

Pattern of Exposure and Measles Mortality in Senegal

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In a rural area of Senegal, 1500 cases of measles and 98 deaths (6.5%) were registered during a 4-year period (1983–1986). For children <5 years old, the acute case fatality ratio (CFR) was 9.6%. Compared with index cases who contracted measles in the village, secondary cases infected within the compound had a significantly higher mortality (odds ratio [OR], 2.9; 95% confidence interval [CI], 1.3–6.1). The CFR of secondary cases increased with the closeness of contact with the index cases; the ORs were 1.9 (CI, 0.6–6.0) for children living in the same compound but not the same household, 2.3 (CI, 1.0–5.7) for children living in the same household but not in the same hut, and 3.8 (CI, 1.7–8.4) for children living in the same hut. In large compounds with many cases, the CFR increased exponentially through the succession of generations; the ORs were 2.3 (CI, 1.0–5.2) in the second generation, 3.7 (CI, 1.1–3.0) in the third generation, 5.5 (CI, 1.7–18.1) in the fourth generation, and 16.1 (CI, 5.6–46.3) in the fifth or later generations. Postmeasles mortality through the year following measles infection was also significantly related to the intensity of exposure. Differences in exposure may be a major determinant of child survival, both at time of acute disease and for the long term impact of measles infection.

Several studies have suggested that overcrowding and intensive exposure are major determinants of acute measles mortality [1, 2]. In these studies, malnutrition had been of less importance. Reanalyses of data collected in Guinea-Bissau [3], Senegal [4], The Gambia [5], Bangladesh [6, 7], the UK [8], and Denmark [9] have consistently found mortality to be higher in families with several cases and higher among secondary cases (i.e., children infected at home). Intensive exposure may increase the severity of infection, possibly due to a dose effect [3, 8]. If this hypothesis is true, differences in exposure patterns may help explain much of the observed variations in measles mortality, for example, why measles case-fatality ratios are higher in West Africa than in developing countries elsewhere, higher in rural areas than in cities, and higher in institutions than in families [1, 3].

Previous studies have reanalyzed existing data where information on exposure was often insufficient. The present study was undertaken in a rural area of Senegal with the objective of studying variations in exposure and their impact on mortality. Two hypotheses were tested among secondary cases in a compound: (1) the closer the contact between a secondary case and its infection source case, the higher the mortality of the secondary case (more intense exposure) and (2) the

more severe the infection of the infecting source case, the higher the mortality of the secondary case (more severe exposure), whether the infecting source case was itself index or secondary within the household.

Subjects and Methods

The environment. The study was conducted in a rural area of Senegal, in a set of 30 villages near Niakhar (region of Fatick). This area of ~24,000 inhabitants has been under demographic surveillance since March 1983. The study area is populated almost exclusively by the Sereer (95.3% of residents). The Sereer are farmers and herders, growing millet and peanuts and raising cattle. The area is a rather dry orchard savannah (400 mm of rainfall/year). Sereer live in small villages, often divided into smaller hamlets of a few compounds. As a result of the scattered settlement pattern, annual measles epidemics occur in only parts of the area, whereas small villages have measles outbreaks only once every 5–10 years. This creates a wide range of ages at infection: from birth to 29 years during the 4 years of investigation (1983–1986).

Sereer compounds have an average of 14.0 persons, an outstandingly large number compared with other societies [10]. There is a wide variety of structures, from the single-person compound (usually an old person) to a very large compound (>100 people) divided into multiple separate households that are defined as people who eat together. Large compounds result from the strong kinship relationships and widespread polygamy, whereby a patriarch can include in his compound his adult sons and his sisters' sons and other relatives. Married men have an average of 1.8 wives (range, 1–7); women have many children (total fertility rate = 7.8 children on the average over a lifetime) and may also care for foster children. Hence compounds often have 5–10 or more children susceptible to measles; a maximum of 21 measles cases was recorded in one compound.

People usually eat outside, sitting on the ground, and use their

Received 13 February 1989; revised 4 January 1990.

Financial support: Unité de Recherche Population et Santé of ORSTOM.

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The Journal of Infectious Diseases 1990;161:1088–1094

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0022-1899/90/6106-0006\$01.00

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hands to get food from the same calabash. Women and young children eat separately from men. They sleep in small huts that have one to three beds and can accommodate 1-8 persons. This is an average of 8.0 persons per household and 2.5 persons per hut.

Vaccine coverage against measles was poor over the study period. There were major vaccination campaigns from 1978 to 1982, at time of the beginning of the Expanded Programme on Immunization, and again from 1987 to 1989 during the so-called "acceleration phase." Over the 1983-1986 period, during which this study was conducted, less than one-third of the susceptible population aged birth to 14 years was protected by vaccination. There is no indication that the prevalence of human immunodeficiency virus (HIV) infection was high over the study period; in 1987 it was found to be 5:1000 among pregnant women. HIV infection is therefore unlikely to have contributed significantly to the high measles mortality.

The investigation of measles transmission. The study started in March 1983 and ended in December 1986. The demographic surveillance system based on annual censuses has been described elsewhere [11-13]. In addition to demographic events, it routinely records cases of measles and pertussis. Sereer people, as do many West African people, recognize measles accurately and pay much attention to transmission of infection. The present study is primarily based on parental report. Previous studies in this area have indicated that >95% acquire measles before age 15, which suggests that under-reporting of measles cases is minimal [14].

All cases reported by parents and examined by a physician were confirmed after a proper clinical examination as in other studies in West Africa [15]. Other cases not seen by a physician were usually epidemiologically linked to cases in the same compound or in the same village. Due to lack of infrastructure, no samples for laboratory confirmation were taken during this period. However, from 1987 to 1989 a measles vaccine trial was undertaken and the same kind of epidemiologic investigation was conducted in the same villages by the same team: All measles cases for which two blood samples were available were serologically confirmed. Death was attributed to measles if it occurred within 6 weeks after the onset of the rash (measles case fatality). For the present analysis, postmeasles mortality at 6-52 weeks after infection was also examined.

Each year after the annual census, we returned and investigated all reported cases of measles to determine the source of infection and the pattern of transmission within the compound. In each compound the list of reported measles cases was checked. The first (index) case was identified and the mother was asked about the probable source of infection. Other children were classified as secondary cases if their rash occurred 6-16 days after the rash of an index case or as coindex cases if their rash occurred within 6 days. Mothers usually had a good recollection of the intervals between different disease episodes: Usually cases occur by generations ~12 days apart, during which children develop measles within 1-3 days from each other. Further, generations can be easily distinguished because mothers traditionally do not wash sick children before the end of the rash (~8 days after onset); it was easy to ask if the next child started his rash before or after the previous one had been washed. In many compounds several parents were interviewed, and there was rarely disagreement about the relative order of events or generations. In a number of cases, intervals between successive generations of cases could be checked and confirmed in dispensary registers.

Cases were classified as (1) index cases in a compound; (2) sec-

ondary case in a compound (living in the same compound but not in the same household, living together but not eating together); (3) secondary case in a household (living in the same household but not in the same hut, eating together but not sleeping together); or (4) secondary case in a hut (living in the same hut, sleeping under the same roof). A few cases of children from the same mother who were not sleeping under the same roof were added to this category because siblings were expected to interact more among themselves than with others.

The three categories of secondary cases reflect important differences in the frequency and closeness of contacts between children that are presumably of increasing intensity. Children who had measles outside the area have not been classified with respect to exposure.

Index cases in the compound were classified into three categories depending on the source of infection: (1) children infected in the village (during a local ceremony, playing with other children in the village, at school); (2) children infected during travel outside the village; and (3) children infected at the dispensary. In the first index category, children presumably had a relatively short contact with the infecting source case. Children infected during travel may have had a short contact while traveling or may have received intensive exposure in another home where they stayed. Children infected at the dispensary were considered a separate category because presumably they were exposed to children who had more severe measles and they were already sick at the time of infection.

As in other studies of transmission of measles [3], the closest source of infection has been considered the most likely. Thus, if a child developed measles within 6-16 days after another case in the same compound, the child is considered a secondary case, even though he or she could have been infected by another child in the village. When several simultaneous sources of infection existed within the compound, the closest one is considered the most likely; for example, if there were two possible index cases, one in the same hut and the other in another hut, the source of infection is considered the child from the same hut. The same holds for index cases; for example, if a child visited the dispensary before onset of measles, he or she is considered to have been infected at the dispensary even if other potential contacts existed in the village.

The study of transmission showed that there could be several generations of measles infection within a compound. A generation was defined as a group of children who developed measles at about the same time, usually from the same person. In small compounds there were commonly two generations: the generation of the index or the few coindex cases, and the generation of the secondary cases infected by the index cases. In large compounds several generations could be identified. For example, an index case could infect two children in the same household; one of these might in turn infect a playmate from another household, who might further infect other roommates sleeping in the same hut. This pattern occurs because parents tend to isolate sick children, efficiently enough to reduce transmission but not to interrupt it. Measles can last for >2 months in large compounds (five generations or more).

The number of cases within the compound was also considered for the statistical analysis as a simple control. The total number of cases in the compound should be correlated with the risk of intensive exposure but is independent of the interpretation of transmission within the compound. The rank within the compound (i.e., the order in which cases occurred, whatever the delay between them)

Table 1. Age-specific case fatality ratios from measles and postmeasles mortality, Niakhar, 1983-1986.

Age at measles onset, years	Measles case fatality			Postmeasles mortality		
	Cases, no.	Deaths, no.	Ratio (:1000)	Cases, no.	Deaths, no.	Ratio (:1000)
0-0.5	36	3	83.3	33	2	60.6
0.5-1.0	129	16	124.0	113	9	79.6
1.0-1.5	140	16	114.3	124	9	72.6
1.5-2.0	127	13	102.4	114	7	61.4
2.0-2.5	102	14	137.3	88	8	90.9
2.5-3.0	111	15	135.1	96	2	20.8
3.0-3.5	90	10	111.1	80	3	37.5
3.5-4.0	73	2	27.4	71	0	
4.0-4.5	77	0		77	0	
4.5-5.0	81	4	49.4	77	3	39.0
5.0-5.5	66	3	45.5	63	1	15.9
5.5-10	341	2	5.9	339	2	5.9
10-15	93	0		93	0	
15-30	34	0		34	0	
All ages	1500	98	65.3	1402	46	32.8

was also considered as a proxy for the risk of intensive and severe exposure. However, these variables do not have any clear epidemiologic interpretation as is the case for intensity and generations.

Statistical methods. The risk of death was analyzed using a linear logistic regression model where the independent variables were age, intensity of exposure, generation, total number of cases, and rank within compound. Data were processed on a microcomputer using SYSTAT supplementary modules (LOGIT).

Results

The pattern of measles transmission. Of the 1500 cases detected, 190 (12.7%) had no adequate information on exposure, usually because the child had measles outside the area. Secondary cases accounted for 60.5% of cases (908) of all ages combined; they were infected in general by a resident member, sometimes by a visitor (4.1% of cases). Of the 402 index cases, 320 (79.6%) were infected in the village: children playing together outside or in another infected compound (77.9%), at school (14.6%), or during a local ceremony or gathering of people (7.5%). Other index cases were infected during a travel in the local buses or during a visit to relatives (14.2%). In rare cases, children were infected at the dispensary (6.2%). An index child infected on the average 3.5 children in the same compound. This number did not vary by pattern of transmission. The high proportion of cases infected within the compound is an important feature of measles transmission in West Africa.

The pattern of transmission varied with age. Young children were more likely to be infected when traveling with their mother or when going to the dispensary. By contrast, older children were more likely to be infected in the village or at school.

Case fatality in acute measles. There were few cases and deaths before age 6 months, all between 4 and 5 months; between 6 and 42 months, the case-fatality ratio reached a high of 12.0%. Mortality was much lower thereafter and only two deaths were recorded at ≥ 66 months (table 1). Since mortality varied strongly with age, four age groups were used for analysis: 4-5 months, where levels of maternal antibodies usually protect the children; 6-41 months, where most deaths occurred; 42-65 months, with a lower mortality rate; and ≥ 66 months, with very few measles deaths.

Acute mortality and exposure. The pattern of acute measles mortality varied greatly according to the source of infection (table 2). For index cases, those infected in the village, usually while playing in the open air with infected children, had the lowest case fatality. They are considered the reference category. For secondary cases, there was a gradual increase in case fatality with increasing intensity of exposure; the odds ratios (ORs) for cases secondary in compound were 1.9 (95% confidence interval [CI], 0.6-6.0) compared with children infected in the village, 2.3 (CI, 1.0-5.7) for secondary cases in household, and 3.8 (CI, 1.7-8.4) for secondary cases in hut. For all secondary cases grouped together, the OR was 2.9 (CI, 1.3-6.1) compared with the index cases infected in the village.

Among other index cases, those infected at the dispensary had the highest case fatality; among them there was a high proportion of children already sick at the time of exposure and they have been analyzed separately. Those infected outside the study area had an average mortality, which presumably reflects their more varied exposure. Some were probably infected in the open air, others in buses, and others were clearly secondary cases in a household outside of the area and for which no proper examination could be conducted.

Table 2. Measles case fatality and age-standardized odds ratios (OR) according to pattern of exposure, Niakhar, 1983-1986.

Pattern of exposure	No. of deaths at <6 weeks/no. of cases by age at measles onset, months				Mantel-Haenszel estimates		
	4-5	6-41	42-65	≥66	OR	χ ²	P
Index cases							
Village	0/4	8/115	0/79	0/122	1.000	(reference)	
Travel	0/0	3/32	0/9	0/16	1.384	0.006	NS
Dispensary	1/3	4/17	0/2	0/3	4.841	4.316	.0378
Subtotal	1/7	15/164	0/90	0/141	1.432	0.337	NS
Secondary cases							
Compound	0/2	10/89	1/50	0/62	1.891	1.189	NS
Household	0/6	18/152	4/66	0/86	2.339	3.526	.0604
Hut	2/15	31/174	4/77	2/129	3.763	11.002	.0009
Subtotal	2/23	59/415	9/193	2/227	2.872	7.352	.0067
Other, unknown	0/6	10/120	0/14	0/50	1.216	0.023	NS
Total	3/36	84/699	9/297	2/468	2.258	4.218	.0400

NOTE. NS, not significant.

Table 3. Postmeasles mortality and age-standardized odds ratios (OR) according to pattern of exposure, Niakhar, 1983-1986.

Pattern of exposure	No. of deaths at 6-52 weeks/no. of cases by age at measles onset, months				Mantel-Haenszel estimates		
	4-5	6-41	42-65	≥66	OR	χ ²	P
Index cases							
Village	0/4	2/107	1/79	0/122	1.000	(reference)	
Travel	0/0	3/29	0/9	0/16	4.779	1.957	NS
Dispensary	0/2	0/13	0/2	0/3	—	—	—
Subtotal	0/6	5/149	1/90	0/141	1.521	0.060	NS
Secondary cases							
Compound	0/2	11/79	0/49	0/62	5.574	6.587	.0103
Household	0/6	4/134	2/62	0/86	2.196	0.688	NS
Hut	1/13	9/143	1/73	2/127	3.564	3.190	.0741
Subtotal	1/21	25/356	3/184	2/275	3.463	3.758	.0526
Other, unknown	1/6	8/110	0/14	0/50	3.916	2.600	NS
Total	2/33	38/615	4/288	2/466	2.954	2.791	NS

NOTE. NS, not significant.

The detailed analysis by age was also striking. Both deaths at >66 months occurred among secondary cases in hut; two of the deaths at <6 months also occurred in the same category and one among the children infected at the dispensary. All nine deaths between 42 and 65 months occurred among secondary cases, four among cases secondary in household and four among cases secondary in hut.

Postmeasles mortality. The pattern was similar for postmeasles mortality (deaths 6-52 weeks after the onset of measles infection). Although the pattern was not as regular, secondary cases had a significantly higher postmeasles mortality than children infected in the village (OR; 3.5; CI, 1.0-12.4; table 3). However, by detailed intensity of exposure, only secondary cases within compound had a significantly higher mortality.

The analysis by number of cases in the compound confirmed these results. For both acute and postmeasles mortality, there was an increase in age-standardized ORs of deaths according to the number of cases that occurred in the compound. Results were significant for a high number of cases: 5-9 and ≥10 cases for acute mortality and ≥10 cases for postmeasles mortality (table 4).

The successive generations effect. The effect of generations was very striking (table 5). Compared with index cases infected in the village, children in the second generation of cases had a mortality OR of 2.3 (CI, 1.0-5.2); the ORs were 3.7 (CI, 1.1-13.0) during the third generation, 5.5 (CI, 1.7-18.1) during the fourth generation, and 16.1 (CI, 5.6-46.3) during the fifth or later generations. All results were highly significant, and the pattern could be fitted accurately with a

Table 4. Measles case fatality, postmeasles mortality, and age-standardized odds ratios (OR) according to number of cases in compound, Niakhar, 1983-1986.

No. of cases	No. of deaths/no. of cases by age at measles onset, months				Mantel-Haenszel estimates		
	4-5	6-41	42-65	≥66	OR	χ ²	P
Measles case fatality							
1	0/2	5/61	0/16	0/21	1.194	0.000	NS
2-4	1/15	22/221	2/97	1/121	1.819	1.613	NS
5-9	2/10	31/192	3/100	0/161	3.027	7.033	.0080
≥10	0/3	16/105	4/70	1/115	3.219	6.779	.0092
Postmeasles mortality							
1	0/2	3/56	1/16	0/21	3.407	1.517	NS
2-4	1/14	9/199	1/95	0/120	2.109	0.707	NS
5-9	0/8	9/161	1/97	1/161	2.619	1.505	NS
≥10	0/3	9/89	1/66	1/114	4.647	5.078	.0242

NOTE. 190 cases with unknown exposure were excluded. NS, not significant.

Table 5. Measles case fatality, postmeasles mortality, and age-standardized odds ratios (OR) according to generation in compound, Niakhar, 1983-1986.

Generation	No. of deaths/no. of cases by age at measles onset, months				Mantel-Haenszel estimates		
	4-5	6-41	42-65	≥66	OR	χ ²	P
Measles case fatality							
First	1/7	15/164	0/90	1/141	1.432	0.337	NS
Second	0/13	36/290	5/142	1/177	2.333	4.091	.0431
Third	2/9	11/90	2/38	1/81	3.695	4.188	.0407
Fourth	0/1	7/24	0/9	0/15	5.507	7.941	.0048
Fifth+	0/0	5/11	2/4	0/4	16.143	27.028	2.0 × 10 ⁻⁷
Postmeasles mortality							
First	0/6	5/149	1/90	0/141	1.521	0.060	NS
Second	1/13	17/254	2/137	2/176	3.468	3.586	.0583
Third	0/7	6/79	0/36	0/80	3.085	1.527	NS
Fourth+	0/1	2/23	1/11	0/19	5.717	3.067	.0799

NOTE. NS, not significant.

LOGIT model, that is, the OR was multiplicative from one generation to the next. This major effect remained stable in multivariate analysis when controlling for number of cases, rank in compound, and other variables measuring intensity of exposure. In fact, when generation was introduced in the LOGIT regression, the net effect of the number of cases disappeared as did the effect of rank within compound.

A multivariate analysis including the generation effect and the intensity of exposure is shown in table 6. When controlling for age and generation, we found that the net effect of intensity of exposure was reduced but remained significant. Other variables being equal, the risk of dying was multiplied by 1.56 at each successive generation.

Discussion

The present study from rural Senegal provides further evidence of the importance of patterns of exposure for the out-

come of measles infection. Mortality rates for secondary cases within the compound were 2.9 times higher than those for index cases infected in the village. This corresponds closely to the risk differences observed in studies from other countries [1]. Further, the case-fatality ratio depended on the intensity of social contact between the infecting and the infected child, the ORs ranging from 1.9 to 3.8 with increasing contact between the children. It seems likely that the variation in social contact corresponds to a variation in the intensity of exposure to infection. Previous studies have distinguished between index and secondary cases only in the household [1, 6-9]. However, the graded mortality differences for secondary cases suggest that a detailed analysis of exposure patterns is useful.

The pattern presented here is based on the assumption that the effective source of infection was the closest contact. At the level of each individual, it cannot be proven that infection was in fact transmitted from the closest contact; for example,

Table 6. Multivariate analysis of the net effect of age, generation, and intensity of exposure (1256 cases, 80 deaths), Niakhar, 1983-1986.

Parameter	Estimate	Standard error	Odds ratio	Test (t or χ^2)	P
Constant	-6.748127	0.7998957		-8.4363	6.5×10^{-14}
Age (months)					
4-5	2.587276	1.025883	13.294	67.097	7.6×10^{-11}
6-41	3.346183	0.7228849	28.394		
42-65	1.976807	0.7882626	7.220		
≥66 (ref)			1.000		
Generation	0.4438147	0.1298495	1.559	3.418	.0003
Intensity					
High	0.8102547	0.4515716	2.248	6.635	.0100
Medium	0.3184904	0.4790414	1.375		
Low	0.1176264	0.5299282	1.125		
Reference			1.000		

NOTE. Log likelihood, -248.825; χ^2 (7) = 97.727 ($P < 10^{-12}$). For definition of intensity and generation see text.

from a sibling sleeping in the same hut rather than from another child in the village. At the level of the whole population, however, the closest contact must be the most frequent. Further, it should be noted that misclassification would tend to diminish rather than exaggerate the differentials. Considering the closest contact as the source case when contamination comes from another source with lower intensity of exposure will decrease the mortality differential of those classified with a high intensity.

It could also be argued that the intensity and severity effects were correlates of socioeconomic status of the family. The number of cases can be used as a proxy for the family status, as among the Sereer large families are the most traditional. However, the number of cases was not significantly related to mortality in the multivariate analysis. On the contrary, the intensity and severity effects remained stable even when we controlled for this proxy of social status. This indicates that the higher case-fatality ratio of secondary cases is not an effect of higher mortality in large families or to other socioeconomic correlates of large families but to a genuine pattern.

The increased mortality associated with closeness to the index case could be explained as a dose-response effect: the closer the contact between cases, the higher the dose of infective particles transmitted and the higher the mortality of the secondary case. Closer contacts presumably implies the absorption of larger doses of virus. In animal studies, a higher dose is associated with a shorter period of incubation and higher mortality. In human studies, the length of incubation had been found to be inversely related to the severity of infection [8, 15]. Therefore, high dose of measles virus is likely to be part of the pathogenic process causing severe infection. Since severe cases of measles have giant cells for a longer period [16], they are likely to excrete more viruses. In this perspective, the generation effect could be due to a process where relatively severe secondary cases, compared with index cases, transmitted more infective particles to the cases

of the third generation, who in turn transmitted ever more to cases of the next generation, and so on.

The role of intercurrent infections in causing severe disease is difficult to delineate because observed complications may reflect the extent of underlying immunosuppression caused by the measles virus rather than the environmental risk of complicating infections. However, a gradual increase with successive generations in the risk of transmission of complicating infections may have played a role in the observed pattern.

Increasing mortality for successive generations within the same families has not previously been described. The gradual increase could be due not only to a dose effect but also to adaptation of the virus to a specific host population of genetically related people. However, mortality has often been reported to increase over time in institutions with unrelated individuals, such as military or refugee camps [1], where changes in virulence could not be attributed to genetic selection. The generation effect within the same compound is more likely to be attributable to a dose effect.

If severe cases transmit more severe infection, children who are less sick should transmit a lighter infection. A similar mechanism could explain, at least in part, the continuous decline in measles mortality in Europe before antibiotics became available. Changes in household structures and living patterns that reduced the risk of household exposure as well as improved nutrition may have started a process in which children were less and less sick on the average and therefore transmitted less and less severe infection to other children.

An effect of exposure on risk of postmeasles mortality has not been reported previously. If confirmed in future studies, it adds further weight to the importance of transmission patterns for the understanding of morbidity and mortality. A likely explanation would be that an initial high dose of infection caused subsequent immunodeficiency and worsened the nutritional status of the child.

These observations from rural Senegal emphasize the importance of sociocultural factors in the determination of mortality patterns. Mortality risk is higher in large families and compounds with many children because of a greater risk of becoming a secondary case. Internationally, West Africa has had the highest measles case-fatality ratio. Much of the explanation can undoubtedly be sought in the fact that West Africa also has the largest households (number of persons) and the highest frequency of polygamy. As a consequence, a very large proportion of all children is likely to be intensively exposed. In the present study as many as 57% of the children <42 months old were secondary cases in the household, whereas in Bangladesh this proportion was only 14% [6].

The generation effect suggests that the parental attempts to isolate the children may inadvertently contribute to an increased case-fatality ratio. If all secondary cases had occurred in the second generation, mortality among secondary cases would have been 40% lower. On the other hand, the fact that there were several generations in large compounds suggests that it might be possible to prevent a significant number of measles cases and deaths by vaccinating all susceptible persons when a case is detected in a compound. Vaccinating even within the first 3 days after exposure has been shown to be effective in preventing the disease [17]. However, improving the general vaccination coverage is obviously the most important public health measure in the control of measles.

Acknowledgment

We thank John Bennett, Ron Gray, and Pierre Cantrelle for comments and suggestions and Carla Obermeyer for carefully reading the manuscript.

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