



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

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2011-000761
Article Type:	Research
Date Submitted by the Author:	14-Dec-2011
Complete List of Authors:	Aaby, Peter; Bandim Health Project, Bandim Health Project Martins, Cesario; Bandim Health Project, Bandim Health Project Garly, May-Lill; Bandim Health Project,, Rodrigues, Amabelia; Bandim Health Project, Bandim Health Project, Benn, Christine; Statens Serum Institut, Department of Epidemiology Research Whittle, Hilton; London School of Hygiene and Tropical Medicine,
Primary Subject Heading:	Global health
Secondary Subject Heading:	Epidemiology, Health policy, Infectious diseases, Paediatrics, Public health
Keywords:	EPIDEMIOLOGY, International health services < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, MEDICAL HISTORY, Public health < INFECTIOUS DISEASES, Community child health < PAEDIATRICS, PUBLIC HEALTH

SCHOLARONE™
Manuscripts

only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

Peter Aaby^{1, 2}, Cesário L Martins¹, May-Lill Garly¹, Amabelia Rodrigues¹, Christine S Benn^{1, 2}, Hilton C Whittle³

1) Bandim Health Project, Indepth Network, Apartado 861, Bissau, Guinea-Bissau

(CL Martins, clinician, PhD student, ML Garly, MD PhD, senior researcher, A Rodrigues, PhD, research director, P Aaby, DMSc, professor). E-mail: p.aaby@bandim.org

2) Bandim Health Project, Danish Epidemiology Science Centre, Statens Serum Institut, Artillerivej 5, 2300 Copenhagen S, Denmark (CS Benn, senior researcher, P Aaby, DMSc, professor)

3) London School of Hygiene and Tropical Medicine, London, United Kingdom (H Whittle, F Med Sci, professor)

Running title: Optimal age of measles vaccination

Word counts: Abstract: 291; Text: 5107

Corresponding author: Peter Aaby, Bandim Health Project, Statens Serum Institut, Artillerivej 5, 2300 Copenhagen S, Denmark

p.aaby@bandim.org

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

1
2
3 cases would occur before the specific age of vaccination (Column 5). In making these
4 calculations it was assumed that “vaccine failures” and unvaccinated measles cases were
5 equally severe (*third assumption*) and that it did not matter whether measles was acquired
6 in infancy or later in childhood (*fourth assumption*). Vaccination at 8, 9, and 10 months
7 of age prevented roughly the same proportion of cases, between 79% and 84% (Column
8 3) (4,6,13). Vaccination at 8 month resulted in considerably more vaccine failures (15%)
9 than vaccination at 9 months (7%). Since vaccine failures were assumed to jeopardize the
10 credibility of the measles immunization programme (*fifth assumption*) (4,6,13), it was
11 concluded that the optimal age for administration of measles vaccine would be 9 months.
12 At the time the EPI assumed that the case fatality in measles infection was 4% in Africa
13 and it will be seen in Column 6 that the number of estimated measles deaths in a birth
14 cohort of a 1000 children would indeed be lowest (between 6.4 and 8.4) for vaccination at
15 8-10 months of age. In making this analysis of the effect of only one dose of measles
16 vaccine (4,6), the EPI assumed that a two-dose policy was infeasible or unjustified (*sixth*
17 *assumption*).
18
19
20
21

22 **Methods**

23 **Selection of studies.** We looked for empirical evidence in African community studies to
24 support or refute these assumptions. The original policy was mainly justified in relation
25 to the epidemiology of measles infection in Africa where the case fatality was clearly
26 higher than in other regions (21-25). Most community studies of measles infection are
27 indeed from Africa.
28
29

30
31 Over the last 20-25 years, several reviews of community studies of the measles case
32 fatality compiled studies of relevance for particularly assumption three and four (21-25).
33 Furthermore, as specified in the supplementary material, we made PubMed searches for
34 additional publications relevant for all assumptions. We included one unpublished report
35 from a large epidemic in Bissau in 1991-1992 which has remained unpublished because
36 the physician (Henning Andersen) handling the epidemic died tragically in an accident
37 shortly after the epidemic.
38
39

40 We distinguished between prospective community studies and surveys retrospectively
41 assessing events since the precision of information on vaccination status and age
42 presumably is better in prospective community studies. Though hospital and health centre
43 studies may have data on the severity of measles infection by vaccination status or age,
44 we have not included these studies in the analysis since biased admission for some groups
45 might have made the result non-representative.
46
47

48 Since the analysis of the assumptions suggested that standard-titre measles vaccination
49 before 9 months of age could be beneficial, we assessed the empirical evidence from
50 studies which assessed the effect of early and later measles vaccination on mortality.
51 Again we used all reviews of community studies and trials assessing the impact of
52 measles vaccination on child mortality (24,26,27). Additional PubMed searches for
53 studies comparing the mortality of measles vaccinated and unvaccinated children did not
54 identify further studies. Studies of medium and high-titre measles vaccines were not
55 included in these analyses as they have been analysed elsewhere (28,29).
56
57
58
59
60

1
2
3
4
5 **Statistical analyses.** The Mantel-Haenszel weighted relative risk stratifying for study or
6 age groups was used to estimate common trends.
7

8 **Ethics.** Since the study is based on review of existing data, approval from an ethical
9 committee was not needed.
10

11 **Results**

12 **Assumption 1: children who seroconvert to measles vaccine have absolute protection**
13 **against measles infection.** A number of smaller studies have documented that a few
14 children do get measles after having seroconverted (30-33). Hence, seroconversion does
15 not give absolute protection. However, there are no general epidemiological studies from
16 Africa and it is therefore difficult to estimate the impact on protection. Since no large
17 series have been reported it seems likely that the effect has been small.
18
19

20
21 **Assumption 2: vaccinated children who do not seroconvert are fully susceptible to**
22 **measles infection.** In a study in Senegal, vaccinated children who were seronegative
23 when exposed to measles infection at home had a 49% (95% CI 21-68%) protection
24 against clinical disease compared with unvaccinated seronegative children exposed under
25 similar conditions (30). It is possible that the children had acquired vaccine-induced
26 measles antibodies earlier but subsequently lost them. Based on the literature search, no
27 other study has tested the susceptibility of “seronegative” vaccinated children. If
28 approximately half the seronegative children have clinical protection it would have major
29 consequences for the calculation of the optimal age of measles vaccine. In animal studies
30 cellular immunity may be obtained without having measurable antibodies (34). There is
31 also good evidence from studies of hepatitis B vaccination that antibody concentration
32 wane with time but the majority of older seronegative children if infected are protected
33 from chronic carriage and its damaging consequences (35).
34
35
36
37

38 The concept of seroconversion to compare the effect of vaccination at different age is in
39 itself problematic. Seroconversion is not the same as seroprotection and the use of the
40 term inevitably disadvantages data from studies that have vaccinated at earlier ages when
41 maternal antibodies are still present. Thus a child immunized at 6 months of age when the
42 maternal antibody level is say 62.5 miU may fail the test for conversion (a four-fold
43 increase) yet still have a protective level of 125 miU at 9 months of age.
44
45

46 **Assumption 3: severity of measles infection in vaccinated children (“vaccine failures”)**
47 **and unvaccinated children is the same.** The EPI perceived “vaccine failures” as due to
48 the vaccine being inactivated by improper storage and handling or due to neutralization of
49 the vaccine by maternal antibodies (11,14). Hence, it was assumed that these children
50 were fully susceptible to measles infection. However, many epidemiological studies in
51 the 1980s and 1990s suggested that measles vaccinated children who contracted measles
52 infection had milder disease (36,37). This would suggest that the children had partial
53 measles immunity, not enough to protect them but enough to modify the severity of the
54 disease. In the community studies of the acute measles case fatality shown in Table 2, the
55 measles case fatality was 2 to 5-fold lower for vaccinated cases (“vaccine failures”) than
56
57
58
59
60

1
2
3 for unvaccinated children with measles infection. The effect was similar in the
4 prospective community studies (case-fatality ratio=0.37 (0.27-0.52)) and the retrospective
5 surveys (case-fatality ratio=0.41 (0.29-0.56)).
6
7

8 All studies with relevant data were included in Table 2 irrespective of whether vaccine
9 efficacy (VE) against measles infection was high or substandard. In several studies, the
10 VE was not high but nonetheless the vaccine appeared to have had an effect; for example,
11 in Kenya VE was only 18% but measles-vaccinated children who developed measles had
12 still 2-fold lower measles mortality than measles unvaccinated children (Table 2). Only
13 one community survey from Niger reported that measles vaccine was not particularly
14 effective against measles infection and that there was no effect of vaccination on the case
15 fatality in measles infection (46).
16
17

18 A few studies followed the children for longer than the one month which is the normal
19 time limit for acute measles deaths. The long-term trend was the same with considerable
20 better survival among vaccinated than unvaccinated children after measles infection
21 (Table 3). Combining the prospective community studies in Tables 2 and 3 would suggest
22 a 3-fold reduction in acute and/or long-term mortality among vaccinated children even
23 though some of the vaccine failures may have been due to inactivated measles vaccines.
24 In the four studies (31,40,49, unpublished) having information on both acute and long-
25 term mortality, mortality was nearly 5-fold lower for the vaccinated cases (mortality
26 ratio= 0.21 (0.13-0.34)). Several hospital or health centre based studies have also
27 compared vaccinated and unvaccinated children and reported that measles vaccinated
28 children had less severe measles infection (50-53). A few community studies from India
29 and PNG have also suggested lower case fatality for vaccinated measles cases (54,55).
30
31
32
33

34 In most of the epidemiological studies (Table 2), it was not possible to control for age
35 given the way the data was reported. However, in 6 studies (17, 36, 38, 40, 42,
36 unpublished data) age could be controlled and there was little difference in the case-
37 fatality ratio in the unadjusted analysis (0.27 (0.17-0.42)) and the age-adjusted analysis
38 (0.30 (0.18-0.49)). It could be speculated that vaccinated children had more health-
39 system-compliant mothers and that they therefore had more care and milder infection.
40 However, in many of the original studies, measles vaccine had been provided in
41 community campaigns and not in routine service and vaccination status depended on
42 whether the mother had been around at the time of the campaign and not on any
43 compliance bias (36). In the studies which controlled for background factors, the
44 differential effect of vaccination on the measles case fatality was increased (36,41).
45 Furthermore, several studies have found that “vaccine failures” occur after high intensity
46 of exposure, i.e. “vaccine failures” are more likely to be secondary cases exposed at home
47 (36,37). Since secondary cases have a higher case fatality than index cases (36,37,56), the
48 milder infection among vaccinated children is even more surprising. The possibility that
49 measles vaccinated children have milder disease due to modified immune responses and
50 not merely due to social confounding is strengthened by the many studies showing that
51 measles vaccination is associated with beneficial effects on overall child survival (26,27).
52 If the severity of measles is not the same in vaccinated and unvaccinated children it
53 would strongly affect the estimated benefit of vaccinations at different ages.
54
55
56
57
58
59
60

1
2
3
4
5 **Assumption 4: severity of measles is the same whether measles infection is acquired in**
6 **infancy or later.** In the hypothetical EPI model in which all children were vaccinated at a
7 specific age, the unvaccinated measles cases would occur in infancy, before measles
8 vaccination, whereas most “vaccine failures” would occur much later after the first year
9 of life. The epidemiological evidence is consistent in suggesting that the case fatality is
10 higher in infancy than among older children in African community studies (Table 4).
11 These studies suggest around a two-fold higher measles case-fatality in infancy, the case
12 fatality ratio being 1.87 (1.63-2.14). The effect was similar before measles vaccine was
13 introduced in these communities (case fatality ratio=2.04 (1.58-2.63)) (see Studies before
14 the introduction of MV, Table 4). If that was indeed the case, it would be more
15 advantageous to have a few vaccine failures later in life rather than leave infants less than
16 9 months of age unprotected.
17
18

19
20 **Assumption 5: vaccine failures lead to lack of credibility of the vaccination**
21 **programme.** Apparently it was assumed that African mothers would lose confidence if
22 measles vaccine did not provide complete and life-long immunity. One study from
23 Tanzania stated that acceptance of measles vaccination was low because of the many
24 failures experienced by children vaccinated before 9 months of age but provided no
25 specific information on how data had been collected (63). In contrast, many African
26 mothers have experienced that vaccinated children have mild measles (36). In cultures
27 where mothers have learnt that everybody has to get measles, the advantage of “mild
28 measles” is easy to see whereas it is difficult to “see” complete “life-long protection” if
29 you still expect your child will get measles some day. In the only community study which
30 examined the credibility of the programme in relation to “vaccine failures”, we showed
31 that the younger siblings of thought to be “vaccine failures” had a significant higher
32 coverage for measles vaccination (95% (33/35)) than siblings of children who had been
33 successfully vaccinated and not had measles infection (78% (630/809)) (relative risk=
34 1.21 (1.11-1.32)) (36). Hence, it may have worked the other way around; seeing your
35 child get mild measles after vaccination strengthened the credibility of the programme.
36
37
38
39

40 **Assumption 6: it had to be a one-dose policy.** The main argument advanced for a one-
41 dose policy was that compliance with the second dose was too low (10,13,62,64). This is
42 surprising since others have described that mothers sought vaccination so eagerly that it
43 was impossible to maintain the age eligibility criteria for vaccinations during campaigns
44 (11). It may have been poor information which meant that mothers did not seek the
45 second dose of measles vaccine in some countries. In Guinea-Bissau, we had very good
46 compliance and improved coverage with a two-dose schedule (65). The two-dose group
47 had better protection against measles infection than the one-dose group (65). A two-dose
48 schedule has also been shown to be effective in Niger (66), India (67) and Saudi Arabia
49 (68). Hence, an early two-dose schedule is both feasible and effective.
50
51
52

53 Only two trials have compared child mortality following two doses of MV, the first being
54 given before 9 months, with mortality after the standard dose of MV at 9 months of age
55 (Table 5). In the small trial from Sudan (69), DTP vaccinations were not controlled and
56 many children received DTP after measles vaccine. DTP administered with or after
57
58
59
60

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

1
2
3 effect on survival. The assumptions were believed to be true, and a small seroconversion
4 study was considered sufficient evidence for the policy (4-6). Thirty-five years ago the
5 six assumptions may have appeared self-evident and programmatic decision apparently
6 had to be taken about the optimal age for measles vaccination. However, all assumptions
7 have been contradicted for years but no change has been made in the policy.
8
9

10 **Strength and weaknesses**

11 The quality of the data and relative strength of these assumptions can be discussed. There
12 are likely to be a few more studies which were not found with the literature search since
13 several of the studies identified in previous reviews were not found by the search terms.
14 However, many reviews over the last 25 years have covered the areas of community
15 studies of measles infection and the impact of MV so it is unlikely that there would be
16 many studies not included. Furthermore, the estimates from different studies were
17 consistent and it is unlikely that the addition of further studies would have a major impact
18 on the estimates.
19
20
21

22 The assumed case fatality of measles infection does not matter for the estimated impact
23 of the optimal policy on measles mortality. With another case fatality level the
24 epidemiological arguments about assumptions 2-4 would still have the same relative
25 effects on the number of deaths prevented. However, as evidenced in Tables 2 and 4,
26 most community studies from Africa suggest that the case fatality may have been higher
27 than 4% and the impact of the optimal measles vaccination strategy on overall mortality
28 may therefore have been even larger. Other assumptions may also have been important;
29 for example, the incidence data were from a rural study rather than from an urban area
30 (16). In an urban area the incidence would have been higher at younger ages and it might
31 have been advantageous to vaccinate even earlier. As maternal measles antibody levels
32 have declined in low-income countries (7), earlier vaccination would also have produced
33 better seroconversion rates and it would have been even more advantageous to vaccinate
34 early.
35
36
37
38

39 **Consistency with previous studies: The non-specific beneficial effects of MV.** The
40 conclusion that earlier measles vaccination is likely to have been better for child survival
41 is based on a reconsideration of the programme's own assumptions about effect on
42 measles mortality. However, what is the evidence for the impact on mortality of measles
43 vaccine before 9 months of age?
44
45

46 Several studies have assessed the impact of measles vaccine before 12 months of age
47 (26,82) but few studies have separately measured the effect on overall mortality of
48 measles vaccination before 9 months of age in an unbiased way (Table 6). In the 1970s,
49 researchers in Congo followed two districts which initially had similar overall mortality
50 and then introduced measles vaccination at 7 months of age in one district (60). Measles
51 vaccination administered at 7 months of age reduced overall mortality between 7 and 21
52 months of age by 71% (2-91%) compared with the neighbouring district which did not
53 get measles vaccination (60). In the early 1980s in Guinea-Bissau, children were
54 vaccinated in annual or biannual campaigns. Hence, it was possible to compare in a
55 "natural experiment" manner the survival of children who had been measles vaccinated
56
57
58
59
60

1
2
3 before 9 months of age and those vaccinated at 9 months of age, the recommended age of
4 measles vaccination. One dose of MV at 4-8 months compared with 9-11 months of age
5 was associated with 31% (-8-54%) lower mortality between 9 months and 5 years of age
6 (72). As mention above the effect was even stronger if they also received a second dose
7 of MV after 9 months of age. During a civil war in Guinea-Bissau in 1998 (73), we
8 followed children who had been randomised to measles vaccination at 6 months of age
9 compared with children who had been randomised to IPV. Due to the war the children
10 did not get the standard measles vaccination at 9 months of age. During the 3 months of
11 intensive fighting when everybody had fled the study area and mortality was high, the
12 measles vaccinated children had 70% (13-92%) lower mortality than the measles-
13 unvaccinated group.
14
15
16

17
18 These studies of one dose of MV before 9 months of age as well as the studies of early
19 two-dose MV suggest that the reduction in mortality from MV before 9 months of age is
20 much larger than can be explained by the prevention of measles infection. WHO
21 estimates that measles deaths caused 10% of under-five deaths (83). However all
22 available studies of the mortality impact of MV (24,26,27,82) suggest that the effect of
23 measles immunization on mortality is much greater than expected. There are several
24 reasons that this beneficial effect is a consistent observation and that the effect can not be
25 explained by the prevention of acute measles infection. First, all studies, in which
26 measles vaccine was not administered with DTP, provided strong evidence of a beneficial
27 effect of measles vaccine on overall mortality (26). Second, all studies censoring for
28 measles infection in the survival analysis to estimate the impact on non-measles related
29 mortality found that prevention of measles-specific deaths explained little and the
30 beneficial effect was due to prevention of non-measles related mortality (26,70,82,84).
31 For example, in the per-protocol analysis of the largest randomised trial (70), measles
32 vaccine at 4.5 and 9 months compared with the standard dose at 9 months of age reduced
33 non-measles related mortality significantly for all children and separately for girls. Third,
34 the beneficial effect of measles vaccine is usually stronger for girls than for boys
35 (70,85,86). Since measles mortality is not higher for girls than boys, this observation
36 suggests sex-differential mechanisms related to immune stimulation. Hence, standard
37 measles vaccine may protect against other infections and have a beneficial effect on child
38 survival even when measles is eliminated.
39
40
41
42
43

44 The possible biological explanations for non-specific beneficial effects of MV have not
45 been explored in humans. In animal studies of heterologous immunity, previous
46 stimulation with infections may have a major effect on the capacity to handle a lethal
47 dose of an unrelated infection (87). Two trials from Bissau suggest that the beneficial
48 effect of MV is better for children vaccinated in the presence of maternal measles
49 antibodies than for children having no measurable maternal antibodies at the time of MV
50 (82,88). This may be the mechanism explaining why MV before 9 months of age is better
51 than later.
52
53

54 **The optimal age of measles vaccination: optimizing seroconversion or impact on**
55 **overall child survival.** The most unfortunate consequence of not testing the optimal age
56 of measles immunization may have been that the beneficial non-specific effects of
57
58
59
60

1
2
3 measles vaccine were not detected (26). To the extent MV has non-specific beneficial
4 effects the question of the optimal age of measles vaccination acquires a new meaning.
5 By lowering the age of measles vaccination, children would benefit not only from earlier
6 protection against measles infection but also from the beneficial non-specific effects
7 against non-measles infections and overall child mortality would be reduced. On the other
8 hand, if the age of vaccination is increased, children would benefit less from the non-
9 specific beneficial effects and overall child mortality would increase. Hence, policies
10 optimizing the non-specific effects clash with those designed to enhance seroconversion.
11
12

14 **Conclusions: Old assumptions linger on**

15 The supplementary immunization activities (SIA) with measles vaccine has eliminated
16 measles infection in Latin America and reduced the incidence in major ways in the rest of
17 the world (1-3). The world is now planning to eradicate measles infection. With the SIA
18 success in measles control, the optimal age of measles immunization is likely to be
19 considered an irrelevant issue. However, as discussed above, measles vaccine has also
20 non-specific effects which need to be taken into consideration in the planning of
21 vaccination programmes. The prevention of all-cause mortality rather than measles
22 mortality should be the primary objective. The evidence for the current policy – or rather
23 the lack thereof - should be properly reviewed and revised by the global and regional
24 immunization programmes. Otherwise old assumptions about seroconversion rates being
25 the basis for the optimal age of immunisation may linger on and continue to influence
26 policy.
27
28
29
30

31 There are major consequences of focusing solely on specific measles mortality. First, as
32 the current policy is mostly determined by our understanding that seroconversion gets
33 better with increasing age, the tendency will be that with improved control of measles
34 infection, age of vaccination will be increased. Following the elimination of measles in
35 Latin America, the recommended age of primary measles immunization was raised to 12
36 months in 1996 (3). Again this decision was based on assumptions and not on studies
37 documenting the overall effect on morbidity and mortality. Following the success of
38 measles campaigns in other continents it has also been recommended by SAGE (the
39 Strategic Advisory Group of Experts) to increase the age of measles vaccination to 12
40 months in areas with low levels of measles transmission (89). The underlying assumption
41 about better seroconversion at higher ages may no longer be valid with the decline in
42 maternal antibody levels (7,90). For example, we have obtained 100% seropositivity and
43 99% protective levels after measles vaccine at 9 months of age with both Schwarz and
44 Edmonston-Zagreb measles vaccine strains in Guinea-Bissau (91).
45
46
47
48

49 However, the most important problem is that measles vaccine has major non-specific
50 beneficial effects and the earlier it is given, the earlier the children will benefit from this
51 advantage (70,82). Increasing the age of measles vaccine from 9 to 12 months may
52 reduce the beneficial effects in the age group between 9 and 12 months of age in which
53 mortality is still high. The lives lost by not having the non-specific beneficial effects of
54 measles vaccine in the 9-11 months age group could well be more than the lives saved by
55 improved measles control. In a sense the studies of early two-dose MV have shown
56
57
58
59
60

1
2
3 precisely that by showing that adding an additional dose of measles vaccine at 4-6
4 months of age reduced overall mortality (70).
5
6

7 Second, in the current paradigm for control of infectious diseases, the ultimate success in
8 public health is to eradicate the disease and then remove the vaccine to reduce economic
9 costs as happened for smallpox and vaccinia in the 1970s (20). This may happen for
10 measles infection and measles vaccine within the next 10-20 years (92). If measles
11 vaccine has major beneficial non-specific effects (70), to remove measles vaccine or
12 reduce its coverage would increase child mortality levels considerably in low-income
13 countries unless we in the meantime find a vaccine which has all the same beneficial
14 immune stimulating effects as measles vaccine.
15
16

17 After 35 years, it may be time to develop a policy for the optimal age of measles
18 immunization – a policy which is based on evidence about the impact on overall health
19 and child-survival and not only on assumptions about the impact of specific prevention
20 against measles infection. A two-dose measles vaccination strategy, providing measles
21 vaccine at 4.5 months of age, after the three DTP vaccines, and again at 9 months of age,
22 may significantly improve child survival and provide a solid basis of immunity which if
23 necessary can be enhanced by supplementary measles immunisation activities at a later
24 age (7,70). Any future changes in the age of measles immunization due to elimination of
25 measles infection, changes in the epidemiology of measles infection, decline in maternal
26 antibody levels, introduction of new measles vaccines or in the timing of other vaccines
27 should be tested in trials to determine their overall impact on child health.
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 **Contributions:** PA and HW have been involved in studies of measles vaccination for
4 more than 30 years in West Africa; MLG, CM, CB and AR have been involved in
5 measles vaccination trials since the early 1990s. The first draft was written by PA; all
6 authors contributed to the final version of the paper. PA will act as guarantor of the study.
7
8

9
10 **Conflict of interest:** nothing to declare
11

12 **Funding:** The Bandim Health Project received support from DANIDA and the Danish
13 National Research Foundation. PA holds a research professorship grant from the Novo
14 Nordisk Foundation. We received no funding specifically for the present study.
15
16

17 **Independence:** The funders had no role in the study design, data collection, data
18 analysis, data interpretation, decision to publish or preparation of the manuscript.
19

20 **Data sharing:** no additional data available
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

References

1. De Quadros CA, Olive JM, Hersh BS, Strassburg MA, Henderson DA, Bandling-Bennett D, Alleyne GA. Measles elimination in the Americas. Evolving strategies. *JAMA* 1996; 275: 224-29
2. Otten M, Kezaala R, Fall A, Masresha B, Martin R, Cairns L, Eggers R, Biellik R, Grabowsky M, Strebel P, Okwo-Bele JM, Nshimirimana. Public-health impact of accelerated measles control in the WHO African Region 2000-03. *Lancet* 2005;366:832-9
3. De Quadros CA, Izurieta H, Venczel L, Carrasco P. Measles eradication in the Americas : Progress to date. *JID* 2004 ;189 (Suppl 1) : S227
4. Expanded Programme on Immunization. Measles immunization. *Weekly Epidemiol Rec* 1979;54:337-9
5. Expanded Programme on Immunization. Global advisory group Meeting. *Weekly Epidemiol Rec* 1981;56:9-16
6. Expanded Programme on Immunization. The optimal age for measles immunization. *Weekly Epidemiol Rec* 1982;57:89-91
7. Martins CL, Garly ML, Balé C, Rodrigues A, Ravn H, Whittle HC, Lisse IM, Aaby P. Protective efficacy of standard Edmonston-Zagreb measles vaccination in infants aged 4.5 months: interim analysis of a randomised clinical trial. *BMJ* 2008;337:a661
8. Foege WH. Measles vaccination in Africa. *Sci Pub PAHO* 1971;228:207-12
9. McBean AM, Foster SO, Herrmann KL, Gateff. Evaluation of mass measles immunisation campaign in Yaoundé, Cameroun. *Trans Roy Soc Trop Med Hyg* 1976;70:206-12
10. Guyer B, McBean AM. The epidemiology and control of measles in Yaoundé, Cameroun, 1968-1975. *Int J Epidemiol* 1981;10:263-9
11. Grigsby ME, Adetosoye JIA. Measles epidemiology and control in Western Nigeria. *J Nat Med Ass* 1973;65:378-85
12. Foster SO, Pifer JM. Mass measles control in West and central Africa. *Afr J Med Sci* 1971;2:151-8
13. Henderson RH. Measles vaccination in Zaire – when and how? *Trans Roy Soc Trop Med Hyg* 1981;75:128-9
14. Wood PB, Soheranda KS, Bracken PM, Houser NE. Measles vaccination in Zaire – when and how? *Trans Roy Soc Trop Med Hyg* 1980;74:381-2
15. Lapeyssonnie L, Omer LA, Nicolas A, Roumiantzeff M. Etude de la response serologique d'enfant soudanais a la vaccination combinee triple (rougeole, tetanos, meningite A). *Med Trop* 1979;39:71-9
16. Collaborative study by the Ministry of Health of Kenya and the World Health Organisation. Measles immunity in the first year after birth and the optimum age for vaccination in Kenyan children. *Bull WHO* 1977;55:21- 31
17. Burström B, Aaby P, Mutie DM, Kimani G, Bjerregaard P. Severe measles outbreak in Western Kenya. *East Afr Med J* 1992; 69:419-423
18. Rosenthal SR, Clements CJ. Two-dose measles vaccination schedules. *Bull WHO* 1993;71:421-8
19. Rolfe M. Measles immunization in the Zambian Copperbelt: cause for concern. *Trans Roy Soc Trop Med Hyg* 1982;76:529-30

- 1
 - 2
 - 3
 - 4
 - 5
 - 6
 - 7
 - 8
 - 9
 - 10
 - 11
 - 12
 - 13
 - 14
 - 15
 - 16
 - 17
 - 18
 - 19
 - 20
 - 21
 - 22
 - 23
 - 24
 - 25
 - 26
 - 27
 - 28
 - 29
 - 30
 - 31
 - 32
 - 33
 - 34
 - 35
 - 36
 - 37
 - 38
 - 39
 - 40
 - 41
 - 42
 - 43
 - 44
 - 45
 - 46
 - 47
 - 48
 - 49
 - 50
 - 51
 - 52
 - 53
 - 54
 - 55
 - 56
 - 57
 - 58
 - 59
 - 60
20. Lancet. Rationalising measles vaccination. *The Lancet* 1981;ii:236-7
21. Aaby P. Malnutrition and overcrowding-exposure in severe measles infection. A review of community studies. *Rev Infect Dis* 1988;10:478-491
22. Aaby P, Clements J, Orinda V Mortality from measles: measuring the impact. Geneva 1991: EPI, WHO
23. Wolfson LJ, Grais RF, Luquero FJ, Birmingham ME, Strebel PM. Estimates of measles case fatality ratios: a comprehensive review of community-based studies. *Int J Epidemiol* 2009;38:192-205
24. Sudfeld CR, Navar AM, Halsey NA. Effectiveness of measles vaccination and vitamin A treatment. *Int J Epidemiol* 2010;39:i48-i55
25. Kouadio IK, Kamigaki T, Oshitani H. Measles outbreaks in displaced populations: a review of transmission, morbidity and mortality associated risk factors. *BMC Int Hlth Hum Rights* 2010;10:5
26. Aaby P, Samb B, Simondon F, Coll Seck AM, Knudsen K, et al. Non-specific beneficial effect of measles immunisation: analysis of mortality studies from developing countries. *Br Med J* 1995;311:481-485
27. Garly ML, Aaby P. The challenge of improving the efficacy of measles vaccine. *Acta Trop* 2003;85:1-17
28. Aaby P, Jensen H, Samb B, Cisse B, Sodeman M, et al. Differences in female-male mortality after high-titre measles vaccine and association with subsequent vaccination with diphtheria-tetanus-pertussis and inactivated poliovirus: reanalysis of West African studies. *Lancet* 2003;361: 2183-88
29. Knudsen KM, Aaby P, Whittle H, Rowe M, Samb B, et al. Child mortality following standard, medium or high titre measles immunization in West Africa. *Int J Epidemiol* 1996;25:665-73
30. Samb B, Aaby P, Whittle H, Coll Seck AM, Rahman S, et al. Serological status and measles attack rates among vaccinated and unvaccinated children in rural Senegal. *Pediatr Inf Dis J* 1995;4:203-9
31. Aaby P, Pedersen IR, Knudsen K, da Silva MC, Mordhorst CH, et al. Child mortality related to seroconversion or lack of seroconversion after measles vaccination. *Pediatr Infect Dis J* 1989;8:197-200
32. Hirose M, Hidaka Y, Miyazaki C, Ueda K, Yoshikawa H. Five cases of measles secondary vaccine failure with confirmed seroconversion after live measles vaccination. *Scand J Inf Dis* 1997;29:187-90
33. Samb B, Aaby P, Whittle H, Coll Seck AW, Simondon F. Protective efficacy of high-titre measles vaccines administered from the age of five months: a community study in rural Senegal. *Trans Roy Soc Trop Med Hyg* 1993;87:697-701
34. Siegrist CA, Barrios C, Martinez X, Brandt C, Berney M, et al. Influence of maternal antibodies on vaccine responses: inhibition of antibody but not T cell responses allows successful early prime-boost strategies in mice. *Eur J Immunol* 1998;28:4138-48
35. van der Sande MA, Waight P, Mendy M, Rayco-Solon P, Hutt P, et al. Long-term protection against carriage of hepatitis B virus after infant vaccination. *J Infect Dis* 2006;193:1528-35
36. Aaby P, Bukh J, Leerhøy J, Lisse IM, Mordhorst CH, et al. Vaccinated children get milder measles infection: a community study from Guinea-Bissau. *J Infect Dis*

- 1986;154:858-63
37. Samb B, Aaby P, Whittle H, Coll Seck AM, Simondon F Decline in measles case fatality ratio after the introduction of measles immunization in rural Senegal. *Am J Epidemiol* 1997;145:51-7
 38. Aaby P, Bukh J, Lisse IM, da Silva CM. Measles mortality decline: Nutrition, age at infection, or exposure? *Br Med* 1988;J 296:1225-1228
 39. Aaby P, Knudsen K, Jensen TG, Thaarup J, Poulsen A, et al. Measles incidence, vaccine efficacy, and mortality in two urban African areas with high vaccination coverage. *J Infect Dis* 1990;162:1043-1048
 40. Aaby P, Whittle H, Cisse B, Jensen H, Samb B, et al. The frailty hypothesis revisited: mainly weak children die of measles: *Vaccine* 2002;20: 949-53
 41. Dollimore N, Cutts F, Binka FN, Ross DA, Morris SS, et al. Measles incidence, case fatality, and delayed mortality in children with or without vitamin A supplementation in rural Ghana. *Am J Epidemiol* 1997;146:646-654
 42. Burström B, Aaby P, Mutie DM Child mortality impact of a measles outbreak in a partially vaccinated rural African community. *Scand J Infect Dis* 1993;25:763-9
 43. Ndikuyeze A, Cook A, Cutts FT, Bennett S. Priorities in global measles control: report of an outbreak in N'djamena, Chad. *Epidemiol Infect* 1995;115:309-14
 44. Grais RF, Dubray C, Gersti S, Guthmann JP, Djibo A, et al. Unacceptably high mortality related to measles epidemics in Niger, Nigeria, and Chad. *PLoS Med* 2007;4:e16
 45. Coronado F, Musa N, Tayeb ESAE, Haithami S, Dabbagh A, et al. Restrospective measles outbreak investigation: Sudan, 2004. *J Trop Pediatr* 2006;52:329-34
 46. Expanded Programme on Immunization. High measles case-fatality during an outbreak in a rural area. *Weekly Epidemiol Rec* 1993;68:142-5
 47. Marufu T, Siziya S, Tshimanga M, Murugasampillay S, Mason E, et al. Factors associated with measles complications in Gweru, Zimbabwe. *East Afr Med J* 2001;78:135-8
 48. Aaby P, Lisse I, Mølbak K, Knudsen K, Whittle H. No persistent T lymphocyte immunosuppression or increased mortality after measles infection: a community study from Guinea-Bissau. *Pediatr Inf Dis J* 1996;5:39-44
 49. Chen RT, Weierbach R, Bisoffi Z, Cutts F, Rhodes P, et al. A 'Post-honeymoon period' measles outbreak in Mayinga Sector, Burundi. *Int J Epidemiol* 1994;23:185-93
 50. Nsungu M. Measles vaccination status, delay in recognizing measles outbreaks and outbreak outcome. *Cent Afr J Med* 1995;41:336-9
 51. Oshitani H, Mpabalwani M, Kosolo F, Mizuta K, Luo NP, et al. Measles infection in hospitalized children in Lusaka, Zambia. *Ann Trop Pediatr* 1995;15:167-72
 52. Yamaguchi S, Dunga A, Broadhead RL, Brabin BJ. Epidemiology of measles in Blantyre, Malawi: analyses of passive surveillance data from 1996 to 1998. *Epidemiol Infect* 2002;129:361-9
 53. Mishra A, Mishra S, Lahariya C, Jain P, Bhadoriya RS, et al. Practical observations from an epidemiological investigation of a measles outbreak in a district of India. *Ind J Comm Med* 2009;34:117-21
 54. Mgone JM, Mgone CS, Duke T, Frank D, Yeka W Control measures and the outcome of the measles epidemic of 1999 in the Eastern Highlands Province. PNG

- 1
2
3 Med J 2000;43:91-7
4
5 55. Aaby P, Bukh J, Lisse IM, Smits AJ. Overcrowding and intensive exposure as
6 determinants of measles mortality. *Am J Epidemiol* 1984;120:49-63
7
8 56. McGregor IA. Measles and child mortality in the Gambia. *West Afr Med J*
9 1964;251-7
10
11 57. Aaby P, Bukh J, Lisse IM, Smits AJ, Gomes J, et al. Determinants of measles
12 mortality in a rural area of Guinea-Bissau: Crowding, age, and malnutrition. *J Trop*
13 *Pediatr* 1984;30:164-69
14
15 58. Muller AS, Voorhoeve AM, 't Mannetje W, Schulpden TWJ. The impact of
16 measles in a rural area of Kenya. *East Afr med J* 1977;54:364-72
17
18 59. Aaby P, Bukh J, Lisse IM, da Silva CM. Measles mortality: Further community
19 studies on the role of overcrowding and intensive exposure. *Rev Infect Dis*
20 1988;10:474-477
21
22 60. The Kasongo Project Team. Influence of measles vaccination on survival pattern
23 of 7-35-month-old children in Kasongo, Zaire. *Lancet* 1981;i:764-7
24
25 61. Nandy R, Handzel T, Zaneidou M, Biey J, Cuddy RZ, et al. Case-fatality rate
26 during a measles outbreak in Eastern Niger in 2003. *Clin Inf Dis* 2006;42:322-8
27
28 62. Hull HF, Williams PJ, Oldfield F. Measles mortality and vaccine efficacy in rural
29 West Africa. *Lancet* 1983;i:972-5
30
31 63. Mandara MP, Remme J. Current measles control in Tanzania. *Rev inf Dis*
32 1983;5:554-7
33
34 64. Heymann DL, Mayben GK, Murphy KR, Guyer B, Foster SO. Measles control in
35 Yaounde: Justification of a one dose, nine month minimum age vaccination policy
36 in tropical Africa. *Lancet* 1983;ii:1470-2
37
38 65. Garly ML, Martins CL, Balé C, da Costa F, Dias F, et al. Early two-dose measles
39 vaccination schedule in Guinea-Bissau: Good protection and coverage in infancy.
40 *Int J Epidemiol* 1999;28:347-52
41
42 66. Kaninda AV, Legros D, Jataou IM, Malfait P, Maisonneuve M, Paquet C, Moren A.
43 Measles vaccine effectiveness in standard and early immunization strategies, Niger,
44 1995. *Pediatr Inf Dis J* 1998;7:1034-9
45
46 67. Phadke MA, Bhargava I, Dhaigude P, Bagade A, Biniwale MA, et al. Efficacy of
47 two dose measles vaccination in a community setting. *Ind Pediatr* 1998;35:723-5
48
49 68. Al-Mazrou YY, Al-Jeffri M, Ahmed OMM, Aziz KMS, Mishkas AH. Measles
50 immunization: Early two-doses policy experience. *J Trop Pediatr* 1999;45:98-104
51
52 69. Aaby P, Ibrahim S, Libman M, Jensen H. The sequence of vaccinations and
53 increased female mortality after high-titre measles vaccine: Trials from rural
54 Sudan and Kinshasa. *Vaccine* 2006;24:2764-71
55
56 70. Aaby P, Martins CL, Garly ML, Bale C, Andersen A, Rodrigues A, Ravn H, Lisse
57 IM, Benn CS, Whittle H. Non-specific effects of standard measles vaccine at 4.5
58 and 9 months of age on childhood mortality: Randomised controlled trial. *BMJ*
59 2010;341:c6495
60
61 71. Aaby P, Garly ML, Jensen H, Martins C, Balé C, et al. Increased female-male
62 mortality ratio associated with inactivated polio and diphtheria-tetanus-pertussis
63 vaccines: Observations from vaccination trials in Guinea-Bissau. *Pediatr Infect*
64 *Dis J* 2007;26:247-52.
65
66 72. Aaby P, Andersen M, Sodemann M, Jakobsen M, Gomes J, et al. Reduced

- 1
2
3 childhood mortality after standard measles vaccination at 4-8 months compared
4 with 9-11 months of age. *Br Med J* 1993;307:1308-1311
- 5
6 73. Aaby P, Garly ML, Balé C, Martins C, Jensen H, et al. Survival of previously
7 measles-vaccinated and measles-unvaccinated children in an emergency situation:
8 An unplanned study. *Pediatr Inf Dis J* 2003;22:798-805
- 9
10 74. Garenne M, Cantrelle P. Rougeole e mortalité au Sénégal : étude de l'impact de la
11 vaccination effectuée à Khombole 1965-1968 sur la survie des enfants. In :
12 Cantrelle P, Dormont S, Fargues P, Goujard J, Guignard J, Rumeau-Rouquette C
13 (eds) : Estimation de la mortalité de jeune enfant (0-5 ans) pour guider les actions
14 de santé dans les pays en développement. Paris : INSERM, 1986 ;145:515-32
- 15
16 75. Aaby P, Bukh J, Lisse IM, Smits AJ. Measles vaccination and reduction in child
17 mortality: a community study from Guinea-Bissau. *J Infect* 1984;8:13-21
- 18
19 76. Velema JP, Alihonou EJ, Gandaho T, Hounye FH. Childhood mortality among
20 users and non- users of primary health care in a rural West African community.
21 *Int J Epidemiol* 1991;20:474- 479
- 22
23 77. Holt EA, Boulos R, Halsey NA, Boulos LM, Boulos C. Childhood survival in
24 Haiti: protective effect of measles vaccination. *Pediatrics* 1990;86:188-94
- 25
26 78. George K, Josph A, Muliyl J, Abraham S, Bhattacharji S, John KR. Measles
27 vaccination before nine months. *Trop Med Int Hlth* 1998;3:751-6
- 28
29 79. Kristensen I, Aaby P, Jensen H. Routine vaccinations and child survival: follow
30 up study in Guinea-Bissau, West Africa. *BMJ* 2000;321:1435-8
- 31
32 80. Lehmann D, Vail J, Firth MJ, de Klerk NH, Alpers MP. Benefits of routine
33 immunisations on childhood survival in Tari, Southern Highlands Province, Papua
34 New Guinea. *Int J Epidemiol* 2004, 10.1093/ije/dyh262
- 35
36 81. Elguero E, Simondon F, Simondon K, Vaugelade J. Non-specific effects of
37 vaccination on survival: a prospective study in Senegal. *Trop Med Int Health*
38 2005;10:956-960
- 39
40 82. Aaby P, Martins CL, Garly ML, Andersen A, Fisker AB, Claesson MH, Ravn H,
41 Rodrigues A, Whittle HC, Benn CS. Measles vaccination in presence of maternal
42 antibodies may increase child survival (submitted)
- 43
44 83. de Quadros CA. Can measles be eradicated globally? *Bull WHO* 2004;82:134-8
- 45
46 84. Aaby P, Bhuyia A, Nahar L, Knudsen K, Francisco A, et al. The survival benefit of
47 measles immunisation may not be explained entirely by the prevention of measles
48 disease. *Int J Epidemiol* 2003;32: 106-115
- 49
50 85. Aaby P, Samb B, Simondon F, Knudsen K, Coll Seck AM, et al. Divergent
51 mortality for male and female recipients of low-titre and high-titre measles vaccines
52 in rural Senegal. *Am J Epidemiol* 1993;138:746-755
- 53
54 86. Desgrées du Loû A, Pison G, Aaby P. The role of immunizations in the recent
55 decline in childhood mortality and the changes in the female/male mortality ratio in
56 rural Senegal. *Am J Epidemiol* 1995;142:643-52
- 57
58 87. Welsh RM, Selin LH. No one is naïve: The significance of heterologous T-cell
59 immunity. *Nat Rev Immunol* 2002; 2: 417-426
- 60
61 88. Aaby P. Measles immunization and child survival: uncontrolled experiments. In:
62 Rashad H, Gray R, Boerma T (eds.) Evaluation of the impact of health
63 interventions, IUSSP, Liege: Derouaux Ordina Editions, 1995, pp 11-45
- 64
65 89. Meeting of the immunization Strategic Advisory Group of experts, November

- 1
2
3 2006 – conclusions and recommendations. *Weekly Epidemiol Rec* 2007;82:1-16
4
5 90. Leuridan E, Hens N, Hutse V, Ieven M, Aerts M, et al. Early waning of maternal
6 measles antibodies in era of measles elimination: longitudinal study. *BMJ*
7 2010;340:c1626
8
9 91. Martins C. Measles vaccination in Guinea-Bissau. Strategies to reduce disease
10 burden and improve child survival. Copenhagen: University of Copenhagen, 2011
11 [PhD Thesis]
12
13 92. Heymann DL, Fine PE, Griffiths UK, Hall AJ, Mounier-Jack S. Measles
14 eradication: past is prologue. *Lancet* 2010;376:1719-20
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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				
	Column 1	Column 2	Column 3	Column 4	Column 5	Column 6	Column 7	Column 8	Column 9	Column 10
	Cumulative measles incidence (%)	Seroconversion 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%

1
2
3
4
5 protection against measles. Hence, the estimated case fatality ratios are 8% for unvaccinated cases occurring in infancy and 1.33% for
6 vaccinated cases but there were fewer vaccinated cases than indicated in column 4.
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

For peer review only

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)*
<i>Bissau (36)¹</i>	<i>1980-82</i>	<i>PCS; urban (only secondary cases)</i>	<i>14%(3/21)</i>	<i>46%(11/24)</i>	<i>0.30 (0.10-0.86)*</i>
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

1
2
3 vaccinated was reported among all cases. It has been assumed that the proportion
4 vaccinated cases was the same among those with follow-up as among all cases.
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

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)

1
2
3 Sources: Reviews of measles case fatality studies (21-25) and PubMed search for
4 community studies of measles mortality/case fatality in infants or by age in Africa (see
5 Supplementary material).
6

7 Notes: MV=measles vaccine; PCS=prospective community study, i.e. the population was
8 known before the epidemic and information is likely to have been obtained for all
9 children; SUR= retrospective survey; # The age grouping is 7-12 months and 12-120
10 months. Measles deaths and total number of children in age group were reported in this
11 study. It has been assumed that all children between 7 and 120 months contracted
12 measles. In this period there were no measles vaccinations available. The last epidemic
13 had occurred 12-13 years earlier; ## The age grouping is 0-8 and 9+ months; ∞ Numbers
14 read from a graph
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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)	1 st vaccine in 2-dose group was Connaught HTMV and 2 nd dose was Schwarz standard MV
	9-36 months	2 nd vs 1 st 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	2 nd vs 1 st 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
<i>Early measles vaccination at 7 months of age compared with children unvaccinated community</i>			
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)
<i>Comparing MV at 4-8 months versus MV at 9-11 months of age</i>			
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)
<i>Comparing children randomised to MV at 6 months versus IPV at 6 months during a war situation</i>			
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 receive 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
----------------------	----	---	---

Page 1 of 2

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: 35 years with a policy based on flawed assumptions

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2011-000761.R1
Article Type:	Research
Date Submitted by the Author:	19-Apr-2012
Complete List of Authors:	Aaby, Peter; Bandim Health Project, Bandim Health Project Martins, Cesario; Bandim Health Project, Bandim Health Project Garly, May-Lill; Bandim Health Project,, Rodrigues, Amabelia; Bandim Health Project, Bandim Health Project, Benn, Christine; Statens Serum Institut, Department of Epidemiology Research Whittle, Hilton; London School of Hygiene and Tropical Medicine,
Primary Subject Heading:	Global health
Secondary Subject Heading:	Epidemiology, Health policy, Infectious diseases, Paediatrics, Public health
Keywords:	EPIDEMIOLOGY, International health services < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, MEDICAL HISTORY, Public health < INFECTIOUS DISEASES, Community child health < PAEDIATRICS, PUBLIC HEALTH

SCHOLARONE™
Manuscripts

only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

Peter Aaby^{1, 2}, Cesário L Martins¹, May-Lill Garly¹, Amabelia Rodrigues¹, Christine S Benn^{1, 2}, Hilton C Whittle³

1) Bandim Health Project, Indepth Network, Apartado 861, Bissau, Guinea-Bissau

(CL Martins, clinician, PhD student, ML Garly, MD PhD, senior researcher, A Rodrigues, PhD, research director, P Aaby, DMSc, professor). E-mail: p.aaby@bandim.org

2) Research Center for Vitamins and Vaccines (CVIVA), Bandim Health Project, Danish Epidemiology Science Centre, Statens Serum Institut, Artillerivej 5, 2300 Copenhagen S, Denmark (CS Benn, senior researcher, P Aaby, DMSc, professor)

3) London School of Hygiene and Tropical Medicine, London, United Kingdom (H Whittle, F Med Sci, honorary professor)

Running title: Optimal age of measles vaccination

Word counts: Abstract: 293; Text: 5685

Corresponding author: Peter Aaby, Bandim Health Project, Statens Serum Institut, Artillerivej 5, 2300 Copenhagen S, Denmark

p.aaby@bandim.org

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

1
2
3 would produce too many vaccine failures and a one-dose programme was considered
4 necessary because mothers would not bring their children back for a second dose (15,25).
5 Therefore, the Expanded Programme on Immunization (EPI) recommended a one-dose
6 policy (6-8,18). In 1980, the Global Advisory Group of EPI endorsed this policy and
7 recommended measles vaccination as early as possible after 9 months of age (7).
8
9

10
11 The recommendation was based on the belief that the expected reduction in mortality
12 could be computed from seroconversion rates (18,26) and the policy was justified several
13 times by analyses of the seroconversion data from Kenya (6,8). In these analyses it was
14 assumed that seroconversion was associated with full protection against measles infection
15 (*assumption 1*) and that non-seroconversion was associated with full susceptibility to
16 measles infection (*assumption 2*). As shown in Table 1 (Column 2), the data from Kenya
17 (21) showed that seroconversion increased with age. This was not unexpected since the
18 calculation of this measure (a fourfold or more increase over baseline) is dependent on
19 level of maternal antibody which wanes as the child ages. Based on cumulative measles
20 incidence figures (Column 1), it was calculated how many measles cases had been
21 prevented assuming everybody was vaccinated at a specific age (Column 3), how many
22 “vaccine failures” would occur after the age of vaccination (Column 4) and how many
23 cases would occur before the specific age of vaccination (Column 5). In making these
24 calculations it was assumed that “vaccine failures” and unvaccinated measles cases were
25 equally severe (*assumption 3*) and that it did not matter whether measles was acquired in
26 infancy or later in childhood (*assumption 4*). Vaccination at 8, 9, and 10 months of age
27 prevented roughly the same proportion of cases, between 79% and 84% (Column 3) (6,8).
28 Vaccination at 8 month resulted in considerably more vaccine failures (15%) than
29 vaccination at 9 months (7%). Since vaccine failures were assumed to jeopardize the
30 credibility of the measles immunization programme (*assumption 5*) (6,8,18), it was
31 concluded that the optimal age for administration of measles vaccine would be 9 months.
32 At the time the EPI assumed that the case fatality in measles infection was 4% in Africa
33 and it will be seen in Column 6 that the number of estimated measles deaths in a birth
34 cohort of a 1000 children would indeed be lowest (between 6.4 and 8.4) for vaccination at
35 8-10 months of age. In making this analysis of the effect of only one dose of measles
36 vaccine (6,8), the EPI assumed that a two-dose policy was not feasible or unjustified
37 (*assumption 6*).
38
39
40
41
42
43

44 **Methods**

45 **Selection of studies.** We looked for empirical evidence in community studies to support
46 or refute these assumptions. The original policy was mainly justified in relation to the
47 epidemiology of measles infection in Africa where the case fatality was clearly higher
48 than in other regions (27-31). Most community studies of measles infection are indeed
49 from Africa and we have therefore restricted the analyses and the tables 2-4 to the
50 African studies. These tables are believed to be exhaustive for Africa and they are not
51 contradicted by community studies from Latin America and Asia. For the analysis of the
52 impact of measles vaccination on child mortality we included all studies from Asia and
53 Latin America.
54
55
56
57
58
59
60

1
2
3 The search strategy has been defined in the supplementary material. Since there are few
4 specific studies to test the six assumptions we have had to use case reports of measles
5 outbreaks to assess their validity. Over the last 20-25 years, several reviews of
6 community studies of the measles case fatality compiled studies of relevance for
7 particularly assumption three and four (27-31). Furthermore, as specified in the
8 supplementary material, we made PubMed searches for additional publications relevant
9 for all assumptions. We included one unpublished report from a large epidemic in Bissau
10 in 1991-1992 which has remained unpublished because the physician (Henning
11 Andersen) handling the epidemic died tragically in an accident shortly after the epidemic.
12
13

14
15 We distinguished between prospective community studies and surveys retrospectively
16 assessing events since the precision of information on vaccination status and age
17 presumably is better in prospective studies. Though hospital and health centre studies
18 may have data on the severity of measles infection by vaccination status or age, we have
19 not included these studies in the analysis since biased admission for some groups might
20 have made the result non-representative.
21
22

23 Since the analysis of the assumptions suggested that measles vaccination before 9 months
24 of age could be beneficial, we assessed the empirical evidence from studies which
25 assessed the effect of early measles vaccination on mortality. Again we used all reviews
26 of community studies and trials assessing the impact of measles vaccination on child
27 mortality (30,32-35). Additional PubMed searches for studies comparing the mortality of
28 measles vaccinated and unvaccinated children did not identify further studies. As
29 explained in the footnote to table 6, we have emphasised the studies in which inactivated
30 vaccines were not administered simultaneously with MV or after MV as such
31 combination or sequences can have a negative effect on child survival (34,36).
32
33

34
35 **Statistical analyses.** The Mantel-Haenszel weighted relative risk stratifying for study or
36 age groups was used to estimate common trends.
37

38
39 **Ethics.** Since the study is based on review of existing data, approval from an ethical
40 committee was not needed.
41

42 **Results**

43
44 ***Assumption 1: children who seroconvert to measles vaccine have absolute protection***
45 ***against measles infection.*** A number of smaller studies have documented that a few
46 children do get measles after having seroconverted (37-40). Hence, seroconversion does
47 not give absolute protection. There are no general epidemiological studies from Africa
48 and it is therefore difficult to estimate the proportion of children who get measles in spite
49 of having seroconverted, but since no large series have been reported it is likely to be
50 small.
51

52
53
54 ***Assumption 2: vaccinated children who do not seroconvert are fully susceptible to***
55 ***measles infection.*** In a study in Senegal, vaccinated children who were seronegative
56 when exposed to measles infection at home had a 49% (95% CI 21-68%) protection
57 against clinical disease compared with unvaccinated seronegative children exposed under
58
59
60

1
2
3 similar conditions (37). It is possible that the children had acquired vaccine-induced
4 measles antibodies earlier but subsequently lost them. Based on the literature search, no
5 other study has tested the susceptibility of vaccinated “seronegative” children. If
6 approximately half the seronegative children have clinical protection it would have major
7 consequences for the calculation of the optimal age of measles vaccine. Cellular
8 immunity may be obtained without having measurable antibodies (41). There is also good
9 evidence from studies of hepatitis B vaccination that antibody concentration wane with
10 time but the majority of older seronegative children if infected are protected from chronic
11 carriage and its damaging consequences (42).
12
13

14
15 The concept of seroconversion to compare the effect of vaccination at different age is in
16 itself problematic. Seroconversion is not the same as seroprotection and the use of the
17 term inevitably disadvantages data from studies that have vaccinated at earlier ages when
18 maternal antibodies are still present. Thus a child immunized at 6 months of age when the
19 maternal antibody level is say 62.5 mIU may fail the test for conversion (a four-fold
20 increase) yet still have a protective level of 125 mIU at 9 months of age.
21
22

23
24 ***Assumption 3: severity of measles infection in vaccinated children (“vaccine failures”)***
25 ***and unvaccinated children is the same.*** The EPI perceived “vaccine failures” as due to
26 the vaccine being inactivated by improper storage and handling or due to neutralization of
27 the vaccine by maternal antibodies (16,19). Hence, it was assumed that these children
28 were fully susceptible to measles infection. However, many epidemiological studies in
29 the 1980s and 1990s suggested that measles vaccinated children who contracted measles
30 infection had milder disease (43,44). This would suggest that the children had partial
31 measles immunity, not enough to protect them but enough to modify the severity of the
32 disease. In the community studies of the acute measles case fatality shown in Table 2, the
33 measles case fatality was 2 to 5-fold lower for vaccinated cases (“vaccine failures”) than
34 for unvaccinated children with measles infection. The effect was similar in the
35 prospective community studies (case-fatality ratio=0.37 (0.27-0.52)) and the retrospective
36 surveys (case-fatality ratio=0.41 (0.29-0.56)).
37
38
39

40 All studies with relevant data were included in Table 2 irrespective of whether vaccine
41 efficacy (VE) against measles infection was high or substandard. In several studies, the
42 VE was not high but nonetheless the vaccine appeared to have had an effect; for example,
43 in Kenya VE was only 18% but measles-vaccinated children who developed measles had
44 still 2-fold lower measles mortality than measles unvaccinated children (Table 2). Only
45 one community survey from Niger reported that measles vaccine was not particularly
46 effective against measles infection and that there was no effect of vaccination on the case
47 fatality in measles infection (53).
48
49

50 A few studies followed the children for longer than the one month which is the normal
51 time limit for acute measles deaths. The long-term trend was the same with considerable
52 better survival among vaccinated than unvaccinated children after measles infection
53 (Table 3). Combining the prospective community studies in Tables 2 and 3 would suggest
54 a 3-fold reduction in acute and/or long-term mortality among vaccinated children even
55 though some of the vaccine failures may have been due to inactivated measles vaccines.
56
57
58
59
60

1
2
3 In the four studies (38,47,56, unpublished) with information on both acute and long-term
4 mortality, mortality was nearly 5-fold lower for the vaccinated cases (mortality ratio=
5 0.21 (0.13-0.34)). Several hospital or health centre based studies have also compared
6 vaccinated and unvaccinated children and reported that measles vaccinated children had
7 less severe measles infection (57-59). A few community studies from India and Papua
8 New Guinea have also suggested lower case fatality for vaccinated measles cases (60,61).
9
10

11
12 In most of the epidemiological studies (Table 2), it was not possible to control for age
13 given the way the data was reported. However, in 6 studies (22, 43, 45, 47, 49,
14 unpublished data) age could be controlled and there was little difference in the case-
15 fatality ratio in the unadjusted analysis (0.27 (0.17-0.42)) and the age-adjusted analysis
16 (0.30 (0.18-0.49)). It could be speculated that vaccinated children had more health-
17 system-compliant mothers and that they therefore had more care and milder infection.
18 However, in many of the original studies from the 1980s, measles vaccine had been
19 provided in community campaigns and not in routine service and vaccination status
20 depended on whether the mother had been around at the time of the campaign and not on
21 bias (43). In the studies which adjusted for background factors, the differential effect of
22 vaccination on the measles case fatality was actually increased (43,48). Furthermore,
23 several studies have found that “vaccine failures” occur after high intensity of exposure,
24 i.e. “vaccine failures” are more likely to be secondary cases exposed at home (43,44).
25 Since secondary cases have a higher case fatality than index cases (43,44,62), the milder
26 infection among vaccinated children is even more surprising. The possibility that measles
27 vaccinated children have milder disease due to modified immune responses and not
28 merely due to social confounding is strengthened by the many studies showing that
29 measles vaccination is associated with beneficial effects on overall child survival (32,33).
30 If the severity of measles is not the same in vaccinated and unvaccinated children it
31 would strongly affect the estimated benefit of vaccinations at different ages.
32
33
34
35
36

37 ***Assumption 4: severity of measles is the same whether measles infection is acquired in***
38 ***infancy or later.*** In the hypothetical EPI model in which all children were vaccinated at a
39 specific age, the unvaccinated measles cases would occur in infancy, before measles
40 vaccination, whereas most “vaccine failures” would occur much later after the first year
41 of life. The epidemiological evidence is consistent in suggesting that the case fatality is
42 higher in infancy than among older children in African community studies (Table 4).
43 These studies suggest around a two-fold higher measles case-fatality in infancy, the case
44 fatality ratio being 1.87 (1.63-2.14). The effect was similar before measles vaccine was
45 introduced in these communities (case fatality ratio=2.04 (1.58-2.63)) (see Studies before
46 the introduction of MV, Table 4). If that was indeed the case, it would be more
47 advantageous to have vaccine failures later in life rather than leave infants less than 9
48 months of age unprotected.
49
50

51
52 ***Assumption 5: vaccine failures lead to lack of credibility of the vaccination***
53 ***programme.*** Apparently it was assumed that African mothers would lose confidence if
54 measles vaccine did not provide complete and life-long immunity. One study from
55 Tanzania stated that acceptance of measles vaccination was low because of the many
56 failures experienced by children vaccinated before 9 months of age but provided no
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

1
2
3 of age was associated with 59% (15-81%) lower mortality between 9 months and 5 years
4 of age (77). Hence, the two-dose studies indicate that a two-dose policy providing the
5 first dose of MV before 9 months of age is associated with major reductions in child
6 mortality.
7
8

9
10 **The implications of the assumptions for the estimated prevention of measles**
11 **mortality.** We calculated how variations in these six assumptions affect the optimal age
12 of MV in terms of reducing measles mortality (Table 1, Columns 7-10). Using the best
13 estimate that the case fatality rate is one-third lower for vaccinated measles cases than for
14 unvaccinated cases (Tables 2 and 3), the number of estimated measles deaths would have
15 been lowest with general vaccination at 8 months (Column 7). Assuming furthermore that
16 infants have 2-fold higher case fatality than older children (Table 4) the estimated number
17 of measles deaths would have been lowest after vaccination at age 7 months (Column 8).
18 Hence, it might have been better to vaccinate at 7 months of age and have some more
19 vaccine failures later in childhood than to have many unvaccinated cases with high
20 mortality in infancy. Adjusting for the possibility that non-seroconverting vaccinated
21 children have some protection from cellular immunity or low levels of antibodies (37),
22 the optimal age for measles immunization in a one-dose strategy would have moved to 6
23 or 7 months of age (Columns 9 and 10).
24
25
26

27 The studies of two doses of MV suggest that both the first and the second dose of measles
28 vaccine are effective and that an early two-dose strategy would be associated with a
29 major reduction in measles and overall mortality (71-76,78). Hence, an early dose at 4-6
30 months of age and a second dose at 9 months of age would have eliminated virtually all
31 measles mortality and significantly reduced mortality from other causes as well..
32
33

34 Discussion

35 The main justification for measles vaccination at 9 months of age in low-income
36 countries was to reduce child mortality from measles infection (18). However, the policy
37 was never tested for its effect on survival. The policy was based on assumptions which
38 were believed to be true, and a small seroconversion study (6-8). Thirty-five years ago
39 the six assumptions appeared self-evident and programmatic decisions had to be taken
40 about the optimal age for measles vaccination. However, though all assumptions have
41 been contradicted for years no change has been made in the policy.
42
43
44

45 Strength and weaknesses

46 Since the six assumptions have not been research issues there are few studies conducted
47 specifically with these topics in mind. We have therefore had to use a search strategy
48 including review articles and case reports to find studies to assess the validity of the
49 original assumptions. There may be a few more studies which were not found with the
50 literature search since several of the studies identified in previous reviews were not found
51 by the search terms. However, many reviews over the last 25 years have covered the
52 areas of community studies of measles infection and the impact of MV on mortality so it
53 is unlikely that there would be many studies not included. Furthermore, the estimates
54 from different studies were consistent and it is unlikely that the addition of further studies
55 would have a major impact on the estimates.
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

1
2
3 lost by this change of schedule could well be more than the lives saved by improved
4 measles control (76).
5
6

7 Second, in the current paradigm for control of infectious diseases, the ultimate success in
8 public health is to eradicate the disease and then remove the vaccine to reduce economic
9 costs as happened for smallpox in the 1970s (26). This may happen for measles infection
10 within the next 10-20 years (98). If measles vaccine has major beneficial non-specific
11 effects (76), to remove measles vaccine or reduce its coverage would increase child
12 mortality levels considerably in low-income countries unless we in the meantime find a
13 vaccine which has all the same beneficial effects as measles vaccine.
14
15

16 After 35 years, it is time to develop a policy for the optimal age of measles immunization.
17 This policy needs to be based on evidence about the impact on overall health and child-
18 survival and not only on assumptions about the impact of specific prevention against
19 measles infection. A two-dose measles vaccination strategy, providing measles vaccine at
20 4.5 months of age, after the three DTP vaccines, and again at 9 months of age, may
21 significantly improve child survival and provide a solid basis of immunity which if
22 necessary can be enhanced by supplementary measles immunisation activities at a later
23 age (76,78). Any future changes in the age of measles immunisation due to elimination of
24 measles infection, changes in the epidemiology of measles infection, decline in maternal
25 antibody levels, introduction of new measles vaccines or in the timing of other vaccines
26 should be tested in trials to determine their overall impact on child health.
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 **Contributions:** PA and HW have been involved in studies of measles vaccination for
4 more than 30 years in West Africa; MLG, CM, CB and AR have been involved in
5 measles vaccination trials since the early 1990s. The first draft was written by PA; all
6 authors contributed to the final version of the paper. PA will act as guarantor of the study.
7
8

9
10 **Conflict of interest:** nothing to declare
11

12 **Funding:** The Bandim Health Project received support from DANIDA and the Danish
13 National Research Foundation. PA holds a research professorship grant from the Novo
14 Nordisk Foundation. We received no funding specifically for the present study.
15
16

17 **Independence:** The funders had no role in the study design, data collection, data
18 analysis, data interpretation, decision to publish or preparation of the manuscript.
19

20 **Data sharing:** no additional data available
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

References

1. De Quadros CA, Olive JM, Hersh BS, Strassburg MA, Henderson DA, Bandling-Bennett D, Alleyne GA. Measles elimination in the Americas. Evolving strategies. *JAMA* 1996; 275: 224-29
2. Otten M, Kezaala R, Fall A, Masresha B, Martin R, Cairns L, Eggers R, Biellik R, Grabowsky M, Strebel P, Okwo-Bele JM, Nshimirimana. Public-health impact of accelerated measles control in the WHO African Region 2000-03. *Lancet* 2005;366:832-9
3. De Quadros CA, Izurieta H, Venczel L, Carrasco P. Measles eradication in the Americas : Progress to date. *JID* 2004 ;189 (Suppl 1) : S227
4. Department of immunization, vaccines and biologicals: Strategic Plan 2010-15. Draft 24 March 2010, World Health Organization
5. Measles vaccines: WHO position paper. *Week Epid Rec* 2009;84:349-60
6. Expanded Programme on Immunization. Measles immunization. *Weekly Epidemiol Rec* 1979;54:337-9
7. Expanded Programme on Immunization. Global advisory group Meeting. *Weekly Epidemiol Rec* 1981;56:9-16
8. Expanded Programme on Immunization. The optimal age for measles immunization. *Weekly Epidemiol Rec* 1982;57:89-91
9. Hendrickse RG. Problems of future measles vaccination in developing countries. *Trans R Soc Trop Med Hyg* 1975;69:31-34
10. Mosley WH. Will primary health care reduce infant and child mortality? A critique of some current strategies. With special reference to Africa and Asia. In: Lopez AD, Vallin J (eds): Health policy, social policy and mortality prospects. Liege: Ordina, 1985;pp 103-37
11. The Kasongo Project Team. Influence of measles vaccination on survival pattern of 7-35-month-old children in Kasongo, Zaire. *Lancet* 1981;i:764-7
12. Meeting of the immunization Strategic Advisory Group of experts, November 2006 – conclusions and recommendations. *Weekly Epidemiol Rec* 2007;82:1-16
13. Foege WH. Measles vaccination in Africa. *Sci Pub PAHO* 1971;228:207-12
14. McBean AM, Foster SO, Herrmann KL, Gateff. Evaluation of mass measles immunisation campaign in Yaoundé, Cameroun. *Trans Roy Soc Trop Med Hyg* 1976;70:206-12
15. Guyer B, McBean AM. The epidemiology and control of measles in Yaoundé, Cameroun, 1968-1975. *Int J Epidemiol* 1981;10:263-9
16. Grigsby ME, Adetosoye JIA. Measles epidemiology and control in Western Nigeria. *J Nat Med Ass* 1973;65:378-85
17. Foster SO, Pifer JM. Mass measles control in West and central Africa. *Afr J Med Sci* 1971;2:151-8
18. Henderson RH. Measles vaccination in Zaire – when and how? *Trans Roy Soc Trop Med Hyg* 1981;75:128-9
19. Wood PB, Soheranda KS, Bracken PM, Houser NE. Measles vaccination in Zaire – when and how? *Trans Roy Soc Trop Med Hyg* 1980;74:381-2
20. Lapeyssonnie L, Omer LA, Nicolas A, Roumiantzeff M. Etude de la réponse serologique d'enfant soudanais a la vaccination combinee triple (rougeole, tetanos, meningite A). *Med Trop* 1979;39:71-9

21. Collaborative study by the Ministry of Health of Kenya and the World Health Organisation. Measles immunity in the first year after birth and the optimum age for vaccination in Kenyan children. *Bull WHO* 1977;55:21- 31
22. Burström B, Aaby P, Mutie DM, Kimani G, Bjerregaard P. Severe measles outbreak in Western Kenya. *East Afr Med J* 1992; 69:419-423
23. Seroconversion rates and measles antibody titers induced by measles vaccine in Latin American children aged 6-12 months of age. Collaborative study by the Ministries of Health of Brazil, Chile, Costa Rica, Ecuador, and the Pan American Health Organization. *Bull Pan Am Health Organ* 1982;16:272-85
24. Rosenthal SR, Clements CJ. Two-dose measles vaccination schedules. *Bull WHO* 1993;71:421-8
25. Rolfe M. Measles immunization in the Zambian Copperbelt: cause for concern. *Trans Roy Soc Trop Med Hyg* 1982;76:529-30
26. Lancet. Rationalising measles vaccination. *The Lancet* 1981;ii:236-7
27. Aaby P. Malnutrition and overcrowding/intensive exposure in severe measles infection: review of community studies. *Rev Infect Dis* 1988;10:478-491
28. Aaby P, Clements J, Orinda V Mortality from measles: measuring the impact. Geneva 1991: EPI, WHO
29. Wolfson LJ, Grais RF, Luquero FJ, Birmingham ME, Strebel PM. Estimates of measles case fatality ratios: a comprehensive review of community-based studies. *Int J Epidemiol* 2009;38:192-205
30. Sudfeld CR, Navar AM, Halsey NA. Effectiveness of measles vaccination and vitamin A treatment. *Int J Epidemiol* 2010;39:i48-i55
31. Kouadio IK, Kamigaki T, Oshitani H. Measles outbreaks in displaced populations: a review of transmission, morbidity and mortality associated risk factors. *BMC Int Hlth Hum Rights* 2010;10:5
32. Aaby P, Samb B, Simondon F, Coll Seck AM, Knudsen K, et al. Non-specific beneficial effect of measles immunisation: analysis of mortality studies from developing countries. *Br Med J* 1995;311:481-485
33. Garly ML, Aaby P. The challenge of improving the efficacy of measles vaccine. *Acta Trop* 2003;85:1-17
34. Aaby P, Jensen H, Samb B, Cisse B, Sodeman M, et al. Differences in female-male mortality after high-titre measles vaccine and association with subsequent vaccination with diphtheria-tetanus-pertussis and inactivated poliovirus: reanalysis of West African studies. *Lancet* 2003;361: 2183-88
35. Knudsen KM, Aaby P, Whittle H, Rowe M, Samb B, et al. Child mortality following standard, medium or high titre measles immunization in West Africa. *Int J Epidemiol* 1996;25:665-73
36. Aaby P, Garly ML, Nielsen J, Ravn H, Martins C, Balé C, et al. Increased female-male mortality ratio associated with inactivated polio and diphtheria-tetanus-pertussis vaccines: Observations from vaccination trials in Guinea-Bissau. *Pediatr Infect Dis J* 2007;26:247-52.
37. Samb B, Aaby P, Whittle H, Coll Seck AM, Rahman S, et al. Serological status and measles attack rates among vaccinated and unvaccinated children in rural Senegal. *Pediatr Inf Dis J* 1995;14:203-9
38. Aaby P, Pedersen IR, Knudsen K, da Silva MC, Mordhorst CH, et al. Child

- mortality related to seroconversion or lack of seroconversion after measles vaccination. *Pediatr Infect Dis J* 1989;8:197-200
39. Hirose M, Hidaka Y, Miyazaki C, Ueda K, Yoshikawa H. Five cases of measles secondary vaccine failure with confirmed seroconversion after live measles vaccination. *Scand J Inf Dis* 1997;29:187-90
40. Samb B, Aaby P, Whittle H, Seck AW, Simondon F. Protective efficacy of high-titre measles vaccines administered from the age of five months: a community study in rural Senegal. *Trans Roy Soc Trop Med Hyg* 1993;87:697-701
41. Siegrist CA, Barrios C, Martinez X, Brandt C, Berney M, et al. Influence of maternal antibodies on vaccine responses: inhibition of antibody but not T cell responses allows successful early prime-boost strategies in mice. *Eur J Immunol* 1998;28:4138-48
42. van der Sande MA, Waight P, Mendy M, Rayco-Solon P, Hutt P, et al. Long-term protection against carriage of hepatitis B virus after infant vaccination. *J Infect Dis* 2006;193:1528-35
43. Aaby P, Bukh J, Leerhøy J, Lisse IM, Mordhorst CH, et al. Vaccinated children get milder measles infection: a community study from Guinea-Bissau. *J Infect Dis* 1986;154:858-63
44. Samb B, Aaby P, Whittle H, Seck AM, Simondon F. Decline in measles case fatality ratio after the introduction of measles immunization in rural Senegal. *Am J Epidemiol* 1997;145:51-7
45. Aaby P, Bukh J, Lisse IM, da Silva CM. Decline in measles mortality: nutrition, age at infection, or exposure? *Br Med J* 1988;296:1225-1228
46. Aaby P, Knudsen K, Jensen TG, Thaarup J, Poulsen A, et al. Measles incidence, vaccine efficacy, and mortality in two urban African areas with high vaccination coverage. *J Infect Dis* 1990;162:1043-1048
47. Aaby P, Whittle H, Cisse B, Samb B, Jensen H, et al. The frailty hypothesis revisited: mainly weak children die of measles. *Vaccine* 2001;20:949-53
48. Dollimore N, Cutts F, Binka FN, Ross DA, Morris SS, et al. Measles incidence, case fatality, and delayed mortality in children with or without vitamin A supplementation in rural Ghana. *Am J Epidemiol* 1997;146:646-654
49. Burström B, Aaby P, Mutie DM. Child mortality impact of a measles outbreak in a partially vaccinated rural African community. *Scand J Infect Dis* 1993;25:763-9
50. Ndikuyeze A, Cook A, Cutts FT, Bennett S. Priorities in global measles control: report of an outbreak in N'djamena, Chad. *Epidemiol Infect* 1995;115:309-14
51. Grais RF, Dubray C, Gersti S, Guthmann JP, Djibo A, et al. Unacceptably high mortality related to measles epidemics in Niger, Nigeria, and Chad. *PLoS Med* 2007;4:e16
52. Coronado F, Musa N, Tayeb ESAE, Haithami S, Dabbagh A, et al. Restrospective measles outbreak investigation: Sudan, 2004. *J Trop Pediatr* 2006;52:329-34
53. Expanded Programme on Immunization. High measles case-fatality during an outbreak in a rural area. *Weekly Epidemiol Rec* 1993;68:142-5
54. Marufu T, Siziya S, Tshimanga M, Murugasampillay S, Mason E, et al. Factors associated with measles complications in Gweru, Zimbabwe. *East Afr Med J* 2001;78:135-8
55. Aaby P, Lisse I, Mølbak K, Knudsen K, Whittle H. No persistent T lymphocyte

- 1
2
3 immunosuppression or increased mortality after measles infection: a community
4 study from Guinea-Bissau. *Pediatr Inf Dis J* 1996;5:39-44
- 5
6 56. Chen RT, Weierbach R, Bisoffi Z, Cutts F, Rhodes P, et al. A 'Post-honeymoon
7 period' measles outbreak in Mayinga Sector, Burundi. *Int J Epidemiol*
8 1994;23:185-93
- 9
10 57. Nsungu M. Measles vaccination status, delay in recognizing measles outbreaks
11 and outbreak outcome. *Cent Afr J Med* 1995;41:336-9
- 12
13 58. Oshitani H, Mpabalwani M, Kosolo F, Mizuta K, Luo NP, et al. Measles infection
14 in hospitalized children in Lusaka, Zambia. *Ann Trop Pediatr* 1995;15:167-72
- 15
16 59. Yamaguchi S, Dunga A, Broadhead RL, Brabin BJ. Epidemiology of measles in
17 Blantyre, Malawi: analyses of passive surveillance data from 1996 to 1998.
18 *Epidemiol Infect* 2002;129:361-9
- 19
20 60. Mishra A, Mishra S, Lahariya C, Jain P, Bhadoriya RS, et al. Practical
21 observations from an epidemiological investigation of a measles outbreak in a
22 district of India. *Ind J Comm Med* 2009;34:117-21
- 23
24 61. Mgone JM, Mgone CS, Duke T, Frank D, Yeka W Control measures and the
25 outcome of the measles epidemic of 1999 in the Eastern Highlands Province. *PNG*
26 *Med J* 2000;43:91-7
- 27
28 62. Aaby P, Bukh J, Lisse IM, Smits AJ. Overcrowding and intensive exposure as
29 determinants of measles mortality. *Am J Epidemiol* 1984;120:49-63
- 30
31 63. McGregor IA. Measles and child mortality in the Gambia. *West Afr Med J*
32 1964;251-7
- 33
34 64. Aaby P, Bukh J, Lisse IM, Smits AJ, Gomes J, et al. Determinants of measles
35 mortality in a rural area of Guinea-Bissau: Crowding, age, and malnutrition. *J Trop*
36 *Pediatr* 1984;30:164-68
- 37
38 65. Muller AS, Voorhoeve AM, 't Mannelje W, Schulpden TWJ. The impact of
39 measles in a rural area of Kenya. *East Afr med J* 1977;54:364-72
- 40
41 66. Aaby P, Bukh J, Lisse IM, da Silva CM. Measles mortality: Further community
42 studies on the role of overcrowding and intensive exposure. *Rev Infect Dis*
43 1988;10:474-477
- 44
45 67. Nandy R, Handzel T, Zaneidou M, Biey J, Cuddy RZ, et al. Case-fatality rate
46 during a measles outbreak in Eastern Niger in 2003. *Clin Inf Dis* 2006;42:322-8
- 47
48 68. Hull HF, Williams PJ, Oldfield F. Measles mortality and vaccine efficacy in rural
49 West Africa. *Lancet* 1983;i:972-5
- 50
51 69. Mandara MP, Remme J. Current measles control in Tanzania. *Rev inf Dis*
52 1983;5:554-7
- 53
54 70. Heymann DL, Mayben GK, Murphy KR, Guyer B, Foster SO. Measles control in
55 Yaounde: Justification of a one dose, nine month minimum age vaccination policy
56 in tropical Africa. *Lancet* 1983;ii:1470-2
- 57
58 71. Garly ML, Martins CL, Balé C, da Costa F, Dias F, et al. Early two-dose measles
59 vaccination schedule in Guinea-Bissau: good protection and coverage in infancy.
60 *Int J Epidemiol* 1999;28:347-52
72. Kaninda AV, Legros D, Jataou IM, Malfait P, Maisonneuve M, Paquet C, Moren A.
Measles vaccine effectiveness in standard and early immunization strategies, Niger,
1995. *Pediatr Inf Dis J* 1998;7:1034-9
73. Phadke MA, Bhargava I, Dhaigude P, Bagade A, Biniwale MA, et al. Efficacy of

- two dose measles vaccination in a community setting. *Ind Pediatr* 1998;35:723-5
74. Al-Mazrou YY, Al-Jeffri M, Ahmed OMM, Aziz KMS, Mishkas AH. Measles immunization: Early two-doses policy experience. *J Trop Pediatr* 1999;45:98-104
75. Aaby P, Ibrahim S, Libman M, Jensen H. The sequence of vaccinations and increased female mortality after high-titre measles vaccine: trials from rural Sudan and Kinshasa. *Vaccine* 2006;24:2764-71
76. Aaby P, Martins CL, Garly ML, Bale C, Andersen A, Rodrigues A, Ravn H, Lisse IM, Benn CS, Whittle H. Non-specific effects of standard measles vaccine at 4.5 and 9 months of age on childhood mortality: Randomised controlled trial. *BMJ* 2010;341:c6495
77. Aaby P, Andersen M, Sodemann M, Jakobsen M, Gomes J, et al. Reduced childhood mortality after standard measles vaccination at 4-8 months compared with 9-11 months of age. *BMJ* 1993;307:1308-1311
78. Martins CL, Garly ML, Balé C, Rodrigues A, Ravn H, Whittle HC, Lisse IM, Aaby P. Protective efficacy of standard Edmonston-Zagreb measles vaccination in infants aged 4.5 months: interim analysis of a randomised clinical trial. *BMJ* 2008;337:a661
79. Aaby P, Garly ML, Balé C, Martins C, Jensen H, et al. Survival of previously measles-vaccinated and measles-unvaccinated children in an emergency situation: an unplanned study. *Pediatr Inf Dis J* 2003;22:798-805
80. Garenne M, Cantrelle P. Rougeole e mortalité au Sénégal : étude de l'impact de la vaccination effectuée à Khombole 1965-1968 sur la survie des enfants. In : Cantrelle P, Dormont S, Fargues P, Goujard J, Guignard J, Rumeau-Rouquette C (eds) : Estimation de la mortalité de jeune enfant (0-5 ans) pour guider les actions de santé dans les pays en développement. Paris : INSERM, 1986 ;145:515-32
81. Aaby P, Bukh J, Lisse IM, Smits AJ. Measles vaccination and reduction in child mortality: a community study from Guinea-Bissau. *J Infect* 1984;8:13-21
82. Velema JP, Alihonou EJ, Gandaho T, Hounye FH. Childhood mortality among users and non- users of primary health care in a rural West African community. *Int J Epidemiol* 1991;20:474- 479
83. Holt EA, Boulos R, Halsey NA, Boulos LM, Boulos C. Childhood survival in Haiti: protective effect of measles vaccination. *Pediatrics* 1990;86:188-94
84. George K, Josphe A, Muliyl J, Abraham S, Bhattacharji S, John KR. Measles vaccination before nine months. *Trop Med Int Hlth* 1998;3:751-6
85. Kristensen I, Aaby P, Jensen H. Routine vaccinations and child survival: follow up study in Guinea-Bissau, West Africa. *BMJ* 2000;321:1435-8
86. Lehmann D, Vail J, Firth MJ, de Klerk NH, Alpers MP. Benefits of routine immunisations on childhood survival in Tari, Southern Highlands Province, Papua New Guinea. *Int J Epidemiol* 2004, 10.1093/ije/dyh262
87. Elguero E, Simondon F, Simondon K, Vaugelade J. Non-specific effects of vaccination on survival: a prospective study in Senegal. *Trop Med Int Health* 2005;10:956-960
88. Aaby P, Martins CL, Garly ML, Andersen A, Fisker AB, Claesson MH, Ravn H, Rodrigues A, Whittle HC, Benn CS. Measles vaccination in presence of maternal antibodies may increase child survival (submitted)
89. de Quadros CA. Can measles be eradicated globally? *Bull WHO* 2004;82:134-8

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
90. Aaby P, Bhuyia A, Nahar L, Knudsen K, Francisco A, et al. The survival benefit of measles immunization may not be explained entirely by the prevention of measles disease: a community study from rural Bangladesh. *Int J Epidemiol* 2003;32: 106-115
 91. Aaby P, Samb B, Simondon F, Knudsen K, Seck AM, et al. Divergent mortality for male and female recipients of low-titer and high-titer measles vaccines in rural Senegal. *Am J Epidemiol* 1993;138:746-755
 92. Desgrées du Loû A, Pison G, Aaby P. The role of immunizations in the recent decline in childhood mortality and the changes in the female/male mortality ratio in rural Senegal. *Am J Epidemiol* 1995;142:643-52
 93. Shann F. The non-specific effects of vaccines. *Arch Dis Child* 2010;95:662-7
 94. Welsh RM, Selin LH. No one is naïve: The significance of heterologous T-cell immunity. *Nat Rev Immunol* 2002; 2: 417-426
 95. Leuridan E, Hens N, Hutse V, Ieven M, Aerts M, et al. Early waning of maternal measles antibodies in era of measles elimination: longitudinal study. *BMJ* 2010;340:c1626
 96. Martins C. Measles vaccination in Guinea-Bissau. Strategies to reduce disease burden and improve child survival. Copenhagen: University of Copenhagen, 2011 [PhD Thesis]
 97. Moxon R, Nossal G, Heymann D, Plotkin S, Levine O. The new decade of vaccines. Authors' reply. *Lancet* 2012;379:27
 98. Heymann DL, Fine PE, Griffiths UK, Hall AJ, Mounier-Jack S. Measles eradication: past is prologue. *Lancet* 2010;376:1719-20

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				
	Column 1	Column 2	Column 3	Column 4	Column 5	Column 6	Column 7	Column 8	Column 9	Column 10
	Cumulative measles incidence (%)	Seroconversion 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%

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

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.

For peer review only

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)*
<i>Bissau (43)¹</i>	<i>1980-82</i>	<i>PCS; urban (only secondary cases)</i>	<i>14%(3/21)</i>	<i>46%(11/24)</i>	<i>0.30 (0.10-0.86)*</i>
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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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.

For peer review only

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)

1
2
3 Sources: Reviews of measles case fatality studies (27-31) and PubMed search for
4 community studies of measles mortality/case fatality in infants or by age in Africa (see
5 Supplementary material).
6

7 Notes: MV=measles vaccine; PCS=prospective community study, i.e. the population was
8 known before the epidemic and information is likely to have been obtained for all
9 children; SUR= retrospective survey; # The age grouping is 7-12 months and 12-120
10 months. Measles deaths and total number of children in age group were reported in this
11 study. It has been assumed that all children between 7 and 120 months contracted
12 measles. In this period there were no measles vaccinations available. The last epidemic
13 had occurred 12-13 years earlier; ## The age grouping is 0-8 and 9+ months; □ Numbers
14 read from a graph
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

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)	1 st vaccine in 2-dose group was Connaught HTMV and 2 nd dose was Schwarz standard MV
	9-36 months	2 nd vs 1 st 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	2 nd vs 1 st 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
<i>Early measles vaccination at 7 months of age compared with children unvaccinated community</i>			
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)
<i>Comparing MV at 4-8 months versus MV at 9-11 months of age</i>			
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)
<i>Comparing children randomised to MV at 6 months versus IPV at 6 months during a war situation</i>			
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 receive 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
----------------------	----	---	---

Page 1 of 2

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

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2011-000761.R2
Article Type:	Research
Date Submitted by the Author:	24-May-2012
Complete List of Authors:	Aaby, Peter; Bandim Health Project, Bandim Health Project Martins, Cesario; Bandim Health Project, Bandim Health Project Garly, May-Lill; Bandim Health Project,, Rodrigues, Amabelia; Bandim Health Project, Bandim Health Project, Benn, Christine; Statens Serum Institut, Department of Epidemiology Research Whittle, Hilton; London School of Hygiene and Tropical Medicine,
Primary Subject Heading:	Global health
Secondary Subject Heading:	Epidemiology, Health policy, Infectious diseases, Paediatrics, Public health
Keywords:	EPIDEMIOLOGY, International health services < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, MEDICAL HISTORY, Public health < INFECTIOUS DISEASES, Community child health < PAEDIATRICS, PUBLIC HEALTH

SCHOLARONE™
Manuscripts

only

1
2
3
4 **The optimal age of measles immunization in low-income countries: A**
5 **secondary analysis of the assumptions underlying the current policy**
6
7

8 Peter Aaby^{1, 2}, Cesário L Martins¹, May-Lill Garly¹, Amabelia Rodrigues¹, Christine S
9 Benn^{1, 2}, Hilton C Whittle³
10
11

12
13
14 **1) Bandim Health Project, Indepth Network, Apartado 861, Bissau, Guinea-Bissau**

15 (CL Martins, clinician, PhD student, ML Garly, MD PhD, senior researcher, A
16 Rodrigues, PhD, research director, P Aaby, DMSc, professor). E-mail:
17 p.aaby@bandim.org
18
19
20
21

22
23 **2) Research Center for Vitamins and Vaccines (CVIVA), Bandim Health Project,**
24 **Danish Epidemiology Science Centre, Statens Serum Institut, Artillerivej 5, 2300**
25 **Copenhagen S, Denmark** (CS Benn, senior researcher, P Aaby, DMSc, professor)
26
27
28

29
30 **3) London School of Hygiene and Tropical Medicine, London, United Kingdom** (H
31 Whittle, F Med Sci, honorary professor)
32
33

34
35 Running title: Optimal age of measles vaccination

36
37 Word counts: Abstract: 300; Text: 6380
38
39

40
41 Corresponding author: Peter Aaby, Bandim Health Project, Statens Serum Institut,
42 Artillerivej 5, 2300 Copenhagen S, Denmark
43

44 p.aaby@bandim.org
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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.

1
2
3 The search strategy has been defined in the Supplementary Material. Since there are few
4 specific studies to test the six assumptions we have had to use case reports of measles
5 outbreaks to assess their validity. Over the last 20-25 years, several reviews of
6 community studies of the measles case fatality compiled studies of relevance for
7 particularly assumption three and four (27-31). Furthermore, as specified in the
8 supplementary material, we made PubMed searches for additional publications relevant
9 for all assumptions. We included one unpublished report from a large epidemic in Bissau
10 in 1991-1992 which has remained unpublished because the physician (Henning
11 Andersen) handling the epidemic died tragically in an accident shortly after the epidemic.
12
13

14
15 We distinguished between prospective community studies and surveys retrospectively
16 assessing events since the precision of information on vaccination status and age
17 presumably is better in prospective studies. Though hospital and health centre studies
18 may have data on the severity of measles infection by vaccination status or age, we have
19 not included these studies in the analysis since biased admission for some groups might
20 have made the result non-representative.
21
22

23
24 Since the analysis of the assumptions suggested that measles vaccination before 9 months
25 of age could be beneficial, we assessed the empirical evidence from studies which
26 assessed the effect of early measles vaccination on mortality. Again we used all reviews
27 of community studies and trials assessing the impact of measles vaccination on child
28 mortality (30,32-35). Additional PubMed searches for studies comparing the mortality of
29 measles vaccinated and unvaccinated children did not identify further studies. As
30 explained in the footnote to table 6, we have emphasised the studies in which inactivated
31 vaccines were not administered simultaneously with MV or after MV as such
32 combination or sequences can have a negative effect on child survival (34,36).
33
34

35 **Presentation.** For each assumption, we briefly outline the background. Next we present
36 the relevant studies found and then analyse the common trends, identifying the secondary
37 analyses which have been made. Finally, we considered whether methodological issues
38 and data quality might question the trends suggested by the analysis.
39
40

41 **Statistical analyses.** In the combined analyses of several studies we used the Mantel-
42 Haenszel (MH) weighted relative risk stratifying for study or age groups to estimate
43 common trends.
44
45

46 **Ethics.** Since the study is a secondary analysis of existing data, approval from an ethical
47 committee was not needed.
48

49 **Results**

50 ***Assumption 1: children who seroconvert to measles vaccine have absolute protection***
51 ***against measles infection.***
52
53

54 ***Background.*** It has usually been assumed that previous measles infection is associated
55 with life-long immunity. This idea was transferred to measles vaccination when the
56
57
58
59
60

1
2
3 vaccine was developed in the 1950s. Hence, if someone had antibodies after vaccination
4 these were also assumed to provide life-long protection.
5

6
7 *Data:* We searched for “measles infection seropositive vaccinated children” and “measles
8 vaccine failure” (Supplementary material). There are many case reports that contradict
9 that seroconverted children have absolute protection but no African community study.
10

11
12 *Analysis.* A number of smaller studies have documented that a few children do get
13 measles after having seroconverted (37-40). Hence, seroconversion does not give
14 absolute protection.
15

16
17 *Considerations.* However, there are no general epidemiological studies from Africa and it
18 is therefore difficult to estimate the proportion of children who get measles in spite of
19 having seroconverted, but since no large series have been reported it is likely to be small.
20

21 ***Assumption 2: vaccinated children who are seronegative are fully susceptible to***
22 ***measles infection.***
23

24
25 *Background.* Measles immunity has generally been considered an either-or phenomenon.
26 If a vaccinated child was seronegative it was assumed that the child was fully susceptible.
27

28
29 *Data:* We searched for “measles infection seronegative vaccinated children” and
30 “measles vaccine failure” (Supplementary material). This provided only one relevant
31 reference (37).
32

33
34 *Analysis.* In a study in Senegal, vaccinated children who were seronegative when exposed
35 to measles infection at home had a 49% (95% CI 21-68%) protection against clinical
36 disease compared with unvaccinated seronegative children exposed under similar
37 conditions (37).
38

39
40 *Considerations.* Apparently, no other study has tested the susceptibility of vaccinated
41 “seronegative” children. It is possible that some children had acquired vaccine-induced
42 measles antibodies earlier but subsequently lost them. Cellular immunity may be obtained
43 without having measurable antibodies (41). There is also good evidence from studies of
44 hepatitis B vaccination that antibody concentration wane with time but the majority of
45 older seronegative children if infected are protected from chronic carriage and its
46 damaging consequences (42).
47

48
49 The concept of seroconversion to compare the effect of vaccination at different age is in
50 itself problematic. Seroconversion is not the same as seroprotection and the use of the
51 term inevitably disadvantages data from studies that have vaccinated at earlier ages when
52 maternal antibodies are still present. Thus a child immunized at 6 months of age when the
53 maternal antibody level is say 62.5 mIU may fail the test for conversion (a four-fold
54 increase) yet still have a protective level of 125 mIU at 9 months of age.
55
56
57
58
59
60

1
2
3 If approximately half the seronegative children have clinical protection it would have
4 major consequences for the calculation of the optimal age of measles vaccine.
5
6

7 ***Assumption 3: severity of measles infection in vaccinated children (“vaccine failures”)***
8 ***and unvaccinated children is the same.***
9

10 *Background.* The EPI perceived “vaccine failures” as due to the vaccine being inactivated
11 by improper storage and handling or due to neutralization of the vaccine by maternal
12 antibodies (16,19). Hence, it was assumed that these children had been fully susceptible
13 to measles infection. However, many epidemiological studies in the 1980s and 1990s
14 suggested that measles vaccinated children who contracted measles infection had milder
15 disease (43,44). This would suggest that the children had partial measles immunity, not
16 enough to protect them but enough to modify the severity of the disease.
17
18

19
20 *Data:* We searched for “measles mortality vaccinated children”, “measles vaccine
21 mortality”, “measles case fatality” and “measles vaccine failure” (Supplementary
22 material). The 18 relevant studies are included in Tables 2 and 3.
23

24
25 *Analysis.* The community studies of the acute measles case fatality are shown in Table 2.
26 Only two African studies (43, 48) have reported significant differences in mortality for
27 vaccinated and unvaccinated measles cases. A combined analysis has not been made
28 previously. The measles case fatality was 2 to 5-fold lower for vaccinated cases (“vaccine
29 failures”) than for unvaccinated children with measles infection in nearly all studies.
30 Using MH weighted relative risk, the effect was similar in the prospective community
31 studies (case-fatality ratio=0.37 (0.27-0.52)) and the retrospective surveys (case-fatality
32 ratio=0.41 (0.29-0.56)).
33
34

35
36 A few studies followed the children for longer than one month which is the normal time
37 limit for acute measles deaths. The long-term trend was the same with considerable better
38 survival among vaccinated than unvaccinated children after measles infection (Table 3).
39 Combining the prospective community studies in Tables 2 and 3 would suggest a 3-fold
40 reduction in acute and/or long-term mortality among vaccinated children even though
41 some of the vaccine failures may have been due to inactivated measles vaccines.
42

43
44 In the four studies (38,47,56, unpublished) with information on both acute and long-term
45 mortality, mortality was nearly 5-fold lower for the vaccinated cases (MH weighted
46 mortality ratio= 0.21 (0.13-0.34)).
47

48
49 *Considerations.* Only two studies did not show lower case fatality among vaccinated
50 children and five of the 18 studies in Tables 2 and 3 showed significantly lower mortality
51 among vaccinated children.
52

53
54 All studies with relevant data were included in Tables 2 and 3 irrespective of whether
55 vaccine efficacy (VE) against measles infection was high or substandard. In several
56 studies, the VE was not high but nonetheless the vaccine appeared to have had an effect;
57 for example, in Kenya VE was only 18% but measles-vaccinated children who developed
58
59
60

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.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

1
2
3 vaccinated children have mild measles infection (43). In cultures where mothers have
4 learnt that everybody has to get measles, the advantage of “mild measles” is easy to see
5 whereas it is difficult to “see” complete “life-long protection” if you still expect your
6 child will get measles some day. Hence, it may have worked the other way around; seeing
7 your child get mild measles after vaccination would be a strong argument for the value of
8 measles vaccination.
9

10
11 ***Assumption 6: it had to be a one-dose policy.***
12

13
14 ***Background.*** The main argument advanced for a one-dose policy was that compliance
15 with the second dose was too low (15,18,68,71). This is surprising since it has been
16 described that mothers sought vaccination so eagerly that it was impossible to maintain
17 the age eligibility criteria for vaccinations during campaigns (16). The reason why
18 mothers did not seek the second dose of measles vaccine in some countries may have
19 been poor information. In Guinea-Bissau, we had very good compliance and improved
20 overall coverage with a two-dose schedule (72). The two-dose group had better protection
21 against measles infection than the one-dose group (72). A two-dose schedule has also
22 been shown to be effective in Niger (73), India (74) and Saudi Arabia (75). Hence, a two-
23 dose schedule is both feasible and effective.
24
25

26
27 ***Data:*** To identify studies comparing the effect on survival of a one-dose and a two-dose
28 policy we used the reviews of measles vaccination and impact on mortality (30,32,33)
29 and searched papers on “Two/2 dose measles vaccine trial”, “Two/2 dose measles
30 vaccination/immunization and mortality/death” and “early measles
31 vaccination/immunization mortality/death”. These procedures identified only two trials
32 of the effect on child survival of a 2-dose measles vaccinations schedule compared with a
33 1-dose schedule (see Table 5) and one observational study (78)
34
35

36
37 ***Analysis.*** Only two trials have compared child mortality following two doses of MV (the
38 first being given before 9 months) with mortality after the standard dose of MV (at 9
39 months of age) (Table 5). In a small trial from Sudan (76), DTP vaccinations were not
40 controlled and many children received DTP after measles vaccine. DTP administered
41 with or after measles vaccine has negative effects on female survival (34,36). We
42 therefore conducted a large randomized trial including only children who had received
43 DTP3 before enrolment and therefore would not receive DTP after MV (77). Among
44 children who had not received neonatal vitamin A supplementation (VAS) which
45 interacted negatively with early MV(76), two doses of MV at 4.5 and 9 months of age
46 compared with the current policy of one dose at 9 months of age reduced mortality
47 between 4.5 and 36 months of age by 50% (22-68%) in the per-protocol analysis (Table
48 5). There was a significant reduction in non-measles related mortality of 45% (14-65%)
49 (77). The combined estimate for the two trials showed that the early two-dose measles
50 vaccination strategy may reduce mortality by as much as 48% (23%-65%) compared with
51 the currently recommended standard dose at 9 months of age. Even if the children
52 receiving neonatal VAS were included, the combined estimate was 31% (9-48%) (Table
53 5).
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

1
2
3 before 9 months of age and those vaccinated at 9 months of age, the recommended age of
4 measles vaccination. One dose of MV at 4-8 months compared with 9-11 months of age
5 was associated with 31% (-8-54%) lower mortality between 9 months and 5 years of age
6 (78). As mention above the effect was even stronger if they also received a second dose
7 of MV after 9 months of age. During a civil war in Guinea-Bissau in 1998 (80), we
8 followed children who had been randomised to measles vaccination at 6 months of age
9 compared with children who had been randomised to inactivated polio vaccine (IPV).
10 Due to the war the children did not get the standard measles vaccination at 9 months of
11 age. During the 3 months of intensive fighting when everybody had fled the study area
12 and mortality was high, the children vaccinated against measles at 6 months of age had
13 70% (13-92%) lower mortality than the unvaccinated group.
14
15
16

17
18 These studies of one dose of MV before 9 months of age as well as the studies of early
19 two-dose MV mentioned above suggest that the reduction in mortality from MV before 9
20 months of age is much larger than can be explained by the prevention of measles
21 infection. WHO estimates that measles deaths caused 10% of under-five deaths (90).
22 However all available studies of the mortality impact of MV (30,32,33) suggest that the
23 effect of measles immunization on mortality is much greater than expected. This
24 beneficial effect is a consistent observation and it can not be explained by the prevention
25 of acute measles infection. First, all studies, in which measles vaccine was not
26 administered with DTP, provided strong evidence of a beneficial effect of measles
27 vaccine on overall mortality (32). Second, all studies censoring for measles infection in
28 the survival analysis to estimate the impact on non-measles related mortality found that
29 prevention of measles-specific deaths explained little and the beneficial effect was due to
30 prevention of non-measles related mortality (32,76,89, 91). For example, in the per-
31 protocol analysis of the largest randomised trial (77), measles vaccine at 4.5 and 9
32 months compared with the standard dose at 9 months of age reduced non-measles related
33 mortality significantly for all children. Third, the beneficial effect of measles vaccine is
34 usually stronger for girls than for boys (77,92,923). Since measles mortality is not higher
35 for girls than boys, this observation suggests sex-differential mechanisms related to
36 immune stimulation. Hence, standard measles vaccine may protect against other
37 infections and have a beneficial effect on child survival even when measles is eliminated.
38
39
40
41

42
43 Though the focus here has been on MV administered before 9 months of age there is also
44 a considerable number of studies indicating that MV administered after 9 months of age
45 have non-specific beneficial effects (32,81-86, 91, 94).
46

47
48 The possible biological explanations for non-specific beneficial effects of MV have not
49 been explored in humans. In animal studies of heterologous immunity, previous
50 stimulation with infections may have a major effect on the capacity to handle a lethal
51 dose of an unrelated infection (95). Two trials from Bissau suggest that the beneficial
52 effect of MV is better for children vaccinated in the presence of maternal measles
53 antibodies than for children having no measurable maternal antibodies at the time of MV
54 (89). This may also help explain why MV before 9 months of age is better than later
55 vaccination.
56
57
58
59
60

1
2
3
4 **The optimal age of measles vaccination: optimizing seroconversion or impact on**
5 **overall child survival.** The most unfortunate consequence of not testing the optimal age
6 of measles immunization may have been that the beneficial non-specific effects of MV
7 were not detected (32). To the extent MV has non-specific beneficial effects the question
8 of the optimal age of measles vaccination acquires a new meaning. By lowering the age
9 of measles vaccination, children would benefit not only from earlier protection against
10 measles infection but also from the beneficial non-specific effects against non-measles
11 infections and overall child mortality would be reduced. On the other hand, if the age of
12 vaccination is increased, children would benefit less from the non-specific beneficial
13 effects and overall child mortality would increase. Hence, policies optimizing the non-
14 specific effects clash with those designed to enhance seroconversion.
15
16

17 18 **Conclusions: Old assumptions linger on**

19 The supplementary immunization activities (SIA) with measles vaccine has eliminated
20 measles infection in Latin America and reduced the incidence in major ways in the rest of
21 the world (1-3). The world is now planning to eliminate and eventually eradicate measles
22 infection (4). With the SIA success in measles control, the optimal age of measles
23 immunization is likely to be considered an irrelevant issue. However, as discussed above,
24 measles vaccine has also non-specific effects which need to be taken into consideration in
25 the planning of vaccination programmes. The prevention of all-cause mortality rather
26 than measles mortality should be the primary objective. In a culture which advocates
27 evidence-based policies (4), the evidence for the current measles vaccination policy – or
28 rather the lack thereof - should be properly reviewed and revised by the global and
29 regional immunization programmes. Otherwise old assumptions about seroconversion
30 rates being the basis for the optimal age of immunisation may linger on and continue to
31 influence policy.
32
33
34

35
36 There are major consequences of focusing solely on specific measles mortality. First, as
37 the current policy is mostly determined by our understanding that seroconversion gets
38 better with increasing age, the tendency will be that with improved control of measles
39 infection, age of vaccination will be increased. Following the elimination of measles in
40 Latin America, the recommended age of primary measles immunization was raised to 12
41 months in 1996 (3). Again this decision was based on assumptions and not on studies
42 documenting the overall effect on morbidity and mortality. Following the success of
43 measles campaigns in other continents it has also been recommended by SAGE (the
44 Strategic Advisory Group of Experts) to increase the age of measles vaccination to 12
45 months in areas with low levels of measles transmission (5,12). The underlying
46 assumption about better seroconversion at higher ages may no longer be valid with the
47 decline in maternal antibody levels (79,96). For example, we have obtained 100%
48 seropositivity and 99% protective levels after measles vaccine at 9 months of age with
49 both Schwarz and Edmonston-Zagreb measles vaccine strains in Guinea-Bissau (97).
50
51
52

53 However, the most important problem is that measles vaccine has major non-specific
54 beneficial effects and the earlier it is given, the earlier the children will benefit from this
55 advantage (11,32,38,76-80,89). There is a tendency to dismiss these observations because
56 randomised trials with overall mortality as an outcome have only been conducted in
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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.

1
2
3 **Contributions:** PA and HW have been involved in studies of measles vaccination for
4 more than 30 years in West Africa; MLG, CM, CB and AR have been involved in
5 measles vaccination trials since the early 1990s. The first draft was written by PA; all
6 authors contributed to the final version of the paper. PA will act as guarantor of the study.
7
8

9
10 **Conflict of interest:** nothing to declare
11

12 **Funding:** The Bandim Health Project received support from DANIDA and the Danish
13 National Research Foundation. PA holds a research professorship grant from the Novo
14 Nordisk Foundation. We received no funding specifically for the present study.
15
16

17 **Independence:** The funders had no role in the study design, data collection, data
18 analysis, data interpretation, decision to publish or preparation of the manuscript.
19

20 **Data sharing:** no additional data available
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

References

1. De Quadros CA, Olive JM, Hersh BS, Strassburg MA, Henderson DA, Bandling-Bennett D, Alleyne GA. Measles elimination in the Americas. Evolving strategies. *JAMA* 1996; 275: 224-29
2. Otten M, Kezaala R, Fall A, Masresha B, Martin R, Cairns L, Eggers R, Biellik R, Grabowsky M, Strebel P, Okwo-Bele JM, Nshimirimana. Public-health impact of accelerated measles control in the WHO African Region 2000-03. *Lancet* 2005;366:832-9
3. De Quadros CA, Izurieta H, Venczel L, Carrasco P. Measles eradication in the Americas : Progress to date. *JID* 2004 ;189 (Suppl 1) : S227
4. Department of immunization, vaccines and biologicals: Strategic Plan 2010-15. Draft 24 March 2010, World Health Organization
5. Measles vaccines: WHO position paper. *Week Epid Rec* 2009;84:349-60
6. Expanded Programme on Immunization. Measles immunization. *Weekly Epidemiol Rec* 1979;54:337-9
7. Expanded Programme on Immunization. Global advisory group Meeting. *Weekly Epidemiol Rec* 1981;56:9-16
8. Expanded Programme on Immunization. The optimal age for measles immunization. *Weekly Epidemiol Rec* 1982;57:89-91
9. Hendrickse RG. Problems of future measles vaccination in developing countries. *Trans R Soc Trop Med Hyg* 1975;69:31-34
10. Mosley WH. Will primary health care reduce infant and child mortality? A critique of some current strategies. With special reference to Africa and Asia. In: Lopez AD, Vallin J (eds): Health policy, social policy and mortality prospects. Liege: Ordina, 1985;pp 103-37
11. The Kasongo Project Team. Influence of measles vaccination on survival pattern of 7-35-month-old children in Kasongo, Zaire. *Lancet* 1981;i:764-7
12. Meeting of the immunization Strategic Advisory Group of experts, November 2006 – conclusions and recommendations. *Weekly Epidemiol Rec* 2007;82:1-16
13. Foege WH. Measles vaccination in Africa. *Sci Pub PAHO* 1971;228:207-12
14. McBean AM, Foster SO, Herrmann KL, Gateff. Evaluation of mass measles immunisation campaign in Yaoundé, Cameroun. *Trans Roy Soc Trop Med Hyg* 1976;70:206-12
15. Guyer B, McBean AM. The epidemiology and control of measles in Yaoundé, Cameroun, 1968-1975. *Int J Epidemiol* 1981;10:263-9
16. Grigsby ME, Adetosoye JIA. Measles epidemiology and control in Western Nigeria. *J Nat Med Ass* 1973;65:378-85
17. Foster SO, Pifer JM. Mass measles control in West and central Africa. *Afr J Med Sci* 1971;2:151-8
18. Henderson RH. Measles vaccination in Zaire – when and how? *Trans Roy Soc Trop Med Hyg* 1981;75:128-9
19. Wood PB, Soheranda KS, Bracken PM, Houser NE. Measles vaccination in Zaire – when and how? *Trans Roy Soc Trop Med Hyg* 1980;74:381-2
20. Lapeyssonnie L, Omer LA, Nicolas A, Roumiantzeff M. Etude de la réponse serologique d'enfant soudanais a la vaccination combinee triple (rougeole, tetanos, meningite A). *Med Trop* 1979;39:71-9

21. Collaborative study by the Ministry of Health of Kenya and the World Health Organisation. Measles immunity in the first year after birth and the optimum age for vaccination in Kenyan children. *Bull WHO* 1977;55:21- 31
22. Burström B, Aaby P, Mutie DM, Kimani G, Bjerregaard P. Severe measles outbreak in Western Kenya. *East Afr Med J* 1992; 69:419-423
23. Seroconversion rates and measles antibody titers induced by measles vaccine in Latin American children aged 6-12 months of age. Collaborative study by the Ministries of Health of Brazil, Chile, Costa Rica, Ecuador, and the Pan American Health Organization. *Bull Pan Am Health Organ* 1982;16:272-85
24. Rosenthal SR, Clements CJ. Two-dose measles vaccination schedules. *Bull WHO* 1993;71:421-8
25. Rolfe M. Measles immunization in the Zambian Copperbelt: cause for concern. *Trans Roy Soc Trop Med Hyg* 1982;76:529-30
26. Lancet. Rationalising measles vaccination. *The Lancet* 1981;ii:236-7
27. Aaby P. Malnutrition and overcrowding/intensive exposure in severe measles infection: review of community studies. *Rev Infect Dis* 1988;10:478-491
28. Aaby P, Clements J, Orinda V Mortality from measles: measuring the impact. Geneva 1991: EPI, WHO
29. Wolfson LJ, Grais RF, Luquero FJ, Birmingham ME, Strebel PM. Estimates of measles case fatality ratios: a comprehensive review of community-based studies. *Int J Epidemiol* 2009;38:192-205
30. Sudfeld CR, Navar AM, Halsey NA. Effectiveness of measles vaccination and vitamin A treatment. *Int J Epidemiol* 2010;39:i48-i55
31. Kouadio IK, Kamigaki T, Oshitani H. Measles outbreaks in displaced populations: a review of transmission, morbidity and mortality associated risk factors. *BMC Int Hlth Hum Rights* 2010;10:5
32. Aaby P, Samb B, Simondon F, Coll Seck AM, Knudsen K, et al. Non-specific beneficial effect of measles immunisation: analysis of mortality studies from developing countries. *Br Med J* 1995;311:481-485
33. Garly ML, Aaby P. The challenge of improving the efficacy of measles vaccine. *Acta Trop* 2003;85:1-17
34. Aaby P, Jensen H, Samb B, Cisse B, Sodeman M, et al. Differences in female-male mortality after high-titre measles vaccine and association with subsequent vaccination with diphtheria-tetanus-pertussis and inactivated poliovirus: reanalysis of West African studies. *Lancet* 2003;361: 2183-88
35. Knudsen KM, Aaby P, Whittle H, Rowe M, Samb B, et al. Child mortality following standard, medium or high titre measles immunization in West Africa. *Int J Epidemiol* 1996;25:665-73
36. Aaby P, Garly ML, Nielsen J, Ravn H, Martins C, Balé C, et al. Increased female-male mortality ratio associated with inactivated polio and diphtheria-tetanus-pertussis vaccines: Observations from vaccination trials in Guinea-Bissau. *Pediatr Infect Dis J* 2007;26:247-52.
37. Samb B, Aaby P, Whittle H, Coll Seck AM, Rahman S, et al. Serological status and measles attack rates among vaccinated and unvaccinated children in rural Senegal. *Pediatr Inf Dis J* 1995;14:203-9
38. Aaby P, Pedersen IR, Knudsen K, da Silva MC, Mordhorst CH, et al. Child

- mortality related to seroconversion or lack of seroconversion after measles vaccination. *Pediatr Infect Dis J* 1989;8:197-200
39. Hirose M, Hidaka Y, Miyazaki C, Ueda K, Yoshikawa H. Five cases of measles secondary vaccine failure with confirmed seroconversion after live measles vaccination. *Scand J Inf Dis* 1997;29:187-90
40. Samb B, Aaby P, Whittle H, Seck AW, Simondon F. Protective efficacy of high-titre measles vaccines administered from the age of five months: a community study in rural Senegal. *Trans Roy Soc Trop Med Hyg* 1993;87:697-701
41. Siegrist CA, Barrios C, Martinez X, Brandt C, Berney M, et al. Influence of maternal antibodies on vaccine responses: inhibition of antibody but not T cell responses allows successful early prime-boost strategies in mice. *Eur J Immunol* 1998;28:4138-48
42. van der Sande MA, Waight P, Mendy M, Rayco-Solon P, Hutt P, et al. Long-term protection against carriage of hepatitis B virus after infant vaccination. *J Infect Dis* 2006;193:1528-35
43. Aaby P, Bukh J, Leerhøy J, Lisse IM, Mordhorst CH, et al. Vaccinated children get milder measles infection: a community study from Guinea-Bissau. *J Infect Dis* 1986;154:858-63
44. Samb B, Aaby P, Whittle H, Seck AM, Simondon F. Decline in measles case fatality ratio after the introduction of measles immunization in rural Senegal. *Am J Epidemiol* 1997;145:51-7
45. Aaby P, Bukh J, Lisse IM, da Silva CM. Decline in measles mortality: nutrition, age at infection, or exposure? *Br Med J* 1988;296:1225-1228
46. Aaby P, Knudsen K, Jensen TG, Thaarup J, Poulsen A, et al. Measles incidence, vaccine efficacy, and mortality in two urban African areas with high vaccination coverage. *J Infect Dis* 1990;162:1043-1048
47. Aaby P, Whittle H, Cisse B, Samb B, Jensen H, et al. The frailty hypothesis revisited: mainly weak children die of measles. *Vaccine* 2001;20:949-53
48. Dollimore N, Cutts F, Binka FN, Ross DA, Morris SS, et al. Measles incidence, case fatality, and delayed mortality in children with or without vitamin A supplementation in rural Ghana. *Am J Epidemiol* 1997;146:646-654
49. Burström B, Aaby P, Mutie DM. Child mortality impact of a measles outbreak in a partially vaccinated rural African community. *Scand J Infect Dis* 1993;25:763-9
50. Ndikuyeze A, Cook A, Cutts FT, Bennett S. Priorities in global measles control: report of an outbreak in N'djamena, Chad. *Epidemiol Infect* 1995;115:309-14
51. Grais RF, Dubray C, Gersti S, Guthmann JP, Djibo A, et al. Unacceptably high mortality related to measles epidemics in Niger, Nigeria, and Chad. *PLoS Med* 2007;4:e16
52. Coronado F, Musa N, Tayeb ESAE, Haithami S, Dabbagh A, et al. Restrospective measles outbreak investigation: Sudan, 2004. *J Trop Pediatr* 2006;52:329-34
53. Expanded Programme on Immunization. High measles case-fatality during an outbreak in a rural area. *Weekly Epidemiol Rec* 1993;68:142-5
54. Marufu T, Siziya S, Tshimanga M, Murugasampillay S, Mason E, et al. Factors associated with measles complications in Gweru, Zimbabwe. *East Afr Med J* 2001;78:135-8
55. Aaby P, Lisse I, Mølbak K, Knudsen K, Whittle H. No persistent T lymphocyte

- 1
2
3 immunosuppression or increased mortality after measles infection: a community
4 study from Guinea-Bissau. *Pediatr Inf Dis J* 1996;5:39-44
- 5
6 56. Chen RT, Weierbach R, Bisoffi Z, Cutts F, Rhodes P, et al. A 'Post-honeymoon
7 period' measles outbreak in Mayinga Sector, Burundi. *Int J Epidemiol*
8 1994;23:185-93
- 9
10 57. Nsungu M. Measles vaccination status, delay in recognizing measles outbreaks
11 and outbreak outcome. *Cent Afr J Med* 1995;41:336-9
- 12
13 58. Oshitani H, Mpabalwani M, Kosolo F, Mizuta K, Luo NP, et al. Measles infection
14 in hospitalized children in Lusaka, Zambia. *Ann Trop Pediatr* 1995;15:167-72
- 15
16 59. Yamaguchi S, Dunga A, Broadhead RL, Brabin BJ. Epidemiology of measles in
17 Blantyre, Malawi: analyses of passive surveillance data from 1996 to 1998.
18 *Epidemiol Infect* 2002;129:361-9
- 19
20 60. Mishra A, Mishra S, Lahariya C, Jain P, Bhadoriya RS, et al. Practical
21 observations from an epidemiological investigation of a measles outbreak in a
22 district of India. *Ind J Comm Med* 2009;34:117-21
- 23
24 61. Mgone JM, Mgone CS, Duke T, Frank D, Yeka W Control measures and the
25 outcome of the measles epidemic of 1999 in the Eastern Highlands Province. *PNG*
26 *Med J* 2000;43:91-7
- 27
28 62. Aaby P, Bukh J, Lisse IM, Smits AJ. Overcrowding and intensive exposure as
29 determinants of measles mortality. *Am J Epidemiol* 1984;120:49-63
- 30
31 63. McGregor IA. Measles and child mortality in the Gambia. *West Afr Med J*
32 1964;251-7
- 33
34 64. Aaby P, Bukh J, Lisse IM, Smits AJ, Gomes J, et al. Determinants of measles
35 mortality in a rural area of Guinea-Bissau: Crowding, age, and malnutrition. *J Trop*
36 *Pediatr* 1984;30:164-68
- 37
38 65. Muller AS, Voorhoeve AM, 't Mannetje W, Schulpden TWJ. The impact of
39 measles in a rural area of Kenya. *East Afr med J* 1977;54:364-72
- 40
41 66. Aaby P, Bukh J, Lisse IM, da Silva CM. Measles mortality: Further community
42 studies on the role of overcrowding and intensive exposure. *Rev Infect Dis*
43 1988;10:474-477
- 44
45 67. Nandy R, Handzel T, Zaneidou M, Biey J, Cuddy RZ, et al. Case-fatality rate
46 during a measles outbreak in Eastern Niger in 2003. *Clin Inf Dis* 2006;42:322-8
- 47
48 68. Hull HF, Williams PJ, Oldfield F. Measles mortality and vaccine efficacy in rural
49 West Africa. *Lancet* 1983;i:972-5
- 50
51 69. Burström B, Aaby P, Maitie DM. Measles in infancy: A review of studies of
52 incidence, vaccine efficacy and mortality in East Africa. *East Afr Med J*
53 1993;72:155-61
- 54
55 70. Mandara MP, Remme J. Current measles control in Tanzania. *Rev inf Dis*
56 1983;5:554-7
- 57
58 71. Heymann DL, Mayben GK, Murphy KR, Guyer B, Foster SO. Measles control in
59 Yaounde: Justification of a one dose, nine month minimum age vaccination policy
60 in tropical Africa. *Lancet* 1983;ii:1470-2
72. Garly ML, Martins CL, Balé C, da Costa F, Dias F, et al. Early two-dose measles
vaccination schedule in Guinea-Bissau: good protection and coverage in infancy.
Int J Epidemiol 1999;28:347-52
73. Kaninda AV, Legros D, Jataou IM, Malfait P, Maisonneuve M, Paquet C, Moren A.

- 1
2
3 Measles vaccine effectiveness in standard and early immunization strategies, Niger,
4 1995. *Pediatr Inf Dis J* 1998;7:1034-9
5
6 74. Phadke MA, Bhargava I, Dhaigude P, Bagade A, Biniwale MA, et al. Efficacy of
7 two dose measles vaccination in a community setting. *Ind Pediatr* 1998;35:723-5
8
9 75. Al-Mazrou YY, Al-Jeffri M, Ahmed OMM, Aziz KMS, Mishkas AH. Measles
10 immunization: Early two-doses policy experience. *J Trop Pediatr* 1999;45:98-104
11
12 76. Aaby P, Ibrahim S, Libman M, Jensen H. The sequence of vaccinations and
13 increased female mortality after high-titre measles vaccine: trials from rural
14 Sudan and Kinshasa. *Vaccine* 2006;24:2764-71
15
16 77. Aaby P, Martins CL, Garly ML, Bale C, Andersen A, Rodrigues A, Ravn H, Lisse
17 IM, Benn CS, Whittle H. Non-specific effects of standard measles vaccine at 4.5
18 and 9 months of age on childhood mortality: Randomised controlled trial. *BMJ*
19 2010;341:c6495
20
21 78. Aaby P, Andersen M, Sodemann M, Jakobsen M, Gomes J, et al. Reduced
22 childhood mortality after standard measles vaccination at 4-8 months compared
23 with 9-11 months of age. *BMJ* 1993;307:1308-1311
24
25 79. Martins CL, Garly ML, Balé C, Rodrigues A, Ravn H, Whittle HC, Lisse IM,
26 Aaby P. Protective efficacy of standard Edmonston-Zagreb measles vaccination in
27 infants aged 4.5 months: interim analysis of a randomised clinical trial. *BMJ*
28 2008;337:a661
29
30 80. Aaby P, Garly ML, Balé C, Martins C, Jensen H, et al. Survival of previously
31 measles-vaccinated and measles-unvaccinated children in an emergency situation:
32 an unplanned study. *Pediatr Inf Dis J* 2003;22:798-805
33
34 81. Garenne M, Cantrelle P. Rougeole e mortalité au Sénégal : étude de l'impact de la
35 vaccination effectuée à Khombole 1965-1968 sur la survie des enfants. In :
36 Cantrelle P, Dormont S, Fargues P, Goujard J, Guignard J, Rumeau-Rouquette C
37 (eds) : Estimation de la mortalité de jeune enfant (0-5 ans) pour guider les actions
38 de santé dans les pays en développement. Paris : INSERM, 1986 ;145:515-32
39
40 82. Aaby P, Bukh J, Lisse IM, Smits AJ. Measles vaccination and reduction in child
41 mortality: a community study from Guinea-Bissau. *J Infect* 1984;8:13-21
42
43 83. Velema JP, Alihonou EJ, Gandaho T, Hounye FH. Childhood mortality among
44 users and non- users of primary health care in a rural West African community.
45 *Int J Epidemiol* 1991;20:474- 479
46
47 84. Holt EA, Boulos R, Halsey NA, Boulos LM, Boulos C. Childhood survival in
48 Haiti: protective effect of measles vaccination. *Pediatrics* 1990;86:188-94
49
50 85. George K, Josph A, Muliyl J, Abraham S, Bhattacharji S, John KR. Measles
51 vaccination before nine months. *Trop Med Int Hlth* 1998;3:751-6
52
53 86. Kristensen I, Aaby P, Jensen H. Routine vaccinations and child survival: follow
54 up study in Guinea-Bissau, West Africa. *BMJ* 2000;321:1435-8
55
56 87. Lehmann D, Vail J, Firth MJ, de Klerk NH, Alpers MP. Benefits of routine
57 immunisations on childhood survival in Tari, Southern Highlands Province, Papua
58 New Guinea. *Int J Epidemiol* 2004, 10.1093/ije/dyh262
59
60 88. Elguero E, Simondon F, Simondon K, Vaugelade J. Non-specific effects of
vaccination on survival: a prospective study in Senegal. *Trop Med Int Health*
2005;10:956-960
89. Aaby P, Martins CL, Garly ML, Andersen A, Fisker AB, Claesson MH, Ravn H,

- Rodrigues A, Whittle HC, Benn CS. Measles vaccination in presence of maternal antibodies may increase child survival (submitted)
90. de Quadros CA. Can measles be eradicated globally? *Bull WHO* 2004;82:134-8
91. Aaby P, Bhuyia A, Nahar L, Knudsen K, Francisco A, et al. The survival benefit of measles immunization may not be explained entirely by the prevention of measles disease: a community study from rural Bangladesh. *Int J Epidemiol* 2003;32: 106-115
92. Aaby P, Samb B, Simondon F, Knudsen K, Seck AM, et al. Divergent mortality for male and female recipients of low-titer and high-titer measles vaccines in rural Senegal. *Am J Epidemiol* 1993;138:746-755
93. Desgrées du Loû A, Pison G, Aaby P. The role of immunizations in the recent decline in childhood mortality and the changes in the female/male mortality ratio in rural Senegal. *Am J Epidemiol* 1995;142:643-52
94. Shann F. The non-specific effects of vaccines. *Arch Dis Child* 2010;95:662-7
95. Welsh RM, Selin LH. No one is naïve: The significance of heterologous T-cell immunity. *Nat Rev Immunol* 2002; 2: 417-426
96. Leuridan E, Hens N, Hutse V, Ieven M, Aerts M, et al. Early waning of maternal measles antibodies in era of measles elimination: longitudinal study. *BMJ* 2010;340:c1626
97. Martins C. Measles vaccination in Guinea-Bissau. Strategies to reduce disease burden and improve child survival. Copenhagen: University of Copenhagen, 2011 [PhD Thesis]
98. Moxon R, Nossal G, Heymann D, Plotkin S, Levine O. The new decade of vaccines. Authors' reply. *Lancet* 2012;379:27
99. Heymann DL, Fine PE, Griffiths UK, Hall AJ, Mounier-Jack S. Measles eradication: past is prologue. *Lancet* 2010;376:1719-20

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				
	Column 1	Column 2	Column 3	Column 4	Column 5	Column 6	Column 7	Column 8	Column 9	Column 10
	Cumulative measles incidence (%)	Seroconversion 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%

1
2
3
4
5 protection against measles. Hence, the estimated case fatality ratios are 8% for unvaccinated cases occurring in infancy and 1.33% for
6 vaccinated cases but there were fewer vaccinated cases than indicated in column 4.
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

For peer review only

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)*
<i>Bissau (43)¹</i>	<i>1980-82</i>	<i>PCS; urban (only secondary cases)</i>	<i>14%(3/21)</i>	<i>46%(11/24)</i>	<i>0.30 (0.10-0.86)*</i>
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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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.

For peer review only

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)

1
2
3 Sources: Reviews of measles case fatality studies (27-31) and PubMed search for
4 community studies of measles mortality/case fatality in infants or by age in Africa (see
5 Supplementary material).
6

7 Notes: MV=measles vaccine; PCS=prospective community study, i.e. the population was
8 known before the epidemic and information is likely to have been obtained for all
9 children; SUR= retrospective survey; # The age grouping is 7-12 months and 12-120
10 months. Measles deaths and total number of children in age group were reported in this
11 study. It has been assumed that all children between 7 and 120 months contracted
12 measles. In this period there were no measles vaccinations available. The last epidemic
13 had occurred 12-13 years earlier; ## The age grouping is 0-8 and 9+ months; ∞ Numbers
14 read from a graph
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

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)	1 st vaccine in 2-dose group was Connaught HTMV and 2 nd dose was Schwarz standard MV
	9-36 months	2 nd vs 1 st 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	2 nd vs 1 st 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
<i>Early measles vaccination at 7 months of age compared with children unvaccinated community</i>			
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)
<i>Comparing MV at 4-8 months versus MV at 9-11 months of age</i>			
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)
<i>Comparing children randomised to MV at 6 months versus IPV at 6 months during a war situation</i>			
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 receive 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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

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
----------------------	----	---	---

Page 1 of 2

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

1
2
3
4
5
6
7
8 **The optimal age of measles immunization in low-income countries: A**
9 **secondary analysis of the assumptions underlying the current policy**
10 **years with a policy based on flawed assumptions**
11

12
13 Peter Aaby^{1, 2}, Cesário L Martins¹, May-Lill Garly¹, Amabelia Rodrigues¹, Christine S
14 Benn^{1, 2}, Hilton C Whittle³
15
16

17
18 **1) Bandim Health Project, Indepth Network, Apartado 861, Bissau, Guinea-Bissau**

19 (CL Martins, clinician, PhD student, ML Garly, MD PhD, senior researcher, A
20 Rodrigues, PhD, research director, P Aaby, DMSc, professor). E-mail:
21 p.aaby@bandim.org
22
23
24

25 **2) Research Center for Vitamins and Vaccines (CVIVA), Bandim Health Project,**
26 **Danish Epidemiology Science Centre, Statens Serum Institut, Artillerivej 5, 2300**
27 **Copenhagen S, Denmark** (CS Benn, senior researcher, P Aaby, DMSc, professor)
28
29
30

31 **3) London School of Hygiene and Tropical Medicine, London, United Kingdom** (H
32 Whittle, F Med Sci, honorary professor)
33
34

35 Running title: Optimal age of measles vaccination

36 Word counts: Abstract: 293; Text: 5685
37
38

39
40 Corresponding author: Peter Aaby, Bandim Health Project, Statens Serum Institut,
41 Artillerivej 5, 2300 Copenhagen S, Denmark
42 p.aaby@bandim.org
43
44
45
46
47
48
49
50
51
52
53
54

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 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. 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-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 recommendation is 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 may lead to an increase in child mortality.

Formatted: Font: Not Bold

Formatted: Font: Not Bold

Formatted: Font: Not Bold

Formatted: Font: Not Bold

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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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, we looked for empirical evidence in community studies to support or refute their validity and 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).

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, 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

Formatted: Font: Italic

Formatted: Font: Not Italic

Formatted: Font: Not Italic

Formatted: Font: Not Italic

Formatted: Font: Not Italic

Formatted: Font: Not Italic

Formatted: Font: Not Italic

Formatted: Font: Not Italic

1
2
3
4
5
6
7
8 conditions (37). It is possible that the children had acquired vaccine-induced measles
9 antibodies earlier but subsequently lost them. Based on the literature search, no other
10 study has tested the susceptibility of vaccinated “seronegative” children. If approximately
11 half the seronegative children have clinical protection it would have major consequences
12 for the calculation of the optimal age of measles vaccine. Cellular immunity may be
13 obtained without having measurable antibodies (41). There is also good evidence from
14 studies of hepatitis B vaccination that antibody concentration wane with time but the
15 majority of older seronegative children if infected are protected from chronic carriage and
16 its damaging consequences (42).

17
18
19 Considerations. Apparently, no other study has tested the susceptibility of vaccinated
20 “seronegative” children. It is possible that some children had acquired vaccine-induced
21 measles antibodies earlier but subsequently lost them. Cellular immunity may be obtained
22 without having measurable antibodies (41). There is also good evidence from studies of
23 hepatitis B vaccination that antibody concentration wane with time but the majority of
24 older seronegative children if infected are protected from chronic carriage and its
25 damaging consequences (42).

Formatted: Font: Not Italic

26
27 The concept of seroconversion to compare the effect of vaccination at different age is in
28 itself problematic. Seroconversion is not the same as seroprotection and the use of the
29 term inevitably disadvantages data from studies that have vaccinated at earlier ages when
30 maternal antibodies are still present. Thus a child immunized at 6 months of age when the
31 maternal antibody level is say 62.5 mIU may fail the test for conversion (a four-fold
32 increase) yet still have a protective level of 125 mIU at 9 months of age.

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

35
36 ***Assumption 3: severity of measles infection in vaccinated children (“vaccine failures”)***
37 ***and unvaccinated children is the same.***

38
39 Background. The EPI perceived “vaccine failures” as due to the vaccine being inactivated
40 by improper storage and handling or due to neutralization of the vaccine by maternal
41 antibodies (16,19). Hence, it was assumed that these children had been fully susceptible
42 to measles infection. However, many epidemiological studies in the 1980s and 1990s
43 suggested that measles vaccinated children who contracted measles infection had milder
44 disease (43,44). This would suggest that the children had partial measles immunity, not
45 enough to protect them but enough to modify the severity of the disease.

46
47 Data: We searched for “measles mortality vaccinated children”, “measles vaccine
48 mortality”, “measles case fatality” and “measles vaccine failure” (Supplementary
49 material). The 18 relevant studies are included in Tables 2 and 3.

50
51 Analysis. The EPI perceived “vaccine failures” as due to the vaccine being inactivated by
52 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 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)).

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 in these studies there 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 this at was indeed higher in infancy the ease, 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.

Formatted: Font: Not Italic

Formatted: Font: Not Italic

Formatted: Font: Not Italic

Formatted: Font: Not Italic

Formatted: Font: Not Italic

Formatted: Font: Not Italic

Formatted: Font: Not Italic

Formatted: Font: Not Italic

Formatted: Font: Not Italic

Formatted: Font: Not Italic

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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 lose 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)

1
2
3
4
5
6
7
8 and searched papers on “Two/2 dose measles vaccine trial”, “Two/2 dose measles
9 vaccination/immunization and mortality/death” and “early measles
10 vaccination/immunization mortality/death”. These procedures identified only two trials
11 of the effect on child survival of a 2-dose measles vaccinations schedule compared with a
12 1-dose schedule (see Table 5) and one observational study (78)
13 The main argument advanced for a one dose policy was that compliance with the second
14 dose was too low (15,18,68,70). This is surprising since it has been described that
15 mothers sought vaccination so eagerly that it was impossible to maintain the age
16 eligibility criteria for vaccinations during campaigns (16). The reason why mothers did
17 not seek the second dose of measles vaccine in some countries may have been poor
18 information. In Guinea Bissau, we had very good compliance and improved overall
19 coverage with a two dose schedule (71). The two dose group had better protection
20 against measles infection than the one dose group (71). A two dose schedule has also
21 been shown to be effective in Niger (72), India (73) and Saudi Arabia (74). Hence, a two-
22 dose schedule is both feasible and effective.

23
24 Analysis. Only two trials have compared child mortality following two doses of MV (the
25 first being given before 9 months) with mortality after the standard dose of MV (at 9
26 months of age) (Table 5). In a small trial from Sudan (756), DTP vaccinations were not
27 controlled and many children received DTP after measles vaccine. DTP administered
28 with or after measles vaccine has negative effects on female survival (34,36). We
29 therefore conducted a large randomized trial including only children who had received
30 DTP3 before enrolment and therefore would not receive DTP after MV (767). Among
31 children who had not received neonatal vitamin A supplementation (VAS) which
32 interacted negatively with early MV(76), two doses of MV at 4.5 and 9 months of age
33 compared with the current policy of one dose at 9 months of age reduced mortality
34 between 4.5 and 36 months of age by 50% (22-68%) in the per-protocol analysis (Table
35 5). There was a significant reduction in non-measles related mortality of 45% (14-65%)
36 (767). The combined estimate for the two trials showed that the early two-dose measles
37 vaccination strategy may reduce mortality by as much as 48% (23%-65%) compared with
38 the currently recommended standard dose at 9 months of age. Even if the children
39 receiving neonatal VAS were included, the combined estimate was 31% (9-48%) (Table
40 5).

41 The only other study to report mortality after two doses of MV is a natural experiment
42 from Guinea-Bissau in the early 1980s. Children were vaccinated in annual or biannual
43 campaigns rather than through routine service. Hence, it was possible to compare in an
44 unbiased way the survival of children who happened to be less than 9 months of age
45 when vaccinated and those vaccinated at the recommended age of 9-11 for MV. MV at 4-
46 8 months and a later dose after 9 months compared with one dose of MV at 9-11 months
47 of age was associated with 59% (15-81%) lower mortality between 9 months and 5 years
48 of age (778). Hence, the two dose studies indicate that a two dose policy providing the
49 first dose of MV before 9 months of age is associated with major reductions in child
50 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 two 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

1
2
3
4
5
6
7
8 is unlikely that there would be many studies not included. Furthermore, the estimates
9 from different studies were consistent and it is unlikely that the addition of further studies
10 would have a major impact on the estimates.
11

12 The assumed case fatality of measles infection does not matter for the estimated impact
13 of the optimal policy on measles mortality. With another case fatality level the
14 epidemiological arguments about assumptions 2-4 would still have the same relative
15 effects on the number of deaths prevented. However, as evident in Tables 2 and 4, most
16 community studies from Africa suggest that the case fatality may have been higher than
17 4% and the impact of the optimal measles vaccination strategy on overall mortality may
18 therefore have been even larger. Other assumptions may also have been important; for
19 example, the incidence data were from a rural study rather than from an urban area (21).
20 In an urban area the incidence would have been higher at younger ages and it might have
21 been advantageous to vaccinate even earlier. As maternal measles antibody levels have
22 declined in low-income countries (788), earlier vaccination would also have produced
23 better seroconversion rates and it would have been even more advantageous to vaccinate
24 early.
25

26 **Consistency with previous studies: The non-specific beneficial effects of MV.** The
27 conclusion that earlier measles vaccination is likely to have been better for child survival
28 is based on a reconsideration of the programme's own assumptions about effect on
29 measles mortality. However, what is the empirical evidence for the impact on mortality of
30 measles vaccine before 9 months of age?
31

32 In marked contradiction to the original fear that children dying of measles would just die
33 of something else and that measles vaccination would therefore only change the cause of
34 death but not the level of mortality (9-11), all subsequent studies measuring the effect on
35 survival have found marked benefit from measles vaccination (32,33,36,778,8079-889).
36 Several studies have assessed the impact of measles vaccine before 12 months of age
37 (30,32,33) but few studies have separately measured the effect on overall mortality of
38 measles vaccination before 9 months of age in an unbiased way (Table 6). In the 1970s,
39 researchers in Congo followed two districts which initially had similar overall mortality
40 levels and then introduced measles vaccination at 7 months of age in one district (11).
41 Measles vaccination administered at 7 months of age reduced overall mortality between 7
42 and 21 months of age by 71% (2-91%) compared with the neighbouring district which
43 did not get measles vaccination (60). In the early 1980s in Guinea-Bissau, children were
44 vaccinated in annual or biannual campaigns. Hence, it was possible to compare in a
45 "natural experiment" manner the survival of children who had been measles vaccinated
46 before 9 months of age and those vaccinated at 9 months of age, the recommended age of
47 measles vaccination. One dose of MV at 4-8 months compared with 9-11 months of age
48 was associated with 31% (-8-54%) lower mortality between 9 months and 5 years of age
49 (778). As mention above the effect was even stronger if they also received a second dose
50 of MV after 9 months of age. During a civil war in Guinea-Bissau in 1998 (8079), we
51 followed children who had been randomised to measles vaccination at 6 months of age
52 compared with children who had been randomised to inactivated polio vaccine (IPV).
53 Due to the war the children did not get the standard measles vaccination at 9 months of
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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 (890). 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 (32,76,88,9,991). 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 (776,924,923). 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

1
2
3
4
5
6
7
8 vaccination is increased, children would benefit less from the non-specific beneficial
9 effects and overall child mortality would increase. Hence, policies optimizing the non-
10 specific effects clash with those designed to enhance seroconversion.
11

12 **Conclusions: Old assumptions linger on**

13 The supplementary immunization activities (SIA) with measles vaccine has eliminated
14 measles infection in Latin America and reduced the incidence in major ways in the rest of
15 the world (1-3). The world is now planning to eliminate and eventually eradicate measles
16 infection (4). With the SIA success in measles control, the optimal age of measles
17 immunization is likely to be considered an irrelevant issue. However, as discussed above,
18 measles vaccine has also non-specific effects which need to be taken into consideration in
19 the planning of vaccination programmes. The prevention of all-cause mortality rather
20 than measles mortality should be the primary objective. In a culture which advocates
21 evidence-based policies (4), the evidence for the current measles vaccination policy – or
22 rather the lack thereof - should be properly reviewed and revised by the global and
23 regional immunization programmes. Otherwise old assumptions about seroconversion
24 rates being the basis for the optimal age of immunisation may linger on and continue to
25 influence policy.
26

27 There are major consequences of focusing solely on specific measles mortality. First, as
28 the current policy is mostly determined by our understanding that seroconversion gets
29 better with increasing age, the tendency will be that with improved control of measles
30 infection, age of vaccination will be increased. Following the elimination of measles in
31 Latin America, the recommended age of primary measles immunization was raised to 12
32 months in 1996 (3). Again this decision was based on assumptions and not on studies
33 documenting the overall effect on morbidity and mortality. Following the success of
34 measles campaigns in other continents it has also been recommended by SAGE (the
35 Strategic Advisory Group of Experts) to increase the age of measles vaccination to 12
36 months in areas with low levels of measles transmission (5,12). The underlying
37 assumption about better seroconversion at higher ages may no longer be valid with the
38 decline in maternal antibody levels (798,965). For example, we have obtained 100%
39 seropositivity and 99% protective levels after measles vaccine at 9 months of age with
40 both Schwarz and Edmonston-Zagreb measles vaccine strains in Guinea-Bissau (976).
41

42 However, the most important problem is that measles vaccine has major non-specific
43 beneficial effects and the earlier it is given, the earlier the children will benefit from this
44 advantage (11,32,38,765-8079,889). There is a tendency to dismiss these observations
45 because randomised trials with overall mortality as an outcome have ~~to-date~~ only been
46 conducted in Guinea-Bissau and it is therefore claimed that the global health community
47 has to wait for verification elsewhere (987). However, the non-specific beneficial effects
48 of MV have been shown in several other countries with high childhood mortality. For
49 example, in a cross-over design, Shann showed that girls receiving standard measles
50 vaccine at 9-10 months of age in five randomised trials in Sudan, Gambia, Senegal and
51 Guinea-Bissau had 47% lower mortality through childhood than control children who
52 received an inactivated vaccine at 9-10 months of age (943). Since the control children
53 had received MV before 9 months of age and did not get measles, the difference in
54

1
2
3
4
5
6
7
8 mortality following MV at 9 months of age was a non-specific beneficial effect not
9 related to prevention of measles infection. Increasing the age of measles vaccine from 9
10 to 12 months may reduce the beneficial effects in the age group between 9 and 12 months
11 of age in which mortality is still high. Thus the lives lost by this change of schedule could
12 well be more than the lives saved by improved measles control (776).
13

14 Second, in the current paradigm for control of infectious diseases, the ultimate success in
15 public health is to eradicate the disease and then remove the vaccine to reduce economic
16 costs as happened for smallpox in the 1970s (26). This may happen for measles infection
17 within the next 10-20 years (989). If measles vaccine has major beneficial non-specific
18 effects (776), to remove measles vaccine or reduce its coverage would increase child
19 mortality levels considerably in low-income countries unless we in the meantime find a
20 vaccine which has all the same beneficial effects as measles vaccine.
21

22 After 35 years, it is time to develop a policy for the optimal age of measles immunization.
23 This policy needs to be based on evidence about the impact on overall health and child-
24 survival and not only on assumptions about the impact of specific prevention against
25 measles infection. A two-dose measles vaccination strategy, providing measles vaccine at
26 4.5 months of age, after the three DTP vaccines, and again at 9 months of age, may
27 significantly improve child survival and provide a solid basis of immunity which if
28 necessary can be enhanced by supplementary measles immunisation activities at a later
29 age (767,789). Any future changes in the age of measles immunisation due to elimination
30 of measles infection, changes in the epidemiology of measles infection, decline in
31 maternal antibody levels, introduction of new measles vaccines or in the timing of other
32 vaccines should be tested in trials to determine their overall impact on child health.
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54

1
2
3
4
5
6
7
8 **Contributions:** PA and HW have been involved in studies of measles vaccination for
9 more than 30 years in West Africa; MLG, CM, CB and AR have been involved in
10 measles vaccination trials since the early 1990s. The first draft was written by PA; all
11 authors contributed to the final version of the paper. PA will act as guarantor of the study.
12

13
14 **Conflict of interest:** nothing to declare

15
16 **Funding:** The Bandim Health Project received support from DANIDA and the Danish
17 National Research Foundation. PA holds a research professorship grant from the Novo
18 Nordisk Foundation. We received no funding specifically for the present study.

19
20 **Independence:** The funders had no role in the study design, data collection, data
21 analysis, data interpretation, decision to publish or preparation of the manuscript.

22
23 **Data sharing:** no additional data available
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54

References

1. De Quadros CA, Olive JM, Hersh BS, Strassburg MA, Henderson DA, Bandling-Bennett D, Alleyne GA. Measles elimination in the Americas. Evolving strategies. *JAMA* 1996; 275: 224-29
2. Otten M, Kezaala R, Fall A, Masresha B, Martin R, Cairns L, Eggers R, Biellik R, Grabowsky M, Strebel P, Okwo-Bele JM, Nshimirimana. Public-health impact of accelerated measles control in the WHO African Region 2000-03. *Lancet* 2005;366:832-9
3. De Quadros CA, Izurieta H, Venczel L, Carrasco P. Measles eradication in the Americas : Progress to date. *JID* 2004 ;189 (Suppl 1) : S227
4. Department of immunization, vaccines and biologicals: Strategic Plan 2010-15. Draft 24 March 2010, World Health Organization
5. Measles vaccines: WHO position paper. *Week Epid Rec* 2009;84:349-60
6. Expanded Programme on Immunization. Measles immunization. *Weekly Epidemiol Rec* 1979;54:337-9
7. Expanded Programme on Immunization. Global advisory group Meeting. *Weekly Epidemiol Rec* 1981;56:9-16
8. Expanded Programme on Immunization. The optimal age for measles immunization. *Weekly Epidemiol Rec* 1982;57:89-91
9. Hendrickse RG. Problems of future measles vaccination in developing countries. *Trans R Soc Trop Med Hyg* 1975;69:31-34
10. Mosley WH. Will primary health care reduce infant and child mortality? A critique of some current strategies. With special reference to Africa and Asia. In: Lopez AD, Vallin J (eds): Health policy, social policy and mortality prospects. Liege: Ordina, 1985;pp 103-37
11. The Kasongo Project Team. Influence of measles vaccination on survival pattern of 7-35-month-old children in Kasongo, Zaire. *Lancet* 1981;i:764-7
12. Meeting of the immunization Strategic Advisory Group of experts, November 2006 – conclusions and recommendations. *Weekly Epidemiol Rec* 2007;82:1-16
13. Foege WH. Measles vaccination in Africa. *Sci Pub PAHO* 1971;228:207-12
14. McBean AM, Foster SO, Herrmann KL, Gateff. Evaluation of mass measles immunisation campaign in Yaoundé, Cameroun. *Trans Roy Soc Trop Med Hyg* 1976;70:206-12
15. Guyer B, McBean AM. The epidemiology and control of measles in Yaoundé, Cameroun, 1968-1975. *Int J Epidemiol* 1981;10:263-9
16. Grigsby ME, Adetosoye JIA. Measles epidemiology and control in Western Nigeria. *J Nat Med Ass* 1973;65:378-85
17. Foster SO, Pifer JM. Mass measles control in West and central Africa. *Afr J Med Sci* 1971;2:151-8
18. Henderson RH. Measles vaccination in Zaire – when and how? *Trans Roy Soc Trop Med Hyg* 1981;75:128-9
19. Wood PB, Soheranda KS, Bracken PM, Houser NE. Measles vaccination in Zaire – when and how? *Trans Roy Soc Trop Med Hyg* 1980;74:381-2
20. Lapeyssonnie L, Omer LA, Nicolas A, Roumiantzeff M. Etude de la response serologique d'enfant soudanais a la vaccination combinee triple (rougeole, tetanos, meningite A). *Med Trop* 1979;39:71-9

Formatted: English (U.S.)

Formatted: French (France)

21. Collaborative study by the Ministry of Health of Kenya and the World Health Organisation. Measles immunity in the first year after birth and the optimum age for vaccination in Kenyan children. *Bull WHO* 1977;55:21- 31
22. Burström B, Aaby P, Mutie DM, Kimani G, Bjerregaard P. Severe measles outbreak in Western Kenya. *East Afr Med J* 1992; 69:419-423
23. Seroconversion rates and measles antibody titers induced by measles vaccine in Latin American children aged 6-12 months of age. Collaborative study by the Ministries of Health of Brazil, Chile, Costa Rica, Ecuador, and the Pan American Health Organization. *Bull Pan Am Health Organ* 1982;16:272-85
24. Rosenthal SR, Clements CJ. Two-dose measles vaccination schedules. *Bull WHO* 1993;71:421-8
25. Rolfe M. Measles immunization in the Zambian Copperbelt: cause for concern. *Trans Roy Soc Trop Med Hyg* 1982;76:529-30
26. *Lancet*. Rationalising measles vaccination. *The Lancet* 1981;ii:236-7
27. Aaby P. Malnutrition and overcrowding/intensive exposure in severe measles infection: review of community studies. *Rev Infect Dis* 1988;10:478-491
28. Aaby P, Clements J, Orinda V. Mortality from measles: measuring the impact. Geneva 1991: EPI, WHO
29. Wolfson LJ, Grais RF, Luquero FJ, Birmingham ME, Strebel PM. Estimates of measles case fatality ratios: a comprehensive review of community-based studies. *Int J Epidemiol* 2009;38:192-205
30. Sudfeld CR, Navar AM, Halsey NA. Effectiveness of measles vaccination and vitamin A treatment. *Int J Epidemiol* 2010;39:i48-i55
31. Kouadio IK, Kamigaki T, Oshitani H. Measles outbreaks in displaced populations: a review of transmission, morbidity and mortality associated risk factors. *BMC Int Hlth Hum Rights* 2010;10:5
32. Aaby P, Samb B, Simondon F, Coll Seck AM, Knudsen K, et al. Non-specific beneficial effect of measles immunisation: analysis of mortality studies from developing countries. *Br Med J* 1995;311:481-485
33. Garly ML, Aaby P. The challenge of improving the efficacy of measles vaccine. *Acta Trop* 2003;85:1-17
34. Aaby P, Jensen H, Samb B, Cisse B, Sodeman M, et al. Differences in female-male mortality after high-titre measles vaccine and association with subsequent vaccination with diphtheria-tetanus-pertussis and inactivated poliovirus: reanalysis of West African studies. *Lancet* 2003;361: 2183-88
35. Knudsen KM, Aaby P, Whittle H, Rowe M, Samb B, et al. Child mortality following standard, medium or high titre measles immunization in West Africa. *Int J Epidemiol* 1996;25:665-73
36. Aaby P, Garly ML, Nielsen J, Ravn H, Martins C, Balé C, et al. Increased female-male mortality ratio associated with inactivated polio and diphtheria-tetanus-pertussis vaccines: Observations from vaccination trials in Guinea-Bissau. *Pediatr Infect Dis J* 2007;26:247-52.
37. Samb B, Aaby P, Whittle H, Coll Seck AM, Rahman S, et al. Serological status and measles attack rates among vaccinated and unvaccinated children in rural Senegal. *Pediatr Inf Dis J* 1995;14:203-9
38. Aaby P, Pedersen IR, Knudsen K, da Silva MC, Mordhorst CH, et al. Child

- mortality related to seroconversion or lack of seroconversion after measles vaccination. *Pediatr Infect Dis J* 1989;8:197-200
39. Hirose M, Hidaka Y, Miyazaki C, Ueda K, Yoshikawa H. Five cases of measles secondary vaccine failure with confirmed seroconversion after live measles vaccination. *Scand J Inf Dis* 1997;29:187-90
40. Samb B, Aaby P, Whittle H, Seck AW, Simondon F. Protective efficacy of high-titre measles vaccines administered from the age of five months: a community study in rural Senegal. *Trans Roy Soc Trop Med Hyg* 1993;87:697-701
41. Siegrist CA, Barrios C, Martinez X, Brandt C, Berney M, et al. Influence of maternal antibodies on vaccine responses: inhibition of antibody but not T cell responses allows successful early prime-boost strategies in mice. *Eur J Immunol* 1998;28:4138-48
42. van der Sande MA, Waight P, Mendy M, Rayco-Solon P, Hutt P, et al. Long-term protection against carriage of hepatitis B virus after infant vaccination. *J Infect Dis* 2006;193:1528-35
43. Aaby P, Bukh J, Leerhøj J, Lisse IM, Mordhorst CH, et al. Vaccinated children get milder measles infection: a community study from Guinea-Bissau. *J Infect Dis* 1986;154:858-63
44. Samb B, Aaby P, Whittle H, Seck AM, Simondon F. Decline in measles case fatality ratio after the introduction of measles immunization in rural Senegal. *Am J Epidemiol* 1997;145:51-7
45. Aaby P, Bukh J, Lisse IM, da Silva CM. Decline in measles mortality: nutrition, age at infection, or exposure? *Br Med J* 1988;296:1225-1228
46. Aaby P, Knudsen K, Jensen TG, Thaarup J, Poulsen A, et al. Measles incidence, vaccine efficacy, and mortality in two urban African areas with high vaccination coverage. *J Infect Dis* 1990;162:1043-1048
47. Aaby P, Whittle H, Cisse B, Samb B, Jensen H, et al. The frailty hypothesis revisited: mainly weak children die of measles. *Vaccine* 2001;20:949-53
48. Dollimore N, Cutts F, Binka FN, Ross DA, Morris SS, et al. Measles incidence, case fatality, and delayed mortality in children with or without vitamin A supplementation in rural Ghana. *Am J Epidemiol* 1997;146:646-654
49. Burström B, Aaby P, Mutie DM. Child mortality impact of a measles outbreak in a partially vaccinated rural African community. *Scand J Infect Dis* 1993;25:763-9
50. Ndikuyeze A, Cook A, Cutts FT, Bennett S. Priorities in global measles control: report of an outbreak in N'djamena, Chad. *Epidemiol Infect* 1995;115:309-14
51. Grais RF, Dubray C, Gersti S, Guthmann JP, Djibo A, et al. Unacceptably high mortality related to measles epidemics in Niger, Nigeria, and Chad. *PLoS Med* 2007;4:e16
52. Coronado F, Musa N, Tayeb ESAE, Haithami S, Dabbagh A, et al. Retrospective measles outbreak investigation: Sudan, 2004. *J Trop Pediatr* 2006;52:329-34
53. Expanded Programme on Immunization. High measles case-fatality during an outbreak in a rural area. *Weekly Epidemiol Rec* 1993;68:142-5
54. Marufu T, Siziya S, Tshimanga M, Murugasampillay S, Mason E, et al. Factors associated with measles complications in Gweru, Zimbabwe. *East Afr Med J* 2001;78:135-8
55. Aaby P, Lisse I, Mølbak K, Knudsen K, Whittle H. No persistent T lymphocyte

- immunosuppression or increased mortality after measles infection: a community study from Guinea-Bissau. *Pediatr Inf Dis J* 1996;5:39-44
56. Chen RT, Weierbach R, Bisoffi Z, Cutts F, Rhodes P, et al. A 'Post-honeymoon period' measles outbreak in Mayinga Sector, Burundi. *Int J Epidemiol* 1994;23:185-93
57. Nsungu M. Measles vaccination status, delay in recognizing measles outbreaks and outbreak outcome. *Cent Afr J Med* 1995;41:336-9
58. Oshitani H, Mpabalwani M, Kosolo F, Mizuta K, Luo NP, et al. Measles infection in hospitalized children in Lusaka, Zambia. *Ann Trop Pediatr* 1995;15:167-72
59. Yamaguchi S, Dunga A, Broadhead RL, Brabin BJ. Epidemiology of measles in Blantyre, Malawi: analyses of passive surveillance data from 1996 to 1998. *Epidemiol Infect* 2002;129:361-9
60. Mishra A, Mishra S, Lahariya C, Jain P, Bhadoriya RS, et al. Practical observations from an epidemiological investigation of a measles outbreak in a district of India. *Ind J Comm Med* 2009;34:117-21
61. Mgone JM, Mgone CS, Duke T, Frank D, Yeka W Control measures and the outcome of the measles epidemic of 1999 in the Eastern Highlands Province. *PNG Med J* 2000;43:91-7
62. Aaby P, Bukh J, Lisse IM, Smits AJ. Overcrowding and intensive exposure as determinants of measles mortality. *Am J Epidemiol* 1984;120:49-63
63. McGregor IA. Measles and child mortality in the Gambia. *West Afr Med J* 1964;251-7
64. Aaby P, Bukh J, Lisse IM, Smits AJ, Gomes J, et al. Determinants of measles mortality in a rural area of Guinea-Bissau: Crowding, age, and malnutrition. *J Trop Pediatr* 1984;30:164-68
65. Muller AS, Voorhoeve AM, 't Mannetje W, Schulpens TWJ. The impact of measles in a rural area of Kenya. *East Afr med J* 1977;54:364-72
66. Aaby P, Bukh J, Lisse IM, da Silva CM. Measles mortality: Further community studies on the role of overcrowding and intensive exposure. *Rev Infect Dis* 1988;10:474-477
67. Nandy R, Handzel T, Zaneidou M, Biey J, Cuddy RZ, et al. Case-fatality rate during a measles outbreak in Eastern Niger in 2003. *Clin Inf Dis* 2006;42:322-8
68. Hull HF, Williams PJ, Oldfield F. Measles mortality and vaccine efficacy in rural West Africa. *Lancet* 1983;i:972-5
69. [Burström B, Aaby P, Muite DM. Measles in infancy: A review of studies of incidence, vaccine efficacy and mortality in East Africa. *East Afr Med J* 1993;72:155-61](#)
70. Mandara MP, Remme J. Current measles control in Tanzania. *Rev inf Dis* 1983;5:554-7
71. Heymann DL, Mayben GK, Murphy KR, Guyer B, Foster SO. Measles control in Yaounde: Justification of a one dose, nine month minimum age vaccination policy in tropical Africa. *Lancet* 1983;ii:1470-2
72. Garly ML, Martins CL, Balé C, da Costa F, Dias F, et al. Early two-dose measles vaccination schedule in Guinea-Bissau: good protection and coverage in infancy. *Int J Epidemiol* 1999;28:347-52
73. Kaninda AV, Legros D, Jataou IM, Malfait P, Maisonneuve M, Paquet C,

Formatted: Bullets and Numbering

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Moren A. Measles vaccine effectiveness in standard and early immunization strategies, Niger, 1995. *Pediatr Inf Dis J* 1998;7:1034-9

~~73-74.~~ Phadke MA, Bhargava I, Dhaigude P, Bagade A, Biniwale MA, et al. Efficacy of two dose measles vaccination in a community setting. *Ind Pediatr* 1998;35:723-5

~~74-75.~~ Al-Mazrou YY, Al-Jeffri M, Ahmed OMM, Aziz KMS, Mishkas AH. Measles immunization: Early two-doses policy experience. *J Trop Pediatr* 1999;45:98-104

~~75-76.~~ Aaby P, Ibrahim S, Libman M, Jensen H. The sequence of vaccinations and increased female mortality after high-titre measles vaccine: trials from rural Sudan and Kinshasa. *Vaccine* 2006;24:2764-71

~~76-77.~~ Aaby P, Martins CL, Garly ML, Bale C, Andersen A, Rodrigues A, Ravn H, Lisse IM, Benn CS, Whittle H. Non-specific effects of standard measles vaccine at 4.5 and 9 months of age on childhood mortality: Randomised controlled trial. *BMJ* 2010;341:c6495

~~77-78.~~ Aaby P, Andersen M, Sodemann M, Jakobsen M, Gomes J, et al. Reduced childhood mortality after standard measles vaccination at 4-8 months compared with 9-11 months of age. *BMJ* 1993;307:1308-1311

~~78-79.~~ Martins CL, Garly ML, Balé C, Rodrigues A, Ravn H, Whittle HC, Lisse IM, Aaby P. Protective efficacy of standard Edmonston-Zagreb measles vaccination in infants aged 4.5 months: interim analysis of a randomised clinical trial. *BMJ* 2008;337:a661

~~79-80.~~ Aaby P, Garly ML, Balé C, Martins C, Jensen H, et al. Survival of previously measles-vaccinated and measles-unvaccinated children in an emergency situation: an unplanned study. *Pediatr Inf Dis J* 2003;22:798-805

~~80-81.~~ Garenne M, Cantrelle P. Rougeole e mortalité au Sénégal : étude de l'impact de la vaccination effectuée à Khombole 1965-1968 sur la survie des enfants. In : Cantrelle P, Dormont S, Fargues P, Goujard J, Guignard J, Rumeau-Rouquette C (eds) : Estimation de la mortalité de jeune enfant (0-5 ans) pour guider les actions de santé dans les pays en développement. Paris : INSERM, 1986 ;145:515-32

~~81-82.~~ Aaby P, Bukh J, Lisse IM, Smits AJ. Measles vaccination and reduction in child mortality: a community study from Guinea-Bissau. *J Infect* 1984;8:13-21

~~82-83.~~ Velema JP, Alihonou EJ, Gandaho T, Hounye FH. Childhood mortality among users and non- users of primary health care in a rural West African community. *Int J Epidemiol* 1991;20:474- 479

~~83-84.~~ Holt EA, Boulos R, Halsey NA, Boulos LM, Boulos C. Childhood survival in Haiti: protective effect of measles vaccination. *Pediatrics* 1990;86:188-94

~~84-85.~~ George K, Josphe A, Mulyil J, Abraham S, Bhattacharji S, John KR. Measles vaccination before nine months. *Trop Med Int Hlth* 1998;3:751-6

~~85-86.~~ Kristensen I, Aaby P, Jensen H. Routine vaccinations and child survival: follow up study in Guinea-Bissau, West Africa. *BMJ* 2000;321:1435-8

~~86-87.~~ Lehmann D, Vail J, Firth MJ, de Klerk NH, Alpers MP. Benefits of routine immunisations on childhood survival in Tari, Southern Highlands Province, Papua New Guinea. *Int J Epidemiol* 2004, 10.1093/ije/dyh262

Formatted: English (U.K.)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

- | [87-88.](#) Elguero E, Simondon F, Simondon K, Vaugelade J. Non-specific effects of vaccination on survival: a prospective study in Senegal. *Trop Med Int Health* 2005;10:956-960
- | [88-89.](#) Aaby P, Martins CL, Garly ML, Andersen A, Fisker AB, Claesson MH, Ravn H, Rodrigues A, Whittle HC, Benn CS. Measles vaccination in presence of maternal antibodies may increase child survival (submitted)
- | [89-90.](#) de Quadros CA. Can measles be eradicated globally? *Bull WHO* 2004;82:134-8
- | [90-91.](#) Aaby P, Bhuyia A, Nahar L, Knudsen K, Francisco A, et al. The survival benefit of measles immunization may not be explained entirely by the prevention of measles disease: a community study from rural Bangladesh. *Int J Epidemiol* 2003;32: 106-115
- | [91-92.](#) Aaby P, Samb B, Simondon F, Knudsen K, Seck AM, et al. Divergent mortality for male and female recipients of low-titer and high-titer measles vaccines in rural Senegal. *Am J Epidemiol* 1993;138:746-755
- | [92-93.](#) Desgrées du Loû A, Pison G, Aaby P. The role of immunizations in the recent decline in childhood mortality and the changes in the female/male mortality ratio in rural Senegal. *Am J Epidemiol* 1995;142:643-52
- | [93-94.](#) Shann F. The non-specific effects of vaccines. *Arch Dis Child* 2010;95:662-7
- | [94-95.](#) Welsh RM, Selin LH. No one is naïve: The significance of heterologous T-cell immunity. *Nat Rev Immunol* 2002; 2: 417-426
- | [95-96.](#) Leuridan E, Hens N, Hutse V, Ieven M, Aerts M, et al. Early waning of maternal measles antibodies in era of measles elimination: longitudinal study. *BMJ* 2010;340:c1626
- | [96-97.](#) Martins C. Measles vaccination in Guinea-Bissau. Strategies to reduce disease burden and improve child survival. Copenhagen: University of Copenhagen, 2011 [PhD Thesis]
- | [97-98.](#) Moxon R, Nossal G, Heymann D, Plotkin S, Levine O. The new decade of vaccines. Authors' reply. *Lancet* 2012;379:27
- | [98-99.](#) Heymann DL, Fine PE, Griffiths UK, Hall AJ, Mounier-Jack S. Measles eradication: past is prologue. *Lancet* 2010;376:1719-20

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					
	Column 1	Column 2	Column 3	Column 4	Column 5	Column 6	Column 7	Column 8	Column 9	Column 10
	Cumulative measles incidence (%)	Seroconversion 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%

1
2
3
4
5
6
7
8 protection against measles. Hence, the estimated case fatality ratios are 8% for unvaccinated cases occurring in infancy and 1.33% for
9 vaccinated cases but there were fewer vaccinated cases than indicated in column 4.
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

For peer review only

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; \$ 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

1
2
3
4
5
6
7
8 vaccinated was reported among all cases. It has been assumed that the proportion
9 vaccinated cases was the same among those with follow-up as among all cases.
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Table 3. ~~M~~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. ~~M~~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)

1
2
3
4
5
6
7
8 Sources: Reviews of measles case fatality studies (27-31) and PubMed search for
9 community studies of measles mortality/case fatality in infants or by age in Africa (see
10 Supplementary material).

11 Notes: MV=measles vaccine; PCS=prospective community study, i.e. the population was
12 known before the epidemic and information is likely to have been obtained for all
13 children; SUR= retrospective survey; # The age grouping is 7-12 months and 12-120
14 months. Measles deaths and total number of children in age group were reported in this
15 study. It has been assumed that all children between 7 and 120 months contracted
16 measles. In this period there were no measles vaccinations available. The last epidemic
17 had occurred 12-13 years earlier; ## The age grouping is 0-8 and 9+ months; □ Numbers
18 read from a graph
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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)	1 st vaccine in 2-dose group was Connaught HTMV and 2 nd dose was Schwarz standard MV
	9-36 months	2 nd vs 1 st 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	2 nd vs 1 st 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 randomised 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).



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

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2011-000761.R3
Article Type:	Research
Date Submitted by the Author:	07-Jun-2012
Complete List of Authors:	Aaby, Peter; Bandim Health Project, Bandim Health Project Martins, Cesario; Bandim Health Project, Bandim Health Project Garly, May-Lill; Bandim Health Project,, Rodrigues, Amabelia; Bandim Health Project, Bandim Health Project, Benn, Christine; Statens Serum Institut, Department of Epidemiology Research Whittle, Hilton; London School of Hygiene and Tropical Medicine,
Primary Subject Heading:	Global health
Secondary Subject Heading:	Epidemiology, Health policy, Infectious diseases, Paediatrics, Public health
Keywords:	EPIDEMIOLOGY, International health services < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, MEDICAL HISTORY, Public health < INFECTIOUS DISEASES, Community child health < PAEDIATRICS, PUBLIC HEALTH

SCHOLARONE™
Manuscripts

only

1
2
3
4 **The optimal age of measles immunization in low-income countries: A**
5 **secondary analysis of the assumptions underlying the current policy**
6
7

8 Peter Aaby^{1, 2}, Cesário L Martins¹, May-Lill Garly¹, Amabelia Rodrigues¹, Christine S
9 Benn^{1, 2}, Hilton C Whittle³
10
11

12
13
14 **1) Bandim Health Project, Indepth Network, Apartado 861, Bissau, Guinea-Bissau**

15 (CL Martins, clinician, PhD student, ML Garly, MD PhD, senior researcher, A
16 Rodrigues, PhD, research director, P Aaby, DMSc, professor). E-mail:
17 p.aaby@bandim.org
18
19
20
21

22
23 **2) Research Center for Vitamins and Vaccines (CVIVA), Bandim Health Project,**
24 **Danish Epidemiology Science Centre, Statens Serum Institut, Artillerivej 5, 2300**
25 **Copenhagen S, Denmark** (CS Benn, senior researcher, P Aaby, DMSc, professor)
26
27
28

29
30 **3) London School of Hygiene and Tropical Medicine, London, United Kingdom** (H
31 Whittle, F Med Sci, honorary professor)
32
33

34
35 Running title: Optimal age of measles vaccination

36
37 Word counts: Abstract: 432; Text: 6513
38
39

40 Corresponding author: Peter Aaby, Bandim Health Project, Statens Serum Institut,
41 Artillerivej 5, 2300 Copenhagen S, Denmark
42
43

44 p.aaby@bandim.org
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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.

1
2
3 Since there are few specific studies to test the six assumptions we have had to use case
4 reports of measles outbreaks to assess their validity. Over the last 20-25 years, several
5 reviews of community studies of the measles case fatality compiled studies of relevance
6 for particularly assumption three and four (27-31), two of these being by the first author
7 (PA). For each assumption we used existing reviews and in December 2011 the first
8 author made a PubMed search for relevant papers as described below. The title and
9 abstract of papers in English, French, Portuguese, Spanish, German and Scandinavian
10 languages was assessed by the first author to ascertain whether the paper was potentially
11 relevant. Potentially relevant papers were read. Most papers were not from Africa but
12 were reviews or case reports and not community based studies and had no information on
13 mortality. We included one unpublished report from a large epidemic in Bissau in 1991-
14 1992 which has remained unpublished because the physician (Henning Andersen)
15 handling the epidemic died tragically in an accident shortly after the epidemic.
16
17
18
19

20
21 We distinguished between prospective community studies and surveys retrospectively
22 assessing events since the precision of information on vaccination status and age
23 presumably is better in prospective studies. Though hospital and health centre studies
24 may have data on the severity of measles infection by vaccination status or age, we have
25 not included these studies in the analysis since biased admission for some groups might
26 have made the result non-representative.
27
28

29 Since the analysis of the assumptions suggested that measles vaccination before 9 months
30 of age could be beneficial, we assessed the empirical evidence from studies which
31 assessed the effect of early measles vaccination on mortality. Again we used all reviews
32 of community studies and trials assessing the impact of measles vaccination on child
33 mortality (30,32-35). Additional PubMed searches for studies comparing the mortality of
34 measles vaccinated and unvaccinated children did not identify further studies. As
35 explained in the footnote to table 6, we have emphasised the studies in which inactivated
36 vaccines were not administered simultaneously with MV or after MV as such
37 combination or sequences can have a negative effect on child survival (34,36).
38
39
40

41 **Presentation.** For each assumption, we briefly outline the background. Next we present
42 the relevant studies found and then analyse the common trends, identifying the secondary
43 analyses which have been made. Finally, we considered whether methodological issues
44 and data quality might question the trends suggested by the analysis.
45
46

47 **Statistical analyses.** Based on cumulative measles incidence data we calculated how
48 many measles cases and measles death had been prevented assuming everybody was
49 vaccinated at a specific age, how many “vaccine failures” would occur after the age of
50 vaccination, and how many cases would occur before the specific age of vaccination. It
51 was estimated how this calculation was influenced by the empirical evidence for the
52 underlying assumptions. In the combined analyses of several studies we used the Mantel-
53 Haenszel (MH) weighted relative risk stratifying for study or age groups to estimate
54 common trends.
55
56
57
58
59
60

1
2
3 **Ethics.** Since the study is a secondary analysis of existing data, approval from an ethical
4 committee was not needed.
5
6

7 **Results**

8 ***Assumption 1: children who seroconvert to measles vaccine have absolute protection***
9 ***against measles infection.***
10

11
12 *Background.* It has usually been assumed that previous measles infection is associated
13 with life-long immunity. This idea was transferred to measles vaccination when the
14 vaccine was developed in the 1950s. Hence, if someone had antibodies after vaccination
15 these were also assumed to provide life-long protection.
16

17
18 *Data:* We searched for “measles infection seropositive vaccinated children” (N=12) and
19 “measles vaccine failure” (N=318). There are many case reports that contradict that
20 seroconverted children have absolute protection but no African community study.
21

22
23 *Analysis.* A number of smaller studies have documented that a few children do get
24 measles after having seroconverted (37-40). Hence, seroconversion does not give
25 absolute protection.
26

27
28 *Considerations.* However, there are no general epidemiological studies from Africa and it
29 is therefore difficult to estimate the proportion of children who get measles in spite of
30 having seroconverted, but since no large series have been reported it is likely to be small.
31

32 ***Assumption 2: vaccinated children who are seronegative are fully susceptible to***
33 ***measles infection.***
34

35
36 *Background.* Measles immunity has generally been considered an either-or phenomenon.
37 If a vaccinated child was seronegative it was assumed that the child was fully susceptible.
38

39
40 *Data:* We searched for “measles infection seronegative vaccinated children” (N=13) and
41 “measles vaccine failure” (N=318). This provided only one relevant reference (37).
42

43
44 *Analysis.* In a study in Senegal, vaccinated children who were seronegative when exposed
45 to measles infection at home had a 49% (95% CI 21-68%) protection against clinical
46 disease compared with unvaccinated seronegative children exposed under similar
47 conditions (37).
48

49
50 *Considerations.* Apparently, no other study has tested the susceptibility of vaccinated
51 “seronegative” children. It is possible that some children had acquired vaccine-induced
52 measles antibodies earlier but subsequently lost them. Cellular immunity may be obtained
53 without having measurable antibodies (41). There is also good evidence from studies of
54 hepatitis B vaccination that antibody concentration wane with time but the majority of
55 older seronegative children if infected are protected from chronic carriage and its
56 damaging consequences (42).
57
58
59
60

1
2
3 The concept of seroconversion to compare the effect of vaccination at different age is in
4 itself problematic. Seroconversion is not the same as seroprotection and the use of the
5 term inevitably disadvantages data from studies that have vaccinated at earlier ages when
6 maternal antibodies are still present. Thus a child immunized at 6 months of age when the
7 maternal antibody level is say 62.5 mIU may fail the test for conversion (a four-fold
8 increase) yet still have a protective level of 125 mIU at 9 months of age.
9
10

11 If approximately half the seronegative children have clinical protection it would have
12 major consequences for the calculation of the optimal age of measles vaccine.
13
14

15 ***Assumption 3: severity of measles infection in vaccinated children (“vaccine failures”)***
16 ***and unvaccinated children is the same.***
17

18 *Background.* The EPI perceived “vaccine failures” as due to the vaccine being inactivated
19 by improper storage and handling or due to neutralization of the vaccine by maternal
20 antibodies (16,19). Hence, it was assumed that these children had been fully susceptible
21 to measles infection. However, many epidemiological studies in the 1980s and 1990s
22 suggested that measles vaccinated children who contracted measles infection had milder
23 disease (43,44). This would suggest that the children had partial measles immunity, not
24 enough to protect them but enough to modify the severity of the disease.
25
26
27

28 *Data:* We searched for “measles mortality vaccinated children” (N=143), “measles
29 vaccine mortality” (N=775), “measles case fatality” (N=161) and “measles vaccine
30 failure” (N=318). The 18 relevant studies are included in Tables 2 and 3.
31
32

33 *Analysis.* The community studies of the acute measles case fatality are shown in Table 2.
34 Only two African studies (43, 48) have reported significant differences in mortality for
35 vaccinated and unvaccinated measles cases. A combined analysis has not been made
36 previously. The measles case fatality was 2 to 5-fold lower for vaccinated cases (“vaccine
37 failures”) than for unvaccinated children with measles infection in nearly all studies.
38 Using MH weighted relative risk, the effect was similar in the prospective community
39 studies (case-fatality ratio=0.37 (0.27-0.52)) and the retrospective surveys (case-fatality
40 ratio=0.41 (0.29-0.56)).
41
42
43

44 A few studies followed the children for longer than one month which is the normal time
45 limit for acute measles deaths. The long-term trend was the same with considerable better
46 survival among vaccinated than unvaccinated children after measles infection (Table 3).
47 Combining the prospective community studies in Tables 2 and 3 would suggest a 3-fold
48 reduction in acute and/or long-term mortality among vaccinated children even though
49 some of the vaccine failures may have been due to inactivated measles vaccines.
50
51

52 In the four studies (38,47,56, unpublished) with information on both acute and long-term
53 mortality, mortality was nearly 5-fold lower for the vaccinated cases (MH weighted
54 mortality ratio= 0.21 (0.13-0.34)).
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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.

1
2
3
4 *Background.* In the hypothetical EPI model in which all children were vaccinated at a
5 specific age, the unvaccinated measles cases would occur in infancy, before measles
6 vaccination, whereas most “vaccine failures” would occur much later after the first year
7 of life. No adjustment was made for how this affected the overall measles mortality. Most
8 infections are more severe in infancy but on the other hand, modification of severity by
9 maternal antibodies could have reduced the case fatality among infants.
10

11 *Data:* We therefore searched for studies of “measles case fatality” (N=161) and “measles
12 mortality/death Africa” (N=620). We found 24 relevant studies (Table 4).
13

14
15 *Analysis.* The African community studies reporting the measles case fatality separately
16 for infants and older children have been presented in Table 4. One review of East African
17 studies of measles have previously emphasised that the case fatality was particularly high
18 in infants (69). However, a comparative analysis of the measles case fatality for infants
19 and older children in all African community studies have not been made before. With a
20 few exceptions, the studies suggested that the case fatality is higher in infancy than
21 among older children (Table 4). These studies suggest around a two-fold higher measles
22 case-fatality in infancy; the MH weighted case fatality ratio for all studies was 1.87 (1.63-
23 2.14). The effect was similar before measles vaccine was introduced in these
24 communities (MH weighted case fatality ratio=2.04 (1.58-2.63)) (see Studies before the
25 introduction of MV, Table 4).
26
27
28

29 *Considerations.* Only three studies did not show higher case fatality in infancy and half
30 the studies showed significantly higher mortality in infancy. Even if a few studies should
31 not have been found by the search terms, it seems unlikely that additional studies would
32 change the tendency.
33
34

35 If the case fatality is indeed higher in infancy, it would be more advantageous to have
36 vaccine failures later in life rather than leave infants less than 9 months of age
37 unprotected.
38

39 ***Assumption 5: vaccine failures lead to lack of credibility of the vaccination***
40 ***programme.***
41

42
43 *Background.* Apparently it was assumed that African mothers – like physicians - would
44 lose confidence if measles vaccine did not provide complete and life-long immunity.
45
46

47 *Data:* We searched “measles vaccine failure” (N=318) and “measles
48 vaccine/vaccination/immunisation credibility” (N=2). This search produced one paper
49 dealing with the relationship between “vaccine failure” and the acceptance or credibility
50 of measles vaccination (70). One study was known from our own research (43).
51
52

53 *Analysis.* One study from Tanzania stated that acceptance of measles vaccination was low
54 because of the many failures experienced by children vaccinated before 9 months of age.
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

1
2
3 interacted negatively with early MV(76), two doses of MV at 4.5 and 9 months of age
4 compared with the current policy of one dose at 9 months of age reduced mortality
5 between 4.5 and 36 months of age by 50% (22-68%) in the per-protocol analysis (Table
6 5). There was a significant reduction in non-measles related mortality of 45% (14-65%)
7 (77). The combined estimate for the two trials showed that the early two-dose measles
8 vaccination strategy may reduce mortality by as much as 48% (23%-65%) compared with
9 the currently recommended standard dose at 9 months of age. Even if the children
10 receiving neonatal VAS were included, the combined estimate was 31% (9-48%) (Table
11 5).
12
13

14
15 The only other study to report mortality after two doses of MV is a natural experiment
16 from Guinea-Bissau in the early 1980s. Children were vaccinated in annual or biannual
17 campaigns rather than through routine service. Hence, it was possible to compare in an
18 unbiased way the survival of children who happened to be less than 9 months of age
19 when vaccinated and those vaccinated at the recommended age of 9-11 for MV. MV at 4-
20 8 months and a later dose after 9 months compared with one dose of MV at 9-11 months
21 of age was associated with 59% (15-81%) lower mortality between 9 months and 5 years
22 of age (78).
23
24

25
26 *Considerations.* The studies indicate that a two-dose policy providing the first dose of
27 MV before 9 months of age is associated with major reductions in child mortality
28 compared with the current one-dose at 9 month policy. The studies indicated that the
29 benefit was not due to better protection against measles infection. Hence, these studies
30 strongly supported that early measles vaccination has non-specific beneficial effects on
31 child survival.
32
33

34 **The implications of the assumptions for the estimated prevention of measles**
35 **mortality.** We calculated how variation in these six assumptions affect the optimal age of
36 MV in terms of reducing measles mortality (Table 1, Columns 7-10). Using the best
37 estimate that the case fatality rate is three-fold lower for vaccinated measles cases than
38 for unvaccinated cases (Tables 2 and 3), the number of estimated measles deaths would
39 have been lowest with one dose of MV at 8 months (Column 7). Assuming furthermore
40 that infants have two-fold higher case fatality than older children (Table 4) the estimated
41 number of measles deaths would have been lowest after vaccination at age 7 months
42 (Column 8). Hence, it might have been better to vaccinate at 7 months of age and have
43 some more vaccine failures later in childhood than to have many unvaccinated cases with
44 high mortality in infancy. Adjusting for the possibility that non-seroconverting vaccinated
45 children have some protection from cellular immunity or low levels of antibodies (37),
46 the optimal age for measles immunization in a one-dose strategy would have moved to 6
47 or 7 months of age (Columns 9 and 10).
48
49
50

51
52 The studies of two doses of MV suggest that both the first and the second dose of measles
53 vaccine are effective and that an early two-dose strategy would be associated with a
54 major reduction in measles and overall mortality (72-77,79). Hence, an early dose at 4-6
55 months of age and a second dose at 9 months of age would have eliminated virtually all
56 measles mortality and significantly reduced mortality from other causes as well.
57
58
59
60

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

1
2
3 death but not the level of mortality (9-11), all subsequent studies measuring the effect on
4 survival have found marked benefit from measles vaccination (32,33,36,78,80-89).
5 Several studies have assessed the impact of measles vaccine before 12 months of age
6 (30,32,33) but few studies have separately measured the effect on overall mortality of
7 measles vaccination before 9 months of age in an unbiased way (Table 6). In the 1970s,
8 researchers in Congo followed two districts which initially had similar overall mortality
9 levels and then introduced measles vaccination at 7 months of age in one district (11).
10 Measles vaccination administered at 7 months of age reduced overall mortality between 7
11 and 21 months of age by 71% (2-91%) compared with the neighbouring district which
12 did not get measles vaccination (60). In the early 1980s in Guinea-Bissau, children were
13 vaccinated in annual or biannual campaigns. Hence, it was possible to compare in a
14 “natural experiment” manner the survival of children who had been measles vaccinated
15 before 9 months of age and those vaccinated at 9 months of age, the recommended age of
16 measles vaccination. One dose of MV at 4-8 months compared with 9-11 months of age
17 was associated with 31% (-8-54%) lower mortality between 9 months and 5 years of age
18 (78). As mention above the effect was even stronger if they also received a second dose
19 of MV after 9 months of age. During a civil war in Guinea-Bissau in 1998 (80), we
20 followed children who had been randomised to measles vaccination at 6 months of age
21 compared with children who had been randomised to inactivated polio vaccine (IPV).
22 Due to the war the children did not get the standard measles vaccination at 9 months of
23 age. During the 3 months of intensive fighting when everybody had fled the study area
24 and mortality was high, the children vaccinated against measles at 6 months of age had
25 70% (13-92%) lower mortality than the unvaccinated group.
26
27
28
29
30

31
32 These studies of one dose of MV before 9 months of age as well as the studies of early
33 two-dose MV mentioned above suggest that the reduction in mortality from MV before 9
34 months of age is much larger than can be explained by the prevention of measles
35 infection. WHO estimates that measles deaths caused 10% of under-five deaths (90).
36 However all available studies of the mortality impact of MV (30,32,33) suggest that the
37 effect of measles immunization on mortality is much greater than expected. This
38 beneficial effect is a consistent observation and it can not be explained by the prevention
39 of acute measles infection. First, all studies, in which measles vaccine was not
40 administered with DTP, provided strong evidence of a beneficial effect of measles
41 vaccine on overall mortality (32). Second, all studies censoring for measles infection in
42 the survival analysis to estimate the impact on non-measles related mortality found that
43 prevention of measles-specific deaths explained little and the beneficial effect was due to
44 prevention of non-measles related mortality (32,76,89, 91). For example, in the per-
45 protocol analysis of the largest randomised trial (77), measles vaccine at 4.5 and 9
46 months compared with the standard dose at 9 months of age reduced non-measles related
47 mortality significantly for all children. Third, the beneficial effect of measles vaccine is
48 usually stronger for girls than for boys (77,92,93). Since measles mortality is not higher
49 for girls than boys, this observation suggests sex-differential mechanisms related to
50 immune stimulation. Hence, standard measles vaccine may protect against other
51 infections and have a beneficial effect on child survival even when measles is eliminated.
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

1
2
3 documenting the overall effect on morbidity and mortality. Following the success of
4 measles campaigns in other continents it has also been recommended by SAGE (the
5 Strategic Advisory Group of Experts) to increase the age of measles vaccination to 12
6 months in areas with low levels of measles transmission (5,12). The underlying
7 assumption about better seroconversion at higher ages may no longer be valid with the
8 decline in maternal antibody levels (79,96). For example, we have obtained 100%
9 seropositivity and 99% protective levels after measles vaccine at 9 months of age with
10 both Schwarz and Edmonston-Zagreb measles vaccine strains in Guinea-Bissau (97).
11
12

13
14 However, the most important problem is that measles vaccine has major non-specific
15 beneficial effects and the earlier it is given, the earlier the children will benefit from this
16 advantage (11,32,38,76-80,89). There is a tendency to dismiss these observations because
17 randomised trials with overall mortality as an outcome have only been conducted in
18 Guinea-Bissau and it is therefore claimed that the global health community has to wait
19 for verification elsewhere (98). However, the beneficial non-specific effects of MV have
20 been shown in several other countries with high childhood mortality. For example, in a
21 cross-over design, Shann showed that girls receiving standard measles vaccine at 9-10
22 months of age in five randomised trials in Sudan, Gambia, Senegal and Guinea-Bissau
23 had 47% lower mortality through childhood than control children who received an
24 inactivated vaccine at 9-10 months of age (94). Since the control children had received
25 MV before 9 months of age and did not get measles, the difference in mortality following
26 MV at 9 months of age was a beneficial non-specific effect not related to prevention of
27 measles infection. Increasing the age of measles vaccine from 9 to 12 months may reduce
28 the beneficial effects in the age group between 9 and 12 months of age in which mortality
29 is still high. Thus the lives lost by this change of schedule could well be more than the
30 lives saved by improved measles control (77).
31
32
33
34

35 Second, in the current paradigm for control of infectious diseases, the ultimate success in
36 public health is to eradicate the disease and then remove the vaccine to reduce economic
37 costs as happened for smallpox in the 1970s (26). This may happen for measles infection
38 within the next 10-20 years (99). If measles vaccine has major beneficial non-specific
39 effects (77), to remove measles vaccine or reduce its coverage would increase child
40 mortality levels considerably in low-income countries unless we in the meantime find a
41 vaccine which has all the same beneficial effects as measles vaccine.
42
43
44

45 After 35 years, it is time to develop a policy for the optimal age of measles immunization.
46 This policy needs to be based on evidence about the impact on overall health and child-
47 survival and not only on assumptions about the impact of specific prevention against
48 measles infection. A two-dose measles vaccination strategy, providing measles vaccine at
49 4.5 months of age, after the three DTP vaccines, and again at 9 months of age, may
50 significantly improve child survival and provide a solid basis of immunity which if
51 necessary can be enhanced by supplementary measles immunisation activities at a later
52 age (77,79). Any future changes in the age of measles immunisation due to elimination of
53 measles infection, changes in the epidemiology of measles infection, decline in maternal
54 antibody levels, introduction of new measles vaccines or in the timing of other vaccines
55 should be tested in trials to determine their overall impact on child health.
56
57
58
59
60

1
2
3 **Contributions:** PA, CSB and HW planned the present study. The first of many drafts
4 was written by PA and all authors contributed critically to the refinement of the
5 arguments and the final version of the paper. All authors approved the final version of the
6 paper. PA will act as guarantor of the study
7
8

9
10 **Conflict of interest:** nothing to declare
11

12 **Funding:** The Bandim Health Project received support from DANIDA and the Danish
13 National Research Foundation. PA holds a research professorship grant from the Novo
14 Nordisk Foundation. We received no funding specifically for the present study.
15
16

17 **Independence:** The funders had no role in the study design, data collection, data
18 analysis, data interpretation, decision to publish or preparation of the manuscript.
19

20 **Data sharing:** no additional data available
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

References

1. De Quadros CA, Olive JM, Hersh BS, *et al.* Measles elimination in the Americas. Evolving strategies. JAMA 1996; 275: 224-29
2. Otten M, Kezaala R, Fall A, *et al.* Public-health impact of accelerated measles control in the WHO African Region 2000-03. Lancet 2005;366:832-9
3. De Quadros CA, Izurieta H, Venczel L, *et al.* Measles eradication in the Americas : Progress to date. JID 2004 ;189 (Suppl 1) : S227
4. Department of immunization, vaccines and biologicals: Strategic Plan 2010-15. Draft 24 March 2010, World Health Organization
5. Measles vaccines: WHO position paper. Week Epid Rec 2009;84:349-60
6. Expanded Programme on Immunization. Measles immunization. Weekly Epidemiol Rec 1979;54:337-9
7. Expanded Programme on Immunization. Global advisory group Meeting. Weekly Epidemiol Rec 1981;56:9-16
8. Expanded Programme on Immunization. The optimal age for measles immunization. Weekly Epidemiol Rec 1982;57:89-91
9. Hendrickse RG. Problems of future measles vaccination in developing countries. Trans R Soc Trop Med Hyg 1975;69:31-34
10. Mosley WH. Will primary health care reduce infant and child mortality? A critique of some current strategies. With special reference to Africa and Asia. In: Lopez AD, Vallin J (eds): Health policy, social policy and mortality prospects. Liege: Ordina, 1985;pp 103-37
11. The Kasongo Project Team. Influence of measles vaccination on survival pattern of 7-35-month-old children in Kasongo, Zaire. Lancet 1981;i:764-7
12. Meeting of the immunization Strategic Advisory Group of experts, November 2006 – conclusions and recommendations. Weekly Epidemiol Rec 2007;82:1-16
13. Foege WH. Measles vaccination in Africa. Sci Pub PAHO 1971;228:207-12
14. McBean AM, Foster SO, Herrmann KL, *et al.* Evaluation of mass measles immunisation campaign in Yaoundé, Cameroun. Trans Roy Soc Trop Med Hyg 1976;70:206-12
15. Guyer B, McBean AM. The epidemiology and control of measles in Yaoundé, Cameroun, 1968-1975. Int J Epidemiol 1981;10:263-9
16. Grigsby ME, Adetosoye JIA. Measles epidemiology and control in Western Nigeria. J Nat Med Ass 1973;65:378-85
17. Foster SO, Pifer JM. Mass measles control in West and central Africa. Afr J Med Sci 1971;2:151-8
18. Henderson RH. Measles vaccination in Zaire – when and how? Trans Roy Soc Trop Med Hyg 1981;75:128-9
19. Wood PB, Soheranda KS, Bracken PM, *et al.* Measles vaccination in Zaire – when and how? Trans Roy Soc Trop Med Hyg 1980;74:381-2
20. Lapeyssonnie L, Omer LA, Nicolas A, *et al.* Etude de la response serologique d'enfant soudanais a la vaccination combinee triple (rougeole, tetanos, meningite A). Med Trop 1979;39:71-9
21. Collaborative study by the Ministry of Health of Kenya and the World Health Organisation. Measles immunity in the first year after birth and the optimum age for vaccination in Kenyan children. Bull WHO 1977;55:21- 31

- 1
 - 2
 - 3
 - 4
 - 5
 - 6
 - 7
 - 8
 - 9
 - 10
 - 11
 - 12
 - 13
 - 14
 - 15
 - 16
 - 17
 - 18
 - 19
 - 20
 - 21
 - 22
 - 23
 - 24
 - 25
 - 26
 - 27
 - 28
 - 29
 - 30
 - 31
 - 32
 - 33
 - 34
 - 35
 - 36
 - 37
 - 38
 - 39
 - 40
 - 41
 - 42
 - 43
 - 44
 - 45
 - 46
 - 47
 - 48
 - 49
 - 50
 - 51
 - 52
 - 53
 - 54
 - 55
 - 56
 - 57
 - 58
 - 59
 - 60
22. Burström B, Aaby P, Mutie DM, *et al.* Severe measles outbreak in Western Kenya. *East Afr Med J* 1992; 69:419-423
23. Seroconversion rates and measles antibody titers induced by measles vaccine in Latin American children aged 6-12 months of age. Collaborative study by the Ministries of Health of Brazil, Chile, Costa Rica, Ecuador, and the Pan American Health Organization. *Bull Pan Am Health Organ* 1982;16:272-85
24. Rosenthal SR, Clements CJ. Two-dose measles vaccination schedules. *Bull WHO* 1993;71:421-8
25. Rolfe M. Measles immunization in the Zambian Copperbelt: cause for concern. *Trans Roy Soc Trop Med Hyg* 1982;76:529-30
26. *Lancet*. Rationalising measles vaccination. *The Lancet* 1981;ii:236-7
27. Aaby P. Malnutrition and overcrowding/intensive exposure in severe measles infection: review of community studies. *Rev Infect Dis* 1988;10:478-491
28. Aaby P, Clements J, Orinda V Mortality from measles: measuring the impact. Geneva 1991: EPI, WHO
29. Wolfson LJ, Grais RF, Luquero FJ, *et al.* Estimates of measles case fatality ratios: a comprehensive review of community-based studies. *Int J Epidemiol* 2009;38:192-205
30. Sudfeld CR, Navar AM, Halsey NA. Effectiveness of measles vaccination and vitamin A treatment. *Int J Epidemiol* 2010;39:i48-i55
31. Kouadio IK, Kamigaki T, Oshitani H. Measles outbreaks in displaced populations: a review of transmission, morbidity and mortality associated risk factors. *BMC Int Hlth Hum Rights* 2010;10:5
32. Aaby P, Samb B, Simondon F, *et al.* Non-specific beneficial effect of measles immunisation: analysis of mortality studies from developing countries. *Br Med J* 1995;311:481-485
33. Garly ML, Aaby P. The challenge of improving the efficacy of measles vaccine. *Acta Trop* 2003;85:1-17
34. Aaby P, Jensen H, Samb B, *et al.* Differences in female-male mortality after high-titre measles vaccine and association with subsequent vaccination with diphtheria-tetanus-pertussis and inactivated poliovirus: reanalysis of West African studies. *Lancet* 2003;361: 2183-88
35. Knudsen KM, Aaby P, Whittle H, *et al.* Child mortality following standard, medium or high titre measles immunization in West Africa. *Int J Epidemiol* 1996;25:665-73
36. Aaby P, Garly ML, Nielsen J, *et al.* Increased female-male mortality ratio associated with inactivated polio and diphtheria-tetanus-pertussis vaccines: Observations from vaccination trials in Guinea-Bissau. *Pediatr Infect Dis J* 2007;26:247-52.
37. Samb B, Aaby P, Whittle H, *et al.* Serological status and measles attack rates among vaccinated and unvaccinated children in rural Senegal. *Pediatr Inf Dis J* 1995;14:203-9
38. Aaby P, Pedersen IR, Knudsen K, *et al.* Child mortality related to seroconversion or lack of seroconversion after measles vaccination. *Pediatr Infect Dis J* 1989;8:197-200
39. Hirose M, Hidaka Y, Miyazaki C, *et al.* Five cases of measles secondary vaccine

- 1
2
3 failure with confirmed seroconversion after live measles vaccination. *Scand J Inf*
4 *Dis* 1997;29:187-90
- 5
6 40. Samb B, Aaby P, Whittle H, *et al.* Protective efficacy of high-titre measles vaccines
7 administered from the age of five months: a community study in rural
8 Senegal. *Trans Roy Soc Trop Med Hyg* 1993;87:697-701
- 9
10 41. Siegrist CA, Barrios C, Martinez X, *et al.* Influence of maternal antibodies on
11 vaccine responses: inhibition of antibody but not T cell responses allows successful
12 early prime-boost strategies in mice. *Eur J Immunol* 1998;28:4138-48
- 13
14 42. van der Sande MA, Waight P, Mendy M, *et al.* Long-term protection against
15 carriage of hepatitis B virus after infant vaccination. *J Infect Dis* 2006;193:1528-
16 35
- 17
18 43. Aaby P, Bukh J, Leerhøy J, *et al.* Vaccinated children get milder measles infection:
19 a community study from Guinea-Bissau. *J Infect Dis* 1986;154:858-63
- 20
21 44. Samb B, Aaby P, Whittle H, *et al.* Decline in measles case fatality ratio after the
22 introduction of measles immunization in rural Senegal. *Am J Epidemiol*
23 1997;145:51-7
- 24
25 45. Aaby P, Bukh J, Lisse IM, *et al.* Decline in measles mortality: nutrition, age at
26 infection, or exposure? *Br Med J* 1988;296:1225-1228
- 27
28 46. Aaby P, Knudsen K, Jensen TG, *et al.* Measles incidence, vaccine efficacy, and
29 mortality in two urban African areas with high vaccination coverage. *J Infect Dis*
30 1990;162:1043-1048
- 31
32 47. Aaby P, Whittle H, Cisse B, *et al.* The frailty hypothesis revisited: mainly weak
33 children die of measles: *Vaccine* 2001;20:949-53
- 34
35 48. Dollimore N, Cutts F, Binka FN, *et al.* Measles incidence, case fatality, and delayed
36 mortality in children with or without vitamin A supplementation in rural Ghana.
37 *Am J Epidemiol* 1997;146:646-654
- 38
39 49. Burström B, Aaby P, Mutie DM Child mortality impact of a measles outbreak in a
40 partially vaccinated rural African community. *Scand J Infect Dis* 1993;25:763-9
- 41
42 50. Ndikuyeze A, Cook A, Cutts FT, *et al.* Priorities in global measles control: report
43 of an outbreak in N'djamena, Chad. *Epidemiol Infect* 1995;115:309-14
- 44
45 51. Grais RF, Dubray C, Gersti S, *et al.* Unacceptably high mortality related to
46 measles epidemics in Niger, Nigeria, and Chad. *PLoS Med* 2007;4:e16
- 47
48 52. Coronado F, Musa N, Tayeb ESAE, *et al.* Restrospective measles outbreak
49 investigation: Sudan, 2004. *J Trop Pediatr* 2006;52:329-34
- 50
51 53. Expanded Programme on Immunization. High measles case-fatality during an
52 outbreak in a rural area. *Weekly Epidemiol Rec* 1993;68:142-5
- 53
54 54. Marufu T, Siziya S, Tshimanga M, *et al.* Factors associated with measles
55 complications in Gweru, Zimbabwe. *East Afr Med J* 2001;78:135-8
- 56
57 55. Aaby P, Lisse I, Mølbak K, *et al.* No persistent T lymphocyte immunosuppression
58 or increased mortality after measles infection: a community study from Guinea-
59 Bissau. *Pediatr Inf Dis J* 1996;5:39-44
- 60
61 56. Chen RT, Weierbach R, Bisoffi Z, *et al.* A 'Post-honeymoon period' measles
62 outbreak in Mayinga Sector, Burundi. *Int J Epidemiol* 1994;23:185-93
- 63
64 57. Aaby P, Bukh J, Lisse IM, *et al.* Overcrowding and intensive exposure as
65 determinants of measles mortality. *Am J Epidemiol* 1984;120:49-63
- 66
67 58. Nsungu M. Measles vaccination status, delay in recognizing measles outbreaks

- and outbreak outcome. *Cent Afr J Med* 1995;41:336-9
59. Oshitani H, Mpabalwani M, Kosolo F, *et al.* Measles infection in hospitalized children in Lusaka, Zambia. *Ann Trop Pediatr* 1995;15:167-72
60. Yamaguchi S, Dunga A, Broadhead RL, *et al.* Epidemiology of measles in Blantyre, Malawi: analyses of passive surveillance data from 1996 to 1998. *Epidemiol Infect* 2002;129:361-9
61. Mishra A, Mishra S, Lahariya C, *et al.* Practical observations from an epidemiological investigation of a measles outbreak in a district of India. *Ind J Comm Med* 2009;34:117-21
62. Mgone JM, Mgone CS, Duke T, *et al.* Control measures and the outcome of the measles epidemic of 1999 in the Eastern Highlands Province. *PNG Med J* 2000;43:91-7
63. McGregor IA. Measles and child mortality in the Gambia. *West Afr Med J* 1964;251-7
64. Aaby P, Bukh J, Lisse IM, *et al.* Determinants of measles mortality in a rural area of Guinea-Bissau: Crowding, age, and malnutrition. *J Trop Pediatr* 1984;30:164-68
65. Muller AS, Voorhoeve AM, 't Mannetje W, *et al.* The impact of measles in a rural area of Kenya. *East Afr med J* 1977;54:364-72
66. Aaby P, Bukh J, Lisse IM, *et al.* Measles mortality: Further community studies on the role of overcrowding and intensive exposure. *Rev Infect Dis* 1988;10:474-477
67. Nandy R, Handzel T, Zaneidou M, *et al.* Case-fatality rate during a measles outbreak in Eastern Niger in 2003. *Clin Inf Dis* 2006;42:322-8
68. Hull HF, Williams PJ, Oldfield F. Measles mortality and vaccine efficacy in rural West Africa. *Lancet* 1983;i:972-5
69. Burström B, Aaby P, Maitie DM. Measles in infancy: A review of studies of incidence, vaccine efficacy and mortality in East Africa. *East Afr Med J* 1993;72:155-61
70. Mandara MP, Remme J. Current measles control in Tanzania. *Rev inf Dis* 1983;5:554-7
71. Heymann DL, Mayben GK, Murphy KR, *et al.* Measles control in Yaounde: Justification of a one dose, nine month minimum age vaccination policy in tropical Africa. *Lancet* 1983;ii:1470-2
72. Garly ML, Martins CL, Balé C, *et al.* Early two-dose measles vaccination schedule in Guinea-Bissau: good protection and coverage in infancy. *Int J Epidemiol* 1999;28:347-52
73. Kaninda AV, Legros D, Jataou IM, *et al.* Measles vaccine effectiveness in standard and early immunization strategies, Niger, 1995. *Pediatr Inf Dis J* 1998;7:1034-9
74. Phadke MA, Bhargava I, Dhaigude P, *et al.* Efficacy of two dose measles vaccination in a community setting. *Ind Pediatr* 1998;35:723-5
75. Al-Mazrou YY, Al-Jeffri M, Ahmed OMM, *et al.* Measles immunization: Early two-doses policy experience. *J Trop Pediatr* 1999;45:98-104
76. Aaby P, Ibrahim S, Libman M, *et al.* The sequence of vaccinations and increased female mortality after high-titre measles vaccine: trials from rural Sudan and Kinshasa. *Vaccine* 2006;24:2764-71
77. Aaby P, Martins CL, Garly ML, *et al.* Non-specific effects of standard measles vaccine at 4.5 and 9 months of age on childhood mortality: Randomised

- controlled trial. *BMJ* 2010;341:c6495
78. Aaby P, Andersen M, Sodemann M, *et al.* Reduced childhood mortality after standard measles vaccination at 4-8 months compared with 9-11 months of age. *BMJ* 1993;307:1308-1311
79. Martins CL, Garly ML, Balé C, *et al.* Protective efficacy of standard Edmonston-Zagreb measles vaccination in infants aged 4.5 months: interim analysis of a randomised clinical trial. *BMJ* 2008;337:a661
80. Aaby P, Garly ML, Balé C, *et al.* Survival of previously measles-vaccinated and measles-unvaccinated children in an emergency situation: an unplanned study. *Pediatr Inf Dis J* 2003;22:798-805
81. Garenne M, Cantrelle P. Rougeole e mortalité au Sénégal : étude de l'impact de la vaccination effectuée à Khombole 1965-1968 sur la survie des enfants. In : Cantrelle P, Dormont S, Fargues P, Goujard J, Guignard J, Rumeau-Rouquette C (eds) : Estimation de la mortalité de jeune enfant (0-5 ans) pour guider les actions de santé dans les pays en développement. Paris : INSERM, 1986 ;145:515-32
82. Aaby P, Bukh J, Lisse IM, *et al.* Measles vaccination and reduction in child mortality: a community study from Guinea-Bissau. *J Infect* 1984;8:13-21
83. Velema JP, Alihonou EJ, Gandaho T, *et al.* Childhood mortality among users and non- users of primary health care in a rural West African community. *Int J Epidemiol* 1991;20:474- 479
84. Holt EA, Boulos R, Halsey NA, *et al.* Childhood survival in Haiti: protective effect of measles vaccination. *Pediatrics* 1990;86:188-94
85. George K, Josph A, Muliyl J, *et al.* Measles vaccination before nine months. *Trop Med Int Hlth* 1998;3:751-6
86. Kristensen I, Aaby P, Jensen H. Routine vaccinations and child survival: follow up study in Guinea-Bissau, West Africa. *BMJ* 2000;321:1435-8
87. Lehmann D, Vail J, Firth MJ, *et al.* Benefits of routine immunisations on childhood survival in Tari, Southern Highlands Province, Papua New Guinea. *Int J Epidemiol* 2004, 10.1093/ije/dyh262
88. Elguero E, Simondon F, Simondon K, *et al.* Non-specific effects of vaccination on survival: a prospective study in Senegal. *Trop Med Int Health* 2005;10:956-960
89. Aaby P, Martins CL, Garly ML, *et al.* Measles vaccination in presence of maternal antibodies may increase child survival (submitted)
90. de Quadros CA. Can measles be eradicated globally? *Bull WHO* 2004;82:134-8
91. Aaby P, Bhuyia A, Nahar L, *et al.* The survival benefit of measles immunization may not be explained entirely by the prevention of measles disease: a community study from rural Bangladesh. *Int J Epidemiol* 2003;32: 106-115
92. Aaby P, Samb B, Simondon F, *et al.* Divergent mortality for male and female recipients of low-titer and high-titer measles vaccines in rural Senegal. *Am J Epidemiol* 1993;138:746-755
93. Desgrées du Loû A, Pison G, Aaby P. The role of immunizations in the recent decline in childhood mortality and the changes in the female/male mortality ratio in rural Senegal. *Am J Epidemiol* 1995;142:643-52
94. Shann F. The non-specific effects of vaccines. *Arch Dis Child* 2010;95:662-7
95. Welsh RM, Selin LH. No one is naïve: The significance of heterologous T-cell

- 1
2
3 immunity. *Nat Rev Immunol* 2002; 2: 417-426
4
5 96. Leuridan E, Hens N, Hutse V, *et al.* Early waning of maternal measles antibodies
6 in era of measles elimination: longitudinal study. *BMJ* 2010;340:c1626
7
8 97. Martins C. Measles vaccination in Guinea-Bissau. Strategies to reduce disease
9 burden and improve child survival. Copenhagen: University of Copenhagen, 2011
10 [PhD Thesis]
11
12 98. Moxon R, Nossal G, Heymann D, *et al.* The new decade of vaccines. Authors'
13 reply. *Lancet* 2012;379:27
14
15 99. Heymann DL, Fine PE, Griffiths UK, *et al.* Measles eradication: past is prologue.
16 *Lancet* 2010;376:1719-20
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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				
	Column 1	Column 2	Column 3	Column 4	Column 5	Column 6	Column 7	Column 8	Column 9	Column 10
	Cumulative measles incidence (%)	Seroconversion 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%

1
2
3
4
5 protection against measles. Hence, the estimated case fatality ratios are 8% for unvaccinated cases occurring in infancy and 1.33% for
6 vaccinated cases but there were fewer vaccinated cases than indicated in column 4.
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

For peer review only

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)*
<i>Bissau (43)¹</i>	<i>1980-82</i>	<i>PCS; urban (only secondary cases)</i>	<i>14%(3/21)</i>	<i>46%(11/24)</i>	<i>0.30 (0.10-0.86)*</i>
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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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.

For peer review only

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)

1
2
3 Sources: Reviews of measles case fatality studies (27-31) and PubMed search for
4 community studies of measles mortality/case fatality in infants or by age in Africa.
5 Notes: MV=measles vaccine; PCS=prospective community study, i.e. the population was
6 known before the epidemic and information is likely to have been obtained for all
7 children; SUR= retrospective survey; # The age grouping is 7-12 months and 12-120
8 months. Measles deaths and total number of children in age group were reported in this
9 study. It has been assumed that all children between 7 and 120 months contracted
10 measles. In this period there were no measles vaccinations available. The last epidemic
11 had occurred 12-13 years earlier; ## The age grouping is 0-8 and 9+ months; ∞ Numbers
12 read from a graph
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

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)	1 st vaccine in 2-dose group was Connaught HTMV and 2 nd dose was Schwarz standard MV
	9-36 months	2 nd vs 1 st 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	2 nd vs 1 st 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
<i>Early measles vaccination at 7 months of age compared with children unvaccinated community</i>			
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)
<i>Comparing MV at 4-8 months versus MV at 9-11 months of age</i>			
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)
<i>Comparing children randomised to MV at 6 months versus IPV at 6 months during a war situation</i>			
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 receive 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.

1
2
3
4 **The optimal age of measles immunization in low-income countries: A**
5 **secondary analysis of the assumptions underlying the current policy**
6
7

8 Peter Aaby^{1, 2}, Cesário L Martins¹, May-Lill Garly¹, Amabelia Rodrigues¹, Christine S
9 Benn^{1, 2}, Hilton C Whittle³
10
11

12
13
14 **1) Bandim Health Project, Indepth Network, Apartado 861, Bissau, Guinea-Bissau**

15 (CL Martins, clinician, PhD student, ML Garly, MD PhD, senior researcher, A
16 Rodrigues, PhD, research director, P Aaby, DMSc, professor). E-mail:
17 p.aaby@bandim.org
18
19
20
21

22
23 **2) Research Center for Vitamins and Vaccines (CVIVA), Bandim Health Project,**
24 **Danish Epidemiology Science Centre, Statens Serum Institut, Artillerivej 5, 2300**
25 **Copenhagen S, Denmark** (CS Benn, senior researcher, P Aaby, DMSc, professor)
26
27
28

29
30 **3) London School of Hygiene and Tropical Medicine, London, United Kingdom** (H
31 Whittle, F Med Sci, honorary professor)
32
33
34

35 Running title: Optimal age of measles vaccination

36
37 | Word counts: Abstract: ~~432300~~; Text: ~~6513380~~
38
39

40 Corresponding author: Peter Aaby, Bandim Health Project, Statens Serum Institut,
41 Artillerivej 5, 2300 Copenhagen S, Denmark
42
43

44 p.aaby@bandim.org
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

1
2
3 | **Supplementary Material**). The present analysis suggests that in retrospect all assumptions
4 were flawed. Had the policy been tested in randomised trials measuring the impact on
5 mortality of vaccination at different ages it is likely that the age of measles vaccination
6 had been changed, with the result that the measles vaccination programme would have
7 had a much larger effect on child survival in low-income countries.
8
9

10 **Methods**

11 **The optimal age of measles immunization: the underlying assumptions**

12 The recommendation was based on the belief that the expected reduction in mortality
13 could be computed from seroconversion rates (18,26) and the policy was justified several
14 times by analyses of the seroconversion data from Kenya (6,8). In these analyses it was
15 assumed that seroconversion was associated with full protection against measles infection
16 (*assumption 1*) and that non-seroconversion was associated with full susceptibility to
17 measles infection (*assumption 2*). As shown in Table 1 (Column 2), the data from Kenya
18 (21) showed that seroconversion increased with age. This was not unexpected since the
19 calculation of this measure (a fourfold or more increase over baseline) is dependent on
20 level of maternal antibody which wanes as the child ages. Based on cumulative measles
21 incidence figures (Column 1), it was calculated how many measles cases had been
22 prevented assuming everybody was vaccinated at a specific age (Column 3), how many
23 “vaccine failures” would occur after the age of vaccination (Column 4) and how many
24 cases would occur before the specific age of vaccination (Column 5). In making these
25 calculations it was assumed that “vaccine failures” and unvaccinated measles cases were
26 equally severe (*assumption 3*) and that it did not matter whether measles was acquired in
27 infancy or later in childhood (*assumption 4*). Vaccination at 8, 9, and 10 months of age
28 prevented roughly the same proportion of cases, between 79% and 84% (Column 3) (6,8).
29 Vaccination at 8 month resulted in considerably more vaccine failures (15%) than
30 vaccination at 9 months (7%). Since vaccine failures were assumed to jeopardize the
31 credibility of the measles immunization programme (*assumption 5*) (6,8,18), it was
32 concluded that the optimal age for administration of measles vaccine would be 9 months.
33 At the time the EPI assumed that the case fatality in measles infection was 4% in Africa
34 and it will be seen in Column 6 that the number of estimated measles deaths in a birth
35 cohort of a 1000 children would indeed be lowest (between 6.4 and 8.4) for vaccination at
36 8-10 months of age. In making this analysis of the effect of only one dose of measles
37 vaccine (6,8), the EPI assumed that a two-dose policy was not feasible or unjustified
38 (*assumption 6*).
39
40
41
42
43
44
45

46 **Selection of studies.** Following the identification of the underlying assumptions, we
47 looked for empirical evidence in community studies to support or refute their validity.
48 The original policy was mainly justified in relation to the epidemiology of measles
49 infection in Africa where the case fatality was clearly higher than in other regions (27-
50 31). Most community studies of measles infection are indeed from Africa and we have
51 therefore restricted the analyses and the tables 2-4 to the African studies. These tables are
52 believed to be exhaustive for Africa and they are not contradicted by community studies
53 from Latin America and Asia. For the analysis of the impact of measles vaccination on
54 child mortality we included all studies from Asia and Latin America.
55
56
57
58
59
60

1
2
3 | ~~The search strategy has been defined in the Supplementary Material.~~ Since there are few
4 specific studies to test the six assumptions we have had to use case reports of measles
5 outbreaks to assess their validity. Over the last 20-25 years, several reviews of
6 community studies of the measles case fatality compiled studies of relevance for
7 particularly assumption three and four (27-31), two of these being by the first author
8 (PA). For each assumption we used existing reviews and in December 2011 the first
9 author made a PubMed search for relevant papers as described below. The title and
10 abstract of papers in English, French, Portuguese, Spanish, German and Scandinavian
11 languages was assessed by the first author to ascertain whether the paper was potentially
12 relevant. Potentially relevant papers were read. Most papers were not from Africa but
13 were reviews or case reports and not community based studies and had no information on
14 mortality. Furthermore, as specified in the supplementary material, we made PubMed
15 searches for additional publications relevant for all assumptions. We included one
16 unpublished report from a large epidemic in Bissau in 1991-1992 which has remained
17 unpublished because the physician (Henning Andersen) handling the epidemic died
18 tragically in an accident shortly after the epidemic.
19
20
21
22
23

24 We distinguished between prospective community studies and surveys retrospectively
25 assessing events since the precision of information on vaccination status and age
26 presumably is better in prospective studies. Though hospital and health centre studies
27 may have data on the severity of measles infection by vaccination status or age, we have
28 not included these studies in the analysis since biased admission for some groups might
29 have made the result non-representative.
30
31
32

33 Since the analysis of the assumptions suggested that measles vaccination before 9 months
34 of age could be beneficial, we assessed the empirical evidence from studies which
35 assessed the effect of early measles vaccination on mortality. Again we used all reviews
36 of community studies and trials assessing the impact of measles vaccination on child
37 mortality (30,32-35). Additional PubMed searches for studies comparing the mortality of
38 measles vaccinated and unvaccinated children did not identify further studies. As
39 explained in the footnote to table 6, we have emphasised the studies in which inactivated
40 vaccines were not administered simultaneously with MV or after MV as such
41 combination or sequences can have a negative effect on child survival (34,36).
42
43
44

45 **Presentation.** For each assumption, we briefly outline the background. Next we present
46 the relevant studies found and then analyse the common trends, identifying the secondary
47 analyses which have been made. Finally, we considered whether methodological issues
48 and data quality might question the trends suggested by the analysis.
49
50

51 **Statistical analyses.** Based on cumulative measles incidence data we calculated how
52 many measles cases and measles death had been prevented assuming everybody was
53 vaccinated at a specific age, how many “vaccine failures” would occur after the age of
54 vaccination, and how many cases would occur before the specific age of vaccination. It
55 was estimated how this calculation was influenced by the empirical evidence for the
56 underlying assumptions. In the combined analyses of several studies we used the Mantel-
57
58
59
60

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

1
2
3 without having measurable antibodies (41). There is also good evidence from studies of
4 hepatitis B vaccination that antibody concentration wane with time but the majority of
5 older seronegative children if infected are protected from chronic carriage and its
6 damaging consequences (42).
7
8

9
10 The concept of seroconversion to compare the effect of vaccination at different age is in
11 itself problematic. Seroconversion is not the same as seroprotection and the use of the
12 term inevitably disadvantages data from studies that have vaccinated at earlier ages when
13 maternal antibodies are still present. Thus a child immunized at 6 months of age when the
14 maternal antibody level is say 62.5 mIU may fail the test for conversion (a four-fold
15 increase) yet still have a protective level of 125 mIU at 9 months of age.
16

17
18 If approximately half the seronegative children have clinical protection it would have
19 major consequences for the calculation of the optimal age of measles vaccine.
20

21 ***Assumption 3: severity of measles infection in vaccinated children (“vaccine failures”)***
22 ***and unvaccinated children is the same.***
23

24
25 *Background.* The EPI perceived “vaccine failures” as due to the vaccine being inactivated
26 by improper storage and handling or due to neutralization of the vaccine by maternal
27 antibodies (16,19). Hence, it was assumed that these children had been fully susceptible
28 to measles infection. However, many epidemiological studies in the 1980s and 1990s
29 suggested that measles vaccinated children who contracted measles infection had milder
30 disease (43,44). This would suggest that the children had partial measles immunity, not
31 enough to protect them but enough to modify the severity of the disease.
32
33

34 *Data:* We searched for “measles mortality vaccinated children” (N=143), “measles
35 vaccine mortality” (N=775), “measles case fatality” (N=161) and “measles vaccine
36 failure” (N=318 ~~Supplementary material~~). The 18 relevant studies are included in Tables 2
37 and 3.
38

39
40 *Analysis.* The community studies of the acute measles case fatality are shown in Table 2.
41 Only two African studies (43, 48) have reported significant differences in mortality for
42 vaccinated and unvaccinated measles cases. A combined analysis has not been made
43 previously. The measles case fatality was 2 to 5-fold lower for vaccinated cases (“vaccine
44 failures”) than for unvaccinated children with measles infection in nearly all studies.
45 Using MH weighted relative risk, the effect was similar in the prospective community
46 studies (case-fatality ratio=0.37 (0.27-0.52)) and the retrospective surveys (case-fatality
47 ratio=0.41 (0.29-0.56)).
48
49

50
51 A few studies followed the children for longer than one month which is the normal time
52 limit for acute measles deaths. The long-term trend was the same with considerable better
53 survival among vaccinated than unvaccinated children after measles infection (Table 3).
54 Combining the prospective community studies in Tables 2 and 3 would suggest a 3-fold
55 reduction in acute and/or long-term mortality among vaccinated children even though
56 some of the vaccine failures may have been due to inactivated measles vaccines.
57
58
59
60

1
2
3
4
5 In the four studies (38,47,56, unpublished) with information on both acute and long-term
6 mortality, mortality was nearly 5-fold lower for the vaccinated cases (MH weighted
7 mortality ratio= 0.21 (0.13-0.34)).
8

9
10 *Considerations.* Only two studies did not show lower case fatality among vaccinated
11 children and five of the 18 studies in Tables 2 and 3 showed significantly lower mortality
12 among vaccinated children.
13

14 All studies with relevant data were included in Tables 2 and 3 irrespective of whether
15 vaccine efficacy (VE) against measles infection was high or substandard. In several
16 studies, the VE was not high but nonetheless the vaccine appeared to have had an effect;
17 for example, in Kenya VE was only 18% but measles-vaccinated children who developed
18 measles had still 2-fold lower measles mortality than measles unvaccinated children
19 (Table 2). Only one community survey from Niger reported that measles vaccine was not
20 particularly effective against measles infection and that there was no effect of vaccination
21 on the case fatality in measles infection (53).
22
23

24
25 In most studies (Table 2), it was not possible to control for age given the way the data
26 was reported. However, in 6 studies (22, 43, 45, 47, 49, unpublished data) age could be
27 controlled. In these studies the crude MH weighted case-fatality ratio was 0.27 (0.17-
28 0.42); when the comparison was stratified by age group, the MH weighted case-fatality
29 ratio became 0.30 (0.18-0.49).
30
31

32 It could be speculated that vaccinated children had more health-system-compliant
33 mothers and that they therefore had more care and milder infection. However, in many of
34 the original studies from the 1980s, measles vaccine had been provided in community
35 campaigns and not in routine service and vaccination status depended on whether the
36 mother had been around at the time of the campaign and not on bias (43). In the studies
37 which adjusted for background factors, the differential effect of vaccination on the
38 measles case fatality was actually increased (43,48). Furthermore, several studies have
39 found that “vaccine failures” occur after high intensity of exposure, i.e. “vaccine failures”
40 are more likely to be secondary cases exposed at home (43,44). Since secondary cases
41 have a higher case fatality than index cases (43,44,62), the milder infection among
42 vaccinated children is even more surprising. The possibility that measles vaccinated
43 children have milder disease due to modified immune responses and not merely due to
44 social confounding is strengthened by the many studies showing that measles vaccination
45 is associated with beneficial effects on overall child survival (32,33).
46
47
48

49 Several hospital or health centre based studies have also compared vaccinated and
50 unvaccinated children and reported that measles vaccinated children had less severe
51 measles infection (57-59). A few community studies from India and Papua New Guinea
52 have also suggested lower case fatality for vaccinated measles cases (60,61).
53
54

55 If the severity of measles is not the same in vaccinated and unvaccinated children it
56 would strongly affect the estimated benefit of vaccinations at different ages.
57
58
59
60

1
2
3
4
5
6
7
Assumption 4: severity of measles is the same whether measles infection is acquired in infancy or later.

8
9
10
11
12
13
14
15
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.

16
17
18
19
20
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](#)).

21
22
23
24
25
26
27
28
29
30
31
32
33
34
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).

35
36
37
38
39
40
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.

41
42
43
44
45
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.

46
47
48
Assumption 5: vaccine failures lead to lack of credibility of the vaccination programme.

49
50
51
52
Background. Apparently it was assumed that African mothers – like physicians - would lose confidence if measles vaccine did not provide complete and life-long immunity.

53
54
55
56
57
58
59
60
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).

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

1
2
3 with or after measles vaccine has negative effects on female survival (34,36). We
4 therefore conducted a large randomized trial including only children who had received
5 DTP3 before enrolment and therefore would not receive DTP after MV (77). Among
6 children who had not received neonatal vitamin A supplementation (VAS) which
7 interacted negatively with early MV(76), two doses of MV at 4.5 and 9 months of age
8 compared with the current policy of one dose at 9 months of age reduced mortality
9 between 4.5 and 36 months of age by 50% (22-68%) in the per-protocol analysis (Table
10 5). There was a significant reduction in non-measles related mortality of 45% (14-65%)
11 (77). The combined estimate for the two trials showed that the early two-dose measles
12 vaccination strategy may reduce mortality by as much as 48% (23%-65%) compared with
13 the currently recommended standard dose at 9 months of age. Even if the children
14 receiving neonatal VAS were included, the combined estimate was 31% (9-48%) (Table
15 5).
16
17
18
19

20 The only other study to report mortality after two doses of MV is a natural experiment
21 from Guinea-Bissau in the early 1980s. Children were vaccinated in annual or biannual
22 campaigns rather than through routine service. Hence, it was possible to compare in an
23 unbiased way the survival of children who happened to be less than 9 months of age
24 when vaccinated and those vaccinated at the recommended age of 9-11 for MV. MV at 4-
25 8 months and a later dose after 9 months compared with one dose of MV at 9-11 months
26 of age was associated with 59% (15-81%) lower mortality between 9 months and 5 years
27 of age (78).
28
29

30 *Considerations.* The studies indicate that a two-dose policy providing the first dose of
31 MV before 9 months of age is associated with major reductions in child mortality
32 compared with the current one-dose at 9 month policy. The studies indicated that the
33 benefit was not due to better protection against measles infection. Hence, these studies
34 strongly supported that early measles vaccination has non-specific beneficial effects on
35 child survival.
36
37
38

39 **The implications of the assumptions for the estimated prevention of measles**
40 **mortality.** We calculated how variation in these six assumptions affect the optimal age of
41 MV in terms of reducing measles mortality (Table 1, Columns 7-10). Using the best
42 estimate that the case fatality rate is three-fold lower for vaccinated measles cases than
43 for unvaccinated cases (Tables 2 and 3), the number of estimated measles deaths would
44 have been lowest with one dose of MV at 8 months (Column 7). Assuming furthermore
45 that infants have two-fold higher case fatality than older children (Table 4) the estimated
46 number of measles deaths would have been lowest after vaccination at age 7 months
47 (Column 8). Hence, it might have been better to vaccinate at 7 months of age and have
48 some more vaccine failures later in childhood than to have many unvaccinated cases with
49 high mortality in infancy. Adjusting for the possibility that non-seroconverting vaccinated
50 children have some protection from cellular immunity or low levels of antibodies (37),
51 the optimal age for measles immunization in a one-dose strategy would have moved to 6
52 or 7 months of age (Columns 9 and 10).
53
54
55
56
57
58
59
60

1
2
3 The studies of two doses of MV suggest that both the first and the second dose of measles
4 vaccine are effective and that an early two-dose strategy would be associated with a
5 major reduction in measles and overall mortality (72-77,79). Hence, an early dose at 4-6
6 months of age and a second dose at 9 months of age would have eliminated virtually all
7 measles mortality and significantly reduced mortality from other causes as well.
8
9

10 Discussion

11 The main justification for measles vaccination at 9 months of age in low-income
12 countries was to reduce child mortality from measles infection (18). However, the policy
13 was never tested for its effect on survival. The policy was based on assumptions which
14 were believed to be true, and a small seroconversion study (6-8). Thirty-five years ago
15 the six assumptions appeared self-evident and programmatic decisions had to be taken
16 about the optimal age for measles vaccination. However, though all assumptions have
17 been contradicted for years no change has been made in the policy.
18
19

20 Strength and weaknesses

21 Since the six assumptions have not been research issues there are few studies conducted
22 specifically with these topics in mind. We have therefore had to use a search strategy
23 including review articles and case reports to find studies to assess the validity of the
24 original assumptions. There may be a few more studies which were not found with the
25 literature search since several of the studies identified in previous reviews were not found
26 by the search terms. However, many reviews over the last 25 years have covered the
27 areas of community studies of measles infection and the impact of MV on mortality so it
28 is unlikely that there would be many studies not included. Furthermore, the estimates
29 from different studies were consistent and it is unlikely that the addition of further studies
30 would have a major impact on the estimates.
31
32
33
34

35 The assumed case fatality of measles infection does not matter for the estimated impact
36 of the optimal policy on measles mortality. With another case fatality level the
37 epidemiological arguments about assumptions 2-4 would still have the same relative
38 effects on the number of deaths prevented. However, as evident in Tables 2 and 4, most
39 community studies from Africa suggest that the case fatality may have been higher than
40 4% and the impact of the optimal measles vaccination strategy on overall mortality may
41 therefore have been even larger. Other assumptions may also have been important; for
42 example, the incidence data were from a rural study rather than from an urban area (21).
43 In an urban area the incidence would have been higher at younger ages and it might have
44 been advantageous to vaccinate even earlier. As maternal measles antibody levels have
45 declined in low-income countries (78), earlier vaccination would also have produced
46 better seroconversion rates and it would have been even more advantageous to vaccinate
47 early.
48
49
50
51

52 **Consistency with previous studies: The non-specific beneficial effects of MV.** The
53 conclusion that earlier measles vaccination is likely to have been better for child survival
54 is based on a reconsideration of the programme's own assumptions about effect on
55 measles mortality. However, what is the empirical evidence for the impact on mortality of
56 measles vaccine before 9 months of age?
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

1
2
3 immune stimulation. Hence, standard measles vaccine may protect against other
4 infections and have a beneficial effect on child survival even when measles is eliminated.
5
6

7 Though the focus here has been on MV administered before 9 months of age there is also
8 a considerable number of studies indicating that MV administered after 9 months of age
9 have non-specific beneficial effects (32,81-86, 91, 94).
10

11 The possible biological explanations for non-specific beneficial effects of MV have not
12 been explored in humans. In animal studies of heterologous immunity, previous
13 stimulation with infections may have a major effect on the capacity to handle a lethal
14 dose of an unrelated infection (95). Two trials from Bissau suggest that the beneficial
15 effect of MV is better for children vaccinated in the presence of maternal measles
16 antibodies than for children having no measurable maternal antibodies at the time of MV
17 (89). This may also help explain why MV before 9 months of age is better than later
18 vaccination.
19
20
21

22 **The optimal age of measles vaccination: optimizing seroconversion or impact on**
23 **overall child survival.** The most unfortunate consequence of not testing the optimal age
24 of measles immunization may have been that the beneficial non-specific effects of MV
25 were not detected (32). To the extent MV has beneficial non-specific ~~beneficial~~ effects
26 the question of the optimal age of measles vaccination acquires a new meaning. By
27 lowering the age of measles vaccination, children would benefit not only from earlier
28 protection against measles infection but also from the beneficial non-specific effects
29 against non-measles infections and overall child mortality would be reduced. On the other
30 hand, if the age of vaccination is increased, children would benefit less from the
31 beneficial non-specific ~~beneficial~~ effects and overall child mortality would increase.
32 Hence, policies optimizing the non-specific effects clash with those designed to enhance
33 seroconversion.
34
35
36
37

38 **Conclusions: Old assumptions linger on**

39 The supplementary immunization activities (SIA) with measles vaccine has eliminated
40 measles infection in Latin America and reduced the incidence in major ways in the rest of
41 the world (1-3). The world is now planning to eliminate and eventually eradicate measles
42 infection (4). With the SIA success in measles control, the optimal age of measles
43 immunization is likely to be considered an irrelevant issue. However, as discussed above,
44 measles vaccine has also non-specific effects which need to be taken into consideration in
45 the planning of vaccination programmes. The prevention of all-cause mortality rather
46 than measles mortality should be the primary objective. In a culture which advocates
47 evidence-based policies (4), the evidence for the current measles vaccination policy – or
48 rather the lack thereof - should be properly reviewed and revised by the global and
49 regional immunization programmes. Otherwise old assumptions about seroconversion
50 rates being the basis for the optimal age of immunisation may linger on and continue to
51 influence policy.
52
53
54

55 There are major consequences of focusing solely on specific measles mortality. First, as
56 the current policy is mostly determined by our understanding that seroconversion gets
57
58
59
60

1
2
3 better with increasing age, the tendency will be that with improved control of measles
4 infection, age of vaccination will be increased. Following the elimination of measles in
5 Latin America, the recommended age of primary measles immunization was raised to 12
6 months in 1996 (3). Again this decision was based on assumptions and not on studies
7 documenting the overall effect on morbidity and mortality. Following the success of
8 measles campaigns in other continents it has also been recommended by SAGE (the
9 Strategic Advisory Group of Experts) to increase the age of measles vaccination to 12
10 months in areas with low levels of measles transmission (5,12). The underlying
11 assumption about better seroconversion at higher ages may no longer be valid with the
12 decline in maternal antibody levels (79,96). For example, we have obtained 100%
13 seropositivity and 99% protective levels after measles vaccine at 9 months of age with
14 both Schwarz and Edmonston-Zagreb measles vaccine strains in Guinea-Bissau (97).
15
16
17

18
19 However, the most important problem is that measles vaccine has major non-specific
20 beneficial effects and the earlier it is given, the earlier the children will benefit from this
21 advantage (11,32,38,76-80,89). There is a tendency to dismiss these observations because
22 randomised trials with overall mortality as an outcome have only been conducted in
23 Guinea-Bissau and it is therefore claimed that the global health community has to wait
24 for verification elsewhere (98). However, the beneficial non-specific ~~beneficial~~ effects of
25 MV have been shown in several other countries with high childhood mortality. For
26 example, in a cross-over design, Shann showed that girls receiving standard measles
27 vaccine at 9-10 months of age in five randomised trials in Sudan, Gambia, Senegal and
28 Guinea-Bissau had 47% lower mortality through childhood than control children who
29 received an inactivated vaccine at 9-10 months of age (94). Since the control children had
30 received MV before 9 months of age and did not get measles, the difference in mortality
31 following MV at 9 months of age was a beneficial non-specific ~~beneficial~~ effect not
32 related to prevention of measles infection. Increasing the age of measles vaccine from 9
33 to 12 months may reduce the beneficial effects in the age group between 9 and 12 months
34 of age in which mortality is still high. Thus the lives lost by this change of schedule could
35 well be more than the lives saved by improved measles control (77).
36
37
38
39

40 Second, in the current paradigm for control of infectious diseases, the ultimate success in
41 public health is to eradicate the disease and then remove the vaccine to reduce economic
42 costs as happened for smallpox in the 1970s (26). This may happen for measles infection
43 within the next 10-20 years (99). If measles vaccine has major beneficial non-specific
44 effects (77), to remove measles vaccine or reduce its coverage would increase child
45 mortality levels considerably in low-income countries unless we in the meantime find a
46 vaccine which has all the same beneficial effects as measles vaccine.
47
48

49 After 35 years, it is time to develop a policy for the optimal age of measles immunization.
50 This policy needs to be based on evidence about the impact on overall health and child-
51 survival and not only on assumptions about the impact of specific prevention against
52 measles infection. A two-dose measles vaccination strategy, providing measles vaccine at
53 4.5 months of age, after the three DTP vaccines, and again at 9 months of age, may
54 significantly improve child survival and provide a solid basis of immunity which if
55 necessary can be enhanced by supplementary measles immunisation activities at a later
56
57
58
59
60

1
2
3 age (77,79). Any future changes in the age of measles immunisation due to elimination of
4 measles infection, changes in the epidemiology of measles infection, decline in maternal
5 antibody levels, introduction of new measles vaccines or in the timing of other vaccines
6 should be tested in trials to determine their overall impact on child health.
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

1
2
3 **Contributions:** PA and HW have been involved in studies of measles vaccination for
4 more than 30 years in West Africa; MLG, CM, CB and AR have been involved in
5 measles vaccination trials since the early 1990s. The first draft was written by PA; all
6 authors contributed to the final version of the paper. PA will act as guarantor of the study.
7
8

9
10 **Conflict of interest:** nothing to declare
11

12 **Funding:** The Bandim Health Project received support from DANIDA and the Danish
13 National Research Foundation. PA holds a research professorship grant from the Novo
14 Nordisk Foundation. We received no funding specifically for the present study.
15
16

17 **Independence:** The funders had no role in the study design, data collection, data
18 analysis, data interpretation, decision to publish or preparation of the manuscript.
19

20 **Data sharing:** no additional data available
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

References

1. De Quadros CA, Olive JM, Hersh BS, Strassburg MA, Henderson DA, Bandling-Bennett D, Alleyne GA. Measles elimination in the Americas. Evolving strategies. *JAMA* 1996; 275: 224-29
2. Otten M, Kezaala R, Fall A, Masresha B, Martin R, Cairns L, Eggers R, Biellik R, Grabowsky M, Strebel P, Okwo-Bele JM, Nshimirimana. Public-health impact of accelerated measles control in the WHO African Region 2000-03. *Lancet* 2005;366:832-9
3. De Quadros CA, Izurieta H, Venczel L, Carrasco P. Measles eradication in the Americas : Progress to date. *JID* 2004 ;189 (Suppl 1) : S227
4. Department of immunization, vaccines and biologicals: Strategic Plan 2010-15. Draft 24 March 2010, World Health Organization
5. Measles vaccines: WHO position paper. *Week Epid Rec* 2009;84:349-60
6. Expanded Programme on Immunization. Measles immunization. *Weekly Epidemiol Rec* 1979;54:337-9
7. Expanded Programme on Immunization. Global advisory group Meeting. *Weekly Epidemiol Rec* 1981;56:9-16
8. Expanded Programme on Immunization. The optimal age for measles immunization. *Weekly Epidemiol Rec* 1982;57:89-91
9. Hendrickse RG. Problems of future measles vaccination in developing countries. *Trans R Soc Trop Med Hyg* 1975;69:31-34
10. Mosley WH. Will primary health care reduce infant and child mortality? A critique of some current strategies. With special reference to Africa and Asia. In: Lopez AD, Vallin J (eds): *Health policy, social policy and mortality prospects*. Liege: Ordina, 1985;pp 103-37
11. The Kasongo Project Team. Influence of measles vaccination on survival pattern of 7-35-month-old children in Kasongo, Zaire. *Lancet* 1981;i:764-7
12. Meeting of the immunization Strategic Advisory Group of experts, November 2006 – conclusions and recommendations. *Weekly Epidemiol Rec* 2007;82:1-16
13. Foege WH. Measles vaccination in Africa. *Sci Pub PAHO* 1971;228:207-12
14. McBean AM, Foster SO, Herrmann KL, Gateff. Evaluation of mass measles immunisation campaign in Yaoundé, Cameroun. *Trans Roy Soc Trop Med Hyg* 1976;70:206-12
15. Guyer B, McBean AM. The epidemiology and control of measles in Yaoundé, Cameroun, 1968-1975. *Int J Epidemiol* 1981;10:263-9
16. Grigsby ME, Adetosoye JIA. Measles epidemiology and control in Western Nigeria. *J Nat Med Ass* 1973;65:378-85
17. Foster SO, Pifer JM. Mass measles control in West and central Africa. *Afr J Med Sci* 1971;2:151-8
18. Henderson RH. Measles vaccination in Zaire – when and how? *Trans Roy Soc Trop Med Hyg* 1981;75:128-9
19. Wood PB, Soheranda KS, Bracken PM, Houser NE. Measles vaccination in Zaire – when and how? *Trans Roy Soc Trop Med Hyg* 1980;74:381-2
20. Lapeyssonnie L, Omer LA, Nicolas A, Roumiantzeff M. Etude de la réponse serologique d'enfant soudanais a la vaccination combinee triple (rougeole, tetanos, meningite A). *Med Trop* 1979;39:71-9

21. Collaborative study by the Ministry of Health of Kenya and the World Health Organisation. Measles immunity in the first year after birth and the optimum age for vaccination in Kenyan children. *Bull WHO* 1977;55:21- 31
22. Burström B, Aaby P, Mutie DM, Kimani G, Bjerregaard P. Severe measles outbreak in Western Kenya. *East Afr Med J* 1992; 69:419-423
23. Seroconversion rates and measles antibody titers induced by measles vaccine in Latin American children aged 6-12 months of age. Collaborative study by the Ministries of Health of Brazil, Chile, Costa Rica, Ecuador, and the Pan American Health Organization. *Bull Pan Am Health Organ* 1982;16:272-85
24. Rosenthal SR, Clements CJ. Two-dose measles vaccination schedules. *Bull WHO* 1993;71:421-8
25. Rolfe M. Measles immunization in the Zambian Copperbelt: cause for concern. *Trans Roy Soc Trop Med Hyg* 1982;76:529-30
26. Lancet. Rationalising measles vaccination. *The Lancet* 1981;ii:236-7
27. Aaby P. Malnutrition and overcrowding/intensive exposure in severe measles infection: review of community studies. *Rev Infect Dis* 1988;10:478-491
28. Aaby P, Clements J, Orinda V Mortality from measles: measuring the impact. Geneva 1991: EPI, WHO
29. Wolfson LJ, Grais RF, Luquero FJ, Birmingham ME, Strebel PM. Estimates of measles case fatality ratios: a comprehensive review of community-based studies. *Int J Epidemiol* 2009;38:192-205
30. Sudfeld CR, Navar AM, Halsey NA. Effectiveness of measles vaccination and vitamin A treatment. *Int J Epidemiol* 2010;39:i48-i55
31. Kouadio IK, Kamigaki T, Oshitani H. Measles outbreaks in displaced populations: a review of transmission, morbidity and mortality associated risk factors. *BMC Int Hlth Hum Rights* 2010;10:5
32. Aaby P, Samb B, Simondon F, Coll Seck AM, Knudsen K, et al. Non-specific beneficial effect of measles immunisation: analysis of mortality studies from developing countries. *Br Med J* 1995;311:481-485
33. Garly ML, Aaby P. The challenge of improving the efficacy of measles vaccine. *Acta Trop* 2003;85:1-17
34. Aaby P, Jensen H, Samb B, Cisse B, Sodeman M, et al. Differences in female-male mortality after high-titre measles vaccine and association with subsequent vaccination with diphtheria-tetanus-pertussis and inactivated poliovirus: reanalysis of West African studies. *Lancet* 2003;361: 2183-88
35. Knudsen KM, Aaby P, Whittle H, Rowe M, Samb B, et al. Child mortality following standard, medium or high titre measles immunization in West Africa. *Int J Epidemiol* 1996;25:665-73
36. Aaby P, Garly ML, Nielsen J, Ravn H, Martins C, Balé C, et al. Increased female-male mortality ratio associated with inactivated polio and diphtheria-tetanus-pertussis vaccines: Observations from vaccination trials in Guinea-Bissau. *Pediatr Infect Dis J* 2007;26:247-52.
37. Samb B, Aaby P, Whittle H, Coll Seck AM, Rahman S, et al. Serological status and measles attack rates among vaccinated and unvaccinated children in rural Senegal. *Pediatr Inf Dis J* 1995;14:203-9
38. Aaby P, Pedersen IR, Knudsen K, da Silva MC, Mordhorst CH, et al. Child

- mortality related to seroconversion or lack of seroconversion after measles vaccination. *Pediatr Infect Dis J* 1989;8:197-200
39. Hirose M, Hidaka Y, Miyazaki C, Ueda K, Yoshikawa H. Five cases of measles secondary vaccine failure with confirmed seroconversion after live measles vaccination. *Scand J Inf Dis* 1997;29:187-90
40. Samb B, Aaby P, Whittle H, Seck AW, Simondon F. Protective efficacy of high-titre measles vaccines administered from the age of five months: a community study in rural Senegal. *Trans Roy Soc Trop Med Hyg* 1993;87:697-701
41. Siegrist CA, Barrios C, Martinez X, Brandt C, Berney M, et al. Influence of maternal antibodies on vaccine responses: inhibition of antibody but not T cell responses allows successful early prime-boost strategies in mice. *Eur J Immunol* 1998;28:4138-48
42. van der Sande MA, Waight P, Mendy M, Rayco-Solon P, Hutt P, et al. Long-term protection against carriage of hepatitis B virus after infant vaccination. *J Infect Dis* 2006;193:1528-35
43. Aaby P, Bukh J, Leerhøy J, Lisse IM, Mordhorst CH, et al. Vaccinated children get milder measles infection: a community study from Guinea-Bissau. *J Infect Dis* 1986;154:858-63
44. Samb B, Aaby P, Whittle H, Seck AM, Simondon F. Decline in measles case fatality ratio after the introduction of measles immunization in rural Senegal. *Am J Epidemiol* 1997;145:51-7
45. Aaby P, Bukh J, Lisse IM, da Silva CM. Decline in measles mortality: nutrition, age at infection, or exposure? *Br Med J* 1988;296:1225-1228
46. Aaby P, Knudsen K, Jensen TG, Thaarup J, Poulsen A, et al. Measles incidence, vaccine efficacy, and mortality in two urban African areas with high vaccination coverage. *J Infect Dis* 1990;162:1043-1048
47. Aaby P, Whittle H, Cisse B, Samb B, Jensen H, et al. The frailty hypothesis revisited: mainly weak children die of measles. *Vaccine* 2001;20:949-53
48. Dollimore N, Cutts F, Binka FN, Ross DA, Morris SS, et al. Measles incidence, case fatality, and delayed mortality in children with or without vitamin A supplementation in rural Ghana. *Am J Epidemiol* 1997;146:646-654
49. Burström B, Aaby P, Mutie DM. Child mortality impact of a measles outbreak in a partially vaccinated rural African community. *Scand J Infect Dis* 1993;25:763-9
50. Ndikuyeze A, Cook A, Cutts FT, Bennett S. Priorities in global measles control: report of an outbreak in N'djamena, Chad. *Epidemiol Infect* 1995;115:309-14
51. Grais RF, Dubray C, Gersti S, Guthmann JP, Djibo A, et al. Unacceptably high mortality related to measles epidemics in Niger, Nigeria, and Chad. *PLoS Med* 2007;4:e16
52. Coronado F, Musa N, Tayeb ESAE, Haithami S, Dabbagh A, et al. Restrospective measles outbreak investigation: Sudan, 2004. *J Trop Pediatr* 2006;52:329-34
53. Expanded Programme on Immunization. High measles case-fatality during an outbreak in a rural area. *Weekly Epidemiol Rec* 1993;68:142-5
54. Marufu T, Siziya S, Tshimanga M, Murugasampillay S, Mason E, et al. Factors associated with measles complications in Gweru, Zimbabwe. *East Afr Med J* 2001;78:135-8
55. Aaby P, Lisse I, Mølbak K, Knudsen K, Whittle H. No persistent T lymphocyte

- immunosuppression or increased mortality after measles infection: a community study from Guinea-Bissau. *Pediatr Inf Dis J* 1996;5:39-44
56. Chen RT, Weierbach R, Bisoffi Z, Cutts F, Rhodes P, et al. A 'Post-honeymoon period' measles outbreak in Mayinga Sector, Burundi. *Int J Epidemiol* 1994;23:185-93
57. Nsungu M. Measles vaccination status, delay in recognizing measles outbreaks and outbreak outcome. *Cent Afr J Med* 1995;41:336-9
58. Oshitani H, Mpabalwani M, Kosolo F, Mizuta K, Luo NP, et al. Measles infection in hospitalized children in Lusaka, Zambia. *Ann Trop Pediatr* 1995;15:167-72
59. Yamaguchi S, Dunga A, Broadhead RL, Brabin BJ. Epidemiology of measles in Blantyre, Malawi: analyses of passive surveillance data from 1996 to 1998. *Epidemiol Infect* 2002;129:361-9
60. Mishra A, Mishra S, Lahariya C, Jain P, Bhadoriya RS, et al. Practical observations from an epidemiological investigation of a measles outbreak in a district of India. *Ind J Comm Med* 2009;34:117-21
61. Mgone JM, Mgone CS, Duke T, Frank D, Yeka W. Control measures and the outcome of the measles epidemic of 1999 in the Eastern Highlands Province. *PNG Med J* 2000;43:91-7
62. Aaby P, Bukh J, Lisse IM, Smits AJ. Overcrowding and intensive exposure as determinants of measles mortality. *Am J Epidemiol* 1984;120:49-63
63. McGregor IA. Measles and child mortality in the Gambia. *West Afr Med J* 1964;25:1-7
64. Aaby P, Bukh J, Lisse IM, Smits AJ, Gomes J, et al. Determinants of measles mortality in a rural area of Guinea-Bissau: Crowding, age, and malnutrition. *J Trop Pediatr* 1984;30:164-68
65. Muller AS, Voorhoeve AM, 't Mannelje W, Schulpden TWJ. The impact of measles in a rural area of Kenya. *East Afr med J* 1977;54:364-72
66. Aaby P, Bukh J, Lisse IM, da Silva CM. Measles mortality: Further community studies on the role of overcrowding and intensive exposure. *Rev Infect Dis* 1988;10:474-477
67. Nandy R, Handzel T, Zaneidou M, Biey J, Cuddy RZ, et al. Case-fatality rate during a measles outbreak in Eastern Niger in 2003. *Clin Inf Dis* 2006;42:322-8
68. Hull HF, Williams PJ, Oldfield F. Measles mortality and vaccine efficacy in rural West Africa. *Lancet* 1983;i:972-5
69. Burström B, Aaby P, Maitie DM. Measles in infancy: A review of studies of incidence, vaccine efficacy and mortality in East Africa. *East Afr Med J* 1993;72:155-61
70. Mandara MP, Remme J. Current measles control in Tanzania. *Rev inf Dis* 1983;5:554-7
71. Heymann DL, Mayben GK, Murphy KR, Guyer B, Foster SO. Measles control in Yaounde: Justification of a one dose, nine month minimum age vaccination policy in tropical Africa. *Lancet* 1983;ii:1470-2
72. Garly ML, Martins CL, Balé C, da Costa F, Dias F, et al. Early two-dose measles vaccination schedule in Guinea-Bissau: good protection and coverage in infancy. *Int J Epidemiol* 1999;28:347-52
73. Kaninda AV, Legros D, Jataou IM, Malfait P, Maisonneuve M, Paquet C, Moren A.

- 1
2
3 Measles vaccine effectiveness in standard and early immunization strategies, Niger,
4 1995. *Pediatr Inf Dis J* 1998;7:1034-9
- 5
6 74. Phadke MA, Bhargava I, Dhaigude P, Bagade A, Biniwale MA, et al. Efficacy of
7 two dose measles vaccination in a community setting. *Ind Pediatr* 1998;35:723-5
- 8
9 75. Al-Mazrou YY, Al-Jeffri M, Ahmed OMM, Aziz KMS, Mishkas AH. Measles
10 immunization: Early two-doses policy experience. *J Trop Pediatr* 1999;45:98-104
- 11
12 76. Aaby P, Ibrahim S, Libman M, Jensen H. The sequence of vaccinations and
13 increased female mortality after high-titre measles vaccine: trials from rural
14 Sudan and Kinshasa. *Vaccine* 2006;24:2764-71
- 15
16 77. Aaby P, Martins CL, Garly ML, Bale C, Andersen A, Rodrigues A, Ravn H, Lisse
17 IM, Benn CS, Whittle H. Non-specific effects of standard measles vaccine at 4.5
18 and 9 months of age on childhood mortality: Randomised controlled trial. *BMJ*
19 2010;341:c6495
- 20
21 78. Aaby P, Andersen M, Sodemann M, Jakobsen M, Gomes J, et al. Reduced
22 childhood mortality after standard measles vaccination at 4-8 months compared
23 with 9-11 months of age. *BMJ* 1993;307:1308-1311
- 24
25 79. Martins CL, Garly ML, Balé C, Rodrigues A, Ravn H, Whittle HC, Lisse IM,
26 Aaby P. Protective efficacy of standard Edmonston-Zagreb measles vaccination in
27 infants aged 4.5 months: interim analysis of a randomised clinical trial. *BMJ*
28 2008;337:a661
- 29
30 80. Aaby P, Garly ML, Balé C, Martins C, Jensen H, et al. Survival of previously
31 measles-vaccinated and measles-unvaccinated children in an emergency situation:
32 an unplanned study. *Pediatr Inf Dis J* 2003;22:798-805
- 33
34 81. Garenne M, Cantrelle P. Rougeole e mortalité au Sénégal : étude de l'impact de la
35 vaccination effectuée à Khombole 1965-1968 sur la survie des enfants. In :
36 Cantrelle P, Dormont S, Fargues P, Goujard J, Guignard J, Rumeau-Rouquette C
37 (eds) : Estimation de la mortalité de jeune enfant (0-5 ans) pour guider les actions
38 de santé dans les pays en développement. Paris : INSERM, 1986 ;145:515-32
- 39
40 82. Aaby P, Bukh J, Lisse IM, Smits AJ. Measles vaccination and reduction in child
41 mortality: a community study from Guinea-Bissau. *J Infect* 1984;8:13-21
- 42
43 83. Velema JP, Alihonou EJ, Gandaho T, Hounye FH. Childhood mortality among
44 users and non- users of primary health care in a rural West African community.
45 *Int J Epidemiol* 1991;20:474- 479
- 46
47 84. Holt EA, Boulos R, Halsey NA, Boulos LM, Boulos C. Childhood survival in
48 Haiti: protective effect of measles vaccination. *Pediatrics* 1990;86:188-94
- 49
50 85. George K, Josph A, Muliyl J, Abraham S, Bhattacharji S, John KR. Measles
51 vaccination before nine months. *Trop Med Int Hlth* 1998;3:751-6
- 52
53 86. Kristensen I, Aaby P, Jensen H. Routine vaccinations and child survival: follow
54 up study in Guinea-Bissau, West Africa. *BMJ* 2000;321:1435-8
- 55
56 87. Lehmann D, Vail J, Firth MJ, de Klerk NH, Alpers MP. Benefits of routine
57 immunisations on childhood survival in Tari, Southern Highlands Province, Papua
58 New Guinea. *Int J Epidemiol* 2004, 10.1093/ije/dyh262
- 59
60 88. Elguero E, Simondon F, Simondon K, Vaugelade J. Non-specific effects of
vaccination on survival: a prospective study in Senegal. *Trop Med Int Health*
2005;10:956-960
89. Aaby P, Martins CL, Garly ML, Andersen A, Fisker AB, Claesson MH, Ravn H,

- Rodrigues A, Whittle HC, Benn CS. Measles vaccination in presence of maternal antibodies may increase child survival (submitted)
90. de Quadros CA. Can measles be eradicated globally? *Bull WHO* 2004;82:134-8
91. Aaby P, Bhuyia A, Nahar L, Knudsen K, Francisco A, et al. The survival benefit of measles immunization may not be explained entirely by the prevention of measles disease: a community study from rural Bangladesh. *Int J Epidemiol* 2003;32: 106-115
92. Aaby P, Samb B, Simondon F, Knudsen K, Seck AM, et al. Divergent mortality for male and female recipients of low-titer and high-titer measles vaccines in rural Senegal. *Am J Epidemiol* 1993;138:746-755
93. Desgrées du Loû A, Pison G, Aaby P. The role of immunizations in the recent decline in childhood mortality and the changes in the female/male mortality ratio in rural Senegal. *Am J Epidemiol* 1995;142:643-52
94. Shann F. The non-specific effects of vaccines. *Arch Dis Child* 2010;95:662-7
95. Welsh RM, Selin LH. No one is naïve: The significance of heterologous T-cell immunity. *Nat Rev Immunol* 2002; 2: 417-426
96. Leuridan E, Hens N, Hutse V, Ieven M, Aerts M, et al. Early waning of maternal measles antibodies in era of measles elimination: longitudinal study. *BMJ* 2010;340:c1626
97. Martins C. Measles vaccination in Guinea-Bissau. Strategies to reduce disease burden and improve child survival. Copenhagen: University of Copenhagen, 2011 [PhD Thesis]
98. Moxon R, Nossal G, Heymann D, Plotkin S, Levine O. The new decade of vaccines. Authors' reply. *Lancet* 2012;379:27
99. Heymann DL, Fine PE, Griffiths UK, Hall AJ, Mounier-Jack S. Measles eradication: past is prologue. *Lancet* 2010;376:1719-20

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				
	Column 1	Column 2	Column 3	Column 4	Column 5	Column 6	Column 7	Column 8	Column 9	Column 10
	Cumulative measles incidence (%)	Seroconversion 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%

1
2
3
4
5 protection against measles. Hence, the estimated case fatality ratios are 8% for unvaccinated cases occurring in infancy and 1.33% for
6 vaccinated cases but there were fewer vaccinated cases than indicated in column 4.
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

For peer review only

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)*
<i>Bissau (43)¹</i>	<i>1980-82</i>	<i>PCS; urban (only secondary cases)</i>	<i>14%(3/21)</i>	<i>46%(11/24)</i>	<i>0.30 (0.10-0.86)*</i>
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

1
2
3 vaccinated was reported among all cases. It has been assumed that the proportion
4 vaccinated cases was the same among those with follow-up as among all cases.
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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)

1
2
3 Sources: Reviews of measles case fatality studies (27-31) and PubMed search for
4 community studies of measles mortality/case fatality in infants or by age in Africa (see
5 [Supplementary material](#)).

6
7 Notes: MV=measles vaccine; PCS=prospective community study, i.e. the population was
8 known before the epidemic and information is likely to have been obtained for all
9 children; SUR= retrospective survey; # The age grouping is 7-12 months and 12-120
10 months. Measles deaths and total number of children in age group were reported in this
11 study. It has been assumed that all children between 7 and 120 months contracted
12 measles. In this period there were no measles vaccinations available. The last epidemic
13 had occurred 12-13 years earlier; ## The age grouping is 0-8 and 9+ months; ∞ Numbers
14 read from a graph
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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)	1 st vaccine in 2-dose group was Connaught HTMV and 2 nd dose was Schwarz standard MV
	9-36 months	2 nd vs 1 st 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	2 nd vs 1 st 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
<i>Early measles vaccination at 7 months of age compared with children unvaccinated community</i>			
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)
<i>Comparing MV at 4-8 months versus MV at 9-11 months of age</i>			
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)
<i>Comparing children randomised to MV at 6 months versus IPV at 6 months during a war situation</i>			
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 receive 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



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
----------------------	----	---	---

Page 1 of 2

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