Epidemiol. Infect. (1996), **117**, 525–531

Nutritional status and delayed mortality following early exposure to measles

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(*Accepted 11 June 1996*)

SUMMARY

Community studies in Guinea-Bissau have found that exposure to measles prior to 6 months of age is associated with delayed mortality later in childhood. In an attempt to understand the underlying mechanism, we examined the role of pre-exposure nutritional status and the impact of exposure to measles on growth and subsequent mortality in these outbreaks. Though exposed children were lighter than controls, there was no association between pre-exposure weight-for-age and subsequent mortality adjusting for age. Although exposure was strongly associated with excess mortality, it did not have a negative impact on growth. Adjustment for state of nutrition did not alter the mortality ratio (MR) between 6 and 59 months of age for exposed children and controls; exposed children examined anthropometrically between 6–17 months had a MR of 3·70 compared with controls. This trend was the same for anthropometric measurements obtained at 18–59 months of age. Among the controls, there was a significant association between weight-for-age and subsequent mortality to the age of 5 years. However, for exposed children there was no association; the relation between weight-for-age and subsequent mortality was significantly different for exposed children compared with controls (tests for interaction between exposure and anthropometric measurements at 6–17 months: $P = 0{\cdot}05$). Growth faltering as a consequence of early exposure to measles does not explain the marked excess mortality among these children. Further studies of the process underlying delayed mortality after early exposure to measles are warranted.

INTRODUCTION

Several studies from West Africa have indicated that measles is associated with both a high acute case fatality rate (c.f.r.) and an important delayed mortality [1–3]. For example, we found in Guinea-Bissau that exposure to natural measles prior to 6 months of age was associated with excess mortality later in life; a 34% mortality risk between 6 months and 5 years of age compared with 11% for unexposed children in the community (1). Some children contract clinical measles despite being below 6 months of age; others get subclinical measles [1, 4]. The difference in mortality between exposed children and controls remained equally strong when socio-economic, demographic and cultural background factors were taken into consideration [1]. In subsequent studies in an urban and a rural area, exposed children were found to have 3·8 and 11·4 times higher mortality than unexposed community controls [3].

These observations suggest that measles may have wider consequences than usually assumed. The area of research on long-term consequences after measles and measles immunization has recently attracted interest because the new high-titre vaccines recommended by WHO (5) compared to standard titre vaccines were

found to be associated with reduced survival for female recipients [6, 7]. Little is known about excess mortality after natural measles, possible confounding factors, its determinants and underlying mechanisms. Intensive exposure and high dose of infection may be important in the pathogenic process. Children who were exposed to measles before 6 months of age are most likely to have been exposed intensively at home through an older sibling and the adverse impact of measles vaccine seems to be related to the dose of vaccine [5]. A high dose of measles virus could possibly induced latent infection and growth faltering. Since exposed children had a marked excess mortality from diarrhoea [1], we speculated that direct exposure or latent infection would aggravate the state of nutrition, leading to higher susceptibility to other infections and subsequent death. In an attempt to clarify the mechanisms underlying the observations on delayed mortality, we examined the role of state of nutrition in the process leading to death. Using data from the regular nutritional surveillance carried out in the study area in Guinea-Bissau, we investigated whether pre-exposure state of nutrition was important for outcome of exposure, and whether exposure had an impact on post-exposure growth patterns and survival.

SUBJECTS AND METHODS

Bandim. Background

Bandim is an urban district in Bissau, the capital of Guinea-Bissau. Since November 1978, Bandim has been the site of a child health and nutrition project. At the initial census in November 1978, the area had 6217 inhabitants (8). Pregnancies were registered during the census, and the listing of pregnancies has subsequently been updated during monthly or bi-monthly interviews in all the houses in the study area. From December 1979, children under 3 years of age have been called for examination and weighing and vaccination every third month. Children who did not attend the examination were visited at home. This procedure makes it unlikely that deaths would remain undetected for long.

Exposed children and controls

We have previously analysed survival data on two cohorts of children exposed to measles before 6 months of age [1, 3]. Exposure to measles was defined as residence in a house where another child had measles. Only children registered before the occurrence of measles were included in the study. Because most houses in Bandim are multi-family houses, exposure could be to a case of measles in the infant's own household or to a case in another family in the same house. In general, the studies have been based on parental diagnosis of measles. During the first epidemic, we documented good correspondence between medical diagnoses and parental recall [8] and subsequent serological surveys have also shown good correspondence between a parental history of measles and the presence of measles antibodies [9, 10]. The two cohorts included children who lived in houses with measles cases during the first epidemic in 1979 [1, 4, 8, 11] and children exposed to measles during the following period 1980–3 [3, 4], after the introduction of measles vaccination in the community.

The 1979 cohort

The first cohort of exposed children and controls included all 314 children born between 1 August 1978 and 31 May 1979 [1]. Bandim experienced a severe measles epidemic between February and June 1979 [8]. Because exposed children were born in the interval August 1978–May 1979, we have included all children born in the community in this period as controls. The older children were registered in the first census and nutritional survey in the community in December 1978 (148), and the younger children (166) were born to mothers registered as pregnant during the first survey. While under 6 months of age, 86 of these 314 children had lived with a child with measles in their own household or in a neighbouring household in the same dwelling and have been considered the exposed group. The follow-up status of the cohort of exposed children and controls has been shown in Table 1. In the 1979-cohort, two children abandoned as 'spirits' (1 exposed, 1 control), and nine twins were excluded from the survival analysis because they have a different mortality risk than singletons [3].

The 1980–3 cohort

Measles vaccination was introduced in Bandim in December 1979 [12] and the subsequent incidence of measles has been considerably lower. However, there were still 72 children who had been exposed to measles before 6 months of age during the period 1980–3 [3]. For each of the exposed children, one age- and sex-matched control was selected. In the 1980–3 cohort, three exposed children (one twin pair and one

Table 1. *Follow-up status of exposed children and controls. Bandim, Guinea-Bissau Cohort/Group*

	Age (months)			
	0–5	6–17	18–59	Total
1979				
Exposed				
Entered	86	71	53	—
Died	11	10	11	32
Moved*	4	8	24	36
Controls				
Entered	228	205	164	—
Died	10	16	10	36
Moved*	13	25	63	101
1980–3				
Exposed				
Entered	72	69	58	—
Died	3	10	11	24
Moved†	—	1	4	5
Controls				
Entered	72	71	65	—
Died	—	3	3	6
Moved†	1	3	8	12

* Moved from original residence.
† Moved out of study area.
In the first years of the study in Bandim (1978–80), there were only annual examinations whereas we introduced 3-monthly examinations of children under 3 years of age in 1980. In the first 1979 cohort, children were considered to have moved when they left their original residence whereas they were subsequently followed to their new residence if they moved within the study area which included the two neighbouring districts, Bandim 2 and Belem. Hence, there was less loss to follow-up in the 1980–3 cohort than in the 1979 cohort.

'abandoned' child) and the corresponding controls were excluded from the survival analysis.

Anthropometric data

The 1979 cohort

In December 1978, at the beginning of the study, all children under 6 years of age were called for an anthropometric examination; 81·3% of the 1462 eligible children attended [8, 11]. In December 1979, all children registered in the first survey as well as children born in the project period were called for another anthropometric examination. Of the 1419 children living in the study area, 1183 (83·4%) attended reexamination. Weight (w), height (h) and mid-upper-arm-circumference (muac) were measured at these examinations [13]. Newborns were registered at home and weighed on a portable Salter scale, 57% (94/166) were weighed within the first week and 81% within the first month. Later weights are available for exposed children and controls of the 1979 cohort from the 3-monthly examinations of children under 3 years of age started in 1980. Information on background factors was collected in connection with both the anthropometric surveys and the birth registration [1].

1980–3 cohort

Weights are available for these children from the regular 3-monthly examinations of children under 3 years of age.

Analysis of anthropometric data

The measurements of weight and height were transformed into a nutritional index in the form of standard deviation scores (z-scores) for weight-for-age (w/a), height-for-age (h/a) and weight-for-height (w/h) using the international WHO/NCHS reference [13]. Comparison of nutritional status for different groups was also carried out with a local standardization using linear regression on muac and on the logarithm to weight and height, adjusting for age and sex. Children in Bandim did not follow the growth pattern of children portrayed in the international nutritional standard. The different age compositions of groups could therefore affect the results if international z-scores were used exclusively for comparison. However, the two types of standardization provided similar results, and we have therefore only displayed the more conventional z-scores.

Survival analysis

All children were included in the survival analyses from the date of first registration until date of leaving Bandim, age 5 years, or death. We discontinued follow-up at measles infection, because we were interested in the impact of early exposure to measles compared with no measles during childhood. Children were considered exposed from the day of exposure, but since the focus was on delayed mortality, exposed children were only considered at risk from 30 days after exposure to measles, thereby excluding acute deaths.

A Cox regression model with age as time scale and stratification for cohort was used to measure differences in mortality and to adjust for background factors [14], effects being expressed as mortality ratios (MR) (95% confidence intervals). The adequacy of

https://doi.org/10.1017/S0950268800059215 Published online by Cambridge University Press

the proportional hazards assumption was examined graphically by comparing log(-log) transformed survival curves. When neonatal and acute measles deaths were excluded, hazards could be assumed to be proportional. The combined effect of exposure and nutritional status on subsequent mortality in the 1979 cohort and the 1980–3 cohort was analysed using a Cox model stratifying by cohort thus allowing for non-proportionality of the underlying hazard in the 2 cohorts.

For each nutritional index, we fitted a model containing exposure status and the nutritional index and extended the model with an interaction term between exposure status and the nutritional index to describe an exposure-specific effect of nutritional state. The MR for nutritional indices expresses the change in the rate of mortality associated with an increase of one unit of z-score (i.e. one standard deviation). We also tested a model where the anthropometric indices were dichotomized; results were essentially the same. In the analysis of the association of nutritional status and subsequent mortality, children have only been included in the analysis from the date of the anthropometric examination. For each of the weight measurements, pre-exposure (age 0–5 months), post-exposure (age 6–17 months), and first weight after 18 months, we performed a separate survival analysis with entry at the time of first weight measurement or age 6 months for pre-exposure measurements. A likelihood ratio test was used to evaluate interaction terms.

RESULTS

Pre-exposure weights and subsequent mortality

Prior to exposure, the exposed children in the 1979 cohort had significantly lower weights than controls (Table 2). We have previously shown that there were significantly more young mothers among the exposed children (1). Younger mothers had lighter children both at birth ($P = 0{\cdot}0006$) and among those registered after the first week of life ($P = 0{\cdot}051$). In the subsequent period from 1980–3, there was a similar tendency for 49 exposed children to be lighter prior to exposure (w/a z-score: −0·26) than 59 controls (w/a z-score: 0·01) ($P = 0{\cdot}196$) [3].

Using a Cox model adjusting for age, there was no relation between pre-exposure weight expressed as z-score and subsequent mortality in either the 1979 cohort (MR = 1±05 (0·78–1·41); $P = 0{\cdot}76$) or the 1980–3 cohort (MR = 0·81 (0·47–1·38), $P = 0{\cdot}44$).

Table 2. *Mean nutritional z-scores at first examination under 6 months of age for exposed children (pre-exposure) and controls. Bandim, Guinea-Bissau 1978–1979*

	Mean z-score (S.D.) (Number of children)		
	Exposed	Controls	*P*
w/a* 0–7 days	−0·65 (1·16) (34)	−0·18 (0·99) (56)	0·047†
w/a* > 7 days	−0·47 (1·14) (45)	0·00 (1·00) (132)	0·009†
h/a*	−0·73 (0·66) (11)	−0·26 (1·04) (74)	0·154†
w/h*	0·20 (1·30) (11)	0·36 (0·79) (74)	0·700‡

* w/a, weight-for-age; h/a, height-for-age; w/h, weight-for-height.
† *t* test, equal variance.
‡ *t* test, unequal variance.

Table 3. *Mean nutritional z-scores at re-examination for exposed children (post-exposure) and controls aged 6–17 months. Bandim, Guinea-Bissau 1979–1980*

	Mean z-score (S.D.) (Number of children)		
	Exposed	Controls	*P*
w/a*	−1·39 (0·96) (44)	−1·24 (1·03) (137)	0·429†
h/a*	−1·19 (0·89) (44)	−1·06 (1·01) (136)	0·479†
w/h*	−0·67 (1·15) (44)	−0·67 (0·92) (136)	0·508†
MUAC*	136 (11·1) (44)	138 (12·8) (136)	0·865†

* w/a, weight-for-age; h/a, height-for-age; w/h, weight-for-height; MUAC, mid-upper-arm-circumference (mm).
† *t* test, equal variance.

Post-exposure nutritional status

In the 1979 cohort, among the exposed children and the controls who participated in a reexamination when they were 6–17 months old, there was no difference in any of the post-exposure anthropometric measurements obtained (Table 3). Similarly, there was no difference in post-exposure w/a for children in the 1980–3 cohort examined between 6 and 17 months of age ($P = 0{\cdot}50$); mean z-score being −1·0 for 57

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Table 4. *Univariate and multivariate Cox regression analyses of exposure to measles before 6 months of age (exposure) and weight-for-age z-score. Bandim, Guinea-Bissau 1979–83*

	Mortality ratio (95% confidence interval)		
Variables	Weight assessment at age 0–5 months	Weight assessment at age 6–17 months	Weight assessment at age 18–59 months
Number of exposed/controls	108/226	99/177	76/113
Exposed *vs.* control	3·41 (1·83–6·38)	4·29 (1·99–9·27)	6·85 (1·90–24·71)
Weight-for-age z-score	0·81 (0·62–1·07)	0·53 (0·37–0·76)	0·49 (0·30–0·80)
Multivariate: Additive			
Exposed *vs.* control	3·26 (1·73–6·16)	3·70 (1·71–8·01)	5·96 (1·65–21·49)
Weight-for-age z-score	0·89 (0·67–1·19)	0·56 (0·39–0·82)	0·51 (0·30–0·87)
Multivariate: Interaction*			
Exposed: Weight-for-age	0·78 (0·55–1·11)	0·75 (0·48–1·17)	0·73 (0·40–1·34)
Controls: Weight-for-age	1·11 (0·70–1·77)	0·36 (0·20–0·65)	0·22 (0·08–0·61)
P-value†	0·24	0·05	0·04

* Estimate for exposed *vs.* controls not shown.
† Likelihood ratio test for no interaction.

exposed children (mean age: 10·2 months) and −0·9 for 59 controls (mean age: 9·5 months).

W/A z-scores in the first examination after 18 months of age were similar in the 1979 cohort (mean z-score: −1·40) and the 1980–3 cohort (mean z-score: −1·50). There was still no difference in w/a between the 79 exposed children (mean z-score: −1·56) and the 132 controls (mean z-score: −1·37) ($P = 0·20$).

Exposure, nutritional status and subsequent mortality

In univariate analyses, exposure showed a strong effect on subsequent mortality which did not diminish over time. The effect of weight-for-age on subsequent mortality was not significant using weight at 0–5 months of age. However, weight-for-age z-scores at age 6–17 months and after 18 months were associated with a 50% reduction in mortality. Since pre-exposure weights were not associated with mortality and post-exposure weights did not differ between exposed and controls, inclusion of both exposure and w/a in a multivariate Cox model had minimal impact on the estimate (Table 4).

When examining the interaction between exposure and w/a, it was seen that the effect of w/a on subsequent mortality was only significant in the control group (Table 4). The interaction term for the effect of w/a z-score in the exposed and the control groups was significant for weighings between 6 and 17 months and after 18 months of age suggesting a marked effect of w/a in the control group but limited effect in the exposure group (Table 4). This tendency was the same if we did not censor at the time of measles infection and included all measles cases in the analysis (data available at request). Data for other anthropometric indices were only available for the 1979 cohort (data not shown). Height-for-age and weight-for-height were not significantly related to mortality. Arm-circumference showed the same pattern as w/a being strongly related to mortality and having a significant interaction term ($P < 0·001$) indicating a marked effect in the control group but no effect in the exposure group.

DISCUSSION

There has been no indication that the marked excess mortality following early exposure to measles could be related to confounding from other socio-cultural factors [1, 3]. Measles is a well-known disease in the area; clinical observations and studies of both antibody levels and secondary attack rates suggest that maternal diagnoses are usually correct [1, 4, 9, 10]. There could be some underreporting of cases, but this form of misclassification would reduce rather than exaggerate the difference between exposed children and controls. Analysis of post-exposure antibody levels for children in the second study cohort [1, 3] suggests that adverse effects of exposure is associated with having high antibody levels to measles virus after exposure. Still, there could be other confounding factors. However, analyses including background factors detected no effect modification; factors differing between exposed children and controls (e.g. maternal age, crowding) did not show a relation to mortality, and those which were related to

https://doi.org/10.1017/S0950268800059215 Published online by Cambridge University Press

mortality (e.g. maternal education, measles vaccination) were equally distributed between the two groups (data not shown). In the present study, we examined whether pre-exposure state of nutrition was a confounding factor. Exposed children weighed less before being exposed than controls. However, this could not explain the excess mortality of the exposure children since there was no association between pre-exposure weight and subsequent risk of dying.

In an attempt to clarify the mechanisms underlying the long-term effects of measles virus, we examined the role of exposure on growth and subsequent mortality. Deaths due to diarrhoea which often has a protracted course, dominated among the exposed children [1]. We therefore expected exposure to have a negative impact on growth, and that those most affected would have increased susceptibility to severe infections and a higher risk of dying, thus producing an association between state of nutrition and mortality risk. However, exposed children grew as well as the controls. But more surprising, the exposed children showed no significant association between w/a and arm-circumference and the subsequent risk of dying, though there were strong associations for the controls. The same pattern was found between 6 and 17 months and between 18 and 59 months of age. Since most children in the study area participated in the anthropometric examinations, it is unlikely that any selection bias in data collection has affected these observations.

The present analysis suggests that exposed children died of diseases unrelated to state of nutrition. The children did not die of measles, which we have previously found to be unrelated to state of nutrition [11]. There are indications from hospital studies in West Africa that severe malaria and meningitis are not related to state of nutrition [15]. Severe malnutrition may, in fact, suppress malaria [16]. Meningitis is unlikely to be a major cause of death [1]. The real impact of malaria infection on mortality is unknown in Bissau. However, since it could be important, we examined whether there was a seasonal difference in the mortality pattern for exposed children and controls, which could suggest a major role of malaria. We found no such tendency (data not shown).

In conclusion, there is no indication that the impact of early exposure to measles can be explained as a result of some confounding. When initial weight was taken into consideration, exposed children were 4–6 times more likely to die than community controls. Maternal education was no different in the exposed children and the control group and inclusion of maternal education in the analysis did not alter the estimate of the MR [1]. The MR remained unchanged when adjustment was made for measles vaccination. Hence, it is not merely the weakest children or those receiving the least attention from the mother who are most affected by exposure. Under the conditions in Bissau, any child can suffer the adverse effects of early intensive exposure. The mechanisms through which early exposure leads to later mortality are not known. From the evidence presented in this paper, growth faltering and subsequent increased susceptibility to other infections is not the prime cause for excess mortality among exposed children. Given the delayed mortality following exposure to measles before 6 month of age [1, 3], following intensive exposure to natural measles [17] and following high-titre measles vaccination [6, 7], further studies of the underlying mechanisms are warranted.

ACKNOWLEDGEMENTS

Data from Guinea-Bissau was collected in a study jointly organized by the Ministry of Health, Guinea-Bissau, and the Swedish Agency for Research Co-operation with Developing Countries (SAREC). The authors wish to thank the following persons: Dr M. Boal and Dr P. Medina of the Ministry of Health, Guinea-Bissau, for their interest in and support of the work; the late Jette Bukh, Dr Ida Lisse, Dr Lars Smedman and Arjon J. Smits, who participated in the first phase of the project; Carolina Barbosa, Flora Co, Matarina Co, Manuel Fernandes, Maria-Rosa Fernandes, Armando Gomes, Joaquim Gomes, Francisco Indi, Joana Lopes, Eugenio Pereira, Angelina da Silva, Mariano Soares da Gama, and Fatima Ture, who assisted in the collection of data; and Dr Kim F. Michaelsen who made helpful comments to a previous version of the manuscript. Support: The study and statistical analyses were supported by the Danish Council for Development Research; the Danish Medical Research Council; the Danish Social Science Research Council, and the Science and Technology for Development Programme of the European Community (TS3*-CT91-0002).

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