

LONDON
SCHOOL of
HYGIENE
& TROPICAL
MEDICINE



LSHTM Research Online

Aaby, P; Martins, CL; Garly, ML; Andersen, A; Fisker, AB; Claesson, MH; Ravn, H; Rodrigues, A; Whittle, HC; Benn, CS; (2014) Measles vaccination in the presence or absence of maternal measles antibody: Impact on child survival. *Clinical infectious diseases*. ISSN 1058-4838 DOI: <https://doi.org/10.1093/cid/ciu354>

Downloaded from: <http://researchonline.lshtm.ac.uk/1726167/>

DOI: <https://doi.org/10.1093/cid/ciu354>

Usage Guidelines:

Please refer to usage guidelines at <http://researchonline.lshtm.ac.uk/policies.html> or alternatively contact researchonline@lshtm.ac.uk.

Available under license: <http://creativecommons.org/licenses/by-nc-nd/2.5/>

<https://researchonline.lshtm.ac.uk>

Measles Vaccination in the Presence or Absence of Maternal Measles Antibody: Impact on Child Survival

Peter Aaby,^{1,2} Cesário L. Martins,¹ May-Lill Garly,¹ Andreas Andersen,^{1,2} Ane B. Fisker,¹ Mogens H. Claesson,³ Henrik Ravn,² Amabelia Rodrigues,¹ Hilton C. Whittle,⁴ and Christine S. Benn^{1,2}

¹Bandim Health Project, Indepth Network, Bissau, Guinea-Bissau; ²Research Centre for Vitamins and Vaccines, Bandim Health Project, Statens Serum Institut, Copenhagen, and ³Institute of International Health, Immunology and Microbiology, Faculty of Health Sciences, University of Copenhagen, Denmark; and ⁴London School of Hygiene and Tropical Medicine, United Kingdom

Background. Measles vaccine (MV) has a greater effect on child survival when administered in early infancy, when maternal antibody may still be present.

Methods. To test whether MV has a greater effect on overall survival if given in the presence of maternal measles antibody, we reanalyzed data from 2 previously published randomized trials of a 2-dose schedule with MV given at 4–6 months and at 9 months of age. In both trials antibody levels had been measured before early measles vaccination.

Results. In trial I (1993–1995), the mortality rate was 0.0 per 1000 person-years among children vaccinated with MV in the presence of maternal antibody and 32.3 per 1000 person-years without maternal antibody (mortality rate ratio [MRR], 0.0; 95% confidence interval [CI], 0–.52). In trial II (2003–2007), the mortality rate was 4.2 per 1000 person-years among children vaccinated in presence of maternal measles antibody and 14.5 per 1000 person-years without measles antibody (MRR, 0.29; 95% CI, .09–.91). Possible confounding factors did not explain the difference. In a combined analysis, children who had measles antibody detected when they received their first dose of MV at 4–6 months of age had lower mortality than children with no maternal antibody, the MRR being 0.22 (95% CI, .07–.64) between 4–6 months and 5 years.

Conclusions. Child mortality in low-income countries may be reduced by vaccinating against measles in the presence of maternal antibody, using a 2-dose schedule with the first dose at 4–6 months (earlier than currently recommended) and a booster dose at 9–12 months of age.

Clinical Trials Registration. NCT00168558.

Keywords. maternal measles antibodies; age of measles vaccination; nonspecific beneficial effects of measles vaccine; 2-dose measles vaccination.

The primary effect of measles vaccination on child survival is assumed to be induction of measles antibody and cellular immunity to prevent measles infection

and related deaths. Hence, the effect on child survival should be proportional to measles vaccine (MV) efficacy [1]. Although measles vaccination in the presence of maternal antibody may induce cellular immune responses to measles, the antibody response is not optimal [2]. It is therefore considered better to provide MV when maternal antibody has waned at 12 months of age or later [3]. To prevent outbreaks in high-incidence areas, the World Health Organization (WHO) recommends MV at 9 months of age in low-income countries [1]. When measles control improves, MV can be delayed to 12 months of age to obtain greater antibody responses [4], as happened in Latin America in 1996 [3].

Received 18 February 2014; accepted 29 April 2014; electronically published 14 May 2014.

Correspondence: Peter Aaby, DMSc, Bandim Health Project, Statens Serum Institut, Artillerivej 5, 2300 Copenhagen S, Denmark (p.aaby@bandim.org).

Clinical Infectious Diseases 2014;59(4):484–92

© The Author 2014. Published by Oxford University Press on behalf of the Infectious Diseases Society of America. This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs licence (<http://creativecommons.org/licenses/by-nc-nd/4.0/>), which permits non-commercial reproduction and distribution of the work, in any medium, provided the original work is not altered or transformed in any way, and that the work properly cited. For commercial re-use, please contact journals.permissions@oup.com.

DOI: 10.1093/cid/ciu354

This policy ignores that MV may have nonspecific beneficial effects on child survival [5–10]. Many observational studies and randomized trials have shown that MV reduces mortality from nonmeasles infections; furthermore, MV reduces the risk of hospital admission for lower respiratory infections [11, 12]. The nonspecific effects are strongest when children are vaccinated early [6–10, 13]. A recent randomized trial tested MV at 4.5 months of age in addition to the recommended vaccination at 9 months of age [5]. Children receiving 2 doses of MV (per-protocol analysis) had 30% (95% confidence interval [CI], 6%–48%) lower mortality between 4.5 and 36 months of age compared with children who followed the normal schedule and received 1 dose at age 9 months. The reduction was 26% (95% CI, 0–45%) when measles cases were censored [5]. Hence, even though many children may have maternal measles antibody at 4–5 months, early MV had a marked effect on survival.

We therefore tested the hypothesis that MV in the presence of maternal measles antibody may enhance the beneficial nonspecific effect on child survival.

METHODS

We reanalyzed data from 2 trials conducted at Bandim Health Project (www.bandim.org) in Guinea-Bissau. In both trials, children were randomized to receive an extra dose of MV at 4–6 months of age in addition to MV at 9 months of age.

Trial I: Early 2-Dose MV and Vitamin A Trial, 1993–1995

In 1993–1995, we enrolled 300 children in the districts Belem and Mindara. The trial examined a 2-dose MV schedule at 6 and 9 months of age compared with 1 dose at 9 months [14]. The control group received inactivated polio vaccine (IPV) at enrollment. The children were also randomized to vitamin A supplementation (VAS) or placebo at 6 and 9 months of age to examine whether VAS enhanced the antibody response to MV. Children with a history of prior measles infection were excluded from the trial. All children had measles antibody assessed at 6 and 18 months of age. In 2000, follow-up was conducted to examine long-term effects of VAS on measles antibody level [15]. The present analysis of survival until 5 years of age is based on the 2000 follow-up. Verbal autopsies were not conducted.

Trial II: Early 2-Dose Trial, 2003–2007

In a recent trial [5], we enrolled children at 4.5 months of age at least 4 weeks after the third dose of diphtheria-tetanus-pertussis vaccine (DTP). Children were randomized to receive either standard-dose Edmonston-Zagreb MV at 4.5 and 9 months of age, or no vaccine at 4.5 months and Edmonston-Zagreb or Schwarz MV at 9 months of age. Between March and October 2004, we measured prevaccination measles antibody in 450

children randomized to MV at 4.5 months; we also measured the antibody levels of their mothers [16]. Antibody samples were not collected from the control group. Children have now been followed to 5 years of age.

Measles Antibody Assay

The antibody level was measured with the hemagglutination inhibition (HAI) test [11, 17]. The HAI assay used a local standard calibrated against WHO's International Reference serum [17]. The HAI assay assesses protection to clinical infection as well as the plaque neutralizing assay [18]. With a 1:2 starting dilution, the minimum detectable level of measles antibody was 31.2 mIU, and the sensitivity of the assay was 15.6 mIU.

Role of Early Life Exposure to Measles Infection

Children exposed to measles infection in the first 6 months of life may have increased child mortality [19, 20]. Hence, children with particularly high prevaccination antibody may have had subclinical measles infection and be at higher risk of dying. This would confound the assessment of possible beneficial effect of receiving MV in presence of maternal antibody. There is no way of knowing whether prevaccination antibody is maternal or due to measles infection, except that maternal antibody will be in the lower range and antibody due to exposure will be in the higher range. In trial II we also tested the measles antibody of 431 mothers of the 450 children. Children with the same or higher level than their mother at 4–5 months of age would have had clinical or subclinical measles infection. In a subgroup analysis, such children were excluded.

Statistical Analyses

Using Cox proportional hazards models with age as underlying time, we compared mortality rates of different subgroups providing mortality rate ratios (MRRs) to assess the importance of maternal antibody at time of measles vaccination; differences between groups were significant at the 5% level if the CI excluded 1.0. In trial I, we compared subsequent mortality of early measles-vaccinated children with and without maternal measles antibody at enrollment and in parallel the mortality of control children with and without measles antibody. One group had no death and we therefore used the log-rank test, and the profile likelihood method for calculating an upper confidence limit for the MRR. In trial II we compared (1) mortality of early MV recipients with and without maternal measles antibody and (2) mortality of early MV recipients with and without maternal measles antibody with control children randomized to MV at 9 months of age. The proportional hazard assumption was assessed graphically, and tested using Schoenfeld residuals ($P = .71$).

Ethical Approval

The protocols for the measles vaccine trials were approved by the Danish Central Ethical Committee, the Gambia/MRC

Table 1. Mortality Until 60 Months of Age in Relation to the Presence of Maternal Measles Antibody at the Time of Measles Vaccination

Measles Antibody Concentration in the Child, ^a mIU/mL	Trial I [14] (N = 150) Death/All, No.	Trial II [5] (N = 450) Death/All, No.
No detectable antibody	16/123 (13%)	11/201 (5%)
Detectable antibody		
31.25		0/85
62.50		1/44
125	0/7	1/46
250	0/5	1/32
500	0/6	0/15
1000	0/7	1/11
2000	0/1	0/7
4000		0/6
8000	0/1	0/2
16 000		0/1
All detectable antibody	0/27 (0%)	4/249 (2%)

^a Only children randomized to early vaccination.

Scientific and Ethics committees, and the Guinean Ministry of Health's Research Coordination Committee.

RESULTS

Trial diagrams for trial I and trial II are shown in [Supplementary Figure 1](#).

Trial I: Early 2-Dose MV and Vitamin A Trial, 1993–1995

Twenty-seven of 150 (18%) children who received MV at 6 months had detectable measles antibody ([Table 1](#)). Between 6 months and 5 years of age, 16 children died. All had undetectable measles antibody levels at 6 months of age; 13 died after the second dose of MV at 9 months of age and before 5 years of age. Among early MV recipients, vaccination in the presence of measles antibody vs vaccination in the absence of measles

antibody was associated with significant survival benefits (MRR, 0 [95% CI, 0–.52]; $P = .048$, log-rank test; [Table 2](#)). No child died of measles infection. The effect was similar for children receiving VAS or placebo with MV (data not shown). In contrast, among IPV recipients, vaccination in presence of measles antibody was not associated with benefits (MRR, 1.74 [95% CI, .57–5.34]).

Trial II: Early 2-Dose Trial, 2003–2007

Among 450 children given MV at 4.5 months of age, 249 (55%) had measles antibody ([Table 1](#)). Controlled for age, children with measles antibody at measles vaccination had significantly lower mortality until 5 years of age than children without measurable measles antibody; the MRR was 0.29 (95% CI, .09–.91; [Figure 1](#)). Nearly all deaths (14/15) occurred after the second dose of MV at 9 months ([Figure 1](#)). No death was due to measles ([Supplementary Table 1](#)).

Some antibody could be due to measles, as there had been a recent epidemic [16]. We therefore conducted an analysis excluding 16 children (1 death) who at 4.5 months had similar or higher titers than their mothers. The result was the same among the remaining 434 children; children with measles antibody at measles vaccination had an MRR of 0.23 (95% CI, .06–.82) compared with children without detectable measles antibody.

Confounding factors, including sex, age of mother, weight-for-age, season, infections, breastfeeding, twinning, high-risk children (twins, motherless, low birth weight and nonbreastfeeding) and decline in titers from mother to child, could not explain why presence of maternal measles antibody had a beneficial effect; the adjusted MRRs varied between 0.22 and 0.33 ([Table 3](#)). Maternal HIV infection is associated with reduced levels of measles antibody in the child. In the early 1990s, the level of human immunodeficiency virus type 1 (HIV-1) infection [21] was very low in Bissau, so HIV-1 infection could not explain higher mortality of children vaccinated in absence of measles antibody in trial I. The expected HIV-1 prevalence among mothers was 4%–5% during trial II [22]. Normally all children are breastfed at 4 months of age in Guinea-Bissau,

Table 2. Mortality Between 6 Months and 5 Years of Age According to Presence of Maternal Measles Antibodies at Time of Randomization to Measles Vaccine or Inactivated Polio Vaccine at 6 Months of Age (Trial I^a)

Early Measles Vaccination			Control Children (IPV Vaccinated)		
Had Measles Antibody ≥ 31.25 mIU/mL ^b	No Detectable Measles Antibody ^b	MRR (95% CI)	Had Measles Antibody ≥ 31.25 mIU/mL ^b	No Detectable Measles Antibody ^b	MRR (95% CI)
0 (0/121) [27]	32.3 (16/495) [123]	0 (0–.52)	44.6 (4/90) [23]	25.2 (13/515) [127]	1.74 (.57–5.34)

The effect of vaccination with measles vaccination or IPV for children with and without maternal antibodies tended to differ statistically ($P = .057$, exact Poisson regression).

Abbreviations: CI, confidence interval; IPV, inactivated polio vaccine; MRR, mortality rate ratio.

^a See [14] for information on the trial.

^b Data are presented as mortality rate/1000 person-years (deaths/person-years) [No.].

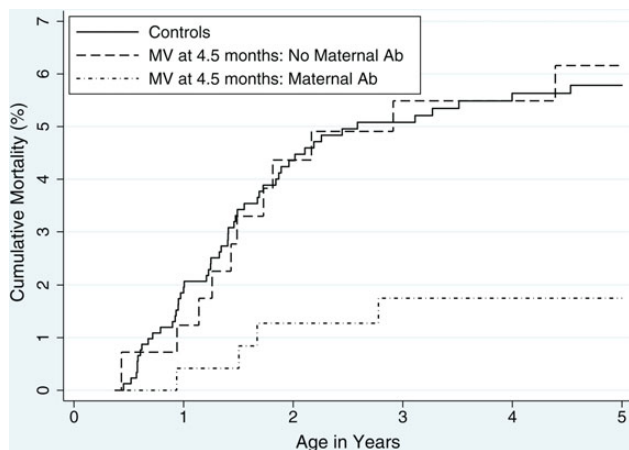


Figure 1. Cumulative mortality between 4.5 months and 5 years of age in relation to age of measles vaccination (MV) and presence of maternal antibody (trial II [5]). Children randomized to MV at 4.5 months received also MV at 9 months of age. Controls received only MV at 9 months of age. Abbreviations: Ab, antibody; MV, measles vaccination.

but during the trial period the nongovernmental organization responsible for prevention of maternal HIV transmission recommended that HIV-infected mothers not breastfeed their children. In trial II, 4% were not breastfed and these children presumably had HIV-infected mothers or mothers who died. Among these children, none of the early recipients died (Table 3). Hence, the beneficial effect of having maternal antibody is not due to HIV-infected children having lower levels and higher mortality.

The 450 measles-vaccinated children were also compared with 948 children enrolled in the same period and randomized to no vaccine at 4.5 months and MV at 9 months of age. Overall, early MV at 4.5 months reduced mortality between 4.5 months and 5 years of age (Table 4). However, the beneficial effect was found only among children who had maternal measles antibody at vaccination (MRR, 0.30 [95% CI, .11–.82]). Children receiving MV at 4.5 months of age without detectable measles antibody had the same mortality as controls who received MV at 9 months of age (MRR, 1.01 [95% CI, .53–1.95]) (Figure 1).

Combined Analysis

The trials were similar in collecting prevaccination samples, having a second MV around 9 months, and having follow-up to 5 years of age. We therefore conducted a combined analysis adjusted for trial; MV at 4–6 months of age in presence of measles antibody was associated with an MRR of 0.22 (95% CI, .07–.64) compared with MV in presence of no measles antibody; the MRR was 0.14 (95% CI, .02–1.09) for girls and 0.26 (95% CI, .07–.91) for boys. After the second dose of MV at 9 months of age, the MRR was 0.24 (95% CI, .08–.73).

DISCUSSION

Childhood survival was better for children who received MV in presence of maternal antibody than for those who had no detectable maternal antibody, and better than for those who received only a single MV at 9 months of age. Control for confounding factors did not explain the finding. In trial I [14], maternal measles antibody had no effect on survival among IPV-vaccinated children.

Confounding Factors and Limitations

Undetectable measles antibody levels could be associated with higher inherent mortality. However, control for potential determinants of antibody levels made no difference to the estimated benefit of MV (Table 3). Importantly, controlling for breastfeeding, which is a proxy for maternal HIV infection in this study setting, did not explain the findings.

High maternal measles antibody levels might be a proxy for generally high maternal antibody levels and protection against other infections. However, in trial I, there was no indication that control children with detectable levels had better survival. Furthermore, if lower mortality was due to protection against other infections, the difference should have occurred before maternal antibody wanes. This was not the case; in both trials the beneficial effect was equally pronounced after the second MV after 9 months of age, when maternal antibody levels are very low. Children having no detectable antibody at MV were not a group with a particularly high mortality. In both trials, children vaccinated early having no maternal measles antibody had a mortality rate similar to controls, who received MV at 9 months of age.

Some children with high prevaccination measles antibody levels may have had antibody due to subclinical or clinical measles infection [16, 19, 20]. When we examined this by excluding children with antibody levels equal to or greater than their mother's, the effect of MV remained unchanged.

The trials were not planned to examine the effect of MV in the presence of measles antibody; for example, we did not collect antibody samples at 4.5 months of age from controls in trial II. Hence, uncontrolled confounding factors for high maternal antibody level could have played a role. Still, both studies supported that vaccination in presence of measles antibody may explain why all epidemiological studies indicate that early MV has a better effect on child survival.

Consistency With Previous Observations

We have previously examined whether vaccination in presence of maternal measles antibody influenced subsequent survival in trials of 1 dose of early MV. We found support for lower mortality after MV in presence of maternal antibody in the first trial of Edmonston-Zagreb in Guinea-Bissau [23]. However, this was

Table 3. Mortality Rate Ratios Between 4.5 and 5 Years of Age for Children With Maternal Measles Antibody Compared With Children Without Detectable Maternal Antibody at the Time of Measles Vaccination at 4.5 Months of Age; Controlled for Potential Confounders in Stratified Analyses (Trial II^a)

Potential Confounding Factor (Definition of Stratum)	Mortality (Deaths/No.), First Strata		Mortality (Deaths/No.), Second Strata		MRR (95% CI)	RR of Having Undetectable Maternal Measles Antibody Levels in the T2 Strata and Comment About Possible Confounding
	Undetectable Antibody	Had Measles Antibody	Undetectable Antibody	Had Measles Antibody		
Unadjusted estimate					0.29 (.09–.91)	
Maternal age ^b (1: 14–24 y; 2: ≥25 y)	4/112	2/122	7/89	2/124	0.27 (.09–.86)	Young mothers may be more likely to have undetectable levels (RR = 1.15 [95% CI, .93–1.41]) and their children could have higher risk of dying.
	MRR = 0.45 (.08–2.47)		MRR = 0.20 (.04–.94)			
Sex (1: male; 2: female)	6/104	3/132	5/97	1/117	0.29 (.09–.90)	There was no difference in risk of undetectable levels for girls and boys (RR = 0.97 [95% CI, .79–1.19]).
	MRR = 0.38 (.10–1.53)		MRR = 0.17 (.02–1.42)			
Weight-for-age z score ^b (1: z score <0; 2: z score ≥0)	6/111	4/142	5/90	0/107	0.27 (.09–.58)	Maternal antibody concentration was not associated with low weight for age (RR = 0.96 [95% CI, .78–1.19]).
	MRR = 0.52 (.15–1.83)		MRR = 0.00			
Season (1: dry; 2: rainy)	5/76	1/127	6/125	3/122	0.29 (.09–.92)	Maternal antibody levels measured in the rainy season were more likely to be undetectable (RR = 1.35 [95% CI, 1.09–1.68]) and mortality could be higher in the rainy season.
	MRR = 0.12 (.01–1.04)		MRR = 0.50 (.12–1.99)			
Breastfeeding at enrollment (1: yes; 2: no)	11/192	4/243	0/9	0/6	0.28 (.09–.89)	Not breastfeeding children, presumably due to the mother being HIV infected, may be more likely to have undetectable levels (RR = 1.36 [95% CI, .89–2.08]); children born to HIV-infected mothers could have higher mortality.
	MRR = 0.28 (.09–.89)		MRR = ND			
Birth weight (1: normal; 2: low)	10/184	3/235	1/17	1/14	0.30 (.09–.93)	Low-birth-weight children are likely to have lower maternal antibody (RR = 1.25 [95% CI, .89–1.75]) and to have higher child mortality.
	MRR = 0.24 (.07–.86)		MRR = 1.14 (.07–18.3)			
Singletons (1: yes; 2: twins)	11/191	4/242	0/10	0/7	0.28 (.09–.89)	Twins are likely to have lower maternal antibody (RR = 1.33 [95% CI, .88–2.01]) and to have higher child mortality.
	MRR = 0.28 (.09–.89)		MRR = ND			
High-risk children (1: no; 2: yes)	10/172	3/224	1/29	1/25	0.29 (.09–.91)	High-risk children (twins, motherless children, nonbreastfeeding, low birth weight) could have lower maternal antibody levels (RR = 1.24 [95% CI, .94–1.62]) and higher child mortality
	MRR = 0.23 (.06–.84)		MRR = 1.10 (.07–17.5)			
Had fever or diarrhea at enrollment (1: yes; 2: no)	1/21	1/14	10/180	3/235	0.30 (.09–.94)	Children who are acutely sick have lower antibody levels (RR = 1.38 [95% CI, 1.03–1.85]) and could have higher subsequent child mortality.
	MRR = 1.62 (.10–26.0)		MRR = 0.22 (.06–.82)			
Decline in titers from mother to child ^{b,c} (1: 0–4-fold; 2: ≥5-fold)	3/63	2/137	8/133	2/98	0.29 (.09–.95)	Children with the most marked decline in antibody level are likely to have lower levels (RR = 1.83 [95% CI, 1.45–2.31]) and could have higher mortality.
	MRR = 0.30 (.05–1.82)		MRR = 0.33 (.07–1.58)			

Table 3 continued.

Potential Confounding Factor (Definition of Stratum)	Mortality (Deaths/No.), First Strata		Mortality (Deaths/No.), Second Strata		RR of Having Undetectable Maternal Measles Antibody Levels in the T2 Strata and Comment About Possible Confounding
	Undetectable Antibody	Had Measles Antibody	Undetectable Antibody	Had Measles Antibody	
Effect after second dose of MV (1: received second MV after 9 mo)	10/191	4/236			As the effect could be due to having higher maternal antibody levels to other infections, we tested the effect after the second dose of MV at 9 mo of age when maternal antibody levels would have waned.
VAS at birth (1: yes; 2: no)	5/78 MRR = 0.18 (.02–1.50)	1/91	6/123 MRR = 0.37 (.09–1.50)	3/158	Because VAS at birth interacted with the overall effect of MV [5], we tested whether neonatal VAS also affected the impact of maternal measles antibody levels.

Controlling for all potential confounders except decline in titer from mother to child, which had missing values, the MRR was 0.25 (95% CI, .08–.82). Controlling for all potential confounders excluding the children whose mothers had missing measles antibody level, the MRR was 0.25 (95% CI, .07–.86).

Abbreviations: CI, confidence interval; MRR, mortality rate ratio; MV, measles vaccination; ND, not defined; RR, relative risk; VAS, vitamin A supplementation.

^a See [5] for information on the trial.

^b Tested as a continuous variable.

^c Nineteen mothers had no antibody titer measured.

not the case in the high-titer measles vaccine trial in Senegal [24], in which the children received DTP-IPV at the same time as MV [25]. We have subsequently shown that DTP administered with MV or after MV reduces the benefit of MV [25, 26]; this could potentially explain the Senegal finding.

Interpretation

The biological mechanisms explaining the beneficial effect of vaccination in presence of measles antibody are unknown. Several not mutually exclusive mechanisms could be important. First, it has been suggested from an early 2-dose study in Sudan that early MV in presence of maternal antibody may prime for a balanced humoral and cellular immune response to subsequent revaccination [27]. Animal studies have suggested that maternal antibody not only confers passive immunity, but also leaves a long-lasting imprint on the immune system of the offspring [28], and that presence of maternal antibody at primary infection is required to ensure long-term protection [29]. Second, maternal antibodies have undergone immune maturation due to somatic hypermutation and gene conversion and are thus guided toward the dominant epitopes on the measles virus. In the presence of such high-affinity maternal antibody, the vaccinated child may respond to the variety of subdominant epitopes, leading to more diverse T- and B-cell repertoires and increased heterologous protection against other pathogens [30–32]. Third, maternal antibody–antigen complexes are powerful immunogens that are readily internalized and processed by antigen-presenting cells, and this could result in enhanced T-cell responses in infants immunized in presence of maternal antibody [32]. Last, recent studies have shown that BCG induces epigenetic changes that reprogram monocytes to enhanced response to unrelated infections [33]. Something similar could presumably happen with MV in presence of maternal antibody [34].

Our results do not mean that nonspecific beneficial effects only occur when the initial MV is provided in the presence of maternal measles antibody. In our studies, early MV was compared with MV at 9 months of age, not with being measles unvaccinated. MV administered later after waning of maternal antibody may also have nonspecific beneficial effects compared with not being measles vaccinated; for example, when MV was introduced after 12 months of age in a community randomized study in Bangladesh, there were significant reductions in mortality that could not be explained by prevention of measles infection [35, 36].

Implications

The current measles vaccination program assumes a better effect of MV when maternal antibody wanes. However, all evidence suggests that early MV has a stronger beneficial effect on child survival than later MV [5–11, 13]. There has been concern that early MV in presence of maternal antibody might

Table 4. Mortality Between 4.5 and 5 Years of Age in Relation to the Presence of Maternal Measles Antibody at the Time of Randomization to Measles Vaccine (MV) or No MV at 4.5 Months of Age (Trial II^a)

Presence of Maternal Antibody, mIU/mL	Mortality Rate per 1000 Person-years (Deaths/Person-years) [No.]		MRR (95% CI)
	Received MV at 4.5 mo	Controls (No MV at 4.5 mo)	
All children	8.7 (15/1716) [450]	14.4 (50/3467) [948]	0.61 (.34–1.09)
No detectable antibody	14.5 (11/760) [201]		1.01 (.53–1.95)
Antibody: 31.25–16 000	4.18 (4/956) [249]		0.30 (.11–.82)
MRR (antibody/no detectable antibody)	0.29 (0.09–0.91)		
Females	7.4 (6/814) [214]	17.9 (28/1562) [436]	0.42 (.17–1.01)
No detectable antibody	13.3 (5/376) [97]		
Antibody: 31.25–16 000	2.3 (1/438) [117]		
MRR (antibody/no detectable antibody)	0.17 (0.02–1.45)		
Males	10.0 (9/901) [236]	11.6 (22/1905) [512]	0.87 (.40–1.89)
No detectable antibody	15.6 (6/383) [104]		
Antibody: 31.25–16 000	5.8 (3/518) [132]		
MRR (antibody/no detectable antibody)	0.38 (0.09–1.51)		

The table includes children enrolled in the trial between March and October 2004—ie, the period in which prevaccination antibody samples were collected. All children were offered the currently recommended MV at 9 months of age. All children have been followed to death, migration, or 5 years of age. Antibody level at 4.5 months of age was only measured in children who received MV at 4.5 months of age and not in the controls who were to receive MV at 9 months of age.

Abbreviations: CI, confidence interval; MRR, mortality rate ratio; MV, measles vaccine.

^a See [5] for information on the trial.

reduce the subsequent protection against measles infection. In trial II, antibody levels were generally lower among early MV recipients than among children vaccinated later [37]. However, the children had very good clinical protection before 9 months of age [38], and following 2 doses at 4.5 and 9 months of age, nearly all children tested had detectable measles antibody at 24 months of age and 97% had protective antibody levels. These children will be followed to assess whether a third dose should be needed [37]. Also, it should be noted that there is no correlation between humoral and cellular responses [39].

The effect of different MV strategies is usually only assessed in terms of its impact on measles antibody levels. However, the most important criterion should be the overall effect on child survival [5–9]. Furthermore, the vaccine should induce sufficient cellular immunity to protect against measles death and sufficient protective antibody levels to maintain herd immunity against measles. An additional early MV would fulfill these criteria, enhancing survival by initiating the nonspecific beneficial effect earlier and by ensuring that more children have maternal antibody at first MV. Early MV has also been shown to reduce measles deaths [38], and in combination with a second dose at 9 months of age it induces protective antibody levels [37]. Hence, early MV in addition to MV at 9 months of age would be a good way to reduce child mortality.

If confirmed in other studies, we would need to understand the biological mechanisms explaining how vaccination in presence of

maternal antibody enhances protection against unrelated infections. The lack of a mechanistic understanding has been used to justify not taking the nonspecific effects into consideration [40]. The results herein suggest that immune enhancement by maternal antibody is an important part of the mechanism explaining the nonspecific beneficial effects of MV for child survival. This area of immunology has not been explored before.

It would be important to know whether the effect is restricted to children who have measles antibody after natural infection of their mother, or is also found when the maternal measles antibody was generated by a previous MV. Because the effect was equally beneficial in the mid-2000s (trial II), when more mothers would have been measles vaccinated, and in the early 1990s (trial I), it seems likely that the effect may also be produced by vaccine-induced maternal antibody. Hence, it should be examined whether a beneficial effect can be obtained by adding passive antibodies at time of measles vaccination to assure that all children have the benefit of MV in the presence of antibody.

Current MV policies may have to be reconsidered [41]. There are several randomized trials from Africa which document that MV provides protection against more than measles infection [5, 8, 41, 42]. There is every reason to use the nonspecific beneficial effects to reduce child mortality in high-mortality countries. We may need to give the first dose of MV earlier rather than later, and any attempt to increase the age of MV may lead to an increase in child mortality.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (<http://cid.oxfordjournals.org>). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

Author contributions. C. S. B. and P. A. developed the hypothesis. H. C. W., A. B. F., and M. H. C. provided input to the hypothesis. M.-L. G., C. L. M., A. R., H. C. W., C. S. B., and P. A. designed and conducted the measles vaccine trials; H. C. W. was responsible for the analysis of measles antibody; P. A. and C. S. B. made the first analysis; A. A. and H. R. was responsible for the statistical analyses; the first draft was written by P. A.; all authors contributed to the final version of the paper. P. A. will act as guarantor of the study.

Disclaimer. The funding agencies had no role in the study design, data collection, data analysis, data interpretation, or the writing of the report.

Financial support. The research on the decline in maternal antibodies that inspired the present trial was funded by the Thrasher Foundation. This work was supported by the Danish Council for Development Research, Ministry of Foreign Affairs, Denmark (grant number 104.Dan.8.f.); Fonden til Lægevidenskabens Fremme; Novo Nordisk Foundation; and European Union FP7 support for OPTIMUNISE (grant number Health-F3-2011-261375). C. S. B. holds a starting grant from the European Research Council (ERC) (ERC-2009-StG-243149). The Research Centre for Vitamins and Vaccines is supported by a grant from the Danish National Research Foundation (DNRF108). P. A. holds a research professorship grant from the Novo Nordisk Foundation.

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

- Expanded Programme on Immunization. The optimal age for measles immunization. *Weekly Epidemiol Rec* **1982**; 57:89–91.
- Gans H, Yasukawa L, Rinki M, et al. Immune responses to measles and mumps vaccination of infants at 6, 9, and 12 months. *J Infect Dis* **2001**; 184:817–26.
- De Quadros CA, Izurieta H, Venczel L, Carrasco P. Measles eradication in the Americas : Progress to date. *J Infect Dis* **2004**; 189(suppl 1): S227.
- Strategic Advisory Group of Experts. Meeting of the immunization Strategic Advisory Group of experts, November 2006—conclusions and recommendations. *Weekly Epidemiol Rec* **2007**; 82:1–16.
- 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.
- 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**; 311:481–5.
- 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. *Br Med J* **1993**; 307:1308–11.
- 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 Infect Dis J* **2003**; 22:798–803.
- 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.
- 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**; 20:474–9.
- Martins CL, Benn CS, Andersen A, et al. A randomized trial of a standard dose of EZ measles vaccine given at 4.5 months of age: effect on total hospital admissions. *J Infect Dis* **2014**; 209:1731–8.
- Sørup S, Benn CS, Poulsen A, Krause T, Aaby P, Ravn H. Live vaccine against measles, mumps, and rubella and the risk of hospital admissions for nontargeted infections. *JAMA* **2014**; 311:826–35.
- Kasongo Project Team. Influence of measles vaccination on survival pattern of 7–35-month-old children in Kasongo, Zaire. *Lancet* **1981**; 1:764–7.
- Benn CS, Aaby P, Balé C, et al. Randomised trial of effect of vitamin A supplementation on antibody response to measles vaccine in Guinea-Bissau, West Africa. *Lancet* **1997**; 350:101–5.
- Benn CS, Balde A, George E, et al. Effect of vitamin A supplementation on measles-specific antibody levels in Guinea-Bissau. *Lancet* **2002**; 359:1313–14.
- Martins C, Carlitos Bale C, Garly ML, et al. Girls may have lower levels of maternal measles antibodies and higher risk of subclinical measles infection before the age of measles vaccination. *Vaccine* **2009**; 27: 5220–5.
- Whittle H, Rowland MG, Mann GF, Lamb WH, Lewis RA. Immunisation of 4–6 month old Gambian infants with Edmonston-Zagreb measles vaccine. *Lancet* **1984**; 2:834–7.
- Samb B, Aaby P, Whittle H, et al. Serological status and measles attack rates among vaccinated and unvaccinated children in rural Senegal. *Pediatr Infect Dis J* **1995**; 14:203–9.
- Aaby P, Bukh J, Kronborg D, Lisse IM, da Silva MC. Delayed excess mortality after exposure to measles during the first six months of life. *Am J Epidemiol* **1990**; 132:211–19.
- Aaby P, Andersen M, Knudsen K. Excess mortality after early exposure to measles. *Int J Epidemiol* **1993**; 22:156–62.
- Poulsen AG, Kvinesdal B, Aaby P, et al. Prevalence of and mortality from human immunodeficiency virus type 2 in Bissau, West Africa. *Lancet* **1989**; 1:827–31.
- da Silva ZJ, Oliveira I, Andersen A, et al. Changes in prevalence and incidence of HIV-1, HIV-2 and dual infections in urban areas of Bissau, Guinea-Bissau. Is HIV-2 disappearing? *AIDS* **2008**; 22: 1195–202.
- Aaby P, Lisse IM, Whittle H, et al. Long-term survival in trial of medium-titre Edmonston-Zagreb measles vaccine in Guinea-Bissau: five year follow-up. *Epidemiol Infect* **1994**; 112:413–20.
- 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: a re-analysis of the West African studies. *Lancet* **2003**; 361: 2183–88.
- Aaby P. Measles immunization and child survival: uncontrolled experiments. In: Rashad H, Gray R, Boerma T, eds. Evaluation of the impact of health interventions, IUSSP. Liege: Derouaux Ordina Editions, **1995**:11–45.
- Aaby P, Biai S, Veirum JE, et al. DTP with or after measles vaccination is associated with increased in-hospital mortality in Guinea-Bissau. *Vaccine* **2007**; 25:1265–9.
- Bertley FM, Ibrahim SA, Libman M, Ward BJ. Measles vaccination in the presence of maternal antibodies primes for a balanced humoral and cellular response to revaccination. *Vaccine* **2004**; 23:444–9.
- Lemke H, Coutinho A, Lange H. Lamarckian inheritance by somatically acquired maternal IgG phenotypes. *Trends Immunol* **2004**; 25: 180–96.
- Navarini AA, Krzyzowski M, Lang KS, et al. Long-lasting immunity by early infection of maternal antibody-protected infants. *Eur J Immunol* **2010**; 40:113–6.
- Shann F. Heterologous immunity and the non-specific effects of vaccines. A major medical advance? *Pediatr Infect Dis J* **2004**; 23:555–8.

31. Siegrist CA. Mechanisms by which maternal antibodies influence infant vaccine responses: review of hypotheses and definition of main determinants. *Vaccine* **2003**; 21:3406–12.
32. Welsh RM, Selin LH. No one is naïve: the significance of heterologous T-cell immunity. *Nat Rev Immunol* **2002**; 2:417–26.
33. Kleinnijenhuis J, Quintin J, Preijers F, et al. Bacille Calmette-Guerin induces NOD2-dependent nonspecific protection from reinfection via epigenetic reprogramming of monocytes. *Proc Natl Acad Sci U S A* **2012**; 109:17537–42.
34. Benn CS, Netea MG, Selin LK, Aaby P. A small jab—a big effect: non-specific immunomodulation by vaccines. *Trends Immunol* **2013**; 34:431–9.
35. Koenig MA, Khan MA, Wojtyniak B, et al. Impact of measles vaccination on childhood mortality in rural Bangladesh. *Bull WHO* **1990**; 68:441–7.
36. Aaby P, Bhuyia A, Nahar L, Knudsen K, de Francisco A, Strong M. 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**; 32:106–15.
37. Martins C, Garly ML, Bale C, et al. Measles antibodies responses after an early two dose schedule with Edmonston-Zagreb standard-titre measles vaccine at 4 1/2 and 9 months of age [Epub ahead of print]. *J Infect Dis* **2014**.
38. 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.
39. Jacobson RM, Ovsyannikova IG, Vierkant RA, Pankratz VS, Poland GA. Independence of measles-specific humoral and cellular immune responses to vaccination. *Hum Immunol* **2012**; 73:474–9.
40. Moxon R, Nossal G, Heymann D, Plotkin S, Levine O. Authors' reply. *Lancet* **2012**; 379:27.
41. Aaby P, Martins CL, Garly ML, Rodrigues A, Benn CS, Whittle HC. The optimal age of measles immunization in low-income countries: a secondary analysis of the assumptions underlying the current policy. *BMJ Open* **2012**; 2:e000761.
42. Shann F. The non-specific effects of vaccines. *Arch Dis Child* **2010**; 95:662–7.