Reduced childhood mortality after standard measles vaccination at 4-8 months compared with 9-11 months of age

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Abstract

Objective—To evaluate the impact on mortality of standard Schwarz measles immunisation before 9 months of age.

Design—Children vaccinated in 1980-3 at 4-5, 6-8, and 9-11 months of age were followed to migration, death, or the age of 5 years.

Setting—One urban district and nine villages in two rural areas of Guinea-Bissau.

Subjects—307 children vaccinated at 4-8 months and 256 at 9-11 months.

Main outcome measures—Mortality from 9 months to 5 years of age for children immunised at 4-5, 6-8, and 9-11 months.

Results—Mortality was significantly lower in children vaccinated at 6-8 months than at 9-11 months (mortality ratio=0.63, (95% confidence interval 0.41 to 0.97), $p=0.047$). As vaccination was provided in semiannual or annual campaigns it is unlikely that age at vaccination reflected a selection bias. The trend was the same in all three study areas. Improved survival after early immunisation was not related to better protection against measles infection. With a Cox multivariate regression model to adjust for age, sex, season at risk, season at birth, measles infection, and region, children vaccinated at 4-8 months had a mortality ratio of 0.61 (0.40 to 0.92, $p=0.020$) compared with children vaccinated at 9-11 months. Reimmunised children tended to have lower mortality than children who received only one vaccine (0.59 (0.28 to 1.27, $p=0.176$)).

Conclusion—Standard measles vaccination before 9 months is not associated with higher childhood mortality than is the currently recommended strategy of immunising from 9 months, and it may reduce mortality. This has implications for measles immunisation strategy in developing countries.

Introduction

In densely populated urban areas 5-10% of children may experience measles before the recommended age of immunisation (9 months).¹ This is a great problem because acute case fatality ratios and long term morbidity and mortality are higher in these children.^{2,3} After trials of medium dose and high dose Edmonston-Zagreb measles vaccine among infants in West Africa and Mexico yielded successful antibody responses^{4,5} and clinical protection⁶ the Global Advisory Group of the Expanded Programme on Immunisation recommended in 1989 that in countries where measles is common before the age of 9 months children should be vaccinated at 6 months of age with high dose Edmonston-Zagreb measles vaccine.¹⁰ Longer follow up in Guinea-Bissau and Senegal showed, however, that girls given high titre measles vaccines mainly before 9 months had higher mortality than girls who received standard Schwarz vaccine after this age.^{11,12} The Global Advisory Group of the Expanded Programme on Immunisation therefore rescinded its recommendation of high titre measles vaccines and

reintroduced the previous policy of one dose of standard Schwarz vaccine at 9 months of age.¹³

The experience with early high titre measles vaccination is likely to raise concerns that vaccination before 9 months could be dangerous. As this may become an impediment to the solution of the important problem of measles before the current age of immunisation, we analysed data from the early 1980s from one urban and two rural areas in Guinea-Bissau where children were vaccinated before 9 months of age. Vaccinations were offered only in annual or biannual campaigns. Different ages at vaccination among infants are therefore unlikely to reflect a selection bias. Children vaccinated before 9 months were offered reimmunisation. We compared mortality of children vaccinated before 9 months and at 9-11 months in these campaigns. The group vaccinated at 9-11 months may be said to represent the current policy of measles immunisation at 9 months,¹³ whereas the group vaccinated before 9 months represents the alternative two dose strategy (at 6 and 9 months) recommended by the Expanded Programme on Immunisation for areas with a high incidence of measles.

Subjects and methods

BACKGROUND

The study of child health and mortality in Guinea-Bissau was started in 1978 in Bandim district in the capital and in some rural areas.^{14,15} In both Bandim and the rural areas, pregnancies, births, anthropometry, vaccinations, infections, and deaths were reported in the routine registration system.¹⁴ In Bandim we also gathered information on certain biological, cultural, and socioeconomic background factors in connection with the registration of births. Children were examined every third month in Bandim and every sixth month in the rural areas. When children were absent from these examinations, home visits were carried out to determine the child's whereabouts. Because of this close follow up it is unlikely that we missed any deaths among children still resident in the study areas. For children who died, information was collected from parents or other relatives on symptoms during the last illness.

MEASLES IMMUNISATION CAMPAIGNS

The initial project proposal emphasised nutritional patterns as determinants of child mortality. During the first years of the study, however, measles epidemics in both Bandim¹⁴ and one rural area, Quinhamel,¹⁵ showed that measles infection could have an enormous impact on mortality in spite of reasonable levels of nutrition among the children. From the beginning of 1980 we introduced measles vaccination campaigns though no functioning national immunisation programme existed in Guinea-Bissau at the time. During these initial (annual or biannual) campaigns, children were vaccinated from the age of 6 months.¹⁵ Some children were immunised at 4-5 months during measles epidemics or due to miscalculation or mis-

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reporting of their age. Children vaccinated below 9 months of age were offered reimmunisation at subsequent campaigns. During the initial campaigns analysed in the present study, only measles vaccine was available for the children. Sick children were not immunised, and children who were absent on the day of the vaccination campaign in their area owing to travel difficulties or lack of information from the village committee could not be immunised until the next campaign.

STUDY POPULATIONS

Bandim—Measles vaccination was introduced in Bandim during December 1979 and January 1980 in connection with the first examination of all children.¹⁶ The second campaign with measles vaccine was carried out from December 1980 to February 1981. From April 1981 onwards, vaccinations were offered more often and different ages of vaccination could reflect selection biases related to maternal knowledge or disease. The analysis has therefore been limited to the children immunised during the first two campaigns.

The first two campaigns reached a total of 287 children vaccinated for the first time between 4 and 11 months of age. Fifty two children were reimmunised, of whom 41 had been under 9 months of age when they received the first vaccination.

TABLE I—Proportion attending when called for measles immunisation according to age, Guinea-Bissau, 1980-3

Area	% (No immunised/No eligible) attending immunisation	
	6-8 Months	9-11 Months
Bandim	76 (132/174)	72 (122/169)
Oio	56 (40/72)	56 (47/84)
Quinhamel	39 (77/196)	44 (86/196)

TABLE II—Mean (SD) values or percentages for biological, cultural, and socioeconomic background factors for children immunised at different ages, Bandim, 1980-1

Background factors	Age at immunisation	
	4-8 months	9-11 months
% (No) boys	50 (165)	51 (122)
Age of mother (years)	24.3 (5.6)	24.4 (5.7)
Birth order	3.8 (2.4)	3.6 (2.0)
No of antenatal visits	2.3 (1.7)	2.1 (2.1)
% (No) exposed to measles at < 6 months of age	11 (165)	12 (122)
% (No) Pelel (ethnic group)	57 (149)	50 (115)
% (No) Polygynous households	33 (144)	33 (144)
Schooling of father (years)	2.0 (2.2)	2.5 (2.3)
Schooling of mother (years)	0.7 (1.7)	0.8 (1.8)
% Of mothers with schooling	20	25
No of households per house	3.0 (1.7)	2.9 (1.6)
No of people in household	8.2 (4.4)	7.9 (3.9)
No of people in house	15.9 (7.8)	15.7 (6.5)
No of rooms per household	2.6 (1.6)	2.5 (2.3)
% Of houses with cement floor	58 (150)	56 (116)
% Of houses with zinc roof	64 (162)	66 (121)

TABLE III—Annual mortality (deaths per person years at risk) from 9 months to 5 years of age according to age at measles immunisation, area, and history of measles infection, Guinea-Bissau, 1980-3

Age at immunisation	All children		Children without measles (9-60 Months)*
	4-8 Months	9-60 Months	
Bandim:			
4-5 Months (n=33)	0 (0/11)	3.1 (3/97)	2.3 (2/88)
6-8 Months (n=132)	11.6 (2/17)	2.7 (11/413)	2.1 (8/377)
9-11 Months (n=122)		4.9 (18/370)	4.2 (14/333)
Mortality ratio (95% confidence interval)†		0.56 (0.28 to 1.13)	0.51 (0.23 to 1.15)
Oio:			
4-5 Months (n=5)	0 (0/2)	0 (0/19)	
6-8 Months (n=40)	0 (0/4)	7.9 (9/114)	
9-11 Months (n=47)		12.8 (15/117)	
Mortality ratio (95% confidence interval)†		0.53 (0.12 to 1.21)	
Quinhamel:			
4-5 Months (n=20)	17.2 (1/6)	10.6 (6/56)	
6-8 Months (n=77)	9.3 (1/11)	5.3 (13/244)	
9-11 Months (n=86)		7.3 (19/260)	
Mortality ratio (95% confidence interval)		0.86 (0.46 to 1.63)	

*Follow up censored at time of measles infection; acute and delayed deaths were excluded.

†Mortality ratio of children immunised at 4-8 months compared to children immunised at 9-11 months of age.

Rural areas—Since 1979, five villages have been followed in the Quinhamel region¹⁵ and four in the Oio region. In the period 1980-3, 400-600 children under 5 years of age were under surveillance in each of these regions. There were no functioning primary health care programmes in Quinhamel and Oio; hence the project team was the only source of measles vaccination in the study villages. Vaccination campaigns were carried out at intervals of 6 months or more. The age at immunisation was changed to 9 months in 1983. Before this change in policy, 275 children were vaccinated between 4 and 11 months of age. Eighty nine children were later reimmunised, of whom 84 had been under 9 months when receiving the first vaccination.

ANALYSIS AND STATISTICAL METHOD

Children were followed to death, migration, or the age of 5 years. We compared mortality from 9 months to 5 years of age for children immunised at 4-5 months, 6-8 months, and 9-11 months. The analysis was limited to these age groups since the children aged 6-11 months would have had only this chance to become immunised. Older children might have had previous possibilities of receiving immunisation where the interval between campaigns was only six months. The group vaccinated at 9-11 months may be said to represent the current policy of measles immunisation at 9 months of age,¹³ whereas the group vaccinated at 6-8 months represents the alternative two dose strategy (at 6 and 9 months) recommended for areas with a high incidence of measles. The group vaccinated at 4-5 months was included in the analysis since immunisation in this age group will occur if the official policy is immunisation at 6 months of age.

The Mantel-Haenszel estimator was used to combine results from different study areas, testing heterogeneity in a multiplicative Poisson model.

As vaccination was offered during campaigns, the main bias is likely to be that children of different ages at vaccination entered the rainy season at different biological ages, which could have affected their susceptibility to infection. We therefore examined mortality by using a multivariate Cox regression model¹⁷ adjusting for season at risk, season at birth, sex, and measles infection. Using the same method, we also analysed whether reimmunisation reduced mortality. Age was used as the time scale in the model, and effects are expressed as mortality ratios (with 95% confidence intervals).

Results

The number of registered children who received immunisation when a vaccination campaign was organised in their area is shown in table I. There was no difference in the proportion of children attending among those aged 6-8 and 9-11 months. Most of the children not immunised were not present at the time of the campaign.

In Bandim, where background information had been collected at the time of birth, it could be tested whether there were any major sociocultural differences between the children immunised at 4-8 and at 9-11 months (table II). For all the biological, cultural, and socioeconomic indicators tested, the two groups had very similar results.

Table III compares mortality between 9 months and 5 years of age for children vaccinated at 4-5 months, 6-8 months, and 9-11 months in the three study areas. Children immunised at 4-5 months had lower mortality than those immunised at 9-11 months, though this was not a significant difference (mortality ratio=0.80; 95% confidence interval 0.39 to 1.63). Children vaccinated at 6-8 months had significantly better survival than children vaccinated at 9-11 months (0.63, 0.41 to 0.97;

TABLE IV—Multivariate Cox regression analysis of mortality ratio (95% confidence interval) for age at vaccination, season, and history of measles infection, Guinea-Bissau, 1980-3

	Mortality ratio (95% confidence interval)	p Value
Age at vaccination (4-8 months/9-11 months)	0.61 (0.40 to 0.92)	0.020
Season (rainy/dry)	1.74 (1.11 to 2.70)	0.015
Measles infection (measles/no measles)	2.66 (1.15 to 6.15)	0.023
Model with reimmunisation:		
Age at vaccination (4-8 months/9-11 months)	0.69 (0.46 to 1.08)	0.101
Season (rainy/dry)	1.70 (1.09 to 2.65)	0.019
Measles infection (measles/no measles)	2.54 (1.09 to 5.87)	0.030
Reimmunisation (yes/no)	0.59 (0.28 to 1.27)	0.176

Analysis stratified for sex and region (Bandim, Oio, Quinhamel). Rainy season is from June to November.

$p=0.047$; test for heterogeneity, $p=0.554$). Compared with the group immunised at 9-11 months, the combined group of children immunised at 4 to 8 months had lower mortality (0.66; 0.44 to 0.99). The tendency was the same for boys and girls (data not shown).

There was no difference in the distribution of causes of death among children vaccinated at 4-8 months of age (fever 35% (16/46), whooping cough and respiratory infections 13% (6/46), diarrhoea and vomiting 13% (6/46), measles 7% (3/46), accidents 2% (1/46), unknown/no information 30% (14/46)) and those vaccinated at 9-11 months of age (fever 38% (20/52), whooping cough and respiratory infections 19% (10/52), diarrhoea and vomiting 13% (7/52), measles 4% (2/52), accidents 2% (1/52), unknown/no information 23% (12/52)).

During the study period, there was little measles in the rural areas. In Bandim, however, 38 of the children immunised between 4 and 11 months subsequently contracted measles: 21 cases among the 165 vaccinated at 4-8 months (13%) and 17 cases among the 122 vaccinated at 9-11 months (14%). The mortality ratio of children vaccinated at 4-8 months of age compared with those immunised at 9-11 months of age (relative risk was not affected by excluding deaths from measles (0.51 (0.23 to 1.15), $p=0.099$; table III).

When a Cox model was used to adjust for age, sex, region, season at risk, and measles infection, children immunised at 4-8 months had a mortality ratio of 0.61 (0.40 to 0.92; $p=0.020$) between 9 months and 5 years of age compared with children immunised at 9-11 months (table IV). Control for season at birth or finer divisions of season at risk had no impact on mortality estimates. The result was identical if history of measles infection was not taken into consideration (0.61 (0.40 to 0.93)). When the effect of age at immunisation was modelled as a linear variable, mortality tended to increase with age, though the trend did not reach significance (1.09 (0.98 to 1.22) per month; $p=0.098$).

If reimmunisations with measles vaccine were included in the Cox analysis (table IV), the mortality ratio of one dose at 4-8 months compared with one at 9-11 months of age was slightly reduced (0.69 (0.46 to 1.08)). Mortality of reimmunised children was lower than the mortality of children who had received only one measles vaccine, though the difference was not significant (0.59 (0.28 to 1.27)). Hence, children vaccinated at 4-8 months and reimmunised had a mortality ratio of 0.41 (0.19 to 0.85) compared with children vaccinated only at 9-11 months.

Discussion

The three data sets from Bandim, Oio, and Quinhamel indicate that vaccination before 9 months of age combined with reimmunisation was associated with better childhood survival than one measles vaccination at 9-11 months of age. Initially, measles vaccine was

the only immunisation available in Guinea-Bissau, so the effect is not due to additional health interventions provided at the same time as measles vaccination. We have previously shown that children who received measles immunisation in the initial measles vaccination campaigns in Bandim¹⁶ and Quinhamel¹⁵ had considerably better survival than the children who did not receive measles vaccine. This difference could be due to a selection bias between those who attended immunisation sessions and those who did not. In the present analysis, comparing groups immunised at different ages, however, a simple selection bias is unlikely to be important. The children were immunised at the age they happened to be when a campaign was organised in their community. There was no indication that participation was different before and after 9 months of age (table I). In Bandim, where information had been collected on various background factors (table II), there were no differences between the children vaccinated at 4-8 months and 9-11 months of age.

Since children vaccinated at different ages were likely to experience the seasons differently, we examined the impact of season on mortality. Season of birth was not significant, whereas the rainy season was associated with higher mortality than the dry season. In the multivariate analysis adjusting for both age and season at risk (table IV), however, there was no modification in the estimate of early measles vaccination.

The children immunised before 9 months of age were more likely to be reimmunised and this could have provided more effective immunity against measles. However, the lower mortality of children immunised at 4-8 months was not related to better protection against measles and its long term consequences as there was no change in the mortality ratio when cases of measles infection were excluded from the analysis.

EARLY VACCINATION

Measles immunisation strategies have been based on the assumption that vaccination before 9 months of age provides suboptimal protection against measles.¹⁸ In communities where measles is an important cause of death, vaccination at 9-11 months should provide better survival than vaccination before 9 months. An unexpected finding in the present study was that children with only one vaccination before 9 months of age tended to have better survival than children immunised after 9 months of age.

A number of other studies have suggested, however, that early measles immunisation is better than later vaccination. In a subsequent period in Bandim (1984-6) we found that mortality during two years of follow up for children vaccinated at 7-11 months of age was zero (0/70) compared with 11% (6/54) for children vaccinated at 12-23 months ($p=0.006$).¹⁹ A study from Benin reported that the protective efficacy of measles vaccination against all cause mortality was 64% (19-84%) for children vaccinated below 13 months of age, whereas there was no difference in survival for children vaccinated after 12 months of age ($p<0.05$, $\chi^2=7.53$, 2 df).²⁰

Furthermore, studies of measles immunisation in developing countries have found large reductions in mortality compared with no vaccination, in most cases 40-50%.^{1,16,21-24} In several of these studies, measles vaccination was introduced before nine months of age.^{16,22,23} All studies indicate that the reduction in mortality is more than should be expected from the proportion of deaths attributed to the acute and delayed consequences of measles in the respective populations.^{1,16,21,24} Therefore, measles immunisation may have a beneficial effect unrelated to prevention of measles.²¹ Possible mechanisms have not been studied,

Public health implications

- High titre measles vaccine given before 9 months of age has been associated with reduced survival
- Standard Schwarz measles vaccine is therefore recommended from 9 months of age in developing countries
- In this study from three areas in Guinea-Bissau, children immunised at 4-8 months of age, many of whom were reimmunised, had lower mortality between 9 months and 5 years of age than children vaccinated at 9-11 months of age
- Improved survival was unrelated to better protection against measles infection and its long term consequences
- Randomised trials are needed to confirm whether measles immunisation before 9 months of age with subsequent reimmunisation is better than the current strategy recommended by the World Health Organisation

but both measles infection and measles immunisation stimulate the immune system, providing protection against other infections.^{25, 26} In certain chronic diseases, BCG vaccine is used to stimulate the immune system.²⁷ Hence the growing immune system in children aged 4-8 months may be stimulated, somehow enhancing resistance to other infections in a critical phase of life.

RECOMMENDATIONS

The Global Advisory Group of the Expanded Programme on Immunisation recommended a schedule of two doses of Schwarz standard vaccine at 6 and 9 months of age only for certain groups at high risk of death from measles, such as infants in refugee camps, infants admitted to hospital, and infants affected by disaster. The relative efficacy of these strategies in terms of reducing mortality was never tested. The recent experience with reduced survival associated with early high titre measles immunisation compared with standard measles immunisation at 9-10 months of age^{11, 12} could raise concern about the safety of measles immunisation among young infants. However, the present study provides some assurance that even when the coverage for a revaccination is low, standard measles immunisation before the recommended age of 9 months is not worse than vaccination at 9 months of age. It may in fact be more effective in reducing mortality.

Further studies of long term survival after measles immunisation at different ages and reimmunisation are warranted. Should the findings from Guinea-Bissau be replicable, they may have important implications for public health and the policy of measles immunisation. As the antibody response is insufficient after early measles immunisation, raising the age at immunisation and relying on herd immunity to protect the youngest children has been recommended.^{28, 29} However, an early two dose measles vaccination strategy may be better in terms of reducing mortality than immunisation from 9 months of age or later. The number and timing of reimmunisation doses may need to be considered. Future assessments of the consequences of measles immunisation at different ages cannot be based exclusively on antibody responses and vaccine efficacy.

It is essential that studies are designed to evaluate the impact on total mortality.³⁰

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