultaneously with MV or after MV as such combination or sequences can have a negative effect on child survival (34,36).

Statistical analyses. The Mantel-Haenszel weighted relative risk stratifying for study or age groups was used to estimate common trends.

Ethics. Since the study is based on review of existing data, approval from an ethical committee was not needed.

Results

Assumption 1: children who seroconvert to measles vaccine have absolute protection against measles infection. A number of smaller studies have documented that a few children do get measles after having seroconverted (37-40). Hence, seroconversion does not give absolute protection. There are no general epidemiological studies from Africa and it is therefore difficult to estimate the proportion of children who get measles in spite of having seroconverted, but since no large series have been reported it is likely to be small.

Assumption 2: vaccinated children who do not seroconvert are fully susceptible to measles infection. In a study in Senegal, vaccinated children who were seronegative when exposed to measles infection at home had a 49% (95% CI 21-68%) protection against clinical disease compared with unvaccinated seronegative children exposed under

similar conditions (37). It is possible that the children had acquired vaccine-induced measles antibodies earlier but subsequently lost them. Based on the literature search, no other study has tested the susceptibility of vaccinated "seronegative" children. If approximately half the seronegative children have clinical protection it would have major consequences for the calculation of the optimal age of measles vaccine. Cellular immunity may be obtained without having measurable antibodies (41). There is also good evidence from studies of hepatitis B vaccination that antibody concentration wane with time but the majority of older seronegative children if infected are protected from chronic carriage and its damaging consequences (42).

The concept of seroconversion to compare the effect of vaccination at different age is in itself problematic. Seroconversion is not the same as seroprotection and the use of the term inevitably disadvantages data from studies that have vaccinated at earlier ages when maternal antibodies are still present. Thus a child immunized at 6 months of age when the maternal antibody level is say 62.5 mIU may fail the test for conversion (a four-fold increase) yet still have a protective level of 125 mIU at 9 months of age.

Assumption 3: severity of measles infection in vaccinated children ("vaccine failures") and unvaccinated children is the same. The EPI perceived "vaccine failures" as due to the vaccine being inactivated by improper storage and handling or due to neutralization of the vaccine by maternal antibodies (16,19). Hence, it was assumed that these children were fully susceptible to measles infection. However, many epidemiological studies in the 1980s and 1990s suggested that measles vaccinated children who contracted measles infection had milder disease (43,44). This would suggest that the children had partial measles immunity, not enough to protect them but enough to modify the severity of the disease. In the community studies of the acute measles case fatality shown in Table 2, the measles case fatality was 2 to 5-fold lower for vaccinated cases ("vaccine failures") than for unvaccinated children with measles infection. The effect was similar in the prospective community studies (case-fatality ratio=0.37 (0.27-0.52)) and the retrospective surveys (case-fatality ratio=0.41 (0.29-0.56)).

All studies with relevant data were included in Table 2 irrespective of whether vaccine efficacy (VE) against measles infection was high or substandard. In several studies, the VE was not high but nonetheless the vaccine appeared to have had an effect; for example, in Kenya VE was only 18% but measles-vaccinated children who developed measles had still 2-fold lower measles mortality than measles unvaccinated children (Table 2). Only one community survey from Niger reported that measles vaccine was not particularly effective against measles infection and that there was no effect of vaccination on the case fatality in measles infection (53).

A few studies followed the children for longer than the one month which is the normal time limit for acute measles deaths. The long-term trend was the same with considerable better survival among vaccinated than unvaccinated children after measles infection (Table 3). Combining the prospective community studies in Tables 2 and 3 would suggest a 3-fold reduction in acute and/or long-term mortality among vaccinated children even though some of the vaccine failures may have been due to inactivated measles vaccines.

In the four studies (38,47,56, unpublished) with information on both acute and long-term mortality, mortality was nearly 5-fold lower for the vaccinated cases (mortality ratio= 0.21 (0.13-0.34)). Several hospital or health centre based studies have also compared vaccinated and unvaccinated children and reported that measles vaccinated children had less severe measles infection (57-59). A few community studies from India and Papua New Guinea have also suggested lower case fatality for vaccinated measles cases (60,61).

In most of the epidemiological studies (Table 2), it was not possible to control for age given the way the data was reported. However, in 6 studies (22, 43, 45, 47, 49, unpublished data) age could be controlled and there was little difference in the case-fatality ratio in the unadjusted analysis (0.27 (0.17-0.42)) and the age-adjusted analysis (0.30 (0.18-0.49)). It could be speculated that vaccinated children had more health-system-compliant mothers and that they therefore had more care and milder infection. However, in many of the original studies from the 1980s, measles vaccine had been provided in community campaigns and not in routine service and vaccination status depended on whether the mother had been around at the time of the campaign and not on bias (43). In the studies which adjusted for background factors, the differential effect of vaccination on the measles case fatality was actually increased (43,48). Furthermore, several studies have found that "vaccine failures" occur after high intensity of exposure, i.e. "vaccine failures" are more likely to be secondary cases exposed at home (43,44). Since secondary cases have a higher case fatality than index cases (43,44,62), the milder infection among vaccinated children is even more surprising. The possibility that measles vaccinated children have milder disease due to modified immune responses and not merely due to social confounding is strengthened by the many studies showing that measles vaccination is associated with beneficial effects on overall child survival (32,33). If the severity of measles is not the same in vaccinated and unvaccinated children it would strongly affect the estimated benefit of vaccinations at different ages.

Assumption 4: severity of measles is the same whether measles infection is acquired in infancy or later. In the hypothetical EPI model in which all children were vaccinated at a specific age, the unvaccinated measles cases would occur in infancy, before measles vaccination, whereas most "vaccine failures" would occur much later after the first year of life. The epidemiological evidence is consistent in suggesting that the case fatality is higher in infancy than among older children in African community studies (Table 4). These studies suggest around a two-fold higher measles case-fatality in infancy, the case fatality ratio being 1.87 (1.63-2.14). The effect was similar before measles vaccine was introduced in these communities (case fatality ratio=2.04 (1.58-2.63)) (see Studies before the introduction of MV, Table 4). If that was indeed the case, it would be more advantageous to have vaccine failures later in life rather than leave infants less than 9 months of age unprotected.

Assumption 5: vaccine failures lead to lack of credibility of the vaccination programme. Apparently it was assumed that African mothers would loose confidence if measles vaccine did not provide complete and life-long immunity. One study from Tanzania stated that acceptance of measles vaccination was low because of the many failures experienced by children vaccinated before 9 months of age but provided no

specific information on how data had been collected (69). In contrast, many African mothers have experienced that vaccinated children have mild measles (43). In cultures where mothers have learnt that everybody has to get measles, the advantage of "mild measles" is easy to see whereas it is difficult to "see" complete "life-long protection" if you still expect your child will get measles some day. In the only community study which examined the credibility of the programme in relation to "vaccine failures", we showed that the younger siblings of "vaccine failures" had a significant higher coverage for measles vaccination (95% (33/35)) than siblings of children who had been successfully vaccinated and not had measles infection (78% (630/809)) (relative risk= 1.21 (1.11-1.32)) (36). Hence, it may have worked the other way around; seeing your child get mild measles after vaccination strengthened the credibility of the programme.

Assumption 6: it had to be a one-dose policy. The main argument advanced for a one-dose policy was that compliance with the second dose was too low (15,18,68,70). This is surprising since it has been described that mothers sought vaccination so eagerly that it was impossible to maintain the age eligibility criteria for vaccinations during campaigns (16). The reason why mothers did not seek the second dose of measles vaccine in some countries may have been poor information. In Guinea-Bissau, we had very good compliance and improved overall coverage with a two-dose schedule (71). The two-dose group had better protection against measles infection than the one-dose group (71). A two-dose schedule has also been shown to be effective in Niger (72), India (73) and Saudi Arabia (74). Hence, a two-dose schedule is both feasible and effective.

Only two trials have compared child mortality following two doses of MV (the first being given before 9 months) with mortality after the standard dose of MV (at 9 months of age) (Table 5). In a small trial from Sudan (75), DTP vaccinations were not controlled and many children received DTP after measles vaccine. DTP administered with or after measles vaccine has negative effects on female survival (34,36). We therefore conducted a large randomized trial including only children who had received DTP3 before enrolment and therefore would not receive DTP after MV (76). Among children who had not received neonatal vitamin A supplementation (VAS) which interacted negatively with early MV(76), two doses of MV at 4.5 and 9 months of age compared with the current policy of one dose at 9 months of age reduced mortality between 4.5 and 36 months of age by 50% (22-68%) in the per-protocol analysis (Table 5). There was a significant reduction in non-measles related mortality of 45% (14-65%) (76). The combined estimate for the two trials showed that the early two-dose measles vaccination strategy may reduce mortality by as much as 48% (23%-65%) compared with the currently recommended standard dose at 9 months of age. Even if the children receiving neonatal VAS were included, the combined estimate was 31% (9-48%) (Table 5).

The only other study to report mortality after two doses of MV is a natural experiment from Guinea-Bissau in the early 1980s. Children were vaccinated in annual or biannual campaigns rather than through routine service. Hence, it was possible to compare in an unbiased way the survival of children who happened to be less than 9 months of age when vaccinated and those vaccinated at the recommended age of 9-11 for MV. MV at 4-8 months and a later dose after 9 months compared with one dose of MV at 9-11 months

of age was associated with 59% (15-81%) lower mortality between 9 months and 5 years of age (77). Hence, the two-dose studies indicate that a two-dose policy providing the first dose of MV before 9 months of age is associated with major reductions in child mortality.

The implications of the assumptions for the estimated prevention of measles mortality. We calculated how variations in these six assumptions affect the optimal age of MV in terms of reducing measles mortality (Table 1, Columns 7-10). Using the best estimate that the case fatality rate is one-third lower for vaccinated measles cases than for unvaccinated cases (Tables 2 and 3), the number of estimated measles deaths would have been lowest with general vaccination at 8 months (Column 7). Assuming furthermore that infants have 2-fold higher case fatality than older children (Table 4) the estimated number of measles deaths would have been lowest after vaccination at age 7 months (Column 8). Hence, it might have been better to vaccinate at 7 months of age and have some more vaccine failures later in childhood than to have many unvaccinated cases with high mortality in infancy. Adjusting for the possibility that non-seroconverting vaccinated children have some protection from cellular immunity or low levels of antibodies (37), the optimal age for measles immunization in a one-dose strategy would have moved to 6 or 7 months of age (Columns 9 and 10).

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 (71-76,78). Hence, an early dose at 4-6 months of age and a second dose at 9 months of age would have eliminated virtually all measles mortality and significantly reduced mortality from other causes as well..

Discussion

The main justification for measles vaccination at 9 months of age in low-income countries was to reduce child mortality from measles infection (18). However, the policy was never tested for its effect on survival. The policy was based on assumptions which were believed to be true, and a small seroconversion study (6-8). Thirty-five years ago the six assumptions appeared self-evident and programmatic decisions had to be taken about the optimal age for measles vaccination. However, though all assumptions have been contradicted for years no change has been made in the policy.

Strength and weaknesses

Since the six assumptions have not been research issues there are few studies conducted specifically with these topics in mind. We have therefore had to use a search strategy including review articles and case reports to find studies to assess the validity of the original assumptions. There may be a few more studies which were not found with the literature search since several of the studies identified in previous reviews were not found by the search terms. However, many reviews over the last 25 years have covered the areas of community studies of measles infection and the impact of MV on mortality so it is unlikely that there would be many studies not included. Furthermore, the estimates from different studies were consistent and it is unlikely that the addition of further studies would have a major impact on the estimates.

The assumed case fatality of measles infection does not matter for the estimated impact of the optimal policy on measles mortality. With another case fatality level the epidemiological arguments about assumptions 2-4 would still have the same relative effects on the number of deaths prevented. However, as evident in Tables 2 and 4, most community studies from Africa suggest that the case fatality may have been higher than 4% and the impact of the optimal measles vaccination strategy on overall mortality may therefore have been even larger. Other assumptions may also have been important; for example, the incidence data were from a rural study rather than from an urban area (21). In an urban area the incidence would have been higher at younger ages and it might have been advantageous to vaccinate even earlier. As maternal measles antibody levels have declined in low-income countries (78), earlier vaccination would also have produced better seroconversion rates and it would have been even more advantageous to vaccinate early.

Consistency with previous studies: The non-specific beneficial effects of MV. The conclusion that earlier measles vaccination is likely to have been better for child survival is based on a reconsideration of the programme´s own assumptions about effect on measles mortality. However, what is the empirical evidence for the impact on mortality of measles vaccine before 9 months of age?

In marked contradiction to the original fear that children dying of measles would just die of something else and that measles vaccination would therefore only change the cause of death but not the level of mortality (9-11), all subsequent studies measuring the effect on survival have found marked benefit from measles vaccination (32,33,36,77,79-88). Several studies have assessed the impact of measles vaccine before 12 months of age (30,32,33) but few studies have separately measured the effect on overall mortality of measles vaccination before 9 months of age in an unbiased way (Table 6). In the 1970s, researchers in Congo followed two districts which initially had similar overall mortality levels and then introduced measles vaccination at 7 months of age in one district (11). Measles vaccination administered at 7 months of age reduced overall mortality between 7 and 21 months of age by 71% (2-91%) compared with the neighbouring district which did not get measles vaccination (60). In the early 1980s in Guinea-Bissau, children were vaccinated in annual or biannual campaigns. Hence, it was possible to compare in a "natural experiment" manner the survival of children who had been measles vaccinated before 9 months of age and those vaccinated at 9 months of age, the recommended age of measles vaccination. One dose of MV at 4-8 months compared with 9-11 months of age was associated with 31% (-8-54%) lower mortality between 9 months and 5 years of age (77). As mention above the effect was even stronger if they also received a second dose of MV after 9 months of age. During a civil war in Guinea-Bissau in 1998 (79), we followed children who had been randomised to measles vaccination at 6 months of age compared with children who had been randomised to inactivated polio vaccine (IPV). Due to the war the children did not get the standard measles vaccination at 9 months of age. During the 3 months of intensive fighting when everybody had fled the study area and mortality was high, the children vaccinated against measles at 6 months of age had 70% (13-92%) lower mortality than the unvaccinated group.

These studies of one dose of MV before 9 months of age as well as the studies of early two-dose MV mentioned above suggest that the reduction in mortality from MV before 9 months of age is much larger than can be explained by the prevention of measles infection. WHO estimates that measles deaths caused 10% of under-five deaths (89). However all available studies of the mortality impact of MV (30,32,33) suggest that the effect of measles immunization on mortality is much greater than expected. This beneficial effect is a consistent observation and it can not be explained by the prevention of acute measles infection. First, all studies, in which measles vaccine was not administered with DTP, provided strong evidence of a beneficial effect of measles vaccine on overall mortality (32). Second, all studies censoring for measles infection in the survival analysis to estimate the impact on non-measles related mortality found that prevention of measles-specific deaths explained little and the beneficial effect was due to prevention of non-measles related mortality (32,76,88,90). For example, in the per-protocol analysis of the largest randomised trial (76), measles vaccine at 4.5 and 9 months compared with the standard dose at 9 months of age reduced non-measles related mortality significantly for all children. Third, the beneficial effect of measles vaccine is usually stronger for girls than for boys (76,91,92). Since measles mortality is not higher for girls than boys, this observation suggests sex-differential mechanisms related to immune stimulation. Hence, standard measles vaccine may protect against other infections and have a beneficial effect on child survival even when measles is eliminated.

Though the focus here has been on MV administered before 9 months of age there is also a considerable number of studies indicating that MV administered after 9 months of age have non-specific beneficial effects (32,80-85, 90, 93).

The possible biological explanations for non-specific beneficial effects of MV have not been explored in humans. In animal studies of heterologous immunity, previous stimulation with infections may have a major effect on the capacity to handle a lethal dose of an unrelated infection (94). Two trials from Bissau suggest that the beneficial effect of MV is better for children vaccinated in the presence of maternal measles antibodies than for children having no measurable maternal antibodies at the time of MV (88). This may also help explain why MV before 9 months of age is better than later vaccination.

The optimal age of measles vaccination: optimizing seroconversion or impact on overall child survival. The most unfortunate consequence of not testing the optimal age of measles immunization may have been that the beneficial non-specific effects of MV were not detected (32). To the extent MV has non-specific beneficial effects the question of the optimal age of measles vaccination acquires a new meaning. By lowering the age of measles vaccination, children would benefit not only from earlier protection against measles infection but also from the beneficial non-specific effects against non-measles infections and overall child mortality would be reduced. On the other hand, if the age of vaccination is increased, children would benefit less from the non-specific beneficial effects and overall child mortality would increase. Hence, policies optimizing the non-specific effects clash with those designed to enhance seroconversion.

Conclusions: Old assumptions linger on

The supplementary immunization activities (SIA) with measles vaccine has eliminated measles infection in Latin America and reduced the incidence in major ways in the rest of the world (1-3). The world is now planning to eliminate and eventually eradicate measles infection (4). With the SIA success in measles control, the optimal age of measles immunization is likely to be considered an irrelevant issue. However, as discussed above, measles vaccine has also non-specific effects which need to be taken into consideration in the planning of vaccination programmes. The prevention of all-cause mortality rather than measles mortality should be the primary objective. In a culture which advocates evidence-based policies (4), the evidence for the current measles vaccination policy – or rather the lack thereof - should be properly reviewed and revised by the global and regional immunization programmes. Otherwise old assumptions about seroconversion rates being the basis for the optimal age of immunisation may linger on and continue to influence policy.

There are major consequences of focusing solely on specific measles mortality. First, as the current policy is mostly determined by our understanding that seroconversion gets better with increasing age, the tendency will be that with improved control of measles infection, age of vaccination will be increased. Following the elimination of measles in Latin America, the recommended age of primary measles immunization was raised to 12 months in 1996 (3). Again this decision was based on assumptions and not on studies documenting the overall effect on morbidity and mortality. Following the success of measles campaigns in other continents it has also been recommended by SAGE (the Strategic Advisory Group of Experts) to increase the age of measles vaccination to 12 months in areas with low levels of measles transmission (5,12). The underlying assumption about better seroconversion at higher ages may no longer be valid with the decline in maternal antibody levels (78,95). For example, we have obtained 100% seropositivity and 99% protective levels after measles vaccine at 9 months of age with both Schwarz and Edmonston-Zagreb measles vaccine strains in Guinea-Bissau (96).

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 (11,32,38,75-79,88). There is a tendency to dismiss these observations because randomised trials with overall mortality as an outcome have to date only been conducted in Guinea-Bissau and it is therefore claimed that the global health community has to wait for verification elsewhere (97). However, the non-specific beneficial effects of MV have been shown in several other countries with high childhood mortality. For example, in a cross-over design, Shann showed that girls receiving standard measles vaccine at 9-10 months of age in five randomised trials in Sudan, Gambia, Senegal and Guinea-Bissau had 47% lower mortality through childhood than control children who received an inactivated vaccine at 9-10 months of age (93). Since the control children had received MV before 9 months of age and did not get measles, the difference in mortality was a non-specific beneficial effect not related to prevention of measles infection. Increasing the age of measles vaccine from 9 to 12 months may reduce the beneficial effects in the age group between 9 and 12 months of age in which mortality is still high. Thus the lives

lost by this change of schedule could well be more than the lives saved by improved measles control (76).

Second, in the current paradigm for control of infectious diseases, the ultimate success in public health is to eradicate the disease and then remove the vaccine to reduce economic costs as happened for smallpox in the 1970s (26). This may happen for measles infection within the next 10-20 years (98). If measles vaccine has major beneficial non-specific effects (76), to remove measles vaccine or reduce its coverage would increase child mortality levels considerably in low-income countries unless we in the meantime find a vaccine which has all the same beneficial effects as measles vaccine.

After 35 years, it is time to develop a policy for the optimal age of measles immunization. This policy needs to be based on evidence about the impact on overall health and child-survival and not only on assumptions about the impact of specific prevention against measles infection. A two-dose measles vaccination strategy, providing measles vaccine at 4.5 months of age, after the three DTP vaccines, and again at 9 months of age, may significantly improve child survival and provide a solid basis of immunity which if necessary can be enhanced by supplementary measles immunisation activities at a later age (76,78). Any future changes in the age of measles immunisation due to elimination of measles infection, changes in the epidemiology of measles infection, decline in maternal antibody levels, introduction of new measles vaccines or in the timing of other vaccines should be tested in trials to determine their overall impact on child health.

Contributions*:* PA and HW have been involved in studies of measles vaccination for more than 30 years in West Africa; MLG, CM, CB and AR have been involved in measles vaccination trials since the early 1990s. The first draft was written by PA; all authors contributed to the final version of the paper. PA will act as guarantor of the study.

Conflict of interest: nothing to declare

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Table 1. Projected reduction in measles cases and measles deaths with measles immunization at ages four to ten months. Machakos, Kenya 1974-1981

Expanded Programme on Immunization model (8)						Estimated number of measles deaths in a cohort of 1000 children				
	Column1	Column 2	Column 3	Column 4	Column 5	Column 6	Column 7	Column 8	Column 9	Column 10
	Cumulative measles incidence (%)	Serocon-version from MV (%)	Prevented cases (%)	Vaccine Failures (%)	Cases prior to MV(%)	EPI assumption: Case fatality 4%	Adjusting vaccination status[1]	Adjusting vaccination status and age of infection[2]	Adjusting vaccination status, age of infection, and seronegative 50% protection[3]	Adjusting vaccination status, age of infection, and seronegative 25% protection[3]
Age 4 months	0.5	15	15	85	0	34	11.3	11.3	5.7	8.5
Age 5 months	1.0	35	35	65	0	26	8.6	8.6	4.3	6.5
Age 6 months	2.8	52	51	48	1	19.6	6.8	7.2	**4.0**	5.6
Age 7 months	6.1	72	69	28	3	12.4	4.9	***6.1***	4.3	**5.2**
Age 8 months	9.5	86	79	15	6	8.4	***4.4***	6.8	5.8	6.3
Age 9 months	14.4	95	84	7	9	***6.4***	4.5	8.1	7.7	7.9
Age 10 months	18.6	98	82	4	14	7.2	6.1	11.7	11.5	11.6

Notes: MV=measles vaccine; The estimated number of measles deaths was obtained by multiplying the number of vaccine failures (column 4) and cases prior to MV (column 5) in a cohort of 1000 children by the case fatality rates as indicated in the following notes: 1. Assumption: The relative case fatality ratio is 1/3 for vaccinated versus unvaccinated cases, i.e. 4% for unvaccinated cases and 1.33% for vaccinated cases. 2. Assumption: The relative case fatality ratio is 1/3 for vaccinated versus unvaccinated cases. The case fatality ratio is twice as high for unvaccinated cases occurring in infancy. Hence, the estimated case fatality ratios are 8% for unvaccinated cases occurring in infancy and 1.33% for vaccinated cases. 3. Assumption: Seronegative children had 50% or 25%

protection against measles. Hence, the estimated case fatality ratios are 8% for unvaccinated cases occurring in infancy and 1.33% for vaccinated cases but there were fewer vaccinated cases than indicated in column 4.

Table 2. Relative acute measles case fatality ratio for measles-vaccinated and measles-unvaccinated cases in African prospective community studies and community surveys

Country	Period	Study	Vaccinated cases (%) (deaths/cases)	Unvaccinated cases (%) (deaths/cases)	Measles case fatality ratio
Bissau (43)	1980-82	PCS; urban	9%(5/53)	17%(18/108)	0.58 (0.23-1.49)*
Bissau (43)[1]	*1980-82*	*PCS; urban (only secondary cases)*	*14%(3/21)*	*46%(11/24)*	*0.30 (0.10-0.86)**
Guinea-Bissau (45)	1983-1984	PCS; urban	4%(4/90)	9%(21/234)	0.41 (0.14-1.22)*
Guinea-Bissau (38)	1984-1987	PCS; 2 year follow-up	0% (0/4)	13% (2/16)	0 (0-23.10)
Bissau (46)	1985-1987	PCS; children < 2yrs; urban	5%(1/22)	11%(10/90)	0.41 (0.06-3.03)#
Bissau (unpublished&)	1991	PCS; children < 10 yrs; urban	2%(10/412)	13%(64/478)	0.24 (0.12-0.49)*
Senegal (47)	1987-1994	PCS; rural	0%(0/127)	2%(18/1085)	0 (0-1.94)*
Ghana (48)	1989-1991	PCS; rural; Vitamin A trial with measles surveillance	10%(15/153)	17%(136/808)	OR=0.42 (0.21-0.83) ##
Kenya (22)	1986	SUR; all ages; rural	2%(2/41)	11%(11/98)	0.51(0.08-3.08)*
Kenya (49)	1988	SUR; Children <5yrs; rural	0%(0/23)	10%(18/182)	0 (0-1.54)*
Chad (50)	1993	SUR; rural	0%(0/23)	8%(61/801)	0 (0-2.18)
Niger (51)	2003-2004	SUR**; urban	0.4%(1/286)	6%(29/481)	0.06 (0.01-0.42)
Chad (51)	2004-2005	SUR** ; urban	0.4%(2/494)	8%(18/212)	0.05 (0.01-0.20)
Nigeria (51)	2004-2005	SUR**; rural	9%(1/11)	7%(79/1131)	1.30 (0.20-8.54)
Sudan (52)	2004	SUR;	0.4%(2/556)	1%(7/568)	0.29 (0.06-1.40)
Niger (53)	1991-1992	SUR; rural	17%(20/118)	15%(61/410)	1.14 (0.72-1.81)
Zimbabwe (54)	1980-1989	SUR; urban	2%(8/335)	7%(20/302)	0.36 (0.16-0.81)
Total					0.39 (0.31-0.49)

Sources: Reviews of measles case fatality studies (27-31) and PubMed search for measles mortality/case fatality in vaccinated children (see Supplementary material); & compiled by Henning Andersen shortly before he died.

Notes: PCS= prospective community studies; SUR= community surveys or outbreak investigations; 1. Mortality is high because only secondary cases are included in the analysis. Since this analysis is a subgroup within the larger study, it has not been included in the combined estimate; *Adjusted for age; # adjusted for district; ## adjusted for age, sex, weight-for-age z-score, paternal education and season; ** Mortality was only reported for children with at least 30 days of follow-up whereas the proportion of

vaccinated was reported among all cases. It has been assumed that the proportion vaccinated cases was the same among those with follow-up as among all cases.

Table 3. Relative measles case-fatality ratio for measles-vaccinated and measles-unvaccinated cases in African prospective community studies and community surveys with long-term follow-up

Country	Period	Study; period of follow-up	Vaccinated cases (%) (deaths/persons)	Unvaccinated cases (%) (deaths/persons)	Mortality ratio
Guinea-Bissau (55)[1]	1988	PCS; 5 year follow-up;	4% (1/23)	16% (8/46)	0.25 (0.03-1.88)
Guinea-Bissau (38)	1984-1987	PCS; 2 year follow-up	0% (0/4)	14% (2/14)	0 (0-20.10)
Burundi (56)[2]	1988-1989	SUR; 7 month follow-up	3/1363 person-months	19/2629 person-months	0.30 (0.09-1.03)
Senegal (47)	1987-1994	PCS; 1 year follow-up	0% (0/127)	1% (15/1055)	0 (0-2.32)
Bissau (unpublished&)	1991-1994	PCS; 3 year follow-up	3% (8/319)	9% (29/338)	0.29 (0.14-0.63)
Total					0.27 (0.14-0.50)

Sources: Reviews of measles case fatality studies (27-31) and PubMed search for measles mortality/case fatality in vaccinated children (see Supplementary material); & compiled by Henning Andersen shortly before he died.
Notes: PCS= prospective community studies; SUR= community surveys or outbreak investigations; 1. There was no data on acute case fatality in the present study since the study only included children who had a convalescent sample collected; 2. This study did not report the acute case fatality but only overall mortality for the 7 months of follow-up.

Table 4. Relative measles case fatality ratio for infants and older children in African prospective community studies and community surveys

Country	Period	Type of study	Infants (%) (deaths/cases)	Children 1+ year (%) (deaths/cases)	Measles case-fatality ratio
Studies before the introduction of MV					
Gambia (63)#	1961	PCS; rural	31%(12/39)	13%(47/356)	2.33 (1.36-4.00)
Guinea-Bissau (45)	1979	PCS; Urban	28%(22/79)	14%(55/380)	1.92 (1.25-2.96)
Guinea-Bissau (64)	1980	PCS; Rural	47%(7/15)	21%(31/147)	2.21 (1.18-4.13)
Senegal (44)	1983-86	PCS; Rural	12%(19/165)	6%(79/1335)	1.95 (1.21-3.13)
Studies after introduction of MV					
Kenya (65)	1974-1976	PCS; rural	6%(4/63)	7%(24/361)	0.96 (0.34-2.66)
Kenya (65)	1976-1977	PCS; rural	4%(5/125)	1%(7/540)	3.09 (1.00-9.56)
Kenya (22)	1986	SUR; rural	17%(5/29)	7%(8/110)	2.37 (0.84-6.71)
Kenya (49)	1988	SUR; rural	22%(9/41)	5%(11/207)	4.13 (1.83-9.33)
Senegal (44)	1987-1990	PCS; rural	2%(1/43)	2%(9/598)	1.55 (0.20-11.9)
Senegal (47)	1991-1994	PCS; rural	6%(4/72)	1%(4/499)	6.93 (1.77-27.1)
Guinea-Bissau (66)	1980-1982	PCS; urban	30%(7/23)	9%(10/115)	3.50 (1.49-8.24)
Guinea-Bissau (45)	1983-1984	PCS; urban	9%(5/56)	7%(20/268)	1.20 (0.47-3.05)
Zaire (11)	1974-1977	PCS; urban	6%(12/194)	6%(53/844)	0.99 (0.54-1.81)
Ghana (48)	1989-1991	PCS; rural	21%(28/131)	15%(123/830)	1.44 (1.00-2.08)
Chad (50)	1993	SUR; urban	6%(9/156)	8%(52/668)	0.74 (0.37-1.47)
Niger (67)	2003	SUR; rural	16%(13/83)	9%(79/862)	1.71 (0.99-2.94)
Niger (53)	1991-1992	SUR; rural	40%(16/40)	13%(65/488)	3.00 (1.93-4.67)
Niger (51)	2003-2004	SUR; urban	7%(8/111)	3%(22/656)	2.15 (0.98-4.71)
Chad (51)	2004-2005	SUR; urban	5%(5/97)	2%(15/609)	2.09 (0.78-5.63)
Nigeria (51)	2004-2005	SUR; rural	11%(5/47)	7%(75/1095)	1.55 (0.66-3.66)
Zimbabwe (54)	1980-1989	SUR; rural	13%(13/103)	3%(15/534)	4.49 (2.20-9.16)
Sudan (52)	2004	SUR;	3%(1/36)	1%(9/1108)	3.42 (0.45-26.28)
Longer follow-up than 1 month					
Burundi (56)##	1989	SUR; rural; 7 months follow-up	14%(2/176 person-months)	6%(20/3816 person-months)	2.17 (0.51-9.20)
Gambia (68)	1981	SUR; rural; 9 months follow-up	64%(7/11)	10%(13/124)	6.07 (3.07-12.0)
Total					1.87 (1.63-2.14)

Sources: Reviews of measles case fatality studies (27-31) and PubMed search for community studies of measles mortality/case fatality in infants or by age in Africa (see Supplementary material).
Notes: MV=measles vaccine; PCS=prospective community study, i.e. the population was known before the epidemic and information is likely to have been obtained for all children; SUR= retrospective survey; # The age grouping is 7-12 months and 12-120 months. Measles deaths and total number of children in age group were reported in this study. It has been assumed that all children between 7 and 120 months contracted measles. In this period there were no measles vaccinations available. The last epidemic had occurred 12-13 years earlier; ## The age grouping is 0-8 and 9+ months; ¤ Numbers read from a graph

Table 5. Vaccine efficacy against overall mortality in randomised trials of an early two-dose measles vaccination schedule compared with the standard dose of measles vaccination at 9 months of age

Country and period	Age interval	Comparison (Vaccines)	Administration of DTP	Deaths/person-years or persons	Mortality rate ratio	Comments
Sudan (75) 1989-1992	5-9 months	MV vs Control (Meningococcal A+C)	DTP not given simultaneous with MV but could have been given after MV	1/60.5 vs 6/61.2	0.18 (0.02-1.54)	1st vaccine in 2-dose group was Connaught HTMV and 2nd dose was Schwarz standard MV
	9-36 months	2nd vs 1st MV		7/371.6 vs 7/355.9	0.96 (0.34-2.73)	
	5-36 months				0.60 (0.25-1.45)#	
Guinea-Bissau (76) 2003-2009	4.5-9 months	MV vs Control (no vaccine)	DTP not given simultaneous with MV and after MV; all had DTP3 one month before enrolment	5/398.8 vs 29/821.8	0.33 (0.13-0.86)	Vitamin A supplementation (VAS) at birth is not official policy. Hence, only results for children who did not receive VAS is presented.#
	9-36 months	2nd vs 1st MV		20/2054.4 vs 67/3881.1	0.56 (0.34-0.93)	
	4.5-36 months				0.50 (0.32-0.78)#	

Source: All studies reporting mortality in trials of two doses of measles vaccine (MV) (30,32,33). Only the per-protocol results have been used comparing children who received two doses of MV with those receiving one dose at 9 months. No additional studies of early two-dose measles vaccination reporting impact on mortality were found by PubMed searches (see Supplementary material).
Note: # The combined estimate (Stata) was 0.52 (0.35-0.77); if the children receiving vitamin A at birth were also included, the combined estimate was 0.69 (0.52-0.91).

Table 6. Vaccine efficacy against overall mortality for one dose of standard-titre measles vaccine before 9 months of age

Country	period	Comparison	Results
Early measles vaccination at 7 months of age compared with children unvaccinated community			
Congo (11)	1974-1977	MV administered at 7 months of age; children followed to 21 and 34 months of age. Mortality from 7 to 21 months of age for vaccinated children (3/230.5 pyrs) compared with unvaccinated children from control area (21/470.7 pyrs)	MRR for 7 to 21 months =0.29 (0.09-0.98) MRR for 7 to 34 months =0.52 (0.21-1.27)
Comparing MV at 4-8 months versus MV at 9-11 months of age			
Guinea-Bissau (77)	1980-1982	Natural experiment: MV at 4-8 versus MV at 9-11 mo compared from 9 to 60 months of age	MRR (MV-4-8mo/MV-9-11mo) 0.69 (0.46-1.08)
Comparing children randomsied to MV at 6 months versus IPV at 6 months during a war situation			
Guinea-Bissau (79)	1998	Children were randomised to MV (4/214) or inactivated polio vaccine (11/219) at 6 months of age. Due to a war they did not received the planned MV at 9 mo. Follow-up for 3 months in a war situation	70% (13 to 92)

Sources: All studies examining the general effect of standard measles vaccine (MV) on child survival (as compiled by all available reviews (30,32,33)) have been screened for information on measles vaccination before 9 months of age. There have been several other studies of the impact of MV before 12 months of age on child survival (80-87) but most of these studies could not distinguish the effect of MV before 9 months of age. However, all studies suggested that early MV had a better effect on child survival than later MV. The studies where children received DTP or IPV with early MV or shortly after MV have not been included in the present table (34-36) since this sequence have unfortunate consequences (34,36). No additional studies of one-dose measles vaccination/immunization before 9 months of age reporting impact on mortality were found by PubMed searches (see Supplementary material).

The optimal age of measles immunization in low-income countries: 35 years with a policy based on flawed assumptions

Search strategy: For each assumption we used existing reviews and in December 2011 we made a PubMed search for relevant papers as described below. The title and abstract of papers in English, French, Portuguese, Spanish, German and Scandinavian languages was assessed to ascertain whether the paper was potentially relevant. Potentially relevant papers were read. The large majority of papers were not from Africa, were reviews or case reports and not community based studies, had no information on mortality, or the vaccine was not single dose measles vaccine.

Assumption 1: children who seroconvert to measles vaccine have absolute protection against measles infection.
We searched for "measles infection seropositive vaccinated children" (N=12) and "measles vaccine failure" (N=318). There are many case reports that contradict that seroconverted children have absolute protection but no African community study.

Assumption 2: vaccinated children who do not seroconvert are fully susceptible to measles infection.
We searched for "measles infection seronegative vaccinated children" (N=13) and "measles vaccine failure" (N=318). This provided only one relevant reference (37).

Assumption 3: severity of measles infection in vaccinated children ("vaccine failures") and unvaccinated children is the same.
We searched for "measles mortality vaccinated children" (N=143), "measles vaccine mortality" (N=775), "measles case fatality" (N=161) and "measles vaccine failure" (N=318). Relevant studies included in Tables 2 and 3.

Assumption 4: severity of measles is the same whether measles infection is acquired in infancy or later.
We searched for "measles case fatality" (N=161) and "measles mortality/death Africa" (N=620). Relevant studies included in Table 4.

Assumption 5: vaccine failures lead to lack of credibility of the vaccination programme.
We searched "measles vaccine failure" (N=318) and "measles vaccine/vaccination/immunisation credibility" (N=2). This search produced one paper dealing with the relationship between "vaccine failure" and the acceptance or credibility of measles vaccination (69). One study was known from our own research (43).

Assumption 6: it had to be a one-dose policy.
We used the reviews of measles vaccination studies (30,32,33) and search papers on *Two/2 dose measles vaccine trial" (N=144), "Two/2 dose measles vaccination/immunization and mortality/death" (N=108) and "early measles vaccination/immunization mortality/death" (N=123). This produced only two trials of the effect on child survival of a 2-dose measles vaccinations schedule compared with a 1-dose schedule (see Table 5).

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE : The optimal age of measles immunization in low-income countries: 35 years with a policy based on flawed assumptions			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Only in abstract, page 2
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4-5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5, supplementary annex
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary annex
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Supplementary annex
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Supplementary annex
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Supplementary annex
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6

PRISMA 2009 Checklist

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency ($e.g., I^2$) for each meta-analysis.	6

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Discussion page 10
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Supplementary annex
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Tables 2-6
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	5,7
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Tables 2-6
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Pages 6-9
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	7,10
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	3,10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	12-14
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	14

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The optimal age of measles immunization in low-income countries: A secondary analysis of the assumptions underlying the current policy

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The optimal age of measles immunization in low-income countries: A secondary analysis of the assumptions underlying the current policy

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Abstract

Background and objective The current policy of measles vaccination at 9 months of age was decided in the mid-1970s. The policy was not tested for impact on child survival. We examined the empirical evidence for the six underlying assumptions.

Data sources and methods These assumptions have not been research issues. Hence, we examined review articles and case reports to assess the empirical evidence for the original assumptions. The search was limited to African community studies of measles infection.

Main outcome The predicted effect on mortality.

Results In retrospect the major assumptions were based on false premises. First, in the single study examining this point seronegative vaccinated children had considerable protection against measles infection. Second, in 18 community studies vaccinated measles cases ("vaccine failures") had three-fold lower case fatality than unvaccinated cases. Third, in 24 community studies, infants had two-fold higher case fatality than older measles cases. Fourth, the only study examining the assumption that "vaccine failures" lead to lack of confidence found the opposite because vaccinated children had milder measles infection. Fifth, a one-dose policy was recommended. However, the two randomised trials of early two-dose measles vaccination compared with one-dose vaccination found significantly reduced mortality until 3 years. Thus current evidence suggests that the optimal age for a single dose of measles vaccine should have been 6 or 7 months resulting in fewer severe unvaccinated cases among infants but more mild "vaccine failures" among older children. Furthermore, the two-dose trials indicate that measles vaccine reduces mortality from other causes than measles infection.

Conclusions Many lives may have been lost by not determining the optimal age of measles vaccination. Despite this the current recommendation is to increase the age of measles vaccination to 12 months in countries with limited measles transmission. This policy may lead to an increase in child mortality.

Article summary

Article focus

- An empirical analysis of the six assumptions underlying the current measles vaccination policy for low-income countries.
- Determine the implications for child survival of not testing the optimal measles vaccination policy.

Key messages

- All six assumptions were flawed; most important were the assumptions that seronegative vaccinated children are fully susceptible to measles infection, that the severity of measles is the same in vaccinated cases ("vaccine failures") and in unvaccinated children, that the severity of measles infection is the same in infancy or later, and that it had to be a one-dose programme.
- The current evidence suggests that the optimal age for a single dose of measles vaccine would probably have been 6 or 7 months of age had the policy been tested.
- An early two-dose schedule at 4-5 months and 9 months of age would have been even better in terms of reducing child mortality.

Strength and limitations

- The current measles vaccination policy for low-income countries is not based on any evidence about the impact on overall child survival.
- There are few studies testing some of the assumptions. However, for the two key assumptions relating to severity of measles in vaccinated infants and children there is ample evidence which suggests that measles is less severe in vaccinated cases.

Introduction

With the spectacular success in measles control in the last 10-15 years(1-3) and the current policy to move ahead with elimination and eventually eradication of measles infection (4), there is now a discussion of when to introduce the second dose of measles vaccine (5). However, few people realize that the key policy of vaccinating against measles at 9 months of age in low-income countries is not based on evidence documenting the optimal age of measles vaccination to reduce overall child mortality.

In the 1970s policy makers found it necessary to formulate a common policy for low-income countries (6-8) since many donors and scientists at the time questioned the value of measles vaccination. Measles infection was believed to kill mainly malnourished children likely to die of other infections if not from measles and hence some people thought that measles vaccine would not reduce overall mortality, but merely change the cause of death (9-11). The policy makers' definition of the optimal age of measles vaccination of 9 months was based on a number of assumptions (6-8). Though these assumptions for vaccinating at age 9 months were not subsequently substantiated the policy has remained in effect. Recently, though, it has been recommended that primary measles vaccination should be at 12 months of age in countries where measles infection has been controlled (12).

In the first measles vaccination campaigns in West and Central Africa in the 1960s children were targeted from 6 months of age (13-17). Initially it was thought that it would be sufficient to conduct campaigns every 2nd or 3rd year to control measles. However, the epidemiologists soon learned that shorter intervals of 6 or 12 months between campaigns were necessary to control measles. In the 1970s, routine vaccination programmes were introduced and the optimal age of routine measles vaccination was debated (18-20). Following the experience with the campaigns, several African countries recommended measles vaccination at 6, 7 or 8 months of age. A study sponsored by the Ministry of Health in Kenya and WHO assessed the seroconversion rates at different ages between 5 and 12 months and recommended measles vaccination at 7½ months of age (21). For several years measles vaccine was administered at 8 months of age in Kenya (22). Similar studies of seroconversion were conducted in Latin America (23). Since some of those vaccinated at 6 months were not protected some countries and many researchers recommended a second dose at 9 months of age or later (20,24). However, there were fears that early vaccination would produce too many vaccine failures and a one-dose programme was considered necessary because mothers would not bring their children back for a second dose (15,25). Therefore, the Expanded Programme on Immunization (EPI) recommended a one-dose policy (6-8,18). In 1980, the Global Advisory Group of EPI endorsed this policy and recommended measles vaccination as early as possible after 9 months of age (7).

Before the global policy is changed to 12 months of age it is timely to examine the empirical basis for the assumptions underlying the current policy. Since these assumptions have not been research issues we have had to use a search strategy including review articles and case reports to assess the validity of the original assumptions (see

Supplementary Material). The present analysis suggests that in retrospect all assumptions were flawed. Had the policy been tested in randomised trials measuring the impact on mortality of vaccination at different ages it is likely that the age of measles vaccination had been changed, with the result that the measles vaccination programme would have had a much larger effect on child survival in low-income countries.

Methods

The optimal age of measles immunization: the underlying assumptions

The recommendation was based on the belief that the expected reduction in mortality could be computed from seroconversion rates (18,26) and the policy was justified several times by analyses of the seroconversion data from Kenya (6,8). In these analyses it was assumed that seroconversion was associated with full protection against measles infection (*assumption 1*) and that non-seroconversion was associated with full susceptibility to measles infection (*assumption 2*). As shown in Table 1 (Column 2), the data from Kenya (21) showed that seroconversion increased with age. This was not unexpected since the calculation of this measure (a fourfold or more increase over baseline) is dependent on level of maternal antibody which wanes as the child ages. Based on cumulative measles incidence figures (Column 1), it was calculated how many measles cases had been prevented assuming everybody was vaccinated at a specific age (Column 3), how many "vaccine failures" would occur after the age of vaccination (Column 4) and how many cases would occur before the specific age of vaccination (Column 5). In making these calculations it was assumed that "vaccine failures" and unvaccinated measles cases were equally severe (*assumption 3*) and that it did not matter whether measles was acquired in infancy or later in childhood (*assumption 4*). Vaccination at 8, 9, and 10 months of age prevented roughly the same proportion of cases, between 79% and 84% (Column 3) (6,8). Vaccination at 8 month resulted in considerably more vaccine failures (15%) than vaccination at 9 months (7%). Since vaccine failures were assumed to jeopardize the credibility of the measles immunization programme (*assumption 5*) (6,8,18), it was concluded that the optimal age for administration of measles vaccine would be 9 months. At the time the EPI assumed that the case fatality in measles infection was 4% in Africa and it will be seen in Column 6 that the number of estimated measles deaths in a birth cohort of a 1000 children would indeed be lowest (between 6.4 and 8.4) for vaccination at 8-10 months of age. In making this analysis of the effect of only one dose of measles vaccine (6,8), the EPI assumed that a two-dose policy was not feasible or unjustified (*assumption 6*).

Selection of studies. Following the identification of the underlying assumptions, we looked for empirical evidence in community studies to support or refute their validity. The original policy was mainly justified in relation to the epidemiology of measles infection in Africa where the case fatality was clearly higher than in other regions (27-31). Most community studies of measles infection are indeed from Africa and we have therefore restricted the analyses and the tables 2-4 to the African studies. These tables are believed to be exhaustive for Africa and they are not contradicted by community studies from Latin America and Asia. For the analysis of the impact of measles vaccination on child mortality we included all studies from Asia and Latin America.

The search strategy has been defined in the Supplementary Material. Since there are few specific studies to test the six assumptions we have had to use case reports of measles outbreaks to assess their validity. Over the last 20-25 years, several reviews of community studies of the measles case fatality compiled studies of relevance for particularly assumption three and four (27-31). Furthermore, as specified in the supplementary material, we made PubMed searches for additional publications relevant for all assumptions. We included one unpublished report from a large epidemic in Bissau in 1991-1992 which has remained unpublished because the physician (Henning Andersen) handling the epidemic died tragically in an accident shortly after the epidemic.

We distinguished between prospective community studies and surveys retrospectively assessing events since the precision of information on vaccination status and age presumably is better in prospective studies. Though hospital and health centre studies may have data on the severity of measles infection by vaccination status or age, we have not included these studies in the analysis since biased admission for some groups might have made the result non-representative.

Since the analysis of the assumptions suggested that measles vaccination before 9 months of age could be beneficial, we assessed the empirical evidence from studies which assessed the effect of early measles vaccination on mortality. Again we used all reviews of community studies and trials assessing the impact of measles vaccination on child mortality (30,32-35). Additional PubMed searches for studies comparing the mortality of measles vaccinated and unvaccinated children did not identify further studies. As explained in the footnote to table 6, we have emphasised the studies in which inactivated vaccines were not administered simultaneously with MV or after MV as such combination or sequences can have a negative effect on child survival (34,36).

Presentation. For each assumption, we briefly outline the background. Next we present the relevant studies found and then analyse the common trends, identifying the secondary analyses which have been made. Finally, we considered whether methodological issues and data quality might question the trends suggested by the analysis.

Statistical analyses. In the combined analyses of several studies we used the Mantel-Haenszel (MH) weighted relative risk stratifying for study or age groups to estimate common trends.

Ethics. Since the study is a secondary analysis of existing data, approval from an ethical committee was not needed.

Results

Assumption 1: children who seroconvert to measles vaccine have absolute protection against measles infection.

Background. It has usually been assumed that previous measles infection is associated with life-long immunity. This idea was transferred to measles vaccination when the

vaccine was developed in the 1950s. Hence, if someone had antibodies after vaccination these were also assumed to provide life-long protection.

Data: We searched for "measles infection seropositive vaccinated children" and "measles vaccine failure" (Supplementary material). There are many case reports that contradict that seroconverted children have absolute protection but no African community study.

Analysis. A number of smaller studies have documented that a few children do get measles after having seroconverted (37-40). Hence, seroconversion does not give absolute protection.

Considerations. However, there are no general epidemiological studies from Africa and it is therefore difficult to estimate the proportion of children who get measles in spite of having seroconverted, but since no large series have been reported it is likely to be small.

Assumption 2: vaccinated children who are seronegative are fully susceptible to measles infection.

Background. Measles immunity has generally been considered an either-or phenomenon. If a vaccinated child was seronegative it was assumed that the child was fully susceptible.

Data: We searched for "measles infection seronegative vaccinated children" and "measles vaccine failure" (Supplementary material). This provided only one relevant reference (37).

Analysis. In a study in Senegal, vaccinated children who were seronegative when exposed to measles infection at home had a 49% (95% CI 21-68%) protection against clinical disease compared with unvaccinated seronegative children exposed under similar conditions (37).

Considerations. Apparently, no other study has tested the susceptibility of vaccinated "seronegative" children. It is possible that some children had acquired vaccine-induced measles antibodies earlier but subsequently lost them. Cellular immunity may be obtained without having measurable antibodies (41). There is also good evidence from studies of hepatitis B vaccination that antibody concentration wane with time but the majority of older seronegative children if infected are protected from chronic carriage and its damaging consequences (42).

The concept of seroconversion to compare the effect of vaccination at different age is in itself problematic. Seroconversion is not the same as seroprotection and the use of the term inevitably disadvantages data from studies that have vaccinated at earlier ages when maternal antibodies are still present. Thus a child immunized at 6 months of age when the maternal antibody level is say 62.5 mIU may fail the test for conversion (a four-fold increase) yet still have a protective level of 125 mIU at 9 months of age.

If approximately half the seronegative children have clinical protection it would have major consequences for the calculation of the optimal age of measles vaccine.

Assumption 3: severity of measles infection in vaccinated children ("vaccine failures") and unvaccinated children is the same.

Background. The EPI perceived "vaccine failures" as due to the vaccine being inactivated by improper storage and handling or due to neutralization of the vaccine by maternal antibodies (16,19). Hence, it was assumed that these children had been fully susceptible to measles infection. However, many epidemiological studies in the 1980s and 1990s suggested that measles vaccinated children who contracted measles infection had milder disease (43,44). This would suggest that the children had partial measles immunity, not enough to protect them but enough to modify the severity of the disease.

Data: We searched for "measles mortality vaccinated children", "measles vaccine mortality", "measles case fatality" and "measles vaccine failure" (Supplementary material). The 18 relevant studies are included in Tables 2 and 3.

Analysis. The community studies of the acute measles case fatality are shown in Table 2. Only two African studies (43, 48) have reported significant differences in mortality for vaccinated and unvaccinated measles cases. A combined analysis has not been made previously. The measles case fatality was 2 to 5-fold lower for vaccinated cases ("vaccine failures") than for unvaccinated children with measles infection in nearly all studies. Using MH weighted relative risk, the effect was similar in the prospective community studies (case-fatality ratio=0.37 (0.27-0.52)) and the retrospective surveys (case-fatality ratio=0.41 (0.29-0.56)).

A few studies followed the children for longer than one month which is the normal time limit for acute measles deaths. The long-term trend was the same with considerable better survival among vaccinated than unvaccinated children after measles infection (Table 3). Combining the prospective community studies in Tables 2 and 3 would suggest a 3-fold reduction in acute and/or long-term mortality among vaccinated children even though some of the vaccine failures may have been due to inactivated measles vaccines.

In the four studies (38,47,56, unpublished) with information on both acute and long-term mortality, mortality was nearly 5-fold lower for the vaccinated cases (MH weighted mortality ratio= 0.21 (0.13-0.34)).

Considerations. Only two studies did not show lower case fatality among vaccinated children and five of the 18 studies in Tables 2 and 3 showed significantly lower mortality among vaccinated children.

All studies with relevant data were included in Tables 2 and 3 irrespective of whether vaccine efficacy (VE) against measles infection was high or substandard. In several studies, the VE was not high but nonetheless the vaccine appeared to have had an effect; for example, in Kenya VE was only 18% but measles-vaccinated children who developed

measles had still 2-fold lower measles mortality than measles unvaccinated children (Table 2). Only one community survey from Niger reported that measles vaccine was not particularly effective against measles infection and that there was no effect of vaccination on the case fatality in measles infection (53).

In most studies (Table 2), it was not possible to control for age given the way the data was reported. However, in 6 studies (22, 43, 45, 47, 49, unpublished data) age could be controlled. In these studies the crude MH weighted case-fatality ratio was 0.27 (0.17-0.42); when the comparison was stratified by age group, the MH weighted case-fatality ratio became 0.30 (0.18-0.49).

It could be speculated that vaccinated children had more health-system-compliant mothers and that they therefore had more care and milder infection. However, in many of the original studies from the 1980s, measles vaccine had been provided in community campaigns and not in routine service and vaccination status depended on whether the mother had been around at the time of the campaign and not on bias (43). In the studies which adjusted for background factors, the differential effect of vaccination on the measles case fatality was actually increased (43,48). Furthermore, several studies have found that "vaccine failures" occur after high intensity of exposure, i.e. "vaccine failures" are more likely to be secondary cases exposed at home (43,44). Since secondary cases have a higher case fatality than index cases (43,44,62), the milder infection among vaccinated children is even more surprising. The possibility that measles vaccinated children have milder disease due to modified immune responses and not merely due to social confounding is strengthened by the many studies showing that measles vaccination is associated with beneficial effects on overall child survival (32,33).

Several hospital or health centre based studies have also compared vaccinated and unvaccinated children and reported that measles vaccinated children had less severe measles infection (57-59). A few community studies from India and Papua New Guinea have also suggested lower case fatality for vaccinated measles cases (60,61).

If the severity of measles is not the same in vaccinated and unvaccinated children it would strongly affect the estimated benefit of vaccinations at different ages.

Assumption 4: severity of measles is the same whether measles infection is acquired in infancy or later.

Background. In the hypothetical EPI model in which all children were vaccinated at a specific age, the unvaccinated measles cases would occur in infancy, before measles vaccination, whereas most "vaccine failures" would occur much later after the first year of life. No adjustment was made for how this affected the overall measles mortality. Most infections are more severe in infancy but on the other hand, modification of severity by maternal antibodies could have reduced the case fatality among infants.

Data: We therefore searched for studies of "measles case fatality" and "measles mortality/death Africa" (Supplementary material). We found 24 relevant studies.

Analysis. The African community studies reporting the measles case fatality separately for infants and older children have been presented in Table 4. One review of East African studies of measles have previously emphasised that the case fatality was particularly high in infants (69). However, a comparative analysis of the measles case fatality for infants and older children in all African community studies have not been made before. With a few exceptions, the studies suggested that the case fatality is higher in infancy than among older children (Table 4). These studies suggest around a two-fold higher measles case-fatality in infancy; the MH weighted case fatality ratio for all studies was 1.87 (1.63-2.14). The effect was similar before measles vaccine was introduced in these communities (MH weighted case fatality ratio=2.04 (1.58-2.63)) (see Studies before the introduction of MV, Table 4).

Considerations. Only three studies did not show higher case fatality in infancy and half the studies showed significantly higher mortality in infancy. Even if a few studies should not have been found by the search terms, it seems unlikely that additional studies would change the tendency.

If the case fatality is indeed higher in infancy, it would be more advantageous to have vaccine failures later in life rather than leave infants less than 9 months of age unprotected.

Assumption 5: vaccine failures lead to lack of credibility of the vaccination programme.

Background. Apparently it was assumed that African mothers – like physicians - would lose confidence if measles vaccine did not provide complete and life-long immunity.

Data: We searched "measles vaccine failure" and "measles vaccine/vaccination/immunisation credibility" This search produced one paper dealing with the relationship between "vaccine failure" and the acceptance or credibility of measles vaccination (70). One study was known from our own research (43).

Analysis. One study from Tanzania stated that acceptance of measles vaccination was low because of the many failures experienced by children vaccinated before 9 months of age.

In the only community study which examined the credibility of the programme in relation to previous experiences with "vaccine failures", younger siblings of "vaccine failures" had a significant higher coverage for measles vaccination (95% (33/35)) than siblings of children who had been successfully vaccinated and not had measles infection (78% (630/809)). Hence, the younger siblings of "vaccine failures" were significantly more likely to have been measles vaccinated (relative risk= 1.21 (1.11-1.32)) (43).

Considerations. The study from Tanzania provided no specific information on how data had been collected and how low acceptance had been measured (70). In contrast to this negative view of measles vaccination, many African mothers have experienced that

vaccinated children have mild measles infection (43). In cultures where mothers have learnt that everybody has to get measles, the advantage of "mild measles" is easy to see whereas it is difficult to "see" complete "life-long protection" if you still expect your child will get measles some day. Hence, it may have worked the other way around; seeing your child get mild measles after vaccination would be a strong argument for the value of measles vaccination.

Assumption 6: it had to be a one-dose policy.

Background. The main argument advanced for a one-dose policy was that compliance with the second dose was too low (15,18,68,71). This is surprising since it has been described that mothers sought vaccination so eagerly that it was impossible to maintain the age eligibility criteria for vaccinations during campaigns (16). The reason why mothers did not seek the second dose of measles vaccine in some countries may have been poor information. In Guinea-Bissau, we had very good compliance and improved overall coverage with a two-dose schedule (72). The two-dose group had better protection against measles infection than the one-dose group (72). A two-dose schedule has also been shown to be effective in Niger (73), India (74) and Saudi Arabia (75). Hence, a two-dose schedule is both feasible and effective.

Data: To identify studies comparing the effect on survival of a one-dose and a two-dose policy we used the reviews of measles vaccination and impact on mortality (30,32,33) and searched papers on "Two/2 dose measles vaccine trial", "Two/2 dose measles vaccination/immunization and mortality/death" and "early measles vaccination/immunization mortality/death". These procedures identified only two trials of the effect on child survival of a 2-dose measles vaccinations schedule compared with a 1-dose schedule (see Table 5) and one observational study (78)

Analysis. Only two trials have compared child mortality following two doses of MV (the first being given before 9 months) with mortality after the standard dose of MV (at 9 months of age) (Table 5). In a small trial from Sudan (76), DTP vaccinations were not controlled and many children received DTP after measles vaccine. DTP administered with or after measles vaccine has negative effects on female survival (34,36). We therefore conducted a large randomized trial including only children who had received DTP3 before enrolment and therefore would not receive DTP after MV (77). Among children who had not received neonatal vitamin A supplementation (VAS) which interacted negatively with early MV(76), two doses of MV at 4.5 and 9 months of age compared with the current policy of one dose at 9 months of age reduced mortality between 4.5 and 36 months of age by 50% (22-68%) in the per-protocol analysis (Table 5). There was a significant reduction in non-measles related mortality of 45% (14-65%) (77). The combined estimate for the two trials showed that the early two-dose measles vaccination strategy may reduce mortality by as much as 48% (23%-65%) compared with the currently recommended standard dose at 9 months of age. Even if the children receiving neonatal VAS were included, the combined estimate was 31% (9-48%) (Table 5).

The only other study to report mortality after two doses of MV is a natural experiment from Guinea-Bissau in the early 1980s. Children were vaccinated in annual or biannual campaigns rather than through routine service. Hence, it was possible to compare in an unbiased way the survival of children who happened to be less than 9 months of age when vaccinated and those vaccinated at the recommended age of 9-11 for MV. MV at 4-8 months and a later dose after 9 months compared with one dose of MV at 9-11 months of age was associated with 59% (15-81%) lower mortality between 9 months and 5 years of age (78).

Considerations. The studies indicate that a two-dose policy providing the first dose of MV before 9 months of age is associated with major reductions in child mortality compared with the current one-dose at 9 month policy. The studies indicated that the benefit was not due to better protection against measles infection. Hence, these studies strongly supported that early measles vaccination has non-specific beneficial effects on child survival.

The implications of the assumptions for the estimated prevention of measles mortality. We calculated how variation in these six assumptions affect the optimal age of MV in terms of reducing measles mortality (Table 1, Columns 7-10). Using the best estimate that the case fatality rate is three-fold lower for vaccinated measles cases than for unvaccinated cases (Tables 2 and 3), the number of estimated measles deaths would have been lowest with one dose of MV at 8 months (Column 7). Assuming furthermore that infants have two-fold higher case fatality than older children (Table 4) the estimated number of measles deaths would have been lowest after vaccination at age 7 months (Column 8). Hence, it might have been better to vaccinate at 7 months of age and have some more vaccine failures later in childhood than to have many unvaccinated cases with high mortality in infancy. Adjusting for the possibility that non-seroconverting vaccinated children have some protection from cellular immunity or low levels of antibodies (37), the optimal age for measles immunization in a one-dose strategy would have moved to 6 or 7 months of age (Columns 9 and 10).

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 (72-77,79). Hence, an early dose at 4-6 months of age and a second dose at 9 months of age would have eliminated virtually all measles mortality and significantly reduced mortality from other causes as well.

Discussion

The main justification for measles vaccination at 9 months of age in low-income countries was to reduce child mortality from measles infection (18). However, the policy was never tested for its effect on survival. The policy was based on assumptions which were believed to be true, and a small seroconversion study (6-8). Thirty-five years ago the six assumptions appeared self-evident and programmatic decisions had to be taken about the optimal age for measles vaccination. However, though all assumptions have been contradicted for years no change has been made in the policy.

Strength and weaknesses

Since the six assumptions have not been research issues there are few studies conducted specifically with these topics in mind. We have therefore had to use a search strategy including review articles and case reports to find studies to assess the validity of the original assumptions. There may be a few more studies which were not found with the literature search since several of the studies identified in previous reviews were not found by the search terms. However, many reviews over the last 25 years have covered the areas of community studies of measles infection and the impact of MV on mortality so it is unlikely that there would be many studies not included. Furthermore, the estimates from different studies were consistent and it is unlikely that the addition of further studies would have a major impact on the estimates.

The assumed case fatality of measles infection does not matter for the estimated impact of the optimal policy on measles mortality. With another case fatality level the epidemiological arguments about assumptions 2-4 would still have the same relative effects on the number of deaths prevented. However, as evident in Tables 2 and 4, most community studies from Africa suggest that the case fatality may have been higher than 4% and the impact of the optimal measles vaccination strategy on overall mortality may therefore have been even larger. Other assumptions may also have been important; for example, the incidence data were from a rural study rather than from an urban area (21). In an urban area the incidence would have been higher at younger ages and it might have been advantageous to vaccinate even earlier. As maternal measles antibody levels have declined in low-income countries (78), earlier vaccination would also have produced better seroconversion rates and it would have been even more advantageous to vaccinate early.

Consistency with previous studies: The non-specific beneficial effects of MV. The conclusion that earlier measles vaccination is likely to have been better for child survival is based on a reconsideration of the programme´s own assumptions about effect on measles mortality. However, what is the empirical evidence for the impact on mortality of measles vaccine before 9 months of age?

In marked contradiction to the original fear that children dying of measles would just die of something else and that measles vaccination would therefore only change the cause of death but not the level of mortality (9-11), all subsequent studies measuring the effect on survival have found marked benefit from measles vaccination (32,33,36,78,80-89). Several studies have assessed the impact of measles vaccine before 12 months of age (30,32,33) but few studies have separately measured the effect on overall mortality of measles vaccination before 9 months of age in an unbiased way (Table 6). In the 1970s, researchers in Congo followed two districts which initially had similar overall mortality levels and then introduced measles vaccination at 7 months of age in one district (11). Measles vaccination administered at 7 months of age reduced overall mortality between 7 and 21 months of age by 71% (2-91%) compared with the neighbouring district which did not get measles vaccination (60). In the early 1980s in Guinea-Bissau, children were vaccinated in annual or biannual campaigns. Hence, it was possible to compare in a "natural experiment" manner the survival of children who had been measles vaccinated

before 9 months of age and those vaccinated at 9 months of age, the recommended age of measles vaccination. One dose of MV at 4-8 months compared with 9-11 months of age was associated with 31% (-8-54%) lower mortality between 9 months and 5 years of age (78). As mention above the effect was even stronger if they also received a second dose of MV after 9 months of age. During a civil war in Guinea-Bissau in 1998 (80), we followed children who had been randomised to measles vaccination at 6 months of age compared with children who had been randomised to inactivated polio vaccine (IPV). Due to the war the children did not get the standard measles vaccination at 9 months of age. During the 3 months of intensive fighting when everybody had fled the study area and mortality was high, the children vaccinated against measles at 6 months of age had 70% (13-92%) lower mortality than the unvaccinated group.

These studies of one dose of MV before 9 months of age as well as the studies of early two-dose MV mentioned above suggest that the reduction in mortality from MV before 9 months of age is much larger than can be explained by the prevention of measles infection. WHO estimates that measles deaths caused 10% of under-five deaths (90). However all available studies of the mortality impact of MV (30,32,33) suggest that the effect of measles immunization on mortality is much greater than expected. This beneficial effect is a consistent observation and it can not be explained by the prevention of acute measles infection. First, all studies, in which measles vaccine was not administered with DTP, provided strong evidence of a beneficial effect of measles vaccine on overall mortality (32). Second, all studies censoring for measles infection in the survival analysis to estimate the impact on non-measles related mortality found that prevention of measles-specific deaths explained little and the beneficial effect was due to prevention of non-measles related mortality (32,76,89, 91). For example, in the per-protocol analysis of the largest randomised trial (77), measles vaccine at 4.5 and 9 months compared with the standard dose at 9 months of age reduced non-measles related mortality significantly for all children. Third, the beneficial effect of measles vaccine is usually stronger for girls than for boys (77,92,923). Since measles mortality is not higher for girls than boys, this observation suggests sex-differential mechanisms related to immune stimulation. Hence, standard measles vaccine may protect against other infections and have a beneficial effect on child survival even when measles is eliminated.

Though the focus here has been on MV administered before 9 months of age there is also a considerable number of studies indicating that MV administered after 9 months of age have non-specific beneficial effects (32,81-86, 91, 94).

The possible biological explanations for non-specific beneficial effects of MV have not been explored in humans. In animal studies of heterologous immunity, previous stimulation with infections may have a major effect on the capacity to handle a lethal dose of an unrelated infection (95). Two trials from Bissau suggest that the beneficial effect of MV is better for children vaccinated in the presence of maternal measles antibodies than for children having no measurable maternal antibodies at the time of MV (89). This may also help explain why MV before 9 months of age is better than later vaccination.

The optimal age of measles vaccination: optimizing seroconversion or impact on overall child survival. The most unfortunate consequence of not testing the optimal age of measles immunization may have been that the beneficial non-specific effects of MV were not detected (32). To the extent MV has non-specific beneficial effects the question of the optimal age of measles vaccination acquires a new meaning. By lowering the age of measles vaccination, children would benefit not only from earlier protection against measles infection but also from the beneficial non-specific effects against non-measles infections and overall child mortality would be reduced. On the other hand, if the age of vaccination is increased, children would benefit less from the non-specific beneficial effects and overall child mortality would increase. Hence, policies optimizing the non-specific effects clash with those designed to enhance seroconversion.

Conclusions: Old assumptions linger on

The supplementary immunization activities (SIA) with measles vaccine has eliminated measles infection in Latin America and reduced the incidence in major ways in the rest of the world (1-3). The world is now planning to eliminate and eventually eradicate measles infection (4). With the SIA success in measles control, the optimal age of measles immunization is likely to be considered an irrelevant issue. However, as discussed above, measles vaccine has also non-specific effects which need to be taken into consideration in the planning of vaccination programmes. The prevention of all-cause mortality rather than measles mortality should be the primary objective. In a culture which advocates evidence-based policies (4), the evidence for the current measles vaccination policy – or rather the lack thereof - should be properly reviewed and revised by the global and regional immunization programmes. Otherwise old assumptions about seroconversion rates being the basis for the optimal age of immunisation may linger on and continue to influence policy.

There are major consequences of focusing solely on specific measles mortality. First, as the current policy is mostly determined by our understanding that seroconversion gets better with increasing age, the tendency will be that with improved control of measles infection, age of vaccination will be increased. Following the elimination of measles in Latin America, the recommended age of primary measles immunization was raised to 12 months in 1996 (3). Again this decision was based on assumptions and not on studies documenting the overall effect on morbidity and mortality. Following the success of measles campaigns in other continents it has also been recommended by SAGE (the Strategic Advisory Group of Experts) to increase the age of measles vaccination to 12 months in areas with low levels of measles transmission (5,12). The underlying assumption about better seroconversion at higher ages may no longer be valid with the decline in maternal antibody levels (79,96). For example, we have obtained 100% seropositivity and 99% protective levels after measles vaccine at 9 months of age with both Schwarz and Edmonston-Zagreb measles vaccine strains in Guinea-Bissau (97).

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 (11,32,38,76-80,89). There is a tendency to dismiss these observations because randomised trials with overall mortality as an outcome have only been conducted in

Guinea-Bissau and it is therefore claimed that the global health community has to wait for verification elsewhere (98). However, the non-specific beneficial effects of MV have been shown in several other countries with high childhood mortality. For example, in a cross-over design, Shann showed that girls receiving standard measles vaccine at 9-10 months of age in five randomised trials in Sudan, Gambia, Senegal and Guinea-Bissau had 47% lower mortality through childhood than control children who received an inactivated vaccine at 9-10 months of age (94). Since the control children had received MV before 9 months of age and did not get measles, the difference in mortality following MV at 9 months of age was a non-specific beneficial effect not related to prevention of measles infection. Increasing the age of measles vaccine from 9 to 12 months may reduce the beneficial effects in the age group between 9 and 12 months of age in which mortality is still high. Thus the lives lost by this change of schedule could well be more than the lives saved by improved measles control (77).

Second, in the current paradigm for control of infectious diseases, the ultimate success in public health is to eradicate the disease and then remove the vaccine to reduce economic costs as happened for smallpox in the 1970s (26). This may happen for measles infection within the next 10-20 years (99). If measles vaccine has major beneficial non-specific effects (77), to remove measles vaccine or reduce its coverage would increase child mortality levels considerably in low-income countries unless we in the meantime find a vaccine which has all the same beneficial effects as measles vaccine.

After 35 years, it is time to develop a policy for the optimal age of measles immunization. This policy needs to be based on evidence about the impact on overall health and child-survival and not only on assumptions about the impact of specific prevention against measles infection. A two-dose measles vaccination strategy, providing measles vaccine at 4.5 months of age, after the three DTP vaccines, and again at 9 months of age, may significantly improve child survival and provide a solid basis of immunity which if necessary can be enhanced by supplementary measles immunisation activities at a later age (77,79). Any future changes in the age of measles immunisation due to elimination of measles infection, changes in the epidemiology of measles infection, decline in maternal antibody levels, introduction of new measles vaccines or in the timing of other vaccines should be tested in trials to determine their overall impact on child health.

Contributions*:* PA and HW have been involved in studies of measles vaccination for more than 30 years in West Africa; MLG, CM, CB and AR have been involved in measles vaccination trials since the early 1990s. The first draft was written by PA; all authors contributed to the final version of the paper. PA will act as guarantor of the study.

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Table 1. Projected reduction in measles cases and measles deaths with measles immunization at ages four to ten months. Machakos, Kenya 1974-1981

Expanded Programme on Immunization model (8)						Estimated number of measles deaths in a cohort of 1000 children				
	Column1	Column 2	Column 3	Column 4	Column 5	Column 6	Column 7	Column 8	Column 9	Column 10
	Cumulative measles incidence (%)	Serocon-version from MV (%)	Prevented cases (%)	Vaccine Failures (%)	Cases prior to MV(%)	EPI assumption: Case fatality 4%	Adjusting vaccination status[1]	Adjusting vaccination status and age of infection[2]	Adjusting vaccination status, age of infection, and seronegative 50% protection[3]	Adjusting vaccination status, age of infection, and seronegative 25% protection[3]
Age 4 months	0.5	15	15	85	0	34	11.3	11.3	5.7	8.5
Age 5 months	1.0	35	35	65	0	26	8.6	8.6	4.3	6.5
Age 6 months	2.8	52	51	48	1	19.6	6.8	7.2	**4.0**	5.6
Age 7 months	6.1	72	69	28	3	12.4	4.9	***6.1***	4.3	**5.2**
Age 8 months	9.5	86	79	15	6	8.4	***4.4***	6.8	5.8	6.3
Age 9 months	14.4	95	84	7	9	***6.4***	4.5	8.1	7.7	7.9
Age 10 months	18.6	98	82	4	14	7.2	6.1	11.7	11.5	11.6

Notes: MV=measles vaccine; The estimated number of measles deaths was obtained by multiplying the number of vaccine failures (column 4) and cases prior to MV (column 5) in a cohort of 1000 children by the case fatality rates as indicated in the following notes: 1. Assumption: The relative case fatality ratio is 1/3 for vaccinated versus unvaccinated cases, i.e. 4% for unvaccinated cases and 1.33% for vaccinated cases. 2. Assumption: The relative case fatality ratio is 1/3 for vaccinated versus unvaccinated cases. The case fatality ratio is twice as high for unvaccinated cases occurring in infancy. Hence, the estimated case fatality ratios are 8% for unvaccinated cases occurring in infancy and 1.33% for vaccinated cases. 3. Assumption: Seronegative children had 50% or 25%

protection against measles. Hence, the estimated case fatality ratios are 8% for unvaccinated cases occurring in infancy and 1.33% for vaccinated cases but there were fewer vaccinated cases than indicated in column 4.

Table 2. Acute measles case fatality ratio for measles-vaccinated and measles-unvaccinated cases in African prospective community studies and community surveys

Country	Period	Study	Vaccinated cases (%) (deaths/cases)	Unvaccinated cases (%) (deaths/cases)	Measles case fatality ratio
Bissau (43)	1980-82	PCS; urban	9%(5/53)	17%(18/108)	0.58 (0.23-1.49)*
Bissau (43)[1]	*1980-82*	*PCS; urban (only secondary cases)*	*14%(3/21)*	*46%(11/24)*	*0.30 (0.10-0.86)**
Guinea-Bissau (45)	1983-1984	PCS; urban	4%(4/90)	9%(21/234)	0.41 (0.14-1.22)*
Guinea-Bissau (38)	1984-1987	PCS; 2 year follow-up	0% (0/4)	13% (2/16)	0 (0-23.10)
Bissau (46)	1985-1987	PCS; children < 2yrs; urban	5%(1/22)	11%(10/90)	0.41 (0.06-3.03)#
Bissau (unpublished&)	1991	PCS; children < 10 yrs; urban	2%(10/412)	13%(64/478)	0.24 (0.12-0.49)*
Senegal (47)	1987-1994	PCS; rural	0%(0/127)	2%(18/1085)	0 (0-1.94)*
Ghana (48)	1989-1991	PCS; rural; Vitamin A trial with measles surveillance	10%(15/153)	17%(136/808)	OR=0.42 (0.21-0.83) $##
Kenya (22)	1986	SUR; all ages; rural	2%(2/41)	11%(11/98)	0.51(0.08-3.08)*
Kenya (49)	1988	SUR; Children <5yrs; rural	0%(0/23)	10%(18/182)	0 (0-1.54)*
Chad (50)	1993	SUR; rural	0%(0/23)	8%(61/801)	0 (0-2.18)
Niger (51)	2003-2004	SUR**; urban	0.4%(1/286)	6%(29/481)	0.06 (0.01-0.42)
Chad (51)	2004-2005	SUR** ; urban	0.4%(2/494)	8%(18/212)	0.05 (0.01-0.20)
Nigeria (51)	2004-2005	SUR**; rural	9%(1/11)	7%(79/1131)	1.30 (0.20-8.54)
Sudan (52)	2004	SUR;	0.4%(2/556)	1%(7/568)	0.29 (0.06-1.40)
Niger (53)	1991-1992	SUR; rural	17%(20/118)	15%(61/410)	1.14 (0.72-1.81)
Zimbabwe (54)	1980-1989	SUR; urban	2%(8/335)	7%(20/302)	0.36 (0.16-0.81)
Total					0.39 (0.31-0.49)

Sources: Reviews of measles case fatality studies (27-31) and PubMed search for measles mortality/case fatality in vaccinated children (see Supplementary material); & compiled by Henning Andersen shortly before he died.

Notes: PCS= prospective community studies; SUR= community surveys or outbreak investigations; 1. Mortality is high because only secondary cases are included in the analysis. Since this analysis is a subgroup within the larger study, it has not been included in the combined estimate; $ case fatality ratio calculated by the authors, the remaining studies have been calculated by us *adjusted for age; # adjusted for district; ## adjusted for age, sex, weight-for-age z-score, paternal education and season; ** Mortality was only reported for children with at least 30 days of follow-up whereas the proportion of

vaccinated was reported among all cases. It has been assumed that the proportion vaccinated cases was the same among those with follow-up as among all cases.

Table 3. Measles case-fatality ratio for measles-vaccinated and measles-unvaccinated cases in African prospective community studies and community surveys with long-term follow-up

Country	Period	Study; period of follow-up	Vaccinated cases (%) (deaths/persons)	Unvaccinated cases (%) (deaths/persons)	Mortality ratio
Guinea-Bissau (55)[1]	1988	PCS; 5 year follow-up;	4% (1/23)	16% (8/46)	0.25 (0.03-1.88)
Guinea-Bissau (38)	1984-1987	PCS; 2 year follow-up	0% (0/4)	14% (2/14)	0 (0-20.10)
Burundi (56) [2]	1988-1989	SUR; 7 month follow-up	3/1363 person-months	19/2629 person-months	0.30 (0.09-1.03)
Senegal (47)	1987-1994	PCS; 1 year follow-up	0% (0/127)	1% (15/1055)	0 (0-2.32)
Bissau (unpublished&)	1991-1994	PCS; 3 year follow-up	3% (8/319)	9% (29/338)	0.29 (0.14-0.63)
Total					0.27 (0.14-0.50)

Sources: Reviews of measles case fatality studies (27-31) and PubMed search for measles mortality/case fatality in vaccinated children (see Supplementary material); & compiled by Henning Andersen shortly before he died.
Notes: PCS= prospective community studies; SUR= community surveys or outbreak investigations; 1. There was no data on acute case fatality in the present study since the study only included children who had a convalescent sample collected; 2. This study did not report the acute case fatality but only overall mortality for the 7 months of follow-up.

Table 4. Measles case fatality ratio for infants and older children in African prospective community studies and community surveys

Country	Period	Type of study	Infants (%) (deaths/cases)	Children 1+ year (%) (deaths/cases)	Measles case-fatality ratio
Studies before the introduction of MV					
Gambia (63)#	1961	PCS; rural	31%(12/39)	13%(47/356)	2.33 (1.36-4.00)
Guinea-Bissau (45)	1979	PCS; Urban	28%(22/79)	14%(55/380)	1.92 (1.25-2.96)
Guinea-Bissau (64)	1980	PCS; Rural	47%(7/15)	21%(31/147)	2.21 (1.18-4.13)
Senegal (44)	1983-86	PCS; Rural	12%(19/165)	6%(79/1335)	1.95 (1.21-3.13)
Studies after introduction of MV					
Kenya (65)	1974-1976	PCS; rural	6%(4/63)	7%(24/361)	0.96 (0.34-2.66)
Kenya (65)	1976-1977	PCS; rural	4%(5/125)	1%(7/540)	3.09 (1.00-9.56)
Kenya (22)	1986	SUR; rural	17%(5/29)	7%(8/110)	2.37 (0.84-6.71)
Kenya (49)	1988	SUR; rural	22%(9/41)	5%(11/207)	4.13 (1.83-9.33)
Senegal (44)	1987-1990	PCS; rural	2%(1/43)	2%(9/598)	1.55 (0.20-11.9)
Senegal (47)	1991-1994	PCS; rural	6%(4/72)	1%(4/499)	6.93 (1.77-27.1)
Guinea-Bissau (66)	1980-1982	PCS; urban	30%(7/23)	9%(10/115)	3.50 (1.49-8.24)
Guinea-Bissau (45)	1983-1984	PCS; urban	9%(5/56)	7%(20/268)	1.20 (0.47-3.05)
Zaire (11)	1974-1977	PCS; urban	6%(12/194)	6%(53/844)	0.99 (0.54-1.81)
Ghana (48)	1989-1991	PCS; rural	21%(28/131)	15%(123/830)	1.44 (1.00-2.08)
Chad (50)	1993	SUR; urban	6%(9/156)	8%(52/668)	0.74 (0.37-1.47)
Niger (67)	2003	SUR; rural	16%(13/83)	9%(79/862)	1.71 (0.99-2.94)
Niger (53)	1991-1992	SUR; rural	40%(16/40)	13%(65/488)	3.00 (1.93-4.67)
Niger (51)	2003-2004	SUR; urban	7%(8/111)	3%(22/656)	2.15 (0.98-4.71)
Chad (51)	2004-2005	SUR; urban	5%(5/97)	2%(15/609)	2.09 (0.78-5.63)
Nigeria (51)	2004-2005	SUR; rural	11%(5/47)	7%(75/1095)	1.55 (0.66-3.66)
Zimbabwe (54)	1980-1989	SUR; rural	13%(13/103)	3%(15/534)	4.49 (2.20-9.16)
Sudan (52)	2004	SUR;	3%(1/36)	1%(9/1108)	3.42 (0.45-26.28)
Longer follow-up than 1 month					
Burundi (56)##	1989	SUR; rural; 7 months follow-up	14%(2/176 person-months)	6%(20/3816 person-months)	2.17 (0.51-9.20)
Gambia (68)	1981	SUR; rural; 9 months follow-up	64%(7/11)	10%(13/124)	6.07 (3.07-12.0)
Total					1.87 (1.63-2.14)

Sources: Reviews of measles case fatality studies (27-31) and PubMed search for community studies of measles mortality/case fatality in infants or by age in Africa (see Supplementary material).
Notes: MV=measles vaccine; PCS=prospective community study, i.e. the population was known before the epidemic and information is likely to have been obtained for all children; SUR= retrospective survey; # The age grouping is 7-12 months and 12-120 months. Measles deaths and total number of children in age group were reported in this study. It has been assumed that all children between 7 and 120 months contracted measles. In this period there were no measles vaccinations available. The last epidemic had occurred 12-13 years earlier; ## The age grouping is 0-8 and 9+ months; ¤ Numbers read from a graph

Table 5. Vaccine efficacy against overall mortality in randomised trials of an early two-dose measles vaccination schedule compared with the standard dose of measles vaccination at 9 months of age

Country and period	Age interval	Comparison (Vaccines)	Administration of DTP	Deaths/person-years or persons	Mortality rate ratio	Comments
Sudan (76) 1989-1992	5-9 months	MV vs Control (Meningococcal A+C)	DTP not given simultaneous with MV but could have been given after MV	1/60.5 vs 6/61.2	0.18 (0.02-1.54)	1st vaccine in 2-dose group was Connaught HTMV and 2nd dose was Schwarz standard MV
	9-36 months	2nd vs 1st MV		7/371.6 vs 7/355.9	0.96 (0.34-2.73)	
	5-36 months				0.60 (0.25-1.45)#	
Guinea-Bissau (77) 2003-2009	4.5-9 months	MV vs Control (no vaccine)	DTP not given simultaneous with MV and after MV; all had DTP3 one month before enrolment	5/398.8 vs 29/821.8	0.33 (0.13-0.86)	Vitamin A supplementation (VAS) at birth is not official policy. Hence, only results for children who did not receive VAS is presented.#
	9-36 months	2nd vs 1st MV		20/2054.4 vs 67/3881.1	0.56 (0.34-0.93)	
	4.5-36 months				0.50 (0.32-0.78)#	

Source: All studies reporting mortality in trials of two doses of measles vaccine (MV) (30,32,33). Only the per-protocol results have been used comparing children who received two doses of MV with those receiving one dose at 9 months. No additional studies of early two-dose measles vaccination reporting impact on mortality were found by PubMed searches (see Supplementary material).
Note: # The combined estimate (Stata) was 0.52 (0.35-0.77); if the children receiving vitamin A at birth were also included, the combined estimate was 0.69 (0.52-0.91).

Table 6. Vaccine efficacy against overall mortality for one dose of standard-titre measles vaccine before 9 months of age

Country	period	Comparison	Results
Early measles vaccination at 7 months of age compared with children unvaccinated community			
Congo (11)	1974-1977	MV administered at 7 months of age; children followed to 21 and 34 months of age. Mortality from 7 to 21 months of age for vaccinated children (3/230.5 pyrs) compared with unvaccinated children from control area (21/470.7 pyrs)	MRR for 7 to 21 months =0.29 (0.09-0.98) MRR for 7 to 34 months =0.52 (0.21-1.27)
Comparing MV at 4-8 months versus MV at 9-11 months of age			
Guinea-Bissau (78)	1980-1982	Natural experiment: MV at 4-8 versus MV at 9-11 mo compared from 9 to 60 months of age	MRR (MV-4-8mo/MV-9-11mo) 0.69 (0.46-1.08)
Comparing children randomsied to MV at 6 months versus IPV at 6 months during a war situation			
Guinea-Bissau (80)	1998	Children were randomised to MV (4/214) or inactivated polio vaccine (11/219) at 6 months of age. Due to a war they did not received the planned MV at 9 mo. Follow-up for 3 months in a war situation	70% (13 to 92)

Sources: All studies examining the general effect of standard measles vaccine (MV) on child survival (as compiled by all available reviews (30,32,33)) have been screened for information on measles vaccination before 9 months of age. There have been several other studies of the impact of MV before 12 months of age on child survival (81-89) but most of these studies could not distinguish the effect of MV before 9 months of age. However, all studies suggested that early MV had a better effect on child survival than later MV. The studies where children received DTP or IPV with early MV or shortly after MV have not been included in the present table (34-36) since this sequence have unfortunate consequences (34,36). No additional studies of one-dose measles vaccination/immunization before 9 months of age reporting impact on mortality were found by PubMed searches (see Supplementary material).

The optimal age of measles immunization in low-income countries: 35 years with a policy based on flawed assumptions

Search strategy: For each assumption we used existing reviews and in December 2011 we made a PubMed search for relevant papers as described below. The title and abstract of papers in English, French, Portuguese, Spanish, German and Scandinavian languages was assessed to ascertain whether the paper was potentially relevant. Potentially relevant papers were read. The large majority of papers were not from Africa, were reviews or case reports and not community based studies, had no information on mortality, or the vaccine was not single dose measles vaccine.

Assumption 1: children who seroconvert to measles vaccine have absolute protection against measles infection.
We searched for "measles infection seropositive vaccinated children" (N=12) and "measles vaccine failure" (N=318). There are many case reports that contradict that seroconverted children have absolute protection but no African community study.

Assumption 2: vaccinated children who do not seroconvert are fully susceptible to measles infection.
We searched for "measles infection seronegative vaccinated children" (N=13) and "measles vaccine failure" (N=318). This provided only one relevant reference (37).

Assumption 3: severity of measles infection in vaccinated children ("vaccine failures") and unvaccinated children is the same.
We searched for "measles mortality vaccinated children" (N=143), "measles vaccine mortality" (N=775), "measles case fatality" (N=161) and "measles vaccine failure" (N=318). Relevant studies included in Tables 2 and 3.

Assumption 4: severity of measles is the same whether measles infection is acquired in infancy or later.
We searched for "measles case fatality" (N=161) and "measles mortality/death Africa" (N=620). Relevant studies included in Table 4.

Assumption 5: vaccine failures lead to lack of credibility of the vaccination programme.
We searched "measles vaccine failure" (N=318) and "measles vaccine/vaccination/immunisation credibility" (N=2). This search produced one paper dealing with the relationship between "vaccine failure" and the acceptance or credibility of measles vaccination (69). One study was known from our own research (43).

Assumption 6: it had to be a one-dose policy.
We used the reviews of measles vaccination studies (30,32,33) and search papers on *Two/2 dose measles vaccine trial" (N=144), "Two/2 dose measles vaccination/immunization and mortality/death" (N=108) and "early measles vaccination/immunization mortality/death" (N=123). This produced only two trials of the effect on child survival of a 2-dose measles vaccinations schedule compared with a 1-dose schedule (see Table 5).

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE : The optimal age of measles immunization in low-income countries: 35 years with a policy based on flawed assumptions			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Only in abstract, page 2
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4-5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5, supplementary annex
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary annex
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Supplementary annex
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Supplementary annex
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Supplementary annex
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6

PRISMA 2009 Checklist

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency ($e.g., I^2$) for each meta-analysis.	6

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Discussion page 10
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Supplementary annex
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Tables 2-6
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	5,7
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Tables 2-6
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Pages 6-9
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	7,10
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	3,10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	12-14
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	14

The optimal age of measles immunization in low-income countries: A secondary analysis of the assumptions underlying the current policy~~35 years with a policy based on flawed assumptions~~

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Running title: Optimal age of measles vaccination

Word counts: Abstract: 293; Text: 5685

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Abstract

Background and objective The current policy of measles vaccination at 9 months of age ~~in low-income countries~~ was decided in the mid-1970s ~~following a study of seroconversion at different ages in Kenya~~. The policy was ~~was~~ not tested for ~~its overall~~ impact on child survival ~~but was based on six assumptions~~. We examined the empirical evidence for the six~~se~~ underlying assumptions.

Data sources and methods These assumptions have not been research issues. Hence, we examined review articles and case reports to assess the empirical evidence for the original assumptions. ~~Existing reviews and additional literature~~ The search was limited to ~~of~~ African community studies of measles infection.

Main outcome The predicted effect on ~~measles and all-cause~~ mortality.

Results In retrospect the major assumptions were based on false premises. First, in the single study examining this point ~~All assumptions were flawed. Most notably,~~ seronegative vaccinated children ~~may have~~ had considerable protection against measles infection. Second, in 18 community studies vaccinated measles cases ("vaccine failures") had three-fold lower ~~have around one-third the~~ case fatality than~~of~~ unvaccinated ~~measles~~ cases. Third, in 24 community studies, infants ~~measles cases have~~ had ~~around~~ two~~2~~-fold higher case fatality than older measles cases. Fourth, the only study examining the assumption that "vaccine failures" ~~did not~~ lead to lack of confidence found the ~~because the~~ opposite because vaccinated children had milder measles infection. Fifth, a one-dose policy was recommended. However, ~~in~~ the two randomised trials of early two-dose measles vaccination compared with one-dose ~~at 9 months of age, mortality was~~ vaccination found significantly reduced mortality until 3 years ~~of age~~. Thus current evidence ~~Had these factors been studied~~ ,suggests that the optimal age for a single dose of measles vaccine ~~would probably~~ should have been 6 or 7 months~~, leading~~ resulting in ~~to more mild "vaccine failures" among older children, but~~ fewer severe unvaccinated cases among infants but more mild "vaccine failures" among older children. Furthermore, the two-dose trials indicate that measles vaccine reduces mortality from other causes than measles infection.

Conclusions Many lives may have been lost by not determining the optimal age of measles vaccination. Despite this ~~The current measles vaccination policy is still based on assumptions about seroconversion and it is now~~ the current recommend~~ed~~ation is to increase the age of measles vaccination to 12 months in countries with limited measles transmission. T~~Based on current evidence t~~his policy ~~is likely to~~ may lead to an increase in child mortality.

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Article summary

Article focus

- An empirical analysis of the six assumptions underlying the current measles vaccination policy for low-income countries.
- Determine the implications for child survival of not testing the optimal measles vaccination policy.

Key messages

- All six assumptions were flawed; most important were the assumptions that seronegative vaccinated children ~~who did not seroconvert~~ are fully susceptible to measles infection, that the severity of measles is the same in vaccinated cases ("vaccine failures") and in unvaccinated children, that the severity of measles infection is the same in infancy or later, and that it had to be a one-dose programme.
- The current evidence suggests that the optimal age for a single dose of measles vaccine would probably have been 6 or 7 months of age had the policy been tested.
- An early two-dose schedule at 4-5 months and 9 months of age would have been even better in terms of reducing child mortality.

Strength and limitations

- The current measles vaccination policy for low-income countries is not based on any evidence about the impact on overall child survival.
- There are few studies testing some of the assumptions. However, for the two key assumptions relating to severity of measles in vaccinated infants and children there is ample evidence which suggests that measles is less severe in vaccinated cases.

Introduction

With the spectacular success in measles control in the last 10-15 years(1-3) and the current policy to move ahead with elimination and eventually eradication of measles infection (4), there is now a discussion of when to introduce the second dose of measles vaccine (5). However, few people realize that the key policy of vaccinating against measles at 9 months of age in low-income countries is not based on evidence documenting the optimal age of measles vaccination to reduce overall child mortality.

In the 1970s policy makers found it necessary to formulate a common policy for low-income countries (6-8) since many donors and scientists at the time questioned the value of measles vaccination. Measles infection was believed to kill mainly malnourished children likely to die of other infections if not from measles and hence some people thought that measles vaccine would not reduce overall mortality, but merely change the cause of death (9-11). The policy makers' definition of the optimal age of measles vaccination of 9 months was based on a number of assumptions (6-8). Though these assumptions for vaccinating at age 9 months were not subsequently substantiated the policy has remained in effect. Recently, though, it has been recommended that primary measles vaccination should be at 12 months of age in countries where measles infection has been controlled (12).

~~Before the global policy is changed it is timely to examine the empirical basis for the assumptions underlying the current policy. Since these assumptions have not been research issues we have had to use a search strategy including review articles and case reports to assess the validity of the original assumptions (see supplementary material). The present analysis suggests that all these assumptions were flawed. Had the policy been tested in randomised trials measuring the impact on mortality of vaccination at different ages it is likely that the age of measles vaccination had been changed, with the result that the measles vaccination programme had had a much larger effect on child survival in low-income countries.~~

~~The optimal age of measles immunization: Six assumptions~~

In the first measles vaccination campaigns in West and Central Africa in the 1960s children were targeted from 6 months of age (13-17). Initially it was thought that it would be sufficient to conduct campaigns every 2nd or 3rd year to control measles. However, the epidemiologists soon learned that shorter intervals of 6 or 12 months between campaigns were necessary to control measles. In the 1970s, routine vaccination programmes were introduced and the optimal age of routine measles vaccination was debated (18-20). Following the experience with the campaigns, several African countries recommended measles vaccination at 6, 7 or 8 months of age. A study sponsored by the Ministry of Health in Kenya and WHO assessed the seroconversion rates at different ages between 5 and 12 months and recommended measles vaccination at 7½ months of age (21). For several years measles vaccine was administered at 8 months of age in Kenya (22). Similar studies of seroconversion were conducted in Latin America (23). Since some of those vaccinated at 6 months were not protected some countries and many researchers recommended a second dose at 9 months of age or later (20,24). However, there were

fears that early vaccination would produce too many vaccine failures and a one-dose programme was considered necessary because mothers would not bring their children back for a second dose (15,25). Therefore, the Expanded Programme on Immunization (EPI) recommended a one-dose policy (6-8,18). In 1980, the Global Advisory Group of EPI endorsed this policy and recommended measles vaccination as early as possible after 9 months of age (7).

Before the global policy is changed to 12 months of age it is timely to examine the empirical basis for the assumptions underlying the current policy. Since these assumptions have not been research issues we have had to use a search strategy including review articles and case reports to assess the validity of the original assumptions (see Supplementary Material). The present analysis suggests that in retrospect all assumptions were flawed. Had the policy been tested in randomised trials measuring the impact on mortality of vaccination at different ages it is likely that the age of measles vaccination had been changed, with the result that the measles vaccination programme would have had a much larger effect on child survival in low-income countries.

Methods

The optimal age of measles immunization: the underlying assumptions

The recommendation was based on the belief that the expected reduction in mortality could be computed from seroconversion rates (18,26) and the policy was justified several times by analyses of the seroconversion data from Kenya (6,8). In these analyses it was assumed that seroconversion was associated with full protection against measles infection (*assumption 1*) and that non-seroconversion was associated with full susceptibility to measles infection (*assumption 2*). As shown in Table 1 (Column 2), the data from Kenya (21) showed that seroconversion increased with age. This was not unexpected since the calculation of this measure (a fourfold or more increase over baseline) is dependent on level of maternal antibody which wanes as the child ages. Based on cumulative measles incidence figures (Column 1), it was calculated how many measles cases had been prevented assuming everybody was vaccinated at a specific age (Column 3), how many "vaccine failures" would occur after the age of vaccination (Column 4) and how many cases would occur before the specific age of vaccination (Column 5). In making these calculations it was assumed that "vaccine failures" and unvaccinated measles cases were equally severe (*assumption 3*) and that it did not matter whether measles was acquired in infancy or later in childhood (*assumption 4*). Vaccination at 8, 9, and 10 months of age prevented roughly the same proportion of cases, between 79% and 84% (Column 3) (6,8). Vaccination at 8 month resulted in considerably more vaccine failures (15%) than vaccination at 9 months (7%). Since vaccine failures were assumed to jeopardize the credibility of the measles immunization programme (*assumption 5*) (6,8,18), it was concluded that the optimal age for administration of measles vaccine would be 9 months. At the time the EPI assumed that the case fatality in measles infection was 4% in Africa and it will be seen in Column 6 that the number of estimated measles deaths in a birth cohort of a 1000 children would indeed be lowest (between 6.4 and 8.4) for vaccination at 8-10 months of age. In making this analysis of the effect of only one dose of measles

vaccine (6,8), the EPI assumed that a two-dose policy was not feasible or unjustified (*assumption 6*).

~~Methods~~

Selection of studies. Following the identification of the underlying assumptions, ~~W~~we looked for empirical evidence in community studies to support or refute their validity~~se assumptions~~. The original policy was mainly justified in relation to the epidemiology of measles infection in Africa where the case fatality was clearly higher than in other regions (27-31). Most community studies of measles infection are indeed from Africa and we have therefore restricted the analyses and the tables 2-4 to the African studies. These tables are believed to be exhaustive for Africa and they are not contradicted by community studies from Latin America and Asia. For the analysis of the impact of measles vaccination on child mortality we included all studies from Asia and Latin America.

The search strategy has been defined in the S~~s~~upplementary M~~m~~aterial. Since there are few specific studies to test the six assumptions we have had to use case reports of measles outbreaks to assess their validity. Over the last 20-25 years, several reviews of community studies of the measles case fatality compiled studies of relevance for particularly assumption three and four (27-31). Furthermore, as specified in the supplementary material, we made PubMed searches for additional publications relevant for all assumptions. We included one unpublished report from a large epidemic in Bissau in 1991-1992 which has remained unpublished because the physician (Henning Andersen) handling the epidemic died tragically in an accident shortly after the epidemic.

We distinguished between prospective community studies and surveys retrospectively assessing events since the precision of information on vaccination status and age presumably is better in prospective studies. Though hospital and health centre studies may have data on the severity of measles infection by vaccination status or age, we have not included these studies in the analysis since biased admission for some groups might have made the result non-representative.

Since the analysis of the assumptions suggested that measles vaccination before 9 months of age could be beneficial, we assessed the empirical evidence from studies which assessed the effect of early measles vaccination on mortality. Again we used all reviews of community studies and trials assessing the impact of measles vaccination on child mortality (30,32-35). Additional PubMed searches for studies comparing the mortality of measles vaccinated and unvaccinated children did not identify further studies. As explained in the footnote to table 6, we have emphasised the studies in which inactivated vaccines were not administered simultaneously with MV or after MV as such combination or sequences can have a negative effect on child survival (34,36).

Presentation. For each assumption, we briefly outline the background. Next we present the relevant studies found and then analyse the common trends, identifying the secondary analyses which have been made. Finally, we considered whether methodological issues and data quality might question the trends suggested by the analysis.

Statistical analyses. In the combined analyses of several studies we used the Mantel-Haenszel (MH) weighted relative risk stratifying for study or age groups to estimate common trends.

~~**Statistical analyses**. The Mantel-Haenszel weighted relative risk stratifying for study or age groups was used to estimate common trends.~~

Ethics. Since the study is a secondary analysis ~~based on review~~ of existing data, approval from an ethical committee was not needed.

Results

Assumption 1: children who seroconvert to measles vaccine have absolute protection against measles infection.

Background. It has usually been assumed that previous measles infection is associated with life-long immunity. This idea was transferred to measles vaccination when the vaccine was developed in the 1950s. Hence, if someone had antibodies after vaccination these were also assumed to provide life-long protection.

Data: We searched for "measles infection seropositive vaccinated children" and "measles vaccine failure" (Supplementary material). There are many case reports that contradict that seroconverted children have absolute protection but no African community study.

Analysis. A number of smaller studies have documented that a few children do get measles after having seroconverted (37-40). Hence, seroconversion does not give absolute protection.

Considerations. However, ~~T~~there are no general epidemiological studies from Africa and it is therefore difficult to estimate the proportion of children who get measles in spite of having seroconverted, but since no large series have been reported it is likely to be small.

Assumption 2: vaccinated children who ~~do not seroconvert~~are seronegative are fully susceptible to measles infection.

Background. Measles immunity has generally been considered an either-or phenomenon. If a vaccinated child was seronegative it was assumed that the child was fully susceptible.

Data: We searched for "measles infection seronegative vaccinated children" and "measles vaccine failure" (Supplementary material). This provided only one relevant reference (37).

Analysis. In a study in Senegal, vaccinated children who were seronegative when exposed to measles infection at home had a 49% (95% CI 21-68%) protection against clinical disease compared with unvaccinated seronegative children exposed under similar

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conditions (37). ~~It is possible that the children had acquired vaccine-induced measles antibodies earlier but subsequently lost them. Based on the literature search, no other study has tested the susceptibility of vaccinated "seronegative" children. If approximately half the seronegative children have clinical protection it would have major consequences for the calculation of the optimal age of measles vaccine. Cellular immunity may be obtained without having measurable antibodies (41). There is also good evidence from studies of hepatitis B vaccination that antibody concentration wane with time but the majority of older seronegative children if infected are protected from chronic carriage and its damaging consequences (42).~~

Considerations. Apparently, no other study has tested the susceptibility of vaccinated "seronegative" children. It is possible that some children had acquired vaccine-induced measles antibodies earlier but subsequently lost them. Cellular immunity may be obtained without having measurable antibodies (41). There is also good evidence from studies of hepatitis B vaccination that antibody concentration wane with time but the majority of older seronegative children if infected are protected from chronic carriage and its damaging consequences (42).

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The concept of seroconversion to compare the effect of vaccination at different age is in itself problematic. Seroconversion is not the same as seroprotection and the use of the term inevitably disadvantages data from studies that have vaccinated at earlier ages when maternal antibodies are still present. Thus a child immunized at 6 months of age when the maternal antibody level is say 62.5 mIU may fail the test for conversion (a four-fold increase) yet still have a protective level of 125 mIU at 9 months of age.

If approximately half the seronegative children have clinical protection it would have major consequences for the calculation of the optimal age of measles vaccine.

Assumption 3: severity of measles infection in vaccinated children ("vaccine failures") and unvaccinated children is the same.

Background. The EPI perceived "vaccine failures" as due to the vaccine being inactivated by improper storage and handling or due to neutralization of the vaccine by maternal antibodies (16,19). Hence, it was assumed that these children had been fully susceptible to measles infection. However, many epidemiological studies in the 1980s and 1990s suggested that measles vaccinated children who contracted measles infection had milder disease (43,44). This would suggest that the children had partial measles immunity, not enough to protect them but enough to modify the severity of the disease.

Data: We searched for "measles mortality vaccinated children", "measles vaccine mortality", "measles case fatality" and "measles vaccine failure" (Supplementary material). The 18 relevant studies are included in Tables 2 and 3.

Analysis. ~~The EPI perceived "vaccine failures" as due to the vaccine being inactivated by improper storage and handling or due to neutralization of the vaccine by maternal~~

~~antibodies (16,19). Hence, it was assumed that these children were fully susceptible to measles infection. However, many epidemiological studies in the 1980s and 1990s suggested that measles-vaccinated children who contracted measles infection had milder disease (43,44). This would suggest that the children had partial measles immunity, not enough to protect them but enough to modify the severity of the disease.~~ TIn the community studies of the acute measles case fatality are shown in Table 2. Only two African studies (43, 48) have reported significant differences in mortality for vaccinated and unvaccinated measles cases. A combined analysis has not been made previously. ~~,~~ T~~t~~he measles case fatality was 2 to 5-fold lower for vaccinated cases ("vaccine failures") than for unvaccinated children with measles infection in nearly all studies. Using MH weighted relative risk, t~~T~~he effect was similar in the prospective community studies (case-fatality ratio=0.37 (0.27-0.52)) and the retrospective surveys (case-fatality ratio=0.41 (0.29-0.56)).

~~All studies with relevant data were included in Table 2 irrespective of whether vaccine efficacy (VE) against measles infection was high or substandard. In several studies, the VE was not high but nonetheless the vaccine appeared to have had an effect; for example, in Kenya VE was only 18% but measles-vaccinated children who developed measles had still 2-fold lower measles mortality than measles-unvaccinated children (Table 2). Only one community survey from Niger reported that measles vaccine was not particularly effective against measles infection and that there was no effect of vaccination on the case fatality in measles infection (53).~~

A few studies followed the children for longer than ~~the~~ one month which is the normal time limit for acute measles deaths. The long-term trend was the same with considerable better survival among vaccinated than unvaccinated children after measles infection (Table 3). Combining the prospective community studies in Tables 2 and 3 would suggest a 3-fold reduction in acute and/or long-term mortality among vaccinated children even though some of the vaccine failures may have been due to inactivated measles vaccines.

In the four studies (38,47,56, unpublished) with information on both acute and long-term mortality, mortality was nearly 5-fold lower for the vaccinated cases (MH weighted mortality ratio= 0.21 (0.13-0.34)). ~~Several hospital or health centre based studies have also compared vaccinated and unvaccinated children and reported that measles vaccinated children had less severe measles infection (57-59). A few community studies from India and Papua New Guinea have also suggested lower case fatality for vaccinated measles cases (60,61).~~

Considerations. Only two studies did not show lower case fatality among vaccinated children and five of the 18 studies in Tables 2 and 3 showed significantly lower mortality among vaccinated children.

All studies with relevant data were included in Tables 2 and 3 irrespective of whether vaccine efficacy (VE) against measles infection was high or substandard. In several studies, the VE was not high but nonetheless the vaccine appeared to have had an effect; for example, in Kenya VE was only 18% but measles-vaccinated children who developed

measles had still 2-fold lower measles mortality than measles unvaccinated children (Table 2). Only one community survey from Niger reported that measles vaccine was not particularly effective against measles infection and that there was no effect of vaccination on the case fatality in measles infection (53).

In most ~~of the epidemiological~~ studies (Table 2), it was not possible to control for age given the way the data was reported. However, in 6 studies (22, 43, 45, 47, 49, unpublished data) age could be controlled. ~~and t~~In these studies ~~here was little difference in~~ the crude MH weighted case-fatality ratio was ~~in the unadjusted analysis (~~0.27 (0.17-0.42)~~)~~; when the comparison was stratified by age group, ~~and the age-adjusted analysis (~~the MH weighted case-fatality ratio became 0.30 (0.18-0.49)~~)~~.

It could be speculated that vaccinated children had more health-system-compliant mothers and that they therefore had more care and milder infection. However, in many of the original studies from the 1980s, measles vaccine had been provided in community campaigns and not in routine service and vaccination status depended on whether the mother had been around at the time of the campaign and not on bias (43). In the studies which adjusted for background factors, the differential effect of vaccination on the measles case fatality was actually increased (43,48). Furthermore, several studies have found that "vaccine failures" occur after high intensity of exposure, i.e. "vaccine failures" are more likely to be secondary cases exposed at home (43,44). Since secondary cases have a higher case fatality than index cases (43,44,62), the milder infection among vaccinated children is even more surprising. The possibility that measles vaccinated children have milder disease due to modified immune responses and not merely due to social confounding is strengthened by the many studies showing that measles vaccination is associated with beneficial effects on overall child survival (32,33).

Several hospital or health centre based studies have also compared vaccinated and unvaccinated children and reported that measles vaccinated children had less severe measles infection (57-59). A few community studies from India and Papua New Guinea have also suggested lower case fatality for vaccinated measles cases (60,61).

If the severity of measles is not the same in vaccinated and unvaccinated children it would strongly affect the estimated benefit of vaccinations at different ages.

Assumption 4: severity of measles is the same whether measles infection is acquired in infancy or later.

Background. In the hypothetical EPI model in which all children were vaccinated at a specific age, the unvaccinated measles cases would occur in infancy, before measles vaccination, whereas most "vaccine failures" would occur much later after the first year of life. No adjustment was made for how this affected the overall measles mortality. Most infections are more severe in infancy but on the other hand, modification of severity by maternal antibodies could have reduced the case fatality among infants.

Data: We therefore searched for studies of "measles case fatality" and "measles mortality/death Africa" (Supplementary material). We found 24 relevant studies.

Analysis. The African community studies reporting the measles case fatality separately for infants and older children have been presented in Table 4. One review of East African studies of measles have previously emphasised that the case fatality was particularly high in infants (69). However, a comparative analysis of the measles case fatality for infants and older children in all African community studies have not been made before. With a few exceptions, the studies suggested that the case fatality is higher in infancy than among older children (Table 4). These studies suggest around a two-fold higher measles case-fatality in infancy; the MH weighted case fatality ratio for all studies was 1.87 (1.63-2.14). The effect was similar before measles vaccine was introduced in these communities (MH weighted case fatality ratio=2.04 (1.58-2.63)) (see Studies before the introduction of MV, Table 4).

Considerations. Only three studies did not show higher case fatality in infancy and half the studies showed significantly higher mortality in infancy. Even if a few studies should not have been found by the search terms, it seems unlikely that additional studies would change the tendency.

~~In the hypothetical EPI model in which all children were vaccinated at a specific age, the unvaccinated measles cases would occur in infancy, before measles vaccination, whereas most "vaccine failures" would occur much later after the first year of life. The epidemiological evidence is consistent in suggesting that the case fatality is higher in infancy than among older children in African community studies (Table 4). These studies suggest around a two-fold higher measles case-fatality in infancy, the case fatality ratio being 1.87 (1.63-2.14). The effect was similar before measles vaccine was introduced in these communities (case fatality ratio=2.04 (1.58-2.63)) (see Studies before the introduction of MV, Table 4).~~ If the case fatality ~~th~~is ~~at was~~ indeed higher in infancy~~the case~~, it would be more advantageous to have vaccine failures later in life rather than leave infants less than 9 months of age unprotected.

Assumption 5: vaccine failures lead to lack of credibility of the vaccination programme.

Background. Apparently it was assumed that African mothers – like physicians - would lose confidence if measles vaccine did not provide complete and life-long immunity.

Data: We searched "measles vaccine failure" and "measles vaccine/vaccination/immunisation credibility" This search produced one paper dealing with the relationship between "vaccine failure" and the acceptance or credibility of measles vaccination (70). One study was known from our own research (43).

Analysis. One study from Tanzania stated that acceptance of measles vaccination was low because of the many failures experienced by children vaccinated before 9 months of age.

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In the only community study which examined the credibility of the programme in relation to previous experiences with "vaccine failures", younger siblings of "vaccine failures" had a significant higher coverage for measles vaccination (95% (33/35)) than siblings of children who had been successfully vaccinated and not had measles infection (78% (630/809)). Hence, the younger siblings of "vaccine failures" were significantly more likely to have been measles vaccinated (relative risk= 1.21 (1.11-1.32)) (43).

Considerations. The study from Tanzania provided no specific information on how data had been collected and how low acceptance had been measured (70). In contrast to this negative view of measles vaccination, many African mothers have experienced that vaccinated children have mild measles infection (43). In cultures where mothers have learnt that everybody has to get measles, the advantage of "mild measles" is easy to see whereas it is difficult to "see" complete "life-long protection" if you still expect your child will get measles some day. ~~Apparently it was assumed that African mothers would loose confidence if measles vaccine did not provide complete and life-long immunity. One study from Tanzania stated that acceptance of measles vaccination was low because of the many failures experienced by children vaccinated before 9 months of age but provided no specific information on how data had been collected (69). In contrast, many African mothers have experienced that vaccinated children have mild measles (43). In cultures where mothers have learnt that everybody has to get measles, the advantage of "mild measles" is easy to see whereas it is difficult to "see" complete "life-long protection" if you still expect your child will get measles some day. In the only community study which examined the credibility of the programme in relation to "vaccine failures", we showed that the younger siblings of "vaccine failures" had a significant higher coverage for measles vaccination (95% (33/35)) than siblings of children who had been successfully vaccinated and not had measles infection (78% (630/809)) (relative risk= 1.21 (1.11-1.32)) (36).~~ Hence, it may have worked the other way around; seeing your child get mild measles after vaccination would be a strong argument for the value of measles vaccination~~strengthened the credibility of the programme~~.

Assumption 6: it had to be a one-dose policy.

Background. The main argument advanced for a one-dose policy was that compliance with the second dose was too low (15,18,68,71). This is surprising since it has been described that mothers sought vaccination so eagerly that it was impossible to maintain the age eligibility criteria for vaccinations during campaigns (16). The reason why mothers did not seek the second dose of measles vaccine in some countries may have been poor information. In Guinea-Bissau, we had very good compliance and improved overall coverage with a two-dose schedule (72). The two-dose group had better protection against measles infection than the one-dose group (72). A two-dose schedule has also been shown to be effective in Niger (73), India (74) and Saudi Arabia (75). Hence, a two-dose schedule is both feasible and effective.

Data: To identify studies comparing the effect on survival of a one-dose and a two-dose policy we used the reviews of measles vaccination and impact on mortality (30,32,33)

and searched papers on "Two/2 dose measles vaccine trial", "Two/2 dose measles vaccination/immunization and mortality/death" and "early measles vaccination/immunization mortality/death". These procedures identified only two trials of the effect on child survival of a 2-dose measles vaccinations schedule compared with a 1-dose schedule (see Table 5) and one observational study (78)

~~The main argument advanced for a one-dose policy was that compliance with the second dose was too low (15,18,68,70). This is surprising since it has been described that mothers sought vaccination so eagerly that it was impossible to maintain the age eligibility criteria for vaccinations during campaigns (16). The reason why mothers did not seek the second dose of measles vaccine in some countries may have been poor information. In Guinea-Bissau, we had very good compliance and improved overall coverage with a two-dose schedule (71). The two-dose group had better protection against measles infection than the one-dose group (71). A two-dose schedule has also been shown to be effective in Niger (72), India (73) and Saudi Arabia (74). Hence, a two-dose schedule is both feasible and effective.~~

Analysis. Only two trials have compared child mortality following two doses of MV (the first being given before 9 months) with mortality after the standard dose of MV (at 9 months of age) (Table 5). In a small trial from Sudan (7~~5~~6), DTP vaccinations were not controlled and many children received DTP after measles vaccine. DTP administered with or after measles vaccine has negative effects on female survival (34,36). We therefore conducted a large randomized trial including only children who had received DTP3 before enrolment and therefore would not receive DTP after MV (7~~6~~7). Among children who had not received neonatal vitamin A supplementation (VAS) which interacted negatively with early MV(76), two doses of MV at 4.5 and 9 months of age compared with the current policy of one dose at 9 months of age reduced mortality between 4.5 and 36 months of age by 50% (22-68%) in the per-protocol analysis (Table 5). There was a significant reduction in non-measles related mortality of 45% (14-65%) (7~~6~~7). The combined estimate for the two trials showed that the early two-dose measles vaccination strategy may reduce mortality by as much as 48% (23%-65%) compared with the currently recommended standard dose at 9 months of age. Even if the children receiving neonatal VAS were included, the combined estimate was 31% (9-48%) (Table 5).

The only other study to report mortality after two doses of MV is a natural experiment from Guinea-Bissau in the early 1980s. Children were vaccinated in annual or biannual campaigns rather than through routine service. Hence, it was possible to compare in an unbiased way the survival of children who happened to be less than 9 months of age when vaccinated and those vaccinated at the recommended age of 9-11 for MV. MV at 4-8 months and a later dose after 9 months compared with one dose of MV at 9-11 months of age was associated with 59% (15-81%) lower mortality between 9 months and 5 years of age (7~~7~~8). ~~Hence, the two-dose studies indicate that a two-dose policy providing the first dose of MV before 9 months of age is associated with major reductions in child mortality.~~

Considerations. The studies indicate that a two-dose policy providing the first dose of MV before 9 months of age is associated with major reductions in child mortality compared with the current one-dose at 9 month policy. The studies indicated that the benefit was not due to better protection against measles infection. Hence, these studies strongly supported that early measles vaccination has non-specific beneficial effects on child survival.

The implications of the assumptions for the estimated prevention of measles mortality. We calculated how variations in these six assumptions affect the optimal age of MV in terms of reducing measles mortality (Table 1, Columns 7-10). Using the best estimate that the case fatality rate is three-fold one third lower for vaccinated measles cases than for unvaccinated cases (Tables 2 and 3), the number of estimated measles deaths would have been lowest with one dose of MV general vaccination at 8 months (Column 7). Assuming furthermore that infants have two2-fold higher case fatality than older children (Table 4) the estimated number of measles deaths would have been lowest after vaccination at age 7 months (Column 8). Hence, it might have been better to vaccinate at 7 months of age and have some more vaccine failures later in childhood than to have many unvaccinated cases with high mortality in infancy. Adjusting for the possibility that non-seroconverting vaccinated children have some protection from cellular immunity or low levels of antibodies (37), the optimal age for measles immunization in a one-dose strategy would have moved to 6 or 7 months of age (Columns 9 and 10).

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 (721–776,798). Hence, an early dose at 4-6 months of age and a second dose at 9 months of age would have eliminated virtually all measles mortality and significantly reduced mortality from other causes as well.

Discussion

The main justification for measles vaccination at 9 months of age in low-income countries was to reduce child mortality from measles infection (18). However, the policy was never tested for its effect on survival. The policy was based on assumptions which were believed to be true, and a small seroconversion study (6-8). Thirty-five years ago the six assumptions appeared self-evident and programmatic decisions had to be taken about the optimal age for measles vaccination. However, though all assumptions have been contradicted for years no change has been made in the policy.

Strength and weaknesses

Since the six assumptions have not been research issues there are few studies conducted specifically with these topics in mind. We have therefore had to use a search strategy including review articles and case reports to find studies to assess the validity of the original assumptions. There may be a few more studies which were not found with the literature search since several of the studies identified in previous reviews were not found by the search terms. However, many reviews over the last 25 years have covered the areas of community studies of measles infection and the impact of MV on mortality so it

is unlikely that there would be many studies not included. Furthermore, the estimates from different studies were consistent and it is unlikely that the addition of further studies would have a major impact on the estimates.

The assumed case fatality of measles infection does not matter for the estimated impact of the optimal policy on measles mortality. With another case fatality level the epidemiological arguments about assumptions 2-4 would still have the same relative effects on the number of deaths prevented. However, as evident in Tables 2 and 4, most community studies from Africa suggest that the case fatality may have been higher than 4% and the impact of the optimal measles vaccination strategy on overall mortality may therefore have been even larger. Other assumptions may also have been important; for example, the incidence data were from a rural study rather than from an urban area (21). In an urban area the incidence would have been higher at younger ages and it might have been advantageous to vaccinate even earlier. As maternal measles antibody levels have declined in low-income countries (7~~8~~8), earlier vaccination would also have produced better seroconversion rates and it would have been even more advantageous to vaccinate early.

Consistency with previous studies: The non-specific beneficial effects of MV. The conclusion that earlier measles vaccination is likely to have been better for child survival is based on a reconsideration of the programme´s own assumptions about effect on measles mortality. However, what is the empirical evidence for the impact on mortality of measles vaccine before 9 months of age?

In marked contradiction to the original fear that children dying of measles would just die of something else and that measles vaccination would therefore only change the cause of death but not the level of mortality (9-11), all subsequent studies measuring the effect on survival have found marked benefit from measles vaccination (32,33,36,7~~7~~8,80~~79~~-8~~8~~9). Several studies have assessed the impact of measles vaccine before 12 months of age (30,32,33) but few studies have separately measured the effect on overall mortality of measles vaccination before 9 months of age in an unbiased way (Table 6). In the 1970s, researchers in Congo followed two districts which initially had similar overall mortality levels and then introduced measles vaccination at 7 months of age in one district (11). Measles vaccination administered at 7 months of age reduced overall mortality between 7 and 21 months of age by 71% (2-91%) compared with the neighbouring district which did not get measles vaccination (60). In the early 1980s in Guinea-Bissau, children were vaccinated in annual or biannual campaigns. Hence, it was possible to compare in a "natural experiment" manner the survival of children who had been measles vaccinated before 9 months of age and those vaccinated at 9 months of age, the recommended age of measles vaccination. One dose of MV at 4-8 months compared with 9-11 months of age was associated with 31% (-8-54%) lower mortality between 9 months and 5 years of age (7~~7~~8). As mention above the effect was even stronger if they also received a second dose of MV after 9 months of age. During a civil war in Guinea-Bissau in 1998 (80~~79~~), we followed children who had been randomised to measles vaccination at 6 months of age compared with children who had been randomised to inactivated polio vaccine (IPV). Due to the war the children did not get the standard measles vaccination at 9 months of

age. During the 3 months of intensive fighting when everybody had fled the study area and mortality was high, the children vaccinated against measles at 6 months of age had 70% (13-92%) lower mortality than the unvaccinated group.

These studies of one dose of MV before 9 months of age as well as the studies of early two-dose MV mentioned above suggest that the reduction in mortality from MV before 9 months of age is much larger than can be explained by the prevention of measles infection. WHO estimates that measles deaths caused 10% of under-five deaths (~~8~~90). However all available studies of the mortality impact of MV (30,32,33) suggest that the effect of measles immunization on mortality is much greater than expected. This beneficial effect is a consistent observation and it can not be explained by the prevention of acute measles infection. First, all studies, in which measles vaccine was not administered with DTP, provided strong evidence of a beneficial effect of measles vaccine on overall mortality (32). Second, all studies censoring for measles infection in the survival analysis to estimate the impact on non-measles related mortality found that prevention of measles-specific deaths explained little and the beneficial effect was due to prevention of non-measles related mortality (32,76,8~~8,~~9, ~~0~~91). For example, in the per-protocol analysis of the largest randomised trial (776), measles vaccine at 4.5 and 9 months compared with the standard dose at 9 months of age reduced non-measles related mortality significantly for all children. Third, the beneficial effect of measles vaccine is usually stronger for girls than for boys (776,921~~,~~923). Since measles mortality is not higher for girls than boys, this observation suggests sex-differential mechanisms related to immune stimulation. Hence, standard measles vaccine may protect against other infections and have a beneficial effect on child survival even when measles is eliminated.

Though the focus here has been on MV administered before 9 months of age there is also a considerable number of studies indicating that MV administered after 9 months of age have non-specific beneficial effects (32,810-865, 910, 943).

The possible biological explanations for non-specific beneficial effects of MV have not been explored in humans. In animal studies of heterologous immunity, previous stimulation with infections may have a major effect on the capacity to handle a lethal dose of an unrelated infection (954). Two trials from Bissau suggest that the beneficial effect of MV is better for children vaccinated in the presence of maternal measles antibodies than for children having no measurable maternal antibodies at the time of MV (898). This may also help explain why MV before 9 months of age is better than later vaccination.

The optimal age of measles vaccination: optimizing seroconversion or impact on overall child survival. The most unfortunate consequence of not testing the optimal age of measles immunization may have been that the beneficial non-specific effects of MV were not detected (32). To the extent MV has non-specific beneficial effects the question of the optimal age of measles vaccination acquires a new meaning. By lowering the age of measles vaccination, children would benefit not only from earlier protection against measles infection but also from the beneficial non-specific effects against non-measles infections and overall child mortality would be reduced. On the other hand, if the age of

vaccination is increased, children would benefit less from the non-specific beneficial effects and overall child mortality would increase. Hence, policies optimizing the non-specific effects clash with those designed to enhance seroconversion.

Conclusions: Old assumptions linger on

The supplementary immunization activities (SIA) with measles vaccine has eliminated measles infection in Latin America and reduced the incidence in major ways in the rest of the world (1-3). The world is now planning to eliminate and eventually eradicate measles infection (4). With the SIA success in measles control, the optimal age of measles immunization is likely to be considered an irrelevant issue. However, as discussed above, measles vaccine has also non-specific effects which need to be taken into consideration in the planning of vaccination programmes. The prevention of all-cause mortality rather than measles mortality should be the primary objective. In a culture which advocates evidence-based policies (4), the evidence for the current measles vaccination policy – or rather the lack thereof - should be properly reviewed and revised by the global and regional immunization programmes. Otherwise old assumptions about seroconversion rates being the basis for the optimal age of immunisation may linger on and continue to influence policy.

There are major consequences of focusing solely on specific measles mortality. First, as the current policy is mostly determined by our understanding that seroconversion gets better with increasing age, the tendency will be that with improved control of measles infection, age of vaccination will be increased. Following the elimination of measles in Latin America, the recommended age of primary measles immunization was raised to 12 months in 1996 (3). Again this decision was based on assumptions and not on studies documenting the overall effect on morbidity and mortality. Following the success of measles campaigns in other continents it has also been recommended by SAGE (the Strategic Advisory Group of Experts) to increase the age of measles vaccination to 12 months in areas with low levels of measles transmission (5,12). The underlying assumption about better seroconversion at higher ages may no longer be valid with the decline in maternal antibody levels (798,965). For example, we have obtained 100% seropositivity and 99% protective levels after measles vaccine at 9 months of age with both Schwarz and Edmonston-Zagreb measles vaccine strains in Guinea-Bissau (976).

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 (11,32,38,765-8079,889). There is a tendency to dismiss these observations because randomised trials with overall mortality as an outcome have ~~to date~~ only been conducted in Guinea-Bissau and it is therefore claimed that the global health community has to wait for verification elsewhere (987). However, the non-specific beneficial effects of MV have been shown in several other countries with high childhood mortality. For example, in a cross-over design, Shann showed that girls receiving standard measles vaccine at 9-10 months of age in five randomised trials in Sudan, Gambia, Senegal and Guinea-Bissau had 47% lower mortality through childhood than control children who received an inactivated vaccine at 9-10 months of age (943). Since the control children had received MV before 9 months of age and did not get measles, the difference in

mortality following MV at 9 months of age was a non-specific beneficial effect not related to prevention of measles infection. Increasing the age of measles vaccine from 9 to 12 months may reduce the beneficial effects in the age group between 9 and 12 months of age in which mortality is still high. Thus the lives lost by this change of schedule could well be more than the lives saved by improved measles control (776).

Second, in the current paradigm for control of infectious diseases, the ultimate success in public health is to eradicate the disease and then remove the vaccine to reduce economic costs as happened for smallpox in the 1970s (26). This may happen for measles infection within the next 10-20 years (989). If measles vaccine has major beneficial non-specific effects (776), to remove measles vaccine or reduce its coverage would increase child mortality levels considerably in low-income countries unless we in the meantime find a vaccine which has all the same beneficial effects as measles vaccine.

After 35 years, it is time to develop a policy for the optimal age of measles immunization. This policy needs to be based on evidence about the impact on overall health and child-survival and not only on assumptions about the impact of specific prevention against measles infection. A two-dose measles vaccination strategy, providing measles vaccine at 4.5 months of age, after the three DTP vaccines, and again at 9 months of age, may significantly improve child survival and provide a solid basis of immunity which if necessary can be enhanced by supplementary measles immunisation activities at a later age (767,789). Any future changes in the age of measles immunisation due to elimination of measles infection, changes in the epidemiology of measles infection, decline in maternal antibody levels, introduction of new measles vaccines or in the timing of other vaccines should be tested in trials to determine their overall impact on child health.

Contributions*:* PA and HW have been involved in studies of measles vaccination for more than 30 years in West Africa; MLG, CM, CB and AR have been involved in measles vaccination trials since the early 1990s. The first draft was written by PA; all authors contributed to the final version of the paper. PA will act as guarantor of the study.

Conflict of interest: nothing to declare

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Table 1. Projected reduction in measles cases and measles deaths with measles immunization at ages four to ten months. Machakos, Kenya 1974-1981

Expanded Programme on Immunization model (8)						Estimated number of measles deaths in a cohort of 1000 children				
	Column1	Column 2	Column 3	Column 4	Column 5	Column 6	Column 7	Column 8	Column 9	Column 10
	Cumulative measles incidence (%)	Serocon-version from MV (%)	Prevented cases (%)	Vaccine Failures (%)	Cases prior to MV(%)	EPI assumption: Case fatality 4%	Adjusting vaccination status[1]	Adjusting vaccination status and age of infection[2]	Adjusting vaccination status, age of infection, and seronegative 50% protection[3]	Adjusting vaccination status, age of infection, and seronegative 25% protection[3]
Age 4 months	0.5	15	15	85	0	34	11.3	11.3	5.7	8.5
Age 5 months	1.0	35	35	65	0	26	8.6	8.6	4.3	6.5
Age 6 months	2.8	52	51	48	1	19.6	6.8	7.2	**4.0**	5.6
Age 7 months	6.1	72	69	28	3	12.4	4.9	***6.1***	4.3	**5.2**
Age 8 months	9.5	86	79	15	6	8.4	***4.4***	6.8	5.8	6.3
Age 9 months	14.4	95	84	7	9	***6.4***	4.5	8.1	7.7	7.9
Age 10 months	18.6	98	82	4	14	7.2	6.1	11.7	11.5	11.6

Notes: MV=measles vaccine; The estimated number of measles deaths was obtained by multiplying the number of vaccine failures (column 4) and cases prior to MV (column 5) in a cohort of 1000 children by the case fatality rates as indicated in the following notes: 1. Assumption: The relative case fatality ratio is 1/3 for vaccinated versus unvaccinated cases, i.e. 4% for unvaccinated cases and 1.33% for vaccinated cases. 2. Assumption: The relative case fatality ratio is 1/3 for vaccinated versus unvaccinated cases. The case fatality ratio is twice as high for unvaccinated cases occurring in infancy. Hence, the estimated case fatality ratios are 8% for unvaccinated cases occurring in infancy and 1.33% for vaccinated cases. 3. Assumption: Seronegative children had 50% or 25%

protection against measles. Hence, the estimated case fatality ratios are 8% for unvaccinated cases occurring in infancy and 1.33% for vaccinated cases but there were fewer vaccinated cases than indicated in column 4.

Table 2. ARelative acute measles case fatality ratio for measles-vaccinated and measles-unvaccinated cases in African prospective community studies and community surveys

Country	Period	Study	Vaccinated cases (%) (deaths/cases)	Unvaccinated cases (%) (deaths/cases)	Measles case fatality ratio
Bissau (43)	1980-82	PCS; urban	9%(5/53)	17%(18/108)	0.58 (0.23-1.49)*
Bissau (43)[1]	*1980-82*	*PCS; urban (only secondary cases)*	*14%(3/21)*	*46%(11/24)*	*0.30 (0.10-0.86)**
Guinea-Bissau (45)	1983-1984	PCS; urban	4%(4/90)	9%(21/234)	0.41 (0.14-1.22)*
Guinea-Bissau (38)	1984-1987	PCS; 2 year follow-up	0% (0/4)	13% (2/16)	0 (0-23.10)
Bissau (46)	1985-1987	PCS; children < 2yrs; urban	5%(1/22)	11%(10/90)	0.41 (0.06-3.03)#
Bissau (unpublished&)	1991	PCS; children < 10 yrs; urban	2%(10/412)	13%(64/478)	0.24 (0.12-0.49)*
Senegal (47)	1987-1994	PCS; rural	0%(0/127)	2%(18/1085)	0 (0-1.94)*
Ghana (48)	1989-1991	PCS; rural; Vitamin A trial with measles surveillance	10%(15/153)	17%(136/808)	OR=0.42 (0.21-0.83) $##
Kenya (22)	1986	SUR; all ages; rural	2%(2/41)	11%(11/98)	0.51(0.08-3.08)*
Kenya (49)	1988	SUR; Children <5yrs; rural	0%(0/23)	10%(18/182)	0 (0-1.54)*
Chad (50)	1993	SUR; rural	0%(0/23)	8%(61/801)	0 (0-2.18)
Niger (51)	2003-2004	SUR**; urban	0.4%(1/286)	6%(29/481)	0.06 (0.01-0.42)
Chad (51)	2004-2005	SUR** ; urban	0.4%(2/494)	8%(18/212)	0.05 (0.01-0.20)
Nigeria (51)	2004-2005	SUR**; rural	9%(1/11)	7%(79/1131)	1.30 (0.20-8.54)
Sudan (52)	2004	SUR;	0.4%(2/556)	1%(7/568)	0.29 (0.06-1.40)
Niger (53)	1991-1992	SUR; rural	17%(20/118)	15%(61/410)	1.14 (0.72-1.81)
Zimbabwe (54)	1980-1989	SUR; urban	2%(8/335)	7%(20/302)	0.36 (0.16-0.81)
Total					0.39 (0.31-0.49)

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Sources: Reviews of measles case fatality studies (27-31) and PubMed search for measles mortality/case fatality in vaccinated children (see Supplementary material); & compiled by Henning Andersen shortly before he died.

Notes: PCS= prospective community studies; SUR= community surveys or outbreak investigations; 1. Mortality is high because only secondary cases are included in the analysis. Since this analysis is a subgroup within the larger study, it has not been included in the combined estimate; $ case fatality ratio calculated by the authors, the remaining studies have been calculated by us *aAdjusted for age; # adjusted for district; ## adjusted for age, sex, weight-for-age z-score, paternal education and season; ** Mortality was only reported for children with at least 30 days of follow-up whereas the proportion of

vaccinated was reported among all cases. It has been assumed that the proportion vaccinated cases was the same among those with follow-up as among all cases.

Table 3. MRelative measles case-fatality ratio for measles-vaccinated and measles-unvaccinated cases in African prospective community studies and community surveys with long-term follow-up

Country	Period	Study; period of follow-up	Vaccinated cases (%) (deaths/persons)	Unvaccinated cases (%) (deaths/persons)	Mortality ratio
Guinea-Bissau (55)[1]	1988	PCS; 5 year follow-up;	4% (1/23)	16% (8/46)	0.25 (0.03-1.88)
Guinea-Bissau (38)	1984-1987	PCS; 2 year follow-up	0% (0/4)	14% (2/14)	0 (0-20.10)
Burundi (56) [2]	1988-1989	SUR; 7 month follow-up	3/1363 person-months	19/2629 person-months	0.30 (0.09-1.03)
Senegal (47)	1987-1994	PCS; 1 year follow-up	0% (0/127)	1% (15/1055)	0 (0-2.32)
Bissau (unpublished&)	1991-1994	PCS; 3 year follow-up	3% (8/319)	9% (29/338)	0.29 (0.14-0.63)
Total					0.27 (0.14-0.50)

Sources: Reviews of measles case fatality studies (27-31) and PubMed search for measles mortality/case fatality in vaccinated children (see Supplementary material); & compiled by Henning Andersen shortly before he died.
Notes: PCS= prospective community studies; SUR= community surveys or outbreak investigations; 1. There was no data on acute case fatality in the present study since the study only included children who had a convalescent sample collected; 2. This study did not report the acute case fatality but only overall mortality for the 7 months of follow-up.

Table 4. MRelative measles case fatality ratio for infants and older children in African prospective community studies and community surveys

Country	Period	Type of study	Infants (%) (deaths/cases)	Children 1+ year (%) (deaths/cases)	Measles case-fatality ratio
Studies before the introduction of MV					
Gambia (63)#	1961	PCS; rural	31%(12/39)	13%(47/356)	2.33 (1.36-4.00)
Guinea-Bissau (45)	1979	PCS; Urban	28%(22/79)	14%(55/380)	1.92 (1.25-2.96)
Guinea-Bissau (64)	1980	PCS; Rural	47%(7/15)	21%(31/147)	2.21 (1.18-4.13)
Senegal (44)	1983-86	PCS; Rural	12%(19/165)	6%(79/1335)	1.95 (1.21-3.13)
Studies after introduction of MV					
Kenya (65)	1974-1976	PCS; rural	6%(4/63)	7%(24/361)	0.96 (0.34-2.66)
Kenya (65)	1976-1977	PCS; rural	4%(5/125)	1%(7/540)	3.09 (1.00-9.56)
Kenya (22)	1986	SUR; rural	17%(5/29)	7%(8/110)	2.37 (0.84-6.71)
Kenya (49)	1988	SUR; rural	22%(9/41)	5%(11/207)	4.13 (1.83-9.33)
Senegal (44)	1987-1990	PCS; rural	2%(1/43)	2%(9/598)	1.55 (0.20-11.9)
Senegal (47)	1991-1994	PCS; rural	6%(4/72)	1%(4/499)	6.93 (1.77-27.1)
Guinea-Bissau (66)	1980-1982	PCS; urban	30%(7/23)	9%(10/115)	3.50 (1.49-8.24)
Guinea-Bissau (45)	1983-1984	PCS; urban	9%(5/56)	7%(20/268)	1.20 (0.47-3.05)
Zaire (11)	1974-1977	PCS; urban	6%(12/194)	6%(53/844)	0.99 (0.54-1.81)
Ghana (48)	1989-1991	PCS; rural	21%(28/131)	15%(123/830)	1.44 (1.00-2.08)
Chad (50)	1993	SUR; urban	6%(9/156)	8%(52/668)	0.74 (0.37-1.47)
Niger (67)	2003	SUR; rural	16%(13/83)	9%(79/862)	1.71 (0.99-2.94)
Niger (53)	1991-1992	SUR; rural	40%(16/40)	13%(65/488)	3.00 (1.93-4.67)
Niger (51)	2003-2004	SUR; urban	7%(8/111)	3%(22/656)	2.15 (0.98-4.71)
Chad (51)	2004-2005	SUR; urban	5%(5/97)	2%(15/609)	2.09 (0.78-5.63)
Nigeria (51)	2004-2005	SUR; rural	11%(5/47)	7%(75/1095)	1.55 (0.66-3.66)
Zimbabwe (54)	1980-1989	SUR; rural	13%(13/103)	3%(15/534)	4.49 (2.20-9.16)
Sudan (52)	2004	SUR;	3%(1/36)	1%(9/1108)	3.42 (0.45-26.28)
Longer follow-up than 1 month					
Burundi (56)##	1989	SUR; rural; 7 months follow-up	14%(2/176 person-months)	6%(20/3816 person-months)	2.17 (0.51-9.20)
Gambia (68)	1981	SUR; rural; 9 months follow-up	64%(7/11)	10%(13/124)	6.07 (3.07-12.0)
Total					1.87 (1.63-2.14)

Sources: Reviews of measles case fatality studies (27-31) and PubMed search for community studies of measles mortality/case fatality in infants or by age in Africa (see Supplementary material).
Notes: MV=measles vaccine; PCS=prospective community study, i.e. the population was known before the epidemic and information is likely to have been obtained for all children; SUR= retrospective survey; # The age grouping is 7-12 months and 12-120 months. Measles deaths and total number of children in age group were reported in this study. It has been assumed that all children between 7 and 120 months contracted measles. In this period there were no measles vaccinations available. The last epidemic had occurred 12-13 years earlier; ## The age grouping is 0-8 and 9+ months; ¤ Numbers read from a graph

Table 5. Vaccine efficacy against overall mortality in randomised trials of an early two-dose measles vaccination schedule compared with the standard dose of measles vaccination at 9 months of age

Country and period	Age interval	Comparison (Vaccines)	Administration of DTP	Deaths/person-years or persons	Mortality rate ratio	Comments
Sudan (756) 1989-1992	5-9 months	MV vs Control (Meningococcal A+C)	DTP not given simultaneous with MV but could have been given after MV	1/60.5 vs 6/61.2	0.18 (0.02-1.54)	1st vaccine in 2-dose group was Connaught HTMV and 2nd dose was Schwarz standard MV
	9-36 months	2nd vs 1st MV		7/371.6 vs 7/355.9	0.96 (0.34-2.73)	
	5-36 months				0.60 (0.25-1.45)#	
Guinea-Bissau (767) 2003-2009	4.5-9 months	MV vs Control (no vaccine)	DTP not given simultaneous with MV and after MV; all had DTP3 one month before enrolment	5/398.8 vs 29/821.8	0.33 (0.13-0.86)	Vitamin A supplementation (VAS) at birth is not official policy. Hence, only results for children who did not receive VAS is presented.#
	9-36 months	2nd vs 1st MV		20/2054.4 vs 67/3881.1	0.56 (0.34-0.93)	
	4.5-36 months				0.50 (0.32-0.78)#	

Source: All studies reporting mortality in trials of two doses of measles vaccine (MV) (30,32,33). Only the per-protocol results have been used comparing children who received two doses of MV with those receiving one dose at 9 months. No additional studies of early two-dose measles vaccination reporting impact on mortality were found by PubMed searches (see Supplementary material).
Note: # The combined estimate (Stata) was 0.52 (0.35-0.77); if the children receiving vitamin A at birth were also included, the combined estimate was 0.69 (0.52-0.91).

Table 6. Vaccine efficacy against overall mortality for one dose of standard-titre measles vaccine before 9 months of age

Country	period	Comparison	Results
Early measles vaccination at 7 months of age compared with children unvaccinated community			
Congo (11)	1974-1977	MV administered at 7 months of age; children followed to 21 and 34 months of age. Mortality from 7 to 21 months of age for vaccinated children (3/230.5 pyrs) compared with unvaccinated children from control area (21/470.7 pyrs)	MRR for 7 to 21 months =0.29 (0.09-0.98) MRR for 7 to 34 months =0.52 (0.21-1.27)
Comparing MV at 4-8 months versus MV at 9-11 months of age			
Guinea-Bissau (787)	1980-1982	Natural experiment: MV at 4-8 versus MV at 9-11 mo compared from 9 to 60 months of age	MRR (MV-4-8mo/MV-9-11mo) 0.69 (0.46-1.08)
Comparing children randomsied to MV at 6 months versus IPV at 6 months during a war situation			
Guinea-Bissau (8079)	1998	Children were randomised to MV (4/214) or inactivated polio vaccine (11/219) at 6 months of age. Due to a war they did not received the planned MV at 9 mo. Follow-up for 3 months in a war situation	70% (13 to 92)

Sources: All studies examining the general effect of standard measles vaccine (MV) on child survival (as compiled by all available reviews (30,32,33)) have been screened for information on measles vaccination before 9 months of age. There have been several other studies of the impact of MV before 12 months of age on child survival (801-897) but most of these studies could not distinguish the effect of MV before 9 months of age. However, all studies suggested that early MV had a better effect on child survival than later MV. The studies where children received DTP or IPV with early MV or shortly after MV have not been included in the present table (34-36) since this sequence have unfortunate consequences (34,36). No additional studies of one-dose measles vaccination/immunization before 9 months of age reporting impact on mortality were found by PubMed searches (see Supplementary material).

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The optimal age of measles immunization in low-income countries: A secondary analysis of the assumptions underlying the current policy

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Abstract

Objective: The current policy of measles vaccination at 9 months of age was decided in the mid-1970s. The policy was not tested for impact on child survival but was based on studies of seroconversion after measles vaccination at different ages. We examined the empirical evidence for the six underlying assumptions.

Design: Secondary analysis

Data sources and methods: These assumptions have not been research issues. Hence, we examined case reports to assess the empirical evidence for the original assumptions. We used existing reviews and in December 2011 we made a PubMed search for relevant papers The title and abstract of papers in English, French, Portuguese, Spanish, German and Scandinavian languages was assessed to ascertain whether the paper was potentially relevant. Based on cumulative measles incidence figures we calculated how many measles cases had been prevented assuming everybody was vaccinated at a specific age, how many "vaccine failures" would occur after the age of vaccination, and how many cases would occur before the specific age of vaccination. In the combined analyses of several studies we used the Mantel-Haenszel (MH) weighted relative risk stratifying for study or age groups to estimate common trends.

Setting and participants: African community studies of measles infection.

Primary and secondary outcomes: Consistency between assumptions and empirical evidence and the predicted effect on mortality.

Results: In retrospect the major assumptions were based on false premises. First, in the single study examining this point, seronegative vaccinated children had considerable protection against measles infection. Second, in 18 community studies vaccinated measles cases ("vaccine failures") had three-fold lower case fatality than unvaccinated cases. Third, in 24 community studies, infants had two-fold higher case fatality than older measles cases. Fourth, the only study examining the assumption that "vaccine failures" lead to lack of confidence found the opposite because vaccinated children had milder measles infection. Fifth, a one-dose policy was recommended. However, the two randomised trials of early two-dose measles vaccination compared with one-dose vaccination found significantly reduced mortality until 3 years of age. Thus current evidence suggests that the optimal age for a single dose of measles vaccine should have been 6 or 7 months resulting in fewer severe unvaccinated cases among infants but more mild "vaccine failures" among older children. Furthermore, the two-dose trials indicate that measles vaccine reduces mortality from other causes than measles infection.

Conclusions: Many lives may have been lost by not determining the optimal age of measles vaccination. Since seroconversion continues to be the basis for policy, the current recommendation is to increase the age of measles vaccination to 12 months in countries with limited measles transmission. This policy may lead to an increase in child mortality.

Article summary

Article focus

- An empirical analysis of the six assumptions underlying the current measles vaccination policy for low-income countries.
- Determine the implications for child survival of not testing the optimal measles vaccination policy.

Key messages

- All six assumptions were flawed; most important were the assumptions that seronegative vaccinated children are fully susceptible to measles infection, that the severity of measles is the same in vaccinated cases ("vaccine failures") and in unvaccinated children, that the severity of measles infection is the same in infancy or later, and that it had to be a one-dose programme.
- The current evidence suggests that the optimal age for a single dose of measles vaccine would probably have been 6 or 7 months of age had the policy been tested.
- An early two-dose schedule at 4-5 months and 9 months of age would have been even better in terms of reducing child mortality.

Strength and limitations

- The current measles vaccination policy for low-income countries is not based on any evidence about the impact on overall child survival.
- The literature search and assessment was only carried out by one researcher. There are few studies testing some of the assumptions. However, for the two key assumptions relating to severity of measles in vaccinated infants and children there is ample evidence which suggests that measles is less severe in vaccinated cases.

Introduction

With the spectacular success in measles control in the last 10-15 years(1-3) and the current policy to move ahead with elimination and eventually eradication of measles infection (4), there is now a discussion of when to introduce the second dose of measles vaccine (5). However, few people realize that the key policy of vaccinating against measles at 9 months of age in low-income countries is not based on evidence documenting the optimal age of measles vaccination to reduce overall child mortality.

In the 1970s policy makers found it necessary to formulate a common policy for low-income countries (6-8) since many donors and scientists at the time questioned the value of measles vaccination. Measles infection was believed to kill mainly malnourished children likely to die of other infections if not from measles and hence some people thought that measles vaccine would not reduce overall mortality, but merely change the cause of death (9-11). The policy makers' definition of the optimal age of measles vaccination of 9 months was based on a number of assumptions (6-8). Though these assumptions for vaccinating at age 9 months were not subsequently substantiated the policy has remained in effect. Recently, though, it has been recommended that primary measles vaccination should be at 12 months of age in countries where measles infection has been controlled (12).

In the first measles vaccination campaigns in West and Central Africa in the 1960s children were targeted from 6 months of age (13-17). Initially it was thought that it would be sufficient to conduct campaigns every 2nd or 3rd year to control measles. However, the epidemiologists soon learned that shorter intervals of 6 or 12 months between campaigns were necessary to control measles. In the 1970s, routine vaccination programmes were introduced and the optimal age of routine measles vaccination was debated (18-20). Following the experience with the campaigns, several African countries recommended measles vaccination at 6, 7 or 8 months of age. A study sponsored by the Ministry of Health in Kenya and WHO assessed the seroconversion rates at different ages between 5 and 12 months and recommended measles vaccination at 7½ months of age (21). For several years measles vaccine was administered at 8 months of age in Kenya (22). Similar studies of seroconversion were conducted in Latin America (23). Since some of those vaccinated at 6 months were not protected some countries and many researchers recommended a second dose at 9 months of age or later (20,24). However, there were fears that early vaccination would produce too many vaccine failures and a one-dose programme was considered necessary because mothers would not bring their children back for a second dose (15,25). Therefore, the Expanded Programme on Immunization (EPI) recommended a one-dose policy (6-8,18). In 1980, the Global Advisory Group of EPI endorsed this policy and recommended measles vaccination as early as possible after 9 months of age (7).

Before the global policy is changed to 12 months of age it is timely to examine the empirical basis for the assumptions underlying the current policy. Since these assumptions have not been research issues we have had to use a search strategy including review articles and case reports to assess the validity of the original assumptions. The present analysis suggests that in retrospect all assumptions were flawed. Had the policy

been tested in randomised trials measuring the impact on mortality of vaccination at different ages it is likely that the age of measles vaccination had been changed, with the result that the measles vaccination programme would have had a much larger effect on child survival in low-income countries.

Methods

The optimal age of measles immunization: the underlying assumptions

The recommendation was based on the belief that the expected reduction in mortality could be computed from seroconversion rates (18,26) and the policy was justified several times by analyses of the seroconversion data from Kenya (6,8). In these analyses it was assumed that seroconversion was associated with full protection against measles infection (*assumption 1*) and that non-seroconversion was associated with full susceptibility to measles infection (*assumption 2*). As shown in Table 1 (Column 2), the data from Kenya (21) showed that seroconversion increased with age. This was not unexpected since the calculation of this measure (a fourfold or more increase over baseline) is dependent on level of maternal antibody which wanes as the child ages. Based on cumulative measles incidence figures (Column 1), it was calculated how many measles cases had been prevented assuming everybody was vaccinated at a specific age (Column 3), how many "vaccine failures" would occur after the age of vaccination (Column 4) and how many cases would occur before the specific age of vaccination (Column 5). In making these calculations it was assumed that "vaccine failures" and unvaccinated measles cases were equally severe (*assumption 3*) and that it did not matter whether measles was acquired in infancy or later in childhood (*assumption 4*). Vaccination at 8, 9, and 10 months of age prevented roughly the same proportion of cases, between 79% and 84% (Column 3) (6,8). Vaccination at 8 month resulted in considerably more vaccine failures (15%) than vaccination at 9 months (7%). Since vaccine failures were assumed to jeopardize the credibility of the measles immunization programme (*assumption 5*) (6,8,18), it was concluded that the optimal age for administration of measles vaccine would be 9 months. At the time the EPI assumed that the case fatality in measles infection was 4% in Africa and it will be seen in Column 6 that the number of estimated measles deaths in a birth cohort of a 1000 children would indeed be lowest (between 6.4 and 8.4) for vaccination at 8-10 months of age. In making this analysis of the effect of only one dose of measles vaccine (6,8), the EPI assumed that a two-dose policy was not feasible or unjustified (*assumption 6*).

Selection of studies. Following the identification of the underlying assumptions, we looked for empirical evidence in community studies to support or refute their validity. The original policy was mainly justified in relation to the epidemiology of measles infection in Africa where the case fatality was clearly higher than in other regions (27-31). Most community studies of measles infection are indeed from Africa and we have therefore restricted the analyses and the tables 2-4 to the African studies. These tables are believed to be exhaustive for Africa and they are not contradicted by community studies from Latin America and Asia. For the analysis of the impact of measles vaccination on child mortality we included all studies from Asia and Latin America.

Since there are few specific studies to test the six assumptions we have had to use case reports of measles outbreaks to assess their validity. Over the last 20-25 years, several reviews of community studies of the measles case fatality compiled studies of relevance for particularly assumption three and four (27-31), two of these being by the first author (PA). For each assumption we used existing reviews and in December 2011 the first author made a PubMed search for relevant papers as described below. The title and abstract of papers in English, French, Portuguese, Spanish, German and Scandinavian languages was assessed by the first author to ascertain whether the paper was potentially relevant. Potentially relevant papers were read. Most papers were not from Africa but were reviews or case reports and not community based studies and had no information on mortality. We included one unpublished report from a large epidemic in Bissau in 1991-1992 which has remained unpublished because the physician (Henning Andersen) handling the epidemic died tragically in an accident shortly after the epidemic.

We distinguished between prospective community studies and surveys retrospectively assessing events since the precision of information on vaccination status and age presumably is better in prospective studies. Though hospital and health centre studies may have data on the severity of measles infection by vaccination status or age, we have not included these studies in the analysis since biased admission for some groups might have made the result non-representative.

Since the analysis of the assumptions suggested that measles vaccination before 9 months of age could be beneficial, we assessed the empirical evidence from studies which assessed the effect of early measles vaccination on mortality. Again we used all reviews of community studies and trials assessing the impact of measles vaccination on child mortality (30,32-35). Additional PubMed searches for studies comparing the mortality of measles vaccinated and unvaccinated children did not identify further studies. As explained in the footnote to table 6, we have emphasised the studies in which inactivated vaccines were not administered simultaneously with MV or after MV as such combination or sequences can have a negative effect on child survival (34,36).

Presentation. For each assumption, we briefly outline the background. Next we present the relevant studies found and then analyse the common trends, identifying the secondary analyses which have been made. Finally, we considered whether methodological issues and data quality might question the trends suggested by the analysis.

Statistical analyses. Based on cumulative measles incidence data we calculated how many measles cases and measles death had been prevented assuming everybody was vaccinated at a specific age, how many "vaccine failures" would occur after the age of vaccination, and how many cases would occur before the specific age of vaccination. It was estimated how this calculation was influenced by the empirical evidence for the underlying assumptions. In the combined analyses of several studies we used the Mantel-Haenszel (MH) weighted relative risk stratifying for study or age groups to estimate common trends.

Ethics. Since the study is a secondary analysis of existing data, approval from an ethical committee was not needed.

Results

Assumption 1: children who seroconvert to measles vaccine have absolute protection against measles infection.

Background. It has usually been assumed that previous measles infection is associated with life-long immunity. This idea was transferred to measles vaccination when the vaccine was developed in the 1950s. Hence, if someone had antibodies after vaccination these were also assumed to provide life-long protection.

Data: We searched for "measles infection seropositive vaccinated children" (N=12) and "measles vaccine failure" (N=318). There are many case reports that contradict that seroconverted children have absolute protection but no African community study.

Analysis. A number of smaller studies have documented that a few children do get measles after having seroconverted (37-40). Hence, seroconversion does not give absolute protection.

Considerations. However, there are no general epidemiological studies from Africa and it is therefore difficult to estimate the proportion of children who get measles in spite of having seroconverted, but since no large series have been reported it is likely to be small.

Assumption 2: vaccinated children who are seronegative are fully susceptible to measles infection.

Background. Measles immunity has generally been considered an either-or phenomenon. If a vaccinated child was seronegative it was assumed that the child was fully susceptible.

Data: We searched for "measles infection seronegative vaccinated children" (N=13) and "measles vaccine failure" (N=318). This provided only one relevant reference (37).

Analysis. In a study in Senegal, vaccinated children who were seronegative when exposed to measles infection at home had a 49% (95% CI 21-68%) protection against clinical disease compared with unvaccinated seronegative children exposed under similar conditions (37).

Considerations. Apparently, no other study has tested the susceptibility of vaccinated "seronegative" children. It is possible that some children had acquired vaccine-induced measles antibodies earlier but subsequently lost them. Cellular immunity may be obtained without having measurable antibodies (41). There is also good evidence from studies of hepatitis B vaccination that antibody concentration wane with time but the majority of older seronegative children if infected are protected from chronic carriage and its damaging consequences (42).

The concept of seroconversion to compare the effect of vaccination at different age is in itself problematic. Seroconversion is not the same as seroprotection and the use of the term inevitably disadvantages data from studies that have vaccinated at earlier ages when maternal antibodies are still present. Thus a child immunized at 6 months of age when the maternal antibody level is say 62.5 mIU may fail the test for conversion (a four-fold increase) yet still have a protective level of 125 mIU at 9 months of age.

If approximately half the seronegative children have clinical protection it would have major consequences for the calculation of the optimal age of measles vaccine.

Assumption 3: severity of measles infection in vaccinated children ("vaccine failures") and unvaccinated children is the same.

Background. The EPI perceived "vaccine failures" as due to the vaccine being inactivated by improper storage and handling or due to neutralization of the vaccine by maternal antibodies (16,19). Hence, it was assumed that these children had been fully susceptible to measles infection. However, many epidemiological studies in the 1980s and 1990s suggested that measles vaccinated children who contracted measles infection had milder disease (43,44). This would suggest that the children had partial measles immunity, not enough to protect them but enough to modify the severity of the disease.

Data: We searched for "measles mortality vaccinated children" (N=143), "measles vaccine mortality" (N=775), "measles case fatality" (N=161) and "measles vaccine failure" (N=318). The 18 relevant studies are included in Tables 2 and 3.

Analysis. The community studies of the acute measles case fatality are shown in Table 2. Only two African studies (43, 48) have reported significant differences in mortality for vaccinated and unvaccinated measles cases. A combined analysis has not been made previously. The measles case fatality was 2 to 5-fold lower for vaccinated cases ("vaccine failures") than for unvaccinated children with measles infection in nearly all studies. Using MH weighted relative risk, the effect was similar in the prospective community studies (case-fatality ratio=0.37 (0.27-0.52)) and the retrospective surveys (case-fatality ratio=0.41 (0.29-0.56)).

A few studies followed the children for longer than one month which is the normal time limit for acute measles deaths. The long-term trend was the same with considerable better survival among vaccinated than unvaccinated children after measles infection (Table 3). Combining the prospective community studies in Tables 2 and 3 would suggest a 3-fold reduction in acute and/or long-term mortality among vaccinated children even though some of the vaccine failures may have been due to inactivated measles vaccines.

In the four studies (38,47,56, unpublished) with information on both acute and long-term mortality, mortality was nearly 5-fold lower for the vaccinated cases (MH weighted mortality ratio= 0.21 (0.13-0.34)).

Considerations. Only two studies did not show lower case fatality among vaccinated children and five of the 18 studies in Tables 2 and 3 showed significantly lower mortality among vaccinated children.

All studies with relevant data were included in Tables 2 and 3 irrespective of whether vaccine efficacy (VE) against measles infection was high or substandard. In several studies, the VE was not high but nonetheless the vaccine appeared to have had an effect; for example, in Kenya VE was only 18% but measles-vaccinated children who developed measles had still 2-fold lower measles mortality than measles unvaccinated children (Table 2). Only one community survey from Niger reported that measles vaccine was not particularly effective against measles infection and that there was no effect of vaccination on the case fatality in measles infection (53).

In most studies (Table 2), it was not possible to control for age given the way the data was reported. However, in 6 studies (22, 43, 45, 47, 49, unpublished data) age could be controlled. In these studies the crude MH weighted case-fatality ratio was 0.27 (0.17-0.42); when the comparison was stratified by age group, the MH weighted case-fatality ratio became 0.30 (0.18-0.49).

It could be speculated that vaccinated children had more health-system-compliant mothers and that they therefore had more care and milder infection. However, in many of the original studies from the 1980s, measles vaccine had been provided in community campaigns and not in routine service and vaccination status depended on whether the mother had been around at the time of the campaign and not on bias (43). In the studies which adjusted for background factors, the differential effect of vaccination on the measles case fatality was actually increased (43,48). Furthermore, several studies have found that "vaccine failures" occur after high intensity of exposure, i.e. "vaccine failures" are more likely to be secondary cases exposed at home (43,44). Since secondary cases have a higher case fatality than index cases (43,44,57), the milder infection among vaccinated children is even more surprising. The possibility that measles vaccinated children have milder disease due to modified immune responses and not merely due to social confounding is strengthened by the many studies showing that measles vaccination is associated with beneficial effects on overall child survival (32,33).

Several hospital or health centre based studies have also compared vaccinated and unvaccinated children and reported that measles vaccinated children had less severe measles infection (58-60). A few community studies from India and Papua New Guinea have also suggested lower case fatality for vaccinated measles cases (61,62).

If the severity of measles is not the same in vaccinated and unvaccinated children it would strongly affect the estimated benefit of vaccinations at different ages.

Assumption 4: severity of measles is the same whether measles infection is acquired in infancy or later.

Background. In the hypothetical EPI model in which all children were vaccinated at a specific age, the unvaccinated measles cases would occur in infancy, before measles vaccination, whereas most "vaccine failures" would occur much later after the first year of life. No adjustment was made for how this affected the overall measles mortality. Most infections are more severe in infancy but on the other hand, modification of severity by maternal antibodies could have reduced the case fatality among infants.

Data: We therefore searched for studies of "measles case fatality" (N=161) and "measles mortality/death Africa" (N=620)). We found 24 relevant studies (Table 4).

Analysis. The African community studies reporting the measles case fatality separately for infants and older children have been presented in Table 4. One review of East African studies of measles have previously emphasised that the case fatality was particularly high in infants (69). However, a comparative analysis of the measles case fatality for infants and older children in all African community studies have not been made before. With a few exceptions, the studies suggested that the case fatality is higher in infancy than among older children (Table 4). These studies suggest around a two-fold higher measles case-fatality in infancy; the MH weighted case fatality ratio for all studies was 1.87 (1.63-2.14). The effect was similar before measles vaccine was introduced in these communities (MH weighted case fatality ratio=2.04 (1.58-2.63)) (see Studies before the introduction of MV, Table 4).

Considerations. Only three studies did not show higher case fatality in infancy and half the studies showed significantly higher mortality in infancy. Even if a few studies should not have been found by the search terms, it seems unlikely that additional studies would change the tendency.

If the case fatality is indeed higher in infancy, it would be more advantageous to have vaccine failures later in life rather than leave infants less than 9 months of age unprotected.

Assumption 5: vaccine failures lead to lack of credibility of the vaccination programme.

Background. Apparently it was assumed that African mothers – like physicians - would lose confidence if measles vaccine did not provide complete and life-long immunity.

Data: We searched "measles vaccine failure" (N=318) and "measles vaccine/vaccination/immunisation credibility" (N=2). This search produced one paper dealing with the relationship between "vaccine failure" and the acceptance or credibility of measles vaccination (70). One study was known from our own research (43).

Analysis. One study from Tanzania stated that acceptance of measles vaccination was low because of the many failures experienced by children vaccinated before 9 months of age.

In the only community study which examined the credibility of the programme in relation to previous experiences with "vaccine failures", younger siblings of "vaccine failures" had a significant higher coverage for measles vaccination (95% (33/35)) than siblings of children who had been successfully vaccinated and not had measles infection (78% (630/809)). Hence, the younger siblings of "vaccine failures" were significantly more likely to have been measles vaccinated (relative risk= 1.21 (1.11-1.32)) (43).

Considerations. The study from Tanzania provided no specific information on how data had been collected and how low acceptance had been measured (70). In contrast to this negative view of measles vaccination, many African mothers have experienced that vaccinated children have mild measles infection (43). In cultures where mothers have learnt that everybody has to get measles, the advantage of "mild measles" is easy to see whereas it is difficult to "see" complete "life-long protection" if you still expect your child will get measles some day. Hence, it may have worked the other way around; seeing your child get mild measles after vaccination would be a strong argument for the value of measles vaccination.

Assumption 6: it had to be a one-dose policy.

Background. The main argument advanced for a one-dose policy was that compliance with the second dose was too low (15,18,68,71). This is surprising since it has been described that mothers sought vaccination so eagerly that it was impossible to maintain the age eligibility criteria for vaccinations during campaigns (16). The reason why mothers did not seek the second dose of measles vaccine in some countries may have been poor information. In Guinea-Bissau, we had very good compliance and improved overall coverage with a two-dose schedule (72). The two-dose group had better protection against measles infection than the one-dose group (72). A two-dose schedule has also been shown to be effective in Niger (73), India (74) and Saudi Arabia (75). Hence, a two-dose schedule is both feasible and effective.

Data: To identify studies comparing the effect on survival of a one-dose and a two-dose policy we used the reviews of measles vaccination and impact on mortality (30,32,33) and searched papers on "Two/2 dose measles vaccine trial" (N=144), "Two/2 dose measles vaccination/immunization and mortality/death" (N=108) and "early measles vaccination/immunization mortality/death" (N=123). These procedures identified only two trials of the effect on child survival of a 2-dose measles vaccinations schedule compared with a 1-dose schedule (see Table 5) and one observational study (78)

Analysis. Only two trials have compared child mortality following two doses of MV (the first being given before 9 months) with mortality after the standard dose of MV (at 9 months of age) (Table 5). In a small trial from Sudan (76), DTP vaccinations were not controlled and many children received DTP after measles vaccine. DTP administered with or after measles vaccine has negative effects on female survival (34,36). We therefore conducted a large randomized trial including only children who had received DTP3 before enrolment and therefore would not receive DTP after MV (77). Among children who had not received neonatal vitamin A supplementation (VAS) which

interacted negatively with early MV(76), two doses of MV at 4.5 and 9 months of age compared with the current policy of one dose at 9 months of age reduced mortality between 4.5 and 36 months of age by 50% (22-68%) in the per-protocol analysis (Table 5). There was a significant reduction in non-measles related mortality of 45% (14-65%) (77). The combined estimate for the two trials showed that the early two-dose measles vaccination strategy may reduce mortality by as much as 48% (23%-65%) compared with the currently recommended standard dose at 9 months of age. Even if the children receiving neonatal VAS were included, the combined estimate was 31% (9-48%) (Table 5).

The only other study to report mortality after two doses of MV is a natural experiment from Guinea-Bissau in the early 1980s. Children were vaccinated in annual or biannual campaigns rather than through routine service. Hence, it was possible to compare in an unbiased way the survival of children who happened to be less than 9 months of age when vaccinated and those vaccinated at the recommended age of 9-11 for MV. MV at 4-8 months and a later dose after 9 months compared with one dose of MV at 9-11 months of age was associated with 59% (15-81%) lower mortality between 9 months and 5 years of age (78).

Considerations. The studies indicate that a two-dose policy providing the first dose of MV before 9 months of age is associated with major reductions in child mortality compared with the current one-dose at 9 month policy. The studies indicated that the benefit was not due to better protection against measles infection. Hence, these studies strongly supported that early measles vaccination has non-specific beneficial effects on child survival.

The implications of the assumptions for the estimated prevention of measles mortality. We calculated how variation in these six assumptions affect the optimal age of MV in terms of reducing measles mortality (Table 1, Columns 7-10). Using the best estimate that the case fatality rate is three-fold lower for vaccinated measles cases than for unvaccinated cases (Tables 2 and 3), the number of estimated measles deaths would have been lowest with one dose of MV at 8 months (Column 7). Assuming furthermore that infants have two-fold higher case fatality than older children (Table 4) the estimated number of measles deaths would have been lowest after vaccination at age 7 months (Column 8). Hence, it might have been better to vaccinate at 7 months of age and have some more vaccine failures later in childhood than to have many unvaccinated cases with high mortality in infancy. Adjusting for the possibility that non-seroconverting vaccinated children have some protection from cellular immunity or low levels of antibodies (37), the optimal age for measles immunization in a one-dose strategy would have moved to 6 or 7 months of age (Columns 9 and 10).

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 (72-77,79). Hence, an early dose at 4-6 months of age and a second dose at 9 months of age would have eliminated virtually all measles mortality and significantly reduced mortality from other causes as well.

Discussion

The main justification for measles vaccination at 9 months of age in low-income countries was to reduce child mortality from measles infection (18). However, the policy was never tested for its effect on survival. The policy was based on assumptions which were believed to be true, and a small seroconversion study (6-8). Thirty-five years ago the six assumptions appeared self-evident and programmatic decisions had to be taken about the optimal age for measles vaccination. However, though all assumptions have been contradicted for years no change has been made in the policy.

Strength and weaknesses

Since the six assumptions have not been research issues there are few studies conducted specifically with these topics in mind. We have therefore had to use a search strategy including review articles and case reports to find studies to assess the validity of the original assumptions. The literature search and assessment was only carried out by one researcher who has followed the topic of measles mortality and measles vaccination in Africa for more than 30 years. There may be a few more studies which were not found with the literature search since several of the studies identified in previous reviews were not found by the search terms. However, many reviews over the last 25 years have covered the areas of community studies of measles infection and the impact of MV on mortality so it is unlikely that there would be many studies not included. Furthermore, the estimates from different studies were consistent and it is unlikely that the addition of further studies would have a major impact on the estimates.

The assumed case fatality of measles infection does not matter for the estimated impact of the optimal policy on measles mortality. With another case fatality level the epidemiological arguments about assumptions 2-4 would still have the same relative effects on the number of deaths prevented. However, as evident in Tables 2 and 4, most community studies from Africa suggest that the case fatality may have been higher than 4% and the impact of the optimal measles vaccination strategy on overall mortality may therefore have been even larger. Other assumptions may also have been important; for example, the incidence data were from a rural study rather than from an urban area (21). In an urban area the incidence would have been higher at younger ages and it might have been advantageous to vaccinate even earlier. As maternal measles antibody levels have declined in low-income countries (78), earlier vaccination would also have produced better seroconversion rates and it would have been even more advantageous to vaccinate early.

Consistency with previous studies: The non-specific beneficial effects of MV. The conclusion that earlier measles vaccination is likely to have been better for child survival is based on a reconsideration of the programme´s own assumptions about effect on measles mortality. However, what is the empirical evidence for the impact on mortality of measles vaccine before 9 months of age?

In marked contradiction to the original fear that children dying of measles would just die of something else and that measles vaccination would therefore only change the cause of

death but not the level of mortality (9-11), all subsequent studies measuring the effect on survival have found marked benefit from measles vaccination (32,33,36,78,80-89). Several studies have assessed the impact of measles vaccine before 12 months of age (30,32,33) but few studies have separately measured the effect on overall mortality of measles vaccination before 9 months of age in an unbiased way (Table 6). In the 1970s, researchers in Congo followed two districts which initially had similar overall mortality levels and then introduced measles vaccination at 7 months of age in one district (11). Measles vaccination administered at 7 months of age reduced overall mortality between 7 and 21 months of age by 71% (2-91%) compared with the neighbouring district which did not get measles vaccination (60). In the early 1980s in Guinea-Bissau, children were vaccinated in annual or biannual campaigns. Hence, it was possible to compare in a "natural experiment" manner the survival of children who had been measles vaccinated before 9 months of age and those vaccinated at 9 months of age, the recommended age of measles vaccination. One dose of MV at 4-8 months compared with 9-11 months of age was associated with 31% (-8-54%) lower mortality between 9 months and 5 years of age (78). As mention above the effect was even stronger if they also received a second dose of MV after 9 months of age. During a civil war in Guinea-Bissau in 1998 (80), we followed children who had been randomised to measles vaccination at 6 months of age compared with children who had been randomised to inactivated polio vaccine (IPV). Due to the war the children did not get the standard measles vaccination at 9 months of age. During the 3 months of intensive fighting when everybody had fled the study area and mortality was high, the children vaccinated against measles at 6 months of age had 70% (13-92%) lower mortality than the unvaccinated group.

These studies of one dose of MV before 9 months of age as well as the studies of early two-dose MV mentioned above suggest that the reduction in mortality from MV before 9 months of age is much larger than can be explained by the prevention of measles infection. WHO estimates that measles deaths caused 10% of under-five deaths (90). However all available studies of the mortality impact of MV (30,32,33) suggest that the effect of measles immunization on mortality is much greater than expected. This beneficial effect is a consistent observation and it can not be explained by the prevention of acute measles infection. First, all studies, in which measles vaccine was not administered with DTP, provided strong evidence of a beneficial effect of measles vaccine on overall mortality (32). Second, all studies censoring for measles infection in the survival analysis to estimate the impact on non-measles related mortality found that prevention of measles-specific deaths explained little and the beneficial effect was due to prevention of non-measles related mortality (32,76,89, 91). For example, in the per-protocol analysis of the largest randomised trial (77), measles vaccine at 4.5 and 9 months compared with the standard dose at 9 months of age reduced non-measles related mortality significantly for all children. Third, the beneficial effect of measles vaccine is usually stronger for girls than for boys (77,92,93). Since measles mortality is not higher for girls than boys, this observation suggests sex-differential mechanisms related to immune stimulation. Hence, standard measles vaccine may protect against other infections and have a beneficial effect on child survival even when measles is eliminated.

Though the focus here has been on MV administered before 9 months of age there is also a considerable number of studies indicating that MV administered after 9 months of age have non-specific beneficial effects (32,81-86, 91, 94).

The possible biological explanations for non-specific beneficial effects of MV have not been explored in humans. In animal studies of heterologous immunity, previous stimulation with infections may have a major effect on the capacity to handle a lethal dose of an unrelated infection (95). Two trials from Bissau suggest that the beneficial effect of MV is better for children vaccinated in the presence of maternal measles antibodies than for children having no measurable maternal antibodies at the time of MV (89). This may also help explain why MV before 9 months of age is better than later vaccination.

The optimal age of measles vaccination: optimizing seroconversion or impact on overall child survival. The most unfortunate consequence of not testing the optimal age of measles immunization may have been that the beneficial non-specific effects of MV were not detected (32). To the extent MV has beneficial non-specific effects the question of the optimal age of measles vaccination acquires a new meaning. By lowering the age of measles vaccination, children would benefit not only from earlier protection against measles infection but also from the beneficial non-specific effects against non-measles infections and overall child mortality would be reduced. On the other hand, if the age of vaccination is increased, children would benefit less from the beneficial non-specific effects and overall child mortality would increase. Hence, policies optimizing the non-specific effects clash with those designed to enhance seroconversion.

Conclusions: Old assumptions linger on

The supplementary immunization activities (SIA) with measles vaccine has eliminated measles infection in Latin America and reduced the incidence in major ways in the rest of the world (1-3). The world is now planning to eliminate and eventually eradicate measles infection (4). With the SIA success in measles control, the optimal age of measles immunization is likely to be considered an irrelevant issue. However, as discussed above, measles vaccine has also non-specific effects which need to be taken into consideration in the planning of vaccination programmes. The prevention of all-cause mortality rather than measles mortality should be the primary objective. In a culture which advocates evidence-based policies (4), the evidence for the current measles vaccination policy – or rather the lack thereof - should be properly reviewed and revised by the global and regional immunization programmes. Otherwise old assumptions about seroconversion rates being the basis for the optimal age of immunisation may linger on and continue to influence policy.

There are major consequences of focusing solely on specific measles mortality. First, as the current policy is mostly determined by our understanding that seroconversion gets better with increasing age, the tendency will be that with improved control of measles infection, age of vaccination will be increased. Following the elimination of measles in Latin America, the recommended age of primary measles immunization was raised to 12 months in 1996 (3). Again this decision was based on assumptions and not on studies

documenting the overall effect on morbidity and mortality. Following the success of measles campaigns in other continents it has also been recommended by SAGE (the Strategic Advisory Group of Experts) to increase the age of measles vaccination to 12 months in areas with low levels of measles transmission (5,12). The underlying assumption about better seroconversion at higher ages may no longer be valid with the decline in maternal antibody levels (79,96). For example, we have obtained 100% seropositivity and 99% protective levels after measles vaccine at 9 months of age with both Schwarz and Edmonston-Zagreb measles vaccine strains in Guinea-Bissau (97).

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 (11,32,38,76-80,89). There is a tendency to dismiss these observations because randomised trials with overall mortality as an outcome have only been conducted in Guinea-Bissau and it is therefore claimed that the global health community has to wait for verification elsewhere (98). However, the beneficial non-specific effects of MV have been shown in several other countries with high childhood mortality. For example, in a cross-over design, Shann showed that girls receiving standard measles vaccine at 9-10 months of age in five randomised trials in Sudan, Gambia, Senegal and Guinea-Bissau had 47% lower mortality through childhood than control children who received an inactivated vaccine at 9-10 months of age (94). Since the control children had received MV before 9 months of age and did not get measles, the difference in mortality following MV at 9 months of age was a beneficial non-specific effect not related to prevention of measles infection. Increasing the age of measles vaccine from 9 to 12 months may reduce the beneficial effects in the age group between 9 and 12 months of age in which mortality is still high. Thus the lives lost by this change of schedule could well be more than the lives saved by improved measles control (77).

Second, in the current paradigm for control of infectious diseases, the ultimate success in public health is to eradicate the disease and then remove the vaccine to reduce economic costs as happened for smallpox in the 1970s (26). This may happen for measles infection within the next 10-20 years (99). If measles vaccine has major beneficial non-specific effects (77), to remove measles vaccine or reduce its coverage would increase child mortality levels considerably in low-income countries unless we in the meantime find a vaccine which has all the same beneficial effects as measles vaccine.

After 35 years, it is time to develop a policy for the optimal age of measles immunization. This policy needs to be based on evidence about the impact on overall health and child-survival and not only on assumptions about the impact of specific prevention against measles infection. A two-dose measles vaccination strategy, providing measles vaccine at 4.5 months of age, after the three DTP vaccines, and again at 9 months of age, may significantly improve child survival and provide a solid basis of immunity which if necessary can be enhanced by supplementary measles immunisation activities at a later age (77,79). Any future changes in the age of measles immunisation due to elimination of measles infection, changes in the epidemiology of measles infection, decline in maternal antibody levels, introduction of new measles vaccines or in the timing of other vaccines should be tested in trials to determine their overall impact on child health.

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Table 1. Projected reduction in measles cases and measles deaths with measles immunization at ages four to ten months. Machakos, Kenya 1974-1981

Expanded Programme on Immunization model (8)						Estimated number of measles deaths in a cohort of 1000 children				
	Column1	Column 2	Column 3	Column 4	Column 5	Column 6	Column 7	Column 8	Column 9	Column 10
	Cumulative measles incidence (%)	Serocon-version from MV (%)	Prevented cases (%)	Vaccine Failures (%)	Cases prior to MV(%)	EPI assumption: Case fatality 4%	Adjusting vaccination status[1]	Adjusting vaccination status and age of infection[2]	Adjusting vaccination status, age of infection, and seronegative 50% protection[3]	Adjusting vaccination status, age of infection, and seronegative 25% protection[3]
Age 4 months	0.5	15	15	85	0	34	11.3	11.3	5.7	8.5
Age 5 months	1.0	35	35	65	0	26	8.6	8.6	4.3	6.5
Age 6 months	2.8	52	51	48	1	19.6	6.8	7.2	**4.0**	5.6
Age 7 months	6.1	72	69	28	3	12.4	4.9	***6.1***	4.3	**5.2**
Age 8 months	9.5	86	79	15	6	8.4	***4.4***	6.8	5.8	6.3
Age 9 months	14.4	95	84	7	9	***6.4***	4.5	8.1	7.7	7.9
Age 10 months	18.6	98	82	4	14	7.2	6.1	11.7	11.5	11.6

Notes: MV=measles vaccine; The estimated number of measles deaths was obtained by multiplying the number of vaccine failures (column 4) and cases prior to MV (column 5) in a cohort of 1000 children by the case fatality rates as indicated in the following notes: 1. Assumption: The relative case fatality ratio is 1/3 for vaccinated versus unvaccinated cases, i.e. 4% for unvaccinated cases and 1.33% for vaccinated cases. 2. Assumption: The relative case fatality ratio is 1/3 for vaccinated versus unvaccinated cases. The case fatality ratio is twice as high for unvaccinated cases occurring in infancy. Hence, the estimated case fatality ratios are 8% for unvaccinated cases occurring in infancy and 1.33% for vaccinated cases. 3. Assumption: Seronegative children had 50% or 25%

protection against measles. Hence, the estimated case fatality ratios are 8% for unvaccinated cases occurring in infancy and 1.33% for vaccinated cases but there were fewer vaccinated cases than indicated in column 4.

Table 2. Acute measles case fatality ratio for measles-vaccinated and measles-unvaccinated cases in African prospective community studies and community surveys

Country	Period	Study	Vaccinated cases (%) (deaths/cases)	Unvaccinated cases (%) (deaths/cases)	Measles case fatality ratio
Bissau (43)	1980-82	PCS; urban	9%(5/53)	17%(18/108)	0.58 (0.23-1.49)*
Bissau (43)[1]	*1980-82*	*PCS; urban (only secondary cases)*	*14%(3/21)*	*46%(11/24)*	*0.30 (0.10-0.86)**
Guinea-Bissau (45)	1983-1984	PCS; urban	4%(4/90)	9%(21/234)	0.41 (0.14-1.22)*
Guinea-Bissau (38)	1984-1987	PCS; 2 year follow-up	0% (0/4)	13% (2/16)	0 (0-23.10)
Bissau (46)	1985-1987	PCS; children < 2yrs; urban	5%(1/22)	11%(10/90)	0.41 (0.06-3.03)#
Bissau (unpublished&)	1991	PCS; children < 10 yrs; urban	2%(10/412)	13%(64/478)	0.24 (0.12-0.49)*
Senegal (47)	1987-1994	PCS; rural	0%(0/127)	2%(18/1085)	0 (0-1.94)*
Ghana (48)	1989-1991	PCS; rural; Vitamin A trial with measles surveillance	10%(15/153)	17%(136/808)	OR=0.42 (0.21-0.83) $##
Kenya (22)	1986	SUR; all ages; rural	2%(2/41)	11%(11/98)	0.51(0.08-3.08)*
Kenya (49)	1988	SUR; Children <5yrs; rural	0%(0/23)	10%(18/182)	0 (0-1.54)*
Chad (50)	1993	SUR; rural	0%(0/23)	8%(61/801)	0 (0-2.18)
Niger (51)	2003-2004	SUR**; urban	0.4%(1/286)	6%(29/481)	0.06 (0.01-0.42)
Chad (51)	2004-2005	SUR** ; urban	0.4%(2/494)	8%(18/212)	0.05 (0.01-0.20)
Nigeria (51)	2004-2005	SUR**; rural	9%(1/11)	7%(79/1131)	1.30 (0.20-8.54)
Sudan (52)	2004	SUR;	0.4%(2/556)	1%(7/568)	0.29 (0.06-1.40)
Niger (53)	1991-1992	SUR; rural	17%(20/118)	15%(61/410)	1.14 (0.72-1.81)
Zimbabwe (54)	1980-1989	SUR; urban	2%(8/335)	7%(20/302)	0.36 (0.16-0.81)
Total					0.39 (0.31-0.49)

Sources: Reviews of measles case fatality studies (27-31) and PubMed search for measles mortality/case fatality in vaccinated children; & compiled by Henning Andersen shortly before he died.

Notes: PCS= prospective community studies; SUR= community surveys or outbreak investigations; 1. Mortality is high because only secondary cases are included in the analysis. Since this analysis is a subgroup within the larger study, it has not been included in the combined estimate; $ case fatality ratio calculated by the authors, the remaining studies have been calculated by us *adjusted for age; # adjusted for district; ## adjusted for age, sex, weight-for-age z-score, paternal education and season; ** Mortality was only reported for children with at least 30 days of follow-up whereas the proportion of

vaccinated was reported among all cases. It has been assumed that the proportion vaccinated cases was the same among those with follow-up as among all cases.

Table 3. Measles case-fatality ratio for measles-vaccinated and measles-unvaccinated cases in African prospective community studies and community surveys with long-term follow-up

Country	Period	Study; period of follow-up	Vaccinated cases (%) (deaths/persons)	Unvaccinated cases (%) (deaths/persons)	Mortality ratio
Guinea-Bissau (55)[1]	1988	PCS; 5 year follow-up;	4% (1/23)	16% (8/46)	0.25 (0.03-1.88)
Guinea-Bissau (38)	1984-1987	PCS; 2 year follow-up	0% (0/4)	14% (2/14)	0 (0-20.10)
Burundi (56) [2]	1988-1989	SUR; 7 month follow-up	3/1363 person-months	19/2629 person-months	0.30 (0.09-1.03)
Senegal (47)	1987-1994	PCS; 1 year follow-up	0% (0/127)	1% (15/1055)	0 (0-2.32)
Bissau (unpublished&)	1991-1994	PCS; 3 year follow-up	3% (8/319)	9% (29/338)	0.29 (0.14-0.63)
Total					0.27 (0.14-0.50)

Sources: Reviews of measles case fatality studies (27-31) and PubMed search for measles mortality/case fatality in vaccinated children; & compiled by Henning Andersen shortly before he died.

Notes: PCS= prospective community studies; SUR= community surveys or outbreak investigations; 1. There was no data on acute case fatality in the present study since the study only included children who had a convalescent sample collected; 2. This study did not report the acute case fatality but only overall mortality for the 7 months of follow-up.

Table 4. Measles case fatality ratio for infants and older children in African prospective community studies and community surveys

Country	Period	Type of study	Infants (%) (deaths/cases)	Children 1+ year (%) (deaths/cases)	Measles case-fatality ratio
Studies before the introduction of MV					
Gambia (63)#	1961	PCS; rural	31%(12/39)	13%(47/356)	2.33 (1.36-4.00)
Guinea-Bissau (45)	1979	PCS; Urban	28%(22/79)	14%(55/380)	1.92 (1.25-2.96)
Guinea-Bissau (64)	1980	PCS; Rural	47%(7/15)	21%(31/147)	2.21 (1.18-4.13)
Senegal (44)	1983-86	PCS; Rural	12%(19/165)	6%(79/1335)	1.95 (1.21-3.13)
Studies after introduction of MV					
Kenya (65)	1974-1976	PCS; rural	6%(4/63)	7%(24/361)	0.96 (0.34-2.66)
Kenya (65)	1976-1977	PCS; rural	4%(5/125)	1%(7/540)	3.09 (1.00-9.56)
Kenya (22)	1986	SUR; rural	17%(5/29)	7%(8/110)	2.37 (0.84-6.71)
Kenya (49)	1988	SUR; rural	22%(9/41)	5%(11/207)	4.13 (1.83-9.33)
Senegal (44)	1987-1990	PCS; rural	2%(1/43)	2%(9/598)	1.55 (0.20-11.9)
Senegal (47)	1991-1994	PCS; rural	6%(4/72)	1%(4/499)	6.93 (1.77-27.1)
Guinea-Bissau (66)	1980-1982	PCS; urban	30%(7/23)	9%(10/115)	3.50 (1.49-8.24)
Guinea-Bissau (45)	1983-1984	PCS; urban	9%(5/56)	7%(20/268)	1.20 (0.47-3.05)
Zaire (11)	1974-1977	PCS; urban	6%(12/194)	6%(53/844)	0.99 (0.54-1.81)
Ghana (48)	1989-1991	PCS; rural	21%(28/131)	15%(123/830)	1.44 (1.00-2.08)
Chad (50)	1993	SUR; urban	6%(9/156)	8%(52/668)	0.74 (0.37-1.47)
Niger (67)	2003	SUR; rural	16%(13/83)	9%(79/862)	1.71 (0.99-2.94)
Niger (53)	1991-1992	SUR; rural	40%(16/40)	13%(65/488)	3.00 (1.93-4.67)
Niger (51)	2003-2004	SUR; urban	7%(8/111)	3%(22/656)	2.15 (0.98-4.71)
Chad (51)	2004-2005	SUR; urban	5%(5/97)	2%(15/609)	2.09 (0.78-5.63)
Nigeria (51)	2004-2005	SUR; rural	11%(5/47)	7%(75/1095)	1.55 (0.66-3.66)
Zimbabwe (54)	1980-1989	SUR; rural	13%(13/103)	3%(15/534)	4.49 (2.20-9.16)
Sudan (52)	2004	SUR;	3%(1/36)	1%(9/1108)	3.42 (0.45-26.28)
Longer follow-up than 1 month					
Burundi (56)##	1989	SUR; rural; 7 months follow-up	14%(2/176 person-months)	6%(20/3816 person-months)	2.17 (0.51-9.20)
Gambia (68)	1981	SUR; rural; 9 months follow-up	64%(7/11)	10%(13/124)	6.07 (3.07-12.0)
Total					1.87 (1.63-2.14)

Sources: Reviews of measles case fatality studies (27-31) and PubMed search for community studies of measles mortality/case fatality in infants or by age in Africa.
Notes: MV=measles vaccine; PCS=prospective community study, i.e. the population was known before the epidemic and information is likely to have been obtained for all children; SUR= retrospective survey; # The age grouping is 7-12 months and 12-120 months. Measles deaths and total number of children in age group were reported in this study. It has been assumed that all children between 7 and 120 months contracted measles. In this period there were no measles vaccinations available. The last epidemic had occurred 12-13 years earlier; ## The age grouping is 0-8 and 9+ months; ¤ Numbers read from a graph

Table 5. Vaccine efficacy against overall mortality in randomised trials of an early two-dose measles vaccination schedule compared with the standard dose of measles vaccination at 9 months of age

Country and period	Age interval	Comparison (Vaccines)	Administration of DTP	Deaths/person-years or persons	Mortality rate ratio	Comments
Sudan (76) 1989-1992	5-9 months	MV vs Control (Meningococcal A+C)	DTP not given simultaneous with MV but could have been given after MV	1/60.5 vs 6/61.2	0.18 (0.02-1.54)	1st vaccine in 2-dose group was Connaught HTMV and 2nd dose was Schwarz standard MV
	9-36 months	2nd vs 1st MV		7/371.6 vs 7/355.9	0.96 (0.34-2.73)	
	5-36 months				0.60 (0.25-1.45)#	
Guinea-Bissau (77) 2003-2009	4.5-9 months	MV vs Control (no vaccine)	DTP not given simultaneous with MV and after MV; all had DTP3 one month before enrolment	5/398.8 vs 29/821.8	0.33 (0.13-0.86)	Vitamin A supplementation (VAS) at birth is not official policy. Hence, only results for children who did not receive VAS is presented.#
	9-36 months	2nd vs 1st MV		20/2054.4 vs 67/3881.1	0.56 (0.34-0.93)	
	4.5-36 months				0.50 (0.32-0.78)#	

Source: All studies reporting mortality in trials of two doses of measles vaccine (MV) (30,32,33). Only the per-protocol results have been used comparing children who received two doses of MV with those receiving one dose at 9 months. No additional studies of early two-dose measles vaccination reporting impact on mortality were found by PubMed searches.
Note: # The combined estimate (Stata) was 0.52 (0.35-0.77); if the children receiving vitamin A at birth were also included, the combined estimate was 0.69 (0.52-0.91).

Table 6. Vaccine efficacy against overall mortality for one dose of standard-titre measles vaccine before 9 months of age

Country	period	Comparison	Results
Early measles vaccination at 7 months of age compared with children unvaccinated community			
Congo (11)	1974-1977	MV administered at 7 months of age; children followed to 21 and 34 months of age. Mortality from 7 to 21 months of age for vaccinated children (3/230.5 pyrs) compared with unvaccinated children from control area (21/470.7 pyrs)	MRR for 7 to 21 months =0.29 (0.09-0.98) MRR for 7 to 34 months =0.52 (0.21-1.27)
Comparing MV at 4-8 months versus MV at 9-11 months of age			
Guinea-Bissau (78)	1980-1982	Natural experiment: MV at 4-8 versus MV at 9-11 mo compared from 9 to 60 months of age	MRR (MV-4-8mo/MV-9-11mo) 0.69 (0.46-1.08)
Comparing children randomsied to MV at 6 months versus IPV at 6 months during a war situation			
Guinea-Bissau (80)	1998	Children were randomised to MV (4/214) or inactivated polio vaccine (11/219) at 6 months of age. Due to a war they did not received the planned MV at 9 mo. Follow-up for 3 months in a war situation	70% (13 to 92)

Sources: All studies examining the general effect of standard measles vaccine (MV) on child survival (as compiled by all available reviews (30,32,33)) have been screened for information on measles vaccination before 9 months of age. There have been several other studies of the impact of MV before 12 months of age on child survival (81-89) but most of these studies could not distinguish the effect of MV before 9 months of age. However, all studies suggested that early MV had a better effect on child survival than later MV. The studies where children received DTP or IPV with early MV or shortly after MV have not been included in the present table (34-36) since this sequence have unfortunate consequences (34,36). No additional studies of one-dose measles vaccination/immunization before 9 months of age reporting impact on mortality were found by PubMed searches.

The optimal age of measles immunization in low-income countries: A secondary analysis of the assumptions underlying the current policy

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Abstract

Background and objective The current policy of measles vaccination at 9 months of age was decided in the mid-1970s. The policy was not tested for impact on child survival but was based on studies of seroconversion after measles vaccination at different ages. We examined the empirical evidence for the six underlying assumptions.

Data sources and methods These assumptions have not been research issues. Hence, we examined case reports to assess the empirical evidence for the original assumptions. We used existing reviews and in December 2011 we made a PubMed search for relevant papers The title and abstract of papers in English, French, Portuguese, Spanish, German and Scandinavian languages was assessed to ascertain whether the paper was potentially relevant. The search was limited to African community studies of measles infection. Based on cumulative measles incidence figures we calculated how many measles cases had been prevented assuming everybody was vaccinated at a specific age, how many "vaccine failures" would occur after the age of vaccination, and how many cases would occur before the specific age of vaccination. In the combined analyses of several studies we used the Mantel-Haenszel (MH) weighted relative risk stratifying for study or age groups to estimate common trends.

~~Hence, we examined review articles and case reports to assess the empirical evidence for the original assumptions. The search was limited to African community studies of measles infection.~~

Main outcome The predicted effect on mortality.

Results In retrospect the major assumptions were based on false premises. First, in the single study examining this point, seronegative vaccinated children had considerable protection against measles infection. Second, in 18 community studies vaccinated measles cases ("vaccine failures") had three-fold lower case fatality than unvaccinated cases. Third, in 24 community studies, infants had two-fold higher case fatality than older measles cases. Fourth, the only study examining the assumption that "vaccine failures" lead to lack of confidence found the opposite because vaccinated children had milder measles infection. Fifth, a one-dose policy was recommended. However, the two randomised trials of early two-dose measles vaccination compared with one-dose vaccination found significantly reduced mortality until 3 years of age. Thus current evidence suggests that the optimal age for a single dose of measles vaccine should have been 6 or 7 months resulting in fewer severe unvaccinated cases among infants but more mild "vaccine failures" among older children. Furthermore, the two-dose trials indicate that measles vaccine reduces mortality from other causes than measles infection.

Conclusions Many lives may have been lost by not determining the optimal age of measles vaccination. Since seroconversion continues to be the basis for policy, ~~Despite this~~ the current recommendation is to increase the age of measles vaccination to 12 months in countries with limited measles transmission. This policy may lead to an increase in child mortality.

Article summary

Article focus

- An empirical analysis of the six assumptions underlying the current measles vaccination policy for low-income countries.
- Determine the implications for child survival of not testing the optimal measles vaccination policy.

Key messages

- All six assumptions were flawed; most important were the assumptions that seronegative vaccinated children are fully susceptible to measles infection, that the severity of measles is the same in vaccinated cases ("vaccine failures") and in unvaccinated children, that the severity of measles infection is the same in infancy or later, and that it had to be a one-dose programme.
- The current evidence suggests that the optimal age for a single dose of measles vaccine would probably have been 6 or 7 months of age had the policy been tested.
- An early two-dose schedule at 4-5 months and 9 months of age would have been even better in terms of reducing child mortality.

Strength and limitations

- The current measles vaccination policy for low-income countries is not based on any evidence about the impact on overall child survival.
- There are few studies testing some of the assumptions. However, for the two key assumptions relating to severity of measles in vaccinated infants and children there is ample evidence which suggests that measles is less severe in vaccinated cases.

Introduction

With the spectacular success in measles control in the last 10-15 years(1-3) and the current policy to move ahead with elimination and eventually eradication of measles infection (4), there is now a discussion of when to introduce the second dose of measles vaccine (5). However, few people realize that the key policy of vaccinating against measles at 9 months of age in low-income countries is not based on evidence documenting the optimal age of measles vaccination to reduce overall child mortality.

In the 1970s policy makers found it necessary to formulate a common policy for low-income countries (6-8) since many donors and scientists at the time questioned the value of measles vaccination. Measles infection was believed to kill mainly malnourished children likely to die of other infections if not from measles and hence some people thought that measles vaccine would not reduce overall mortality, but merely change the cause of death (9-11). The policy makers' definition of the optimal age of measles vaccination of 9 months was based on a number of assumptions (6-8). Though these assumptions for vaccinating at age 9 months were not subsequently substantiated the policy has remained in effect. Recently, though, it has been recommended that primary measles vaccination should be at 12 months of age in countries where measles infection has been controlled (12).

In the first measles vaccination campaigns in West and Central Africa in the 1960s children were targeted from 6 months of age (13-17). Initially it was thought that it would be sufficient to conduct campaigns every 2nd or 3rd year to control measles. However, the epidemiologists soon learned that shorter intervals of 6 or 12 months between campaigns were necessary to control measles. In the 1970s, routine vaccination programmes were introduced and the optimal age of routine measles vaccination was debated (18-20). Following the experience with the campaigns, several African countries recommended measles vaccination at 6, 7 or 8 months of age. A study sponsored by the Ministry of Health in Kenya and WHO assessed the seroconversion rates at different ages between 5 and 12 months and recommended measles vaccination at 7½ months of age (21). For several years measles vaccine was administered at 8 months of age in Kenya (22). Similar studies of seroconversion were conducted in Latin America (23). Since some of those vaccinated at 6 months were not protected some countries and many researchers recommended a second dose at 9 months of age or later (20,24). However, there were fears that early vaccination would produce too many vaccine failures and a one-dose programme was considered necessary because mothers would not bring their children back for a second dose (15,25). Therefore, the Expanded Programme on Immunization (EPI) recommended a one-dose policy (6-8,18). In 1980, the Global Advisory Group of EPI endorsed this policy and recommended measles vaccination as early as possible after 9 months of age (7).

Before the global policy is changed to 12 months of age it is timely to examine the empirical basis for the assumptions underlying the current policy. Since these assumptions have not been research issues we have had to use a search strategy including review articles and case reports to assess the validity of the original assumptions ~~(see~~

Supplementary Material). The present analysis suggests that in retrospect all assumptions were flawed. Had the policy been tested in randomised trials measuring the impact on mortality of vaccination at different ages it is likely that the age of measles vaccination had been changed, with the result that the measles vaccination programme would have had a much larger effect on child survival in low-income countries.

Methods

The optimal age of measles immunization: the underlying assumptions

The recommendation was based on the belief that the expected reduction in mortality could be computed from seroconversion rates (18,26) and the policy was justified several times by analyses of the seroconversion data from Kenya (6,8). In these analyses it was assumed that seroconversion was associated with full protection against measles infection (*assumption 1*) and that non-seroconversion was associated with full susceptibility to measles infection (*assumption 2*). As shown in Table 1 (Column 2), the data from Kenya (21) showed that seroconversion increased with age. This was not unexpected since the calculation of this measure (a fourfold or more increase over baseline) is dependent on level of maternal antibody which wanes as the child ages. Based on cumulative measles incidence figures (Column 1), it was calculated how many measles cases had been prevented assuming everybody was vaccinated at a specific age (Column 3), how many "vaccine failures" would occur after the age of vaccination (Column 4) and how many cases would occur before the specific age of vaccination (Column 5). In making these calculations it was assumed that "vaccine failures" and unvaccinated measles cases were equally severe (*assumption 3*) and that it did not matter whether measles was acquired in infancy or later in childhood (*assumption 4*). Vaccination at 8, 9, and 10 months of age prevented roughly the same proportion of cases, between 79% and 84% (Column 3) (6,8). Vaccination at 8 month resulted in considerably more vaccine failures (15%) than vaccination at 9 months (7%). Since vaccine failures were assumed to jeopardize the credibility of the measles immunization programme (*assumption 5*) (6,8,18), it was concluded that the optimal age for administration of measles vaccine would be 9 months. At the time the EPI assumed that the case fatality in measles infection was 4% in Africa and it will be seen in Column 6 that the number of estimated measles deaths in a birth cohort of a 1000 children would indeed be lowest (between 6.4 and 8.4) for vaccination at 8-10 months of age. In making this analysis of the effect of only one dose of measles vaccine (6,8), the EPI assumed that a two-dose policy was not feasible or unjustified (*assumption 6*).

Selection of studies. Following the identification of the underlying assumptions, we looked for empirical evidence in community studies to support or refute their validity. The original policy was mainly justified in relation to the epidemiology of measles infection in Africa where the case fatality was clearly higher than in other regions (27-31). Most community studies of measles infection are indeed from Africa and we have therefore restricted the analyses and the tables 2-4 to the African studies. These tables are believed to be exhaustive for Africa and they are not contradicted by community studies from Latin America and Asia. For the analysis of the impact of measles vaccination on child mortality we included all studies from Asia and Latin America.

~~The search strategy has been defined in the Supplementary Material.~~ Since there are few specific studies to test the six assumptions we have had to use case reports of measles outbreaks to assess their validity. Over the last 20-25 years, several reviews of community studies of the measles case fatality compiled studies of relevance for particularly assumption three and four (27-31), two of these being by the first author (PA). For each assumption we used existing reviews and in December 2011 the first author made a PubMed search for relevant papers as described below. The title and abstract of papers in English, French, Portuguese, Spanish, German and Scandinavian languages was assessed by the first author to ascertain whether the paper was potentially relevant. Potentially relevant papers were read. Most papers were not from Africa but were reviews or case reports and not community based studies and had no information on mortality. ~~Furthermore, as specified in the supplementary material, we made PubMed searches for additional publications relevant for all assumptions.~~ We included one unpublished report from a large epidemic in Bissau in 1991-1992 which has remained unpublished because the physician (Henning Andersen) handling the epidemic died tragically in an accident shortly after the epidemic.

We distinguished between prospective community studies and surveys retrospectively assessing events since the precision of information on vaccination status and age presumably is better in prospective studies. Though hospital and health centre studies may have data on the severity of measles infection by vaccination status or age, we have not included these studies in the analysis since biased admission for some groups might have made the result non-representative.

Since the analysis of the assumptions suggested that measles vaccination before 9 months of age could be beneficial, we assessed the empirical evidence from studies which assessed the effect of early measles vaccination on mortality. Again we used all reviews of community studies and trials assessing the impact of measles vaccination on child mortality (30,32-35). Additional PubMed searches for studies comparing the mortality of measles vaccinated and unvaccinated children did not identify further studies. As explained in the footnote to table 6, we have emphasised the studies in which inactivated vaccines were not administered simultaneously with MV or after MV as such combination or sequences can have a negative effect on child survival (34,36).

Presentation. For each assumption, we briefly outline the background. Next we present the relevant studies found and then analyse the common trends, identifying the secondary analyses which have been made. Finally, we considered whether methodological issues and data quality might question the trends suggested by the analysis.

Statistical analyses. Based on cumulative measles incidence data we calculated how many measles cases and measles death had been prevented assuming everybody was vaccinated at a specific age, how many "vaccine failures" would occur after the age of vaccination, and how many cases would occur before the specific age of vaccination. It was estimated how this calculation was influenced by the empirical evidence for the underlying assumptions. In the combined analyses of several studies we used the Mantel-

Haenszel (MH) weighted relative risk stratifying for study or age groups to estimate common trends.

Ethics. Since the study is a secondary analysis of existing data, approval from an ethical committee was not needed.

Results

Assumption 1: children who seroconvert to measles vaccine have absolute protection against measles infection.

Background. It has usually been assumed that previous measles infection is associated with life-long immunity. This idea was transferred to measles vaccination when the vaccine was developed in the 1950s. Hence, if someone had antibodies after vaccination these were also assumed to provide life-long protection.

Data: We searched for "measles infection seropositive vaccinated children" (N=12) and "measles vaccine failure" (N=318~~Supplementary material~~). There are many case reports that contradict that seroconverted children have absolute protection but no African community study.

Analysis. A number of smaller studies have documented that a few children do get measles after having seroconverted (37-40). Hence, seroconversion does not give absolute protection.

Considerations. However, there are no general epidemiological studies from Africa and it is therefore difficult to estimate the proportion of children who get measles in spite of having seroconverted, but since no large series have been reported it is likely to be small.

Assumption 2: vaccinated children who are seronegative are fully susceptible to measles infection.

Background. Measles immunity has generally been considered an either-or phenomenon. If a vaccinated child was seronegative it was assumed that the child was fully susceptible.

Data: We searched for "measles infection seronegative vaccinated children" (N=13) and "measles vaccine failure" (N=318~~Supplementary material~~). This provided only one relevant reference (37).

Analysis. In a study in Senegal, vaccinated children who were seronegative when exposed to measles infection at home had a 49% (95% CI 21-68%) protection against clinical disease compared with unvaccinated seronegative children exposed under similar conditions (37).

Considerations. Apparently, no other study has tested the susceptibility of vaccinated "seronegative" children. It is possible that some children had acquired vaccine-induced measles antibodies earlier but subsequently lost them. Cellular immunity may be obtained

without having measurable antibodies (41). There is also good evidence from studies of hepatitis B vaccination that antibody concentration wane with time but the majority of older seronegative children if infected are protected from chronic carriage and its damaging consequences (42).

The concept of seroconversion to compare the effect of vaccination at different age is in itself problematic. Seroconversion is not the same as seroprotection and the use of the term inevitably disadvantages data from studies that have vaccinated at earlier ages when maternal antibodies are still present. Thus a child immunized at 6 months of age when the maternal antibody level is say 62.5 mIU may fail the test for conversion (a four-fold increase) yet still have a protective level of 125 mIU at 9 months of age.

If approximately half the seronegative children have clinical protection it would have major consequences for the calculation of the optimal age of measles vaccine.

Assumption 3: severity of measles infection in vaccinated children ("vaccine failures") and unvaccinated children is the same.

Background. The EPI perceived "vaccine failures" as due to the vaccine being inactivated by improper storage and handling or due to neutralization of the vaccine by maternal antibodies (16,19). Hence, it was assumed that these children had been fully susceptible to measles infection. However, many epidemiological studies in the 1980s and 1990s suggested that measles vaccinated children who contracted measles infection had milder disease (43,44). This would suggest that the children had partial measles immunity, not enough to protect them but enough to modify the severity of the disease.

Data: We searched for "measles mortality vaccinated children" (N=143), "measles vaccine mortality" (N=775), "measles case fatality" (N=161) and "measles vaccine failure" (N=318~~Supplementary material~~). The 18 relevant studies are included in Tables 2 and 3.

Analysis. The community studies of the acute measles case fatality are shown in Table 2. Only two African studies (43, 48) have reported significant differences in mortality for vaccinated and unvaccinated measles cases. A combined analysis has not been made previously. The measles case fatality was 2 to 5-fold lower for vaccinated cases ("vaccine failures") than for unvaccinated children with measles infection in nearly all studies. Using MH weighted relative risk, the effect was similar in the prospective community studies (case-fatality ratio=0.37 (0.27-0.52)) and the retrospective surveys (case-fatality ratio=0.41 (0.29-0.56)).

A few studies followed the children for longer than one month which is the normal time limit for acute measles deaths. The long-term trend was the same with considerable better survival among vaccinated than unvaccinated children after measles infection (Table 3). Combining the prospective community studies in Tables 2 and 3 would suggest a 3-fold reduction in acute and/or long-term mortality among vaccinated children even though some of the vaccine failures may have been due to inactivated measles vaccines.

In the four studies (38,47,56, unpublished) with information on both acute and long-term mortality, mortality was nearly 5-fold lower for the vaccinated cases (MH weighted mortality ratio= 0.21 (0.13-0.34)).

Considerations. Only two studies did not show lower case fatality among vaccinated children and five of the 18 studies in Tables 2 and 3 showed significantly lower mortality among vaccinated children.

All studies with relevant data were included in Tables 2 and 3 irrespective of whether vaccine efficacy (VE) against measles infection was high or substandard. In several studies, the VE was not high but nonetheless the vaccine appeared to have had an effect; for example, in Kenya VE was only 18% but measles-vaccinated children who developed measles had still 2-fold lower measles mortality than measles unvaccinated children (Table 2). Only one community survey from Niger reported that measles vaccine was not particularly effective against measles infection and that there was no effect of vaccination on the case fatality in measles infection (53).

In most studies (Table 2), it was not possible to control for age given the way the data was reported. However, in 6 studies (22, 43, 45, 47, 49, unpublished data) age could be controlled. In these studies the crude MH weighted case-fatality ratio was 0.27 (0.17-0.42); when the comparison was stratified by age group, the MH weighted case-fatality ratio became 0.30 (0.18-0.49).

It could be speculated that vaccinated children had more health-system-compliant mothers and that they therefore had more care and milder infection. However, in many of the original studies from the 1980s, measles vaccine had been provided in community campaigns and not in routine service and vaccination status depended on whether the mother had been around at the time of the campaign and not on bias (43). In the studies which adjusted for background factors, the differential effect of vaccination on the measles case fatality was actually increased (43,48). Furthermore, several studies have found that "vaccine failures" occur after high intensity of exposure, i.e. "vaccine failures" are more likely to be secondary cases exposed at home (43,44). Since secondary cases have a higher case fatality than index cases (43,44,62), the milder infection among vaccinated children is even more surprising. The possibility that measles vaccinated children have milder disease due to modified immune responses and not merely due to social confounding is strengthened by the many studies showing that measles vaccination is associated with beneficial effects on overall child survival (32,33).

Several hospital or health centre based studies have also compared vaccinated and unvaccinated children and reported that measles vaccinated children had less severe measles infection (57-59). A few community studies from India and Papua New Guinea have also suggested lower case fatality for vaccinated measles cases (60,61).

If the severity of measles is not the same in vaccinated and unvaccinated children it would strongly affect the estimated benefit of vaccinations at different ages.

Assumption 4: severity of measles is the same whether measles infection is acquired in infancy or later.

Background. In the hypothetical EPI model in which all children were vaccinated at a specific age, the unvaccinated measles cases would occur in infancy, before measles vaccination, whereas most "vaccine failures" would occur much later after the first year of life. No adjustment was made for how this affected the overall measles mortality. Most infections are more severe in infancy but on the other hand, modification of severity by maternal antibodies could have reduced the case fatality among infants.

Data: We therefore searched for studies of "measles case fatality" (N=161) and "measles mortality/death Africa" (N=620)~~Supplementary material~~). We found 24 relevant studies (Table 4).

Analysis. The African community studies reporting the measles case fatality separately for infants and older children have been presented in Table 4. One review of East African studies of measles have previously emphasised that the case fatality was particularly high in infants (69). However, a comparative analysis of the measles case fatality for infants and older children in all African community studies have not been made before. With a few exceptions, the studies suggested that the case fatality is higher in infancy than among older children (Table 4). These studies suggest around a two-fold higher measles case-fatality in infancy; the MH weighted case fatality ratio for all studies was 1.87 (1.63-2.14). The effect was similar before measles vaccine was introduced in these communities (MH weighted case fatality ratio=2.04 (1.58-2.63)) (see Studies before the introduction of MV, Table 4).

Considerations. Only three studies did not show higher case fatality in infancy and half the studies showed significantly higher mortality in infancy. Even if a few studies should not have been found by the search terms, it seems unlikely that additional studies would change the tendency.

If the case fatality is indeed higher in infancy, it would be more advantageous to have vaccine failures later in life rather than leave infants less than 9 months of age unprotected.

Assumption 5: vaccine failures lead to lack of credibility of the vaccination programme.

Background. Apparently it was assumed that African mothers – like physicians - would lose confidence if measles vaccine did not provide complete and life-long immunity.

Data: We searched "measles vaccine failure" (N=318) and "measles vaccine/vaccination/immunisation credibility" (N=2). This search produced one paper dealing with the relationship between "vaccine failure" and the acceptance or credibility of measles vaccination (70). One study was known from our own research (43).

Analysis. One study from Tanzania stated that acceptance of measles vaccination was low because of the many failures experienced by children vaccinated before 9 months of age.

In the only community study which examined the credibility of the programme in relation to previous experiences with "vaccine failures", younger siblings of "vaccine failures" had a significant higher coverage for measles vaccination (95% (33/35)) than siblings of children who had been successfully vaccinated and not had measles infection (78% (630/809)). Hence, the younger siblings of "vaccine failures" were significantly more likely to have been measles vaccinated (relative risk= 1.21 (1.11-1.32)) (43).

Considerations. The study from Tanzania provided no specific information on how data had been collected and how low acceptance had been measured (70). In contrast to this negative view of measles vaccination, many African mothers have experienced that vaccinated children have mild measles infection (43). In cultures where mothers have learnt that everybody has to get measles, the advantage of "mild measles" is easy to see whereas it is difficult to "see" complete "life-long protection" if you still expect your child will get measles some day. Hence, it may have worked the other way around; seeing your child get mild measles after vaccination would be a strong argument for the value of measles vaccination.

Assumption 6: it had to be a one-dose policy.

Background. The main argument advanced for a one-dose policy was that compliance with the second dose was too low (15,18,68,71). This is surprising since it has been described that mothers sought vaccination so eagerly that it was impossible to maintain the age eligibility criteria for vaccinations during campaigns (16). The reason why mothers did not seek the second dose of measles vaccine in some countries may have been poor information. In Guinea-Bissau, we had very good compliance and improved overall coverage with a two-dose schedule (72). The two-dose group had better protection against measles infection than the one-dose group (72). A two-dose schedule has also been shown to be effective in Niger (73), India (74) and Saudi Arabia (75). Hence, a two-dose schedule is both feasible and effective.

Data: To identify studies comparing the effect on survival of a one-dose and a two-dose policy we used the reviews of measles vaccination and impact on mortality (30,32,33) and searched papers on "Two/2 dose measles vaccine trial" (N=144), "Two/2 dose measles vaccination/immunization and mortality/death" (N=108) and "early measles vaccination/immunization mortality/death" (N=123). These procedures identified only two trials of the effect on child survival of a 2-dose measles vaccinations schedule compared with a 1-dose schedule (see Table 5) and one observational study (78)

Analysis. Only two trials have compared child mortality following two doses of MV (the first being given before 9 months) with mortality after the standard dose of MV (at 9 months of age) (Table 5). In a small trial from Sudan (76), DTP vaccinations were not controlled and many children received DTP after measles vaccine. DTP administered

with or after measles vaccine has negative effects on female survival (34,36). We therefore conducted a large randomized trial including only children who had received DTP3 before enrolment and therefore would not receive DTP after MV (77). Among children who had not received neonatal vitamin A supplementation (VAS) which interacted negatively with early MV(76), two doses of MV at 4.5 and 9 months of age compared with the current policy of one dose at 9 months of age reduced mortality between 4.5 and 36 months of age by 50% (22-68%) in the per-protocol analysis (Table 5). There was a significant reduction in non-measles related mortality of 45% (14-65%) (77). The combined estimate for the two trials showed that the early two-dose measles vaccination strategy may reduce mortality by as much as 48% (23%-65%) compared with the currently recommended standard dose at 9 months of age. Even if the children receiving neonatal VAS were included, the combined estimate was 31% (9-48%) (Table 5).

The only other study to report mortality after two doses of MV is a natural experiment from Guinea-Bissau in the early 1980s. Children were vaccinated in annual or biannual campaigns rather than through routine service. Hence, it was possible to compare in an unbiased way the survival of children who happened to be less than 9 months of age when vaccinated and those vaccinated at the recommended age of 9-11 for MV. MV at 4-8 months and a later dose after 9 months compared with one dose of MV at 9-11 months of age was associated with 59% (15-81%) lower mortality between 9 months and 5 years of age (78).

Considerations. The studies indicate that a two-dose policy providing the first dose of MV before 9 months of age is associated with major reductions in child mortality compared with the current one-dose at 9 month policy. The studies indicated that the benefit was not due to better protection against measles infection. Hence, these studies strongly supported that early measles vaccination has non-specific beneficial effects on child survival.

The implications of the assumptions for the estimated prevention of measles mortality. We calculated how variation in these six assumptions affect the optimal age of MV in terms of reducing measles mortality (Table 1, Columns 7-10). Using the best estimate that the case fatality rate is three-fold lower for vaccinated measles cases than for unvaccinated cases (Tables 2 and 3), the number of estimated measles deaths would have been lowest with one dose of MV at 8 months (Column 7). Assuming furthermore that infants have two-fold higher case fatality than older children (Table 4) the estimated number of measles deaths would have been lowest after vaccination at age 7 months (Column 8). Hence, it might have been better to vaccinate at 7 months of age and have some more vaccine failures later in childhood than to have many unvaccinated cases with high mortality in infancy. Adjusting for the possibility that non-seroconverting vaccinated children have some protection from cellular immunity or low levels of antibodies (37), the optimal age for measles immunization in a one-dose strategy would have moved to 6 or 7 months of age (Columns 9 and 10).

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 (72-77,79). Hence, an early dose at 4-6 months of age and a second dose at 9 months of age would have eliminated virtually all measles mortality and significantly reduced mortality from other causes as well.

Discussion

The main justification for measles vaccination at 9 months of age in low-income countries was to reduce child mortality from measles infection (18). However, the policy was never tested for its effect on survival. The policy was based on assumptions which were believed to be true, and a small seroconversion study (6-8). Thirty-five years ago the six assumptions appeared self-evident and programmatic decisions had to be taken about the optimal age for measles vaccination. However, though all assumptions have been contradicted for years no change has been made in the policy.

Strength and weaknesses

Since the six assumptions have not been research issues there are few studies conducted specifically with these topics in mind. We have therefore had to use a search strategy including review articles and case reports to find studies to assess the validity of the original assumptions. There may be a few more studies which were not found with the literature search since several of the studies identified in previous reviews were not found by the search terms. However, many reviews over the last 25 years have covered the areas of community studies of measles infection and the impact of MV on mortality so it is unlikely that there would be many studies not included. Furthermore, the estimates from different studies were consistent and it is unlikely that the addition of further studies would have a major impact on the estimates.

The assumed case fatality of measles infection does not matter for the estimated impact of the optimal policy on measles mortality. With another case fatality level the epidemiological arguments about assumptions 2-4 would still have the same relative effects on the number of deaths prevented. However, as evident in Tables 2 and 4, most community studies from Africa suggest that the case fatality may have been higher than 4% and the impact of the optimal measles vaccination strategy on overall mortality may therefore have been even larger. Other assumptions may also have been important; for example, the incidence data were from a rural study rather than from an urban area (21). In an urban area the incidence would have been higher at younger ages and it might have been advantageous to vaccinate even earlier. As maternal measles antibody levels have declined in low-income countries (78), earlier vaccination would also have produced better seroconversion rates and it would have been even more advantageous to vaccinate early.

Consistency with previous studies: The non-specific beneficial effects of MV. The conclusion that earlier measles vaccination is likely to have been better for child survival is based on a reconsideration of the programme´s own assumptions about effect on measles mortality. However, what is the empirical evidence for the impact on mortality of measles vaccine before 9 months of age?

In marked contradiction to the original fear that children dying of measles would just die of something else and that measles vaccination would therefore only change the cause of death but not the level of mortality (9-11), all subsequent studies measuring the effect on survival have found marked benefit from measles vaccination (32,33,36,78,80-89). Several studies have assessed the impact of measles vaccine before 12 months of age (30,32,33) but few studies have separately measured the effect on overall mortality of measles vaccination before 9 months of age in an unbiased way (Table 6). In the 1970s, researchers in Congo followed two districts which initially had similar overall mortality levels and then introduced measles vaccination at 7 months of age in one district (11). Measles vaccination administered at 7 months of age reduced overall mortality between 7 and 21 months of age by 71% (2-91%) compared with the neighbouring district which did not get measles vaccination (60). In the early 1980s in Guinea-Bissau, children were vaccinated in annual or biannual campaigns. Hence, it was possible to compare in a "natural experiment" manner the survival of children who had been measles vaccinated before 9 months of age and those vaccinated at 9 months of age, the recommended age of measles vaccination. One dose of MV at 4-8 months compared with 9-11 months of age was associated with 31% (-8-54%) lower mortality between 9 months and 5 years of age (78). As mention above the effect was even stronger if they also received a second dose of MV after 9 months of age. During a civil war in Guinea-Bissau in 1998 (80), we followed children who had been randomised to measles vaccination at 6 months of age compared with children who had been randomised to inactivated polio vaccine (IPV). Due to the war the children did not get the standard measles vaccination at 9 months of age. During the 3 months of intensive fighting when everybody had fled the study area and mortality was high, the children vaccinated against measles at 6 months of age had 70% (13-92%) lower mortality than the unvaccinated group.

These studies of one dose of MV before 9 months of age as well as the studies of early two-dose MV mentioned above suggest that the reduction in mortality from MV before 9 months of age is much larger than can be explained by the prevention of measles infection. WHO estimates that measles deaths caused 10% of under-five deaths (90). However all available studies of the mortality impact of MV (30,32,33) suggest that the effect of measles immunization on mortality is much greater than expected. This beneficial effect is a consistent observation and it can not be explained by the prevention of acute measles infection. First, all studies, in which measles vaccine was not administered with DTP, provided strong evidence of a beneficial effect of measles vaccine on overall mortality (32). Second, all studies censoring for measles infection in the survival analysis to estimate the impact on non-measles related mortality found that prevention of measles-specific deaths explained little and the beneficial effect was due to prevention of non-measles related mortality (32,76,89, 91). For example, in the per-protocol analysis of the largest randomised trial (77), measles vaccine at 4.5 and 9 months compared with the standard dose at 9 months of age reduced non-measles related mortality significantly for all children. Third, the beneficial effect of measles vaccine is usually stronger for girls than for boys (77,92,923). Since measles mortality is not higher for girls than boys, this observation suggests sex-differential mechanisms related to

immune stimulation. Hence, standard measles vaccine may protect against other infections and have a beneficial effect on child survival even when measles is eliminated.

Though the focus here has been on MV administered before 9 months of age there is also a considerable number of studies indicating that MV administered after 9 months of age have non-specific beneficial effects (32,81-86, 91, 94).

The possible biological explanations for non-specific beneficial effects of MV have not been explored in humans. In animal studies of heterologous immunity, previous stimulation with infections may have a major effect on the capacity to handle a lethal dose of an unrelated infection (95). Two trials from Bissau suggest that the beneficial effect of MV is better for children vaccinated in the presence of maternal measles antibodies than for children having no measurable maternal antibodies at the time of MV (89). This may also help explain why MV before 9 months of age is better than later vaccination.

The optimal age of measles vaccination: optimizing seroconversion or impact on overall child survival. The most unfortunate consequence of not testing the optimal age of measles immunization may have been that the beneficial non-specific effects of MV were not detected (32). To the extent MV has beneficial non-specific ~~beneficial~~ effects the question of the optimal age of measles vaccination acquires a new meaning. By lowering the age of measles vaccination, children would benefit not only from earlier protection against measles infection but also from the beneficial non-specific effects against non-measles infections and overall child mortality would be reduced. On the other hand, if the age of vaccination is increased, children would benefit less from the beneficial non-specific ~~beneficial~~ effects and overall child mortality would increase. Hence, policies optimizing the non-specific effects clash with those designed to enhance seroconversion.

Conclusions: Old assumptions linger on

The supplementary immunization activities (SIA) with measles vaccine has eliminated measles infection in Latin America and reduced the incidence in major ways in the rest of the world (1-3). The world is now planning to eliminate and eventually eradicate measles infection (4). With the SIA success in measles control, the optimal age of measles immunization is likely to be considered an irrelevant issue. However, as discussed above, measles vaccine has also non-specific effects which need to be taken into consideration in the planning of vaccination programmes. The prevention of all-cause mortality rather than measles mortality should be the primary objective. In a culture which advocates evidence-based policies (4), the evidence for the current measles vaccination policy – or rather the lack thereof - should be properly reviewed and revised by the global and regional immunization programmes. Otherwise old assumptions about seroconversion rates being the basis for the optimal age of immunisation may linger on and continue to influence policy.

There are major consequences of focusing solely on specific measles mortality. First, as the current policy is mostly determined by our understanding that seroconversion gets

better with increasing age, the tendency will be that with improved control of measles infection, age of vaccination will be increased. Following the elimination of measles in Latin America, the recommended age of primary measles immunization was raised to 12 months in 1996 (3). Again this decision was based on assumptions and not on studies documenting the overall effect on morbidity and mortality. Following the success of measles campaigns in other continents it has also been recommended by SAGE (the Strategic Advisory Group of Experts) to increase the age of measles vaccination to 12 months in areas with low levels of measles transmission (5,12). The underlying assumption about better seroconversion at higher ages may no longer be valid with the decline in maternal antibody levels (79,96). For example, we have obtained 100% seropositivity and 99% protective levels after measles vaccine at 9 months of age with both Schwarz and Edmonston-Zagreb measles vaccine strains in Guinea-Bissau (97).

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 (11,32,38,76-80,89). There is a tendency to dismiss these observations because randomised trials with overall mortality as an outcome have only been conducted in Guinea-Bissau and it is therefore claimed that the global health community has to wait for verification elsewhere (98). However, the beneficial non-specific ~~beneficial~~ effects of MV have been shown in several other countries with high childhood mortality. For example, in a cross-over design, Shann showed that girls receiving standard measles vaccine at 9-10 months of age in five randomised trials in Sudan, Gambia, Senegal and Guinea-Bissau had 47% lower mortality through childhood than control children who received an inactivated vaccine at 9-10 months of age (94). Since the control children had received MV before 9 months of age and did not get measles, the difference in mortality following MV at 9 months of age was a beneficial non-specific ~~beneficial~~ effect not related to prevention of measles infection. Increasing the age of measles vaccine from 9 to 12 months may reduce the beneficial effects in the age group between 9 and 12 months of age in which mortality is still high. Thus the lives lost by this change of schedule could well be more than the lives saved by improved measles control (77).

Second, in the current paradigm for control of infectious diseases, the ultimate success in public health is to eradicate the disease and then remove the vaccine to reduce economic costs as happened for smallpox in the 1970s (26). This may happen for measles infection within the next 10-20 years (99). If measles vaccine has major beneficial non-specific effects (77), to remove measles vaccine or reduce its coverage would increase child mortality levels considerably in low-income countries unless we in the meantime find a vaccine which has all the same beneficial effects as measles vaccine.

After 35 years, it is time to develop a policy for the optimal age of measles immunization. This policy needs to be based on evidence about the impact on overall health and child-survival and not only on assumptions about the impact of specific prevention against measles infection. A two-dose measles vaccination strategy, providing measles vaccine at 4.5 months of age, after the three DTP vaccines, and again at 9 months of age, may significantly improve child survival and provide a solid basis of immunity which if necessary can be enhanced by supplementary measles immunisation activities at a later

age (77,79). Any future changes in the age of measles immunisation due to elimination of measles infection, changes in the epidemiology of measles infection, decline in maternal antibody levels, introduction of new measles vaccines or in the timing of other vaccines should be tested in trials to determine their overall impact on child health.

Contributions*:* PA and HW have been involved in studies of measles vaccination for more than 30 years in West Africa; MLG, CM, CB and AR have been involved in measles vaccination trials since the early 1990s. The first draft was written by PA; all authors contributed to the final version of the paper. PA will act as guarantor of the study.

Conflict of interest: nothing to declare

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Table 1. Projected reduction in measles cases and measles deaths with measles immunization at ages four to ten months. Machakos, Kenya 1974-1981

Expanded Programme on Immunization model (8)						Estimated number of measles deaths in a cohort of 1000 children				
	Column1	Column 2	Column 3	Column 4	Column 5	Column 6	Column 7	Column 8	Column 9	Column 10
	Cumulative measles incidence (%)	Serocon-version from MV (%)	Prevented cases (%)	Vaccine Failures (%)	Cases prior to MV(%)	EPI assumption: Case fatality 4%	Adjusting vaccination status[1]	Adjusting vaccination status and age of infection[2]	Adjusting vaccination status, age of infection, and seronegative 50% protection[3]	Adjusting vaccination status, age of infection, and seronegative 25% protection[3]
Age 4 months	0.5	15	15	85	0	34	11.3	11.3	5.7	8.5
Age 5 months	1.0	35	35	65	0	26	8.6	8.6	4.3	6.5
Age 6 months	2.8	52	51	48	1	19.6	6.8	7.2	**4.0**	5.6
Age 7 months	6.1	72	69	28	3	12.4	4.9	***6.1***	4.3	**5.2**
Age 8 months	9.5	86	79	15	6	8.4	***4.4***	6.8	5.8	6.3
Age 9 months	14.4	95	84	7	9	***6.4***	4.5	8.1	7.7	7.9
Age 10 months	18.6	98	82	4	14	7.2	6.1	11.7	11.5	11.6

Notes: MV=measles vaccine; The estimated number of measles deaths was obtained by multiplying the number of vaccine failures (column 4) and cases prior to MV (column 5) in a cohort of 1000 children by the case fatality rates as indicated in the following notes: 1. Assumption: The relative case fatality ratio is 1/3 for vaccinated versus unvaccinated cases, i.e. 4% for unvaccinated cases and 1.33% for vaccinated cases. 2. Assumption: The relative case fatality ratio is 1/3 for vaccinated versus unvaccinated cases. The case fatality ratio is twice as high for unvaccinated cases occurring in infancy. Hence, the estimated case fatality ratios are 8% for unvaccinated cases occurring in infancy and 1.33% for vaccinated cases. 3. Assumption: Seronegative children had 50% or 25%

protection against measles. Hence, the estimated case fatality ratios are 8% for unvaccinated cases occurring in infancy and 1.33% for vaccinated cases but there were fewer vaccinated cases than indicated in column 4.

Table 2. Acute measles case fatality ratio for measles-vaccinated and measles-unvaccinated cases in African prospective community studies and community surveys

Country	Period	Study	Vaccinated cases (%) (deaths/cases)	Unvaccinated cases (%) (deaths/cases)	Measles case fatality ratio
Bissau (43)	1980-82	PCS; urban	9%(5/53)	17%(18/108)	0.58 (0.23-1.49)*
Bissau (43)[1]	*1980-82*	*PCS; urban (only secondary cases)*	*14%(3/21)*	*46%(11/24)*	*0.30 (0.10-0.86)**
Guinea-Bissau (45)	1983-1984	PCS; urban	4%(4/90)	9%(21/234)	0.41 (0.14-1.22)*
Guinea-Bissau (38)	1984-1987	PCS; 2 year follow-up	0% (0/4)	13% (2/16)	0 (0-23.10)
Bissau (46)	1985-1987	PCS; children < 2yrs; urban	5%(1/22)	11%(10/90)	0.41 (0.06-3.03)#
Bissau (unpublished&)	1991	PCS; children < 10 yrs; urban	2%(10/412)	13%(64/478)	0.24 (0.12-0.49)*
Senegal (47)	1987-1994	PCS; rural	0%(0/127)	2%(18/1085)	0 (0-1.94)*
Ghana (48)	1989-1991	PCS; rural; Vitamin A trial with measles surveillance	10%(15/153)	17%(136/808)	OR=0.42 (0.21-0.83) $##
Kenya (22)	1986	SUR; all ages; rural	2%(2/41)	11%(11/98)	0.51(0.08-3.08)*
Kenya (49)	1988	SUR; Children <5yrs; rural	0%(0/23)	10%(18/182)	0 (0-1.54)*
Chad (50)	1993	SUR; rural	0%(0/23)	8%(61/801)	0 (0-2.18)
Niger (51)	2003-2004	SUR**; urban	0.4%(1/286)	6%(29/481)	0.06 (0.01-0.42)
Chad (51)	2004-2005	SUR** ; urban	0.4%(2/494)	8%(18/212)	0.05 (0.01-0.20)
Nigeria (51)	2004-2005	SUR**; rural	9%(1/11)	7%(79/1131)	1.30 (0.20-8.54)
Sudan (52)	2004	SUR;	0.4%(2/556)	1%(7/568)	0.29 (0.06-1.40)
Niger (53)	1991-1992	SUR; rural	17%(20/118)	15%(61/410)	1.14 (0.72-1.81)
Zimbabwe (54)	1980-1989	SUR; urban	2%(8/335)	7%(20/302)	0.36 (0.16-0.81)
Total					0.39 (0.31-0.49)

Sources: Reviews of measles case fatality studies (27-31) and PubMed search for measles mortality/case fatality in vaccinated children ~~(see Supplementary material)~~; & compiled by Henning Andersen shortly before he died.

Notes: PCS= prospective community studies; SUR= community surveys or outbreak investigations; 1. Mortality is high because only secondary cases are included in the analysis. Since this analysis is a subgroup within the larger study, it has not been included in the combined estimate; $ case fatality ratio calculated by the authors, the remaining studies have been calculated by us *adjusted for age; # adjusted for district; ## adjusted for age, sex, weight-for-age z-score, paternal education and season; ** Mortality was only reported for children with at least 30 days of follow-up whereas the proportion of

vaccinated was reported among all cases. It has been assumed that the proportion vaccinated cases was the same among those with follow-up as among all cases.

Table 3. Measles case-fatality ratio for measles-vaccinated and measles-unvaccinated cases in African prospective community studies and community surveys with long-term follow-up

Country	Period	Study; period of follow-up	Vaccinated cases (%) (deaths/persons)	Unvaccinated cases (%) (deaths/persons)	Mortality ratio
Guinea-Bissau (55)[1]	1988	PCS; 5 year follow-up;	4% (1/23)	16% (8/46)	0.25 (0.03-1.88)
Guinea-Bissau (38)	1984-1987	PCS; 2 year follow-up	0% (0/4)	14% (2/14)	0 (0-20.10)
Burundi (56) [2]	1988-1989	SUR; 7 month follow-up	3/1363 person-months	19/2629 person-months	0.30 (0.09-1.03)
Senegal (47)	1987-1994	PCS; 1 year follow-up	0% (0/127)	1% (15/1055)	0 (0-2.32)
Bissau (unpublished&)	1991-1994	PCS; 3 year follow-up	3% (8/319)	9% (29/338)	0.29 (0.14-0.63)
Total					0.27 (0.14-0.50)

Sources: Reviews of measles case fatality studies (27-31) and PubMed search for measles mortality/case fatality in vaccinated children ~~(see Supplementary material)~~; & compiled by Henning Andersen shortly before he died.
Notes: PCS= prospective community studies; SUR= community surveys or outbreak investigations; 1. There was no data on acute case fatality in the present study since the study only included children who had a convalescent sample collected; 2. This study did not report the acute case fatality but only overall mortality for the 7 months of follow-up.

Table 4. Measles case fatality ratio for infants and older children in African prospective community studies and community surveys

Country	Period	Type of study	Infants (%) (deaths/cases)	Children 1+ year (%) (deaths/cases)	Measles case-fatality ratio
Studies before the introduction of MV					
Gambia (63)#	1961	PCS; rural	31%(12/39)	13%(47/356)	2.33 (1.36-4.00)
Guinea-Bissau (45)	1979	PCS; Urban	28%(22/79)	14%(55/380)	1.92 (1.25-2.96)
Guinea-Bissau (64)	1980	PCS; Rural	47%(7/15)	21%(31/147)	2.21 (1.18-4.13)
Senegal (44)	1983-86	PCS; Rural	12%(19/165)	6%(79/1335)	1.95 (1.21-3.13)
Studies after introduction of MV					
Kenya (65)	1974-1976	PCS; rural	6%(4/63)	7%(24/361)	0.96 (0.34-2.66)
Kenya (65)	1976-1977	PCS; rural	4%(5/125)	1%(7/540)	3.09 (1.00-9.56)
Kenya (22)	1986	SUR; rural	17%(5/29)	7%(8/110)	2.37 (0.84-6.71)
Kenya (49)	1988	SUR; rural	22%(9/41)	5%(11/207)	4.13 (1.83-9.33)
Senegal (44)	1987-1990	PCS; rural	2%(1/43)	2%(9/598)	1.55 (0.20-11.9)
Senegal (47)	1991-1994	PCS; rural	6%(4/72)	1%(4/499)	6.93 (1.77-27.1)
Guinea-Bissau (66)	1980-1982	PCS; urban	30%(7/23)	9%(10/115)	3.50 (1.49-8.24)
Guinea-Bissau (45)	1983-1984	PCS; urban	9%(5/56)	7%(20/268)	1.20 (0.47-3.05)
Zaire (11)	1974-1977	PCS; urban	6%(12/194)	6%(53/844)	0.99 (0.54-1.81)
Ghana (48)	1989-1991	PCS; rural	21%(28/131)	15%(123/830)	1.44 (1.00-2.08)
Chad (50)	1993	SUR; urban	6%(9/156)	8%(52/668)	0.74 (0.37-1.47)
Niger (67)	2003	SUR; rural	16%(13/83)	9%(79/862)	1.71 (0.99-2.94)
Niger (53)	1991-1992	SUR; rural	40%(16/40)	13%(65/488)	3.00 (1.93-4.67)
Niger (51)	2003-2004	SUR; urban	7%(8/111)	3%(22/656)	2.15 (0.98-4.71)
Chad (51)	2004-2005	SUR; urban	5%(5/97)	2%(15/609)	2.09 (0.78-5.63)
Nigeria (51)	2004-2005	SUR; rural	11%(5/47)	7%(75/1095)	1.55 (0.66-3.66)
Zimbabwe (54)	1980-1989	SUR; rural	13%(13/103)	3%(15/534)	4.49 (2.20-9.16)
Sudan (52)	2004	SUR;	3%(1/36)	1%(9/1108)	3.42 (0.45-26.28)
Longer follow-up than 1 month					
Burundi (56)##	1989	SUR; rural; 7 months follow-up	14%(2/176 person-months)	6%(20/3816 person-months)	2.17 (0.51-9.20)
Gambia (68)	1981	SUR; rural; 9 months follow-up	64%(7/11)	10%(13/124)	6.07 (3.07-12.0)
Total					1.87 (1.63-2.14)

Sources: Reviews of measles case fatality studies (27-31) and PubMed search for community studies of measles mortality/case fatality in infants or by age in Africaa ~~(see Supplementary material)~~.

Notes: MV=measles vaccine; PCS=prospective community study, i.e. the population was known before the epidemic and information is likely to have been obtained for all children; SUR= retrospective survey; # The age grouping is 7-12 months and 12-120 months. Measles deaths and total number of children in age group were reported in this study. It has been assumed that all children between 7 and 120 months contracted measles. In this period there were no measles vaccinations available. The last epidemic had occurred 12-13 years earlier; ## The age grouping is 0-8 and 9+ months; ¤ Numbers read from a graph

Table 5. Vaccine efficacy against overall mortality in randomised trials of an early two-dose measles vaccination schedule compared with the standard dose of measles vaccination at 9 months of age

Country and period	Age interval	Comparison (Vaccines)	Administration of DTP	Deaths/person-years or persons	Mortality rate ratio	Comments
Sudan (76) 1989-1992	5-9 months	MV vs Control (Meningococcal A+C)	DTP not given simultaneous with MV but could have been given after MV	1/60.5 vs 6/61.2	0.18 (0.02-1.54)	1st vaccine in 2-dose group was Connaught HTMV and 2nd dose was Schwarz standard MV
	9-36 months	2nd vs 1st MV		7/371.6 vs 7/355.9	0.96 (0.34-2.73)	
	5-36 months				0.60 (0.25-1.45)#	
Guinea-Bissau (77) 2003-2009	4.5-9 months	MV vs Control (no vaccine)	DTP not given simultaneous with MV and after MV; all had DTP3 one month before enrolment	5/398.8 vs 29/821.8	0.33 (0.13-0.86)	Vitamin A supplementation (VAS) at birth is not official policy. Hence, only results for children who did not receive VAS is presented.#
	9-36 months	2nd vs 1st MV		20/2054.4 vs 67/3881.1	0.56 (0.34-0.93)	
	4.5-36 months				0.50 (0.32-0.78)#	

Source: All studies reporting mortality in trials of two doses of measles vaccine (MV) (30,32,33). Only the per-protocol results have been used comparing children who received two doses of MV with those receiving one dose at 9 months. No additional studies of early two-dose measles vaccination reporting impact on mortality were found by PubMed searches ~~(see Supplementary material)~~.
Note: # The combined estimate (Stata) was 0.52 (0.35-0.77); if the children receiving vitamin A at birth were also included, the combined estimate was 0.69 (0.52-0.91).

Table 6. Vaccine efficacy against overall mortality for one dose of standard-titre measles vaccine before 9 months of age

Country	period	Comparison	Results
Early measles vaccination at 7 months of age compared with children unvaccinated community			
Congo (11)	1974-1977	MV administered at 7 months of age; children followed to 21 and 34 months of age. Mortality from 7 to 21 months of age for vaccinated children (3/230.5 pyrs) compared with unvaccinated children from control area (21/470.7 pyrs)	MRR for 7 to 21 months =0.29 (0.09-0.98) MRR for 7 to 34 months =0.52 (0.21-1.27)
Comparing MV at 4-8 months versus MV at 9-11 months of age			
Guinea-Bissau (78)	1980-1982	Natural experiment: MV at 4-8 versus MV at 9-11 mo compared from 9 to 60 months of age	MRR (MV-4-8mo/MV-9-11mo) 0.69 (0.46-1.08)
Comparing children randomsied to MV at 6 months versus IPV at 6 months during a war situation			
Guinea-Bissau (80)	1998	Children were randomised to MV (4/214) or inactivated polio vaccine (11/219) at 6 months of age. Due to a war they did not received the planned MV at 9 mo. Follow-up for 3 months in a war situation	70% (13 to 92)

Sources: All studies examining the general effect of standard measles vaccine (MV) on child survival (as compiled by all available reviews (30,32,33)) have been screened for information on measles vaccination before 9 months of age. There have been several other studies of the impact of MV before 12 months of age on child survival (81-89) but most of these studies could not distinguish the effect of MV before 9 months of age. However, all studies suggested that early MV had a better effect on child survival than later MV. The studies where children received DTP or IPV with early MV or shortly after MV have not been included in the present table (34-36) since this sequence have unfortunate consequences (34,36). No additional studies of one-dose measles vaccination/immunization before 9 months of age reporting impact on mortality were found by PubMed searches ~~(see Supplementary material)~~.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE : The optimal age of measles immunization in low-income countries: 35 years with a policy based on flawed assumptions			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Only in abstract, page 2
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4-5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5, supplementary annex
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary annex
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Supplementary annex
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Supplementary annex
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Supplementary annex
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6

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Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency ($e.g., I^2$) for each meta-analysis.	6

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Discussion page 10
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Supplementary annex
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Tables 2-6
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	5,7
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Tables 2-6
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Pages 6-9
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	7,10
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	3,10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	12-14
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	14