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No Long-term Excess Mortality after Measles Infection: A Community Study from Senegal

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Because measles immunization has been found in all studies to reduce mortality with more than the share of deaths attributed to acute measles, the authors examined mortality after measles infection in a study in a rural area of Senegal that included 6,924 unimmunized children, of whom 1,118 developed measles. Age-adjusted post-measles mortality was similar to the mortality of unvaccinated, uninfected children (mortality ratio (MR) = 1.04, 95% confidence interval (CI) 0.80–1.35). When controlling for source of infection, mortality rate was significantly different for children who contracted measles from a person outside the home (index cases vs. unvaccinated, uninfected MR = 0.27, 95% CI 0.09–0.85) and for children infected at home (secondary cases vs. unvaccinated, uninfected MR = 1.10, 95% CI 0.80–1.51). Hence, secondary cases had markedly higher long-term mortality than did index cases (MR = 4.13, 95% CI 1.26–13.58). These estimates were essentially unchanged when the effects of season, period, separation from mother, size of community, and size of compound were investigated using a multivariate Cox regression model. The authors conclude that measles infection was not associated with increased mortality after the acute phase of infection and that index cases had lower mortality than uninfected, unvaccinated children. The reduction in mortality after measles immunization can therefore not be explained by the prevention of post-measles mortality. *Am J Epidemiol* 1996;143:1035–41.

immunization; infection; measles

Studies from West Africa have reported measles infection to be associated with major delayed mortality after the acute phase (1–3). In studies from many developing countries, including Guinea-Bissau (2, 4), Zaire (5), Senegal (6), Bangladesh (7), and Haiti (8), measles immunization has been associated with reductions in overall childhood mortality of 30 percent or more, which is considerably more than the share of all deaths attributed to acute measles. This extra benefit from measles immunization has been ascribed to the prevention of the negative long-term consequences of measles infection (2, 3, 7).

However, studies of long-term mortality after measles infection have had small numbers and have not adjusted for possible confounding factors, particularly the impact of immunization status (3). Furthermore, to our knowledge, no study has examined prospectively the timing, extent, and risk factors associated with excess mortality.

Studies of long-term mortality after measles have acquired additional interest, because recent studies of high-titer measles vaccines from West Africa and Haiti have reported increased mortality for the recipients of high-titer vaccines compared with children who received standard low-titer or medium-titer measles vaccine (6, 9, 10). This tendency has not been found in areas with low background mortality (11, 12). It has been speculated (10, 13) that high-titer vaccine could possibly have a long-term negative impact on the immune system, as also suspected after measles infection. The present study examines long-term survival after measles infection in a rural area of Senegal, Niakhar, where measles transmission and acute mortality was studied between 1983 and 1986 (14, 15).

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Abbreviations: CI, confidence interval; df, degrees of freedom; MR, mortality ratio.

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MATERIALS AND METHODS

Background

The study area, which has a population of 24,000 inhabitants, has been under demographic surveillance since March 1983 (14). The demographic surveillance system included annual censuses in all compounds in the study area to detect new births, migrations, mar-

riages, and deaths. Information on infections (measles and whooping cough) and immunizations was also obtained on this occasion. The area is populated almost exclusively by the Sereer, who live in compounds with an average of 14 persons. Larger compounds are usually divided into multiple separate households. Within a household, people may sleep in different huts.

Investigation of measles epidemiology and measles immunization

As described in detail elsewhere (14, 15), all cases of measles reported in the annual census were investigated during home visits to determine the source of infection and the pattern of transmission within the compound. A total of 1,500 cases were detected in the period from 1983 to 1986. As a result of long intervals between epidemics of measles, the age at infection proved to be high (14–16). The present study is based primarily on parental reports. However, these reports are likely to be correct as there are very few reports of reinfections with measles among children with a previous history of measles; during 1987–1990, when virtually all cases were confirmed by a physician (17), 62 children who had measles during 1983–1986 were exposed to measles again and only one child developed measles (15). There are other indications that parental diagnoses are reliable, i.e., high secondary attack rates and high cumulative incidence (14, 16).

The first case (index case) was identified, and the mother was asked about the probable source of infection. Children were classified as secondary cases if their rash occurred 6 or more days following the rash of an index case. In the main analysis, we have distinguished only between index and secondary cases in the compound. Exposure was classified for 87.3 percent of the documented cases. Children with unknown exposure status had mostly contracted measles outside the study area (14).

Measles vaccine coverage was poor during the period studied (14). A few well-defined campaigns were carried out in certain villages by development projects, mainly during the dry seasons in 1979, 1981, 1982, and 1983. Information on immunizations both inside and outside the study area was obtained in the annual censuses.

Study population: measles cases and controls

The present study compares post-measles mortality of unimmunized children with mortality of unimmunized children who had not had measles. In order to maximize the number of controls, all children were included as controls until they developed measles, received immunization, or were censored for other reasons. Hence, children who received measles immunization or developed measles infection were excluded from the control group from the date of immunization or infection.

In previous analyses of the determinants of mortality (14, 15), children who died within 6 weeks were considered acute deaths. The present study examines post-measles mortality, i.e., the mortality from 43 days after measles. Because few children had measles before 6 months of age (14), the comparison was only made from 6 months of age. After the initiation of the national immunization campaign at the end of 1986, mortality levels changed dramatically in the study area. It was therefore decided to censor follow-up in December 1986. Post-measles cases were followed from 43 days after infection to death, migration, or December 1986. Controls were followed from the first census in 1983 or age 6 months, if born during the period of surveillance, to death, immunization against measles, migration, or December 1986.

In the initial census in 1983, information on measles infection prior to the study was only obtained systematically for children born since 1978. Because we wanted to analyze mortality after 6 months of age for children who had not had measles prior to the study, the analysis was restricted to children born from January 1978 onward. Children born during the study until March 1986 were also included in the analysis. The youngest child who had measles in the period 1983–1986 was born in March 1986. A total of 8,892 children born between January 1978 and March 1986 were registered in the study area. After exclusion of children registered after December 1, 1986, children who were censored before 6 months of age, and children who had measles or had been immunized before entry, 6,924 children remained for the survival analysis. Children who were immunized against measles before the end of the study were excluded from the day they received measles vaccine. Of the 1,500 measles cases registered between 1983 and 1986 (14, 15), 1,118 belonged to the group born from January 1978 onward and who had not been immunized against measles.

Statistical methods

Crude analyses of differences in long-term post-measles mortality were based on deaths in relation to person-years-at-risk in different age groups. Multivariate Cox regression analyses (18) were used to control for the effect of background factors. Age is used as the time scale in the Cox regression model. The analyses were stratified for sex to allow for non-proportional mortality for each sex. A child was considered under

risk from 6 months of age or from the age at entry if after 6 months of age, until death, migration, or December 1986. A child with measles was considered at risk for post-measles mortality from 42 days after the onset of measles infection. Effects are expressed as mortality ratios and 95 percent confidence intervals. The post-measles mortality effect was modeled using a time-dependent covariate. The effect of time-since-measles (time-dependent: 0–12 months, >12 months), and risk factors for severity of acute measles infection (time-independent: sex, age at infection, intensity of exposure (10), generation within the compound (10), and cross-sex transmission (11)) have been modeled by the interaction of the factor and the time-dependent post-measles variable. The analysis also included factors known to affect measles incidence (time-independent: size of village) and child mortality (time-dependent: season (July-October (rain) vs. November-June (dry)), and separation from the mother; time-independent: size of compound, maternal education, and period (first and second half of the period from 1983 to 1986)). To evaluate the effect of exposure, a separate analysis was performed where children with unknown exposure were excluded. Because the study included cases between 1983 and 1986 and follow-up was censored in December 1986, maximum follow-up was 3.7 years. The median follow-up after the acute phase of measles was 523 days (range, 1–1,348 days).

RESULTS

Study population and incidence of measles

In the study from 1983 to 1986 of acute measles mortality (14), there were 1,500 cases, of whom 1,118 were unimmunized children born after January 1978. The median age at infection was 43 months. For unimmunized children, the cumulative incidence of measles was 19.2 percent and 33.2 percent, respectively, at ages 3 and 5 years. At age 3 years, there was no difference in cumulative incidence (20.3 percent vs. 19.2 percent) using data from the children born during the study and the children born before the beginning of the study in March 1983. The acute case fatality ratio was 8.6 percent for unimmunized children (table 1); secondary cases had a much higher case fatality ratio than index cases in the compound (mortality ratio (MR) = 2.48, 95 percent confidence interval (CI) 1.22–5.04).

Of the 1,118 unimmunized measles cases born after January 1978, 96 children died in the acute phase and 13 had no post-measles follow-up because they were guests or moved at the time of measles infection, leaving 1,009 children to be included in the post-measles survival analysis; 199 children were index cases, 695 were secondary cases, and 185 had unknown exposure.

Crude analysis of post-measles mortality

Mortality in the post-measles period and in the control group of unimmunized children is indicated in table 2. There was no excess mortality in the post-measles groups compared with unvaccinated controls (MR = 1.04, 95 percent CI 0.80–1.35) (table 2). Because we have previously found (14) that intensity of exposure was important for acute mortality and mortality during the first year after infection, long-term survival has also been examined in relation to the intensity of exposure to measles. Index cases had significantly lower mortality than community controls without a history of measles (MR = 0.27, 95 percent CI 0.09–0.85), whereas secondary cases had the same mortality as controls (MR = 1.10, 95 percent CI 0.80–1.51). Hence, secondary cases had markedly higher long-term mortality than did index cases (MR = 4.13, 95 percent CI 1.26–13.58). Postmortem interviews (6) have shown that most childhood deaths in Niakhar are related to diarrhea, malaria, pneumonia, and malnutrition. Apparently, index cases had lower mortality for all of these causes. However, with the

TABLE 1. Acute case fatality ratios for measles cases according to exposure, Niakhar, Senegal, 1983–1986

Age group	No. of deaths/no. of cases (case fatality ratio)			
	Index	Secondary	Other cases*	All cases
0–5 months	0/4 (0.0)	2/23 (0.087)	1/9 (0.111)	3/35 (0.086)
6–23 months	4/61 (0.066)	30/212 (0.142)	11/115 (0.096)	45/389 (0.116)
2–4 years	4/95 (0.042)	35/345 (0.101)	6/66 (0.091)	45/506 (0.089)
5–9 years	0/52 (0.0)	3/118 (0.025)	0/18 (0.0)	3/188 (0.016)
Total	8/212 (0.038)	70/698 (0.100)	18/208 (0.087)	96/1,118 (0.086)

* Cases infected at a health center/hospital or cases without information on exposure. Most of these cases had measles outside the study area.

TABLE 2. Numbers of deaths, person-years-at risk, and annual mortality rates for post-measles cases, according to exposure, and unvaccinated controls, Niakhar, Senegal, 1983–1986

Age group	No. of deaths/person-years-at-risk (no.*) (annual mortality rate)				
	Index	Secondary	Other cases†	All cases	Controls
Girls					
6–23 months	0/13.1 (21) (0.000)	5/57.0 (81) (0.088)	8/24.5 (54) (0.331)	13/94.3 (156) (0.138)	188/2,231.2 (2,345) (0.084)
2–4 years	2/68.9 (59) (0.029)	12/214.5 (212) (0.056)	4/70.3 (68) (0.057)	18/353.7 (339) (0.051)	113/2,766.4 (2,165) (0.041)
5–9 years	1/48.1 (42) (0.021)	2/173.4 (145) (0.012)	0/15.4 (18) (0.000)	3/236.9 (205) (0.013)	15/1,272.3 (833) (0.012)
Boys					
6–23 months	0/20.6 (32) (0.000)	7/76.4 (111) (0.092)	3/30.3 (47) (0.099)	10/127.3 (190) (0.079)	186/2,378.1 (2,483) (0.078)
2–4 years	0/70.4 (71) (0.000)	13/254.3 (241) (0.051)	3/70.4 (70) (0.043)	16/395.1 (382) (0.040)	158/2,724.9 (2,198) (0.058)
5–9 years	0/94.0 (60) (0.000)	2/177.1 (150) (0.011)	0/23.0 (22) (0.000)	2/294.1 (232) (0.007)	9/1,273.8 (808) (0.007)
Total					
6–23 months	0/33.7 (53) (0.000)	12/133.3 (192) (0.090)	11/54.5 (101) (0.202)	23/221.5 (346) (0.104)	374/4,609.3 (4,828) (0.081)
2–4 years	2/139.3 (130) (0.014)	25/468.8 (453) (0.053)	7/140.7 (138) (0.050)	34/748.8 (721) (0.045)	271/5,491.3 (4,363) (0.049)
5–9 years	1/142.1 (102) (0.007)	4/350.5 (295) (0.011)	0/38.5 (40) (0.000)	5/531.1 (437) (0.009)	24/2,546.0 (1,641) (0.009)

* Number of children who contributed to person-years-at-risk in this age group. Because a child may have contributed to follow-up time in several age groups or may have been a control first only to become a case later, numbers do not add up to the total number of children in the study.

† Cases without information on exposure. Most of these cases had measles outside the study area.

limited number of index cases, there was little power to detect differences by type of pathology.

Because girls in Niakhar have been found to have higher acute measles mortality (15) and to have higher mortality after high-titer measles vaccination (6), differences in post-measles mortality by sex were also examined (table 2). Although not a significant difference, girls tended to have higher post-measles mortality than boys (MR = 1.47, 95 percent CI 0.89–2.44). However, when the children were followed for another 5 years, to February 1992, there were 21 male deaths and eight female deaths among post-measles cases, of whom at least nine had been immunized during the campaign in 1986–1987. Hence, there was no sign of a long-term difference in post-measles mortality by sex.

Multivariate analyses

Season and separation from mother were significant determinants of mortality. Neither size of compound, size of village, period, maternal education, age at infection, time-since-measles, nor interaction between sex and post-measles mortality were significant. Adjusting for the significant background factors (table 3), the mortality ratio for all post-measles cases was 1.04 (95 percent CI 0.80–1.35) compared with uninfected children. Because age was the time scale and the Cox model was stratified for sex, estimates were also adjusted for age and sex. There was no significant difference between mortality ratios for post-measles girls (MR = 1.34, 95 percent CI 0.94–1.93) and post-measles boys (MR = 0.81, 95 percent CI 0.55–1.20) (likelihood-ratio test: chi-square = 3.49, degrees of freedom (df) = 1, $p = 0.062$). Neither cross-sex transmission nor generation was associated with significant variation in post-measles mortality levels among secondary cases.

When only measles cases with known exposure were included, the mortality ratio for index and secondary cases compared with uninfected children was 0.94 (95 percent CI 0.69–1.28). When the interaction between post-measles mortality and exposure was included (table 3), it was found that the estimates were significantly different (likelihood ratio test: chi-square = 8.23, df = 1, $p < 0.01$), with index cases having lower mortality (MR = 0.28, 95 percent CI 0.09–0.87) than unvaccinated controls and secondary cases having a mortality ratio similar to that of controls (MR = 1.14, 95 percent CI 0.83–1.57).

TABLE 3. Multivariate Cox regression analysis of the mortality ratios (95% confidence intervals (CI)) for post-measles cases compared with unvaccinated controls, controlling for background factors, Niakhar, Senegal, 1983–1986

Case status or background factor	All measles cases		Only cases with known exposure	
	Mortality ratio	95% CI	Mortality ratio	95% CI
Baseline: no measles	1.00		1.00	
Post-measles	1.04	0.80–1.35		
Index cases			0.28	0.09–0.87
Secondary cases			1.14	0.83–1.57
Season				
Baseline: dry	1.00		1.00	
Rainy	1.73	1.50–2.00	1.72	1.49–1.99
Separation from mother				
Baseline: with mother	1.00		1.00	
Not with mother	2.44	1.54–3.86	2.05	1.22–3.42

DISCUSSION

Several studies have suggested that measles is associated with delayed mortality (1–3, 7). Post-measles excess mortality has been assumed to explain why measles immunization reduces mortality with more than the share of all deaths attributed to acute measles (2, 3, 7). Our observations from rural Senegal contradict these assumptions. Among children who had measles between 1983 and 1986, post-measles cases did not have higher mortality than unimmunized controls. Adjustment for risk factors for child mortality made no difference to the mortality rate ratios between post-measles cases and unvaccinated, uninfected controls (table 3).

Apart from possible misclassifications in the original assessment of exposure status (14), there seem to be few methodological reasons to question the observation that index cases had significantly lower post-measles mortality than secondary cases. However, the comparison of post-measles cases with uninfected, unimmunized children could be biased if many unreported measles deaths, measles cases, or measles immunizations had occurred in the comparison group. Unreported measles deaths in the comparison group would mean that post-measles cases did have higher mortality than uninfected children. However, measles disease is a well-recognized disease in this area (14–16), and deaths from clinical measles are unlikely to have been missed, because interviews about the cause of death were conducted with the parents of all children who died. If connected with high mortality, many subclinical measles infections could lead to an exaggerated mortality rate in the comparison group because subclinical cases would only be found in this group. However, subclinical cases are milder and most occur before 6 months of age while the children still have maternal antibodies (19) and would therefore not affect the present comparison from 6 months of age. Because the cases detected during the study did not have excess mortality after measles, it seems unlikely that the reclassification of controls misclassified as uninfected would fundamentally change the mortality ratio between post-measles cases and uninfected children.

In a study conducted in Niakhar between 1987 and 1990, 33 percent of the "uninfected, unimmunized" children exposed to measles had antibodies to measles (17). These children were significantly older, had lower levels of measles antibodies, and higher secondary attack rates after exposure to measles at home than other children with documented immunization and measles antibodies. Because children are expected to have higher antibody levels and better protection after natural measles, it seems most likely that these uninfected, unimmunized children acquired measles antibodies through undocumented immunization during campaigns (6) or outside the study area in the past. Although many of these immunizations may have been a result of the accelerated immunization campaigns in the beginning of 1987 (6), undocumented immunizations may also have occurred in the 1983–1986 period covered by the present study. Measles immunization is associated with low mortality (6, 7), so that adjustment for an important underreporting of immunizations would mean higher mortality among unimmunized, uninfected children compared with post-measles cases.

Given annual reporting of the measles cases, the delay between infection and subsequent death could have been misreported by the parents with the effect of increasing acute mortality and reducing post-measles mortality. However, parents or guardians were asked

specifically about the delay between measles disease and death. Furthermore, a similar reporting bias could not produce low mortality for index cases in both the acute phase (table 1) and the post-measles period (table 2).

The age at infection was high in the present community study and this could have influenced the estimate of post-measles mortality. There was no interaction between age at measles infection and post-measles mortality. However, post-measles mortality could be somewhat greater for children who had measles at an early age (table 2). Only larger studies will be able to assess whether young age at infection is important for the long-term impact of measles.

The contrast between the present study and previous studies that have reported higher post-measles mortality (1–3) is hard to judge because these studies mainly compared post-measles cases and immunized controls. For example, post-measles cases in Guinea-Bissau had significantly higher mortality than community controls who had received measles vaccine (2). However, compared with unimmunized controls, post-measles cases tended to have lower mortality (MR = 0.45, 95 percent CI 0.14–1.43)) (2). Subsequent studies from Guinea-Bissau, Senegal, Bangladesh (unpublished observations), and Burundi (20) have likewise failed to find higher post-measles mortality.

Index cases had very low post-measles mortality (table 2). Even allowing for some misclassification of infection and immunization status, it seems unlikely that the mortality level in the group of uninfected, unimmunized children would come near the level among post-measles index cases. Because index cases had low mortality in the acute phase of measles, low post-measles mortality among index cases cannot be due to a "selection" of stronger children, the weak ones having died already during measles infection. We may therefore have to look for another explanation of the low post-measles mortality among index cases. While measles may be associated with adverse long-term consequences in some individuals, e.g., aggravation of tuberculosis (21), measles infection and measles vaccine may also stimulate the immune system (22), for example, reducing prevalence and density of malaria parasitemia during acute infection (23). The net impact of such immune activation could be beneficial.

The absence of excess post-measles mortality questions current beliefs about measles infection and immunization. If prevention of excess mortality after measles infection does not explain the marked reductions in childhood mortality associated with standard measles vaccination (2–8), live measles vaccine may have nonspecific beneficial effects on the immune system, providing some protection against other infections than measles (24, 25). The lack of increased post-measles mortality makes it unlikely that the reduced survival after high-titer vaccine (6, 9, 10) should be a result of persistent immunosuppression due to the vaccine (11, 13, 26). Whereas high-titer vaccines were associated with reduced survival only for girls (6), there was no long-term difference in post-measles mortality by sex in the present study. Hence, an alternative explanation of the surprising increase in mortality after high-titer measles vaccine could be that high-titer vaccine does not have the same beneficial effect as standard vaccine (25), an effect which may be particularly strong for girls (6, 27).

In the Niakhar study, the net impact of measles was negative because acute mortality was high (14). However, it should be noted that even if the eight acute and the three post-measles deaths were combined, there was no excess mortality for index cases compared with uninfected children. Although this may rarely occur in developing countries, the net impact of natural measles might be beneficial in situations with no acute mortality and many index cases. If infections and immunizations can protect against more than the specific disease, it is not enough to measure seroconversion after vaccination to decide on the best immunization policy. It will be necessary to assess the total impact of a new vaccine on morbidity and mortality (28).

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