Decline in Measles Case Fatality Ratio after the Introduction of Measles Immunization in Rural Senegal

Badara Samb,1,2 Peter Aaby,1,3 Hilton Whittle,4 Awa Marie Coll Seck,5 and Francois Simondon1

The epidemiology of measles has been investigated in Niakhar, a rural area of Senegal, during two periods, 1983–1986 and 1987–1990. Following a major increase in immunization coverage beginning in 1987, the case fatality ratio for all ages declined fourfold from the first to the second period (relative risk (RR) = 0.24, 95% confidence interval (CI) 0.13–0.46). The measles incidence for children under 10 years of age declined by 69% (95% CI 65–72) and the risk of dying of measles by 91% (95% CI 82–95). Vaccinated children who contracted measles had significantly lower case fatality ratio than unvaccinated children with measles (p = 0.038). Children infected by an immunized case tended to have lower case fatality ratio than those infected by an unimmunized index case (p = 0.104) and immunized index cases generated fewer secondary cases than unimmunized index cases (p < 0.001). Respiratory complications were more common in secondary cases infected by an index case with respiratory complications than by an index case without such complications (RR = 1.60, 95% CI 1.08–2.37), which suggests that severe cases give rise to further severe cases. As expected, there was a significant increase in the proportion of vaccinated cases in the second period (RR = 1.41, 95% CI 1.00–1.98). Mean age at infection increased from 4 to 7 years between the two periods and the change in age structure accounted for 20% of the decline in case fatality ratio. Measles immunization may contribute to lower mortality directly through reduced incidence and indirectly through increases in age at infection, less severe infection for immunized cases and changes in transmission patterns leading to reduced severity of measles. Am J Epidemiol 1997;145:51–7.

immunization; infection; measles; mortality

During the latter part of the 1980s, measles was responsible for 1–2 million deaths per year, most of these in the developing countries (1). In the industrialized countries, the decline in the case fatality of measles seems to have been correlated with major socioeconomic changes including improved housing, reduced family size, changing patterns of transmission (2), as well as improved treatment, isolation of cases, and prophylactic use of convalescent serum among high risk groups (3). The importance of housing and exposure is supported by the many studies from developing countries and historical studies from Europe which have shown that the case fatality ratio is associated with the degree of overcrowding and intensity of exposure (4).

In most countries in Africa, it is unrealistic to expect major socioeconomic improvements in the immediate future which could lead to a reduction in the fatality from measles infection. Nonetheless, the World Health Assembly has set a goal of 90 percent reduction in measles incidence and 95 percent in measles mortality by year 2000 (5) and is thus assuming that case fatality will simultaneously drop to 50 percent of its present value. This assumption could be overoptimistic if the children who remain unimmunized are those likely to have a high case fatality ratio. Therefore, it is important to identify possible mechanisms for reduction in the case fatality ratio which may not depend on a total change in the socioeconomic situation or a 100 percent immunization coverage. The investigation of measles during the last decade in a rural area of Niakhar, Senegal (6–8), has permitted us to examine this question because a major reduction in case fatality ratio occurred during the period.
MATERIALS AND METHODS

Study population and demographic surveillance

The study was carried out in Niakhar, Senegal, in a rural area with a population of around 25,000 persons living in 30 villages (9, 10). The population and the demographic surveillance system in the area have been described in detail elsewhere (9-11). From 1983 to 1986, the surveillance system was based on annual censuses collecting information on births, marriages, migrations, vaccinations, infections, and deaths. Since 1987, the system has been based on a weekly visit by field assistants to all 1,800 compounds in the study area. The work of the 12 assistants was controlled by two supervisors who had contact with each assistant at least twice a week.

Measles surveillance and study periods

From 1983 to 1986, information on measles cases was collected in annual censuses and subsequently interviews were carried out with parents to determine the pattern of transmission within the compound (6, 12). From July 1987, cases were registered through the weekly morbidity surveillance system and by a physician who carried out bi-weekly examinations in compounds with reported measles cases (7). Information on measles cases was also obtained in each census; most cases reported only in the census had occurred outside the study area. Hence, the investigation was mainly based on parental diagnoses in the first period whereas both parental and medical diagnoses were used in the latter period (6, 8).

The present study compares cases occurring between March 1983 and December 1986 (6, 12) and from July 1987 to December 1990 (7, 8). There was no epidemiologic study in the period from January to June 1987. Included in the present study are all cases occurring in the study zone as well as cases occurring outside the study area among children registered in Niakhar. As in the previous studies (6, 12), death was attributed to measles if it occurred within 6 weeks of the onset of a measles rash. No death in this period was related to trauma.

Clinical examination and treatment

During 1983–1986, treatment was only available at the three local dispensaries, one private Catholic center staffed by nuns and two public centers. From 1987, compounds with measles cases were visited by a physician. All children under 3 years of age seen during the prodromes or the acute phase of infection were given prophylactic antibiotic treatment (cotrimoxazole) (13). Older children were treated with antibiot-ics when signs of complicating infections developed. In the period 1987–1990, vitamin A had not yet been recommended as routine treatment for measles cases and it was not used in the study area (13).

All clinical examinations included auscultation and respiratory complications were classified as "none," "light," "moderate," or "severe." The prevalence of respiratory complications was highest from day 5–11 after the onset of symptoms, corresponding approximately to the first week after the rash. The analysis of determinants of respiratory complications was therefore restricted to the period with the highest prevalence, i.e., 5–11 days after the onset of symptoms (13).

Intensity of exposure

A child who developed measles more than 6 days after another case in the same compound was classified as a secondary case (6–8, 12). The closest source of infection was considered the most likely, e.g., if there were two possible index cases, one in the same hut and the other one in a different hut, the child from the same hut was considered the source. Secondary cases were noted as to whether they lived in the same hut as the index case, in the same household but not the same hut or in the same compound but not in the same household (6). These categories reflect levels of decreasing contacts among children.

Measles immunization

There were yearly measles vaccination campaigns, usually in the dry season, in the period 1979 to 1983 in Niakhar and again during the acceleration phase of the Expanded Programme on Immunization (EPI) between November 1986 and February 1987. Between 1983 and 1985, no mass immunization was organized in the study area. From mid-1987, vaccination was offered systematically by the project at immunization sessions organized once a month at each of the three health centers as part of a trial of measles vaccines (7, 14, 15). Children with onset of disease within 2 weeks of a measles vaccination have been classified as unvaccinated.

Comparisons and statistics

The case fatality ratios have been compared for the 1983–1986 and the 1987–1990 periods. Since the mode of infection was undocumented for the children who contracted measles when travelling, the main comparison concerns index and secondary cases infected in the study area. To detect any general change in mortality levels between the two periods, we have compared all cause mortality between 12 and 59 months of age for all children vaccinated before 12
months of age between 1983 and 1985 with standard titer measles vaccine with the similar group of children immunized with standard titer measles vaccine between 1987 and 1989. In the campaigns some of the vaccines had been given as early as 5–6 months of age. In the period 1987–1989, the children who had received high-titer vaccines were not included in the analysis.

The EPI INFO program (USD Inc., Stone Mountain, Georgia) was used for calculation of relative risks and 95 percent confidence intervals. The Mantel-Haenszel estimator was used to produce combined estimates for various subgroups (16). To examine how much of the decline could be explained by changes in the epidemiology of measles, we calculated crude and adjusted relative risks for the two periods. The change introduced in the relative risk after adjustment for a given factor, e.g., age or vaccination status, indicates how much of the change between the two periods can be accounted for by this factor.

RESULTS
Epidemic periods and decline in acute case fatality ratio

The measles immunization coverage for the children aged 1–4 years increased from 12 percent in 1986 to 78 percent in 1990. There was therefore a major drop in the number of cases from 1,500 during the first period to 630 during the second (figure 1). Of the 630 cases detected in the second period, 554 (88 percent) had been diagnosed by both the mother and a physician. The number of acute measles deaths dropped from 98 to 10 between the two periods (table 1). The case fatality ratio for all ages was 6.5 percent during 1983–1986 against only 1.6 percent in the second period (table 1) (relative risk (RR) = 0.24, 95 percent confidence interval (CI) 0.13–0.46, p < 0.0001). Allowing for the number of person-years-at-risk in the two periods, there was a 69 percent (95 percent CI 65–72) decline in incidence for children under 10 years of age and the decline in measles deaths was 91 percent (95 percent CI 82–95).
As shown in figure 1, measles occurred in several distinct epidemics. Due to scattered settlement patterns, these epidemics depended mostly on contacts out of the community and on the prevalence of measles in the society at large. The case fatality ratio was highest in the first epidemic in 1983 (table 2) which was the tail of an epidemic since the first census was started in the middle of an epidemic. The first complete epidemic occurred in 1984. A major decline in case fatality ratio only occurred after the introduction of the accelerated expanded immunization program in 1986–1987. In the inter-epidemic periods (table 2, periods 5 and 7), there was a significantly higher proportion of the children who were infected outside the community and on the prevalence of measles in the society at large. The case fatality ratio was lower than in the epidemic periods (table 2, periods 1–4 and 6).

For children aged 1–4 years who had received measles immunization before one year of age, the non-measles-related mortality declined between 1983–1986 and 1987–1990, the mortality ratio being 0.63 (95 percent CI 0.43–0.93).

### Decline in severity: measles immunization

No child with a record of measles immunization died of acute measles and, standardized for age and period, the vaccinated cases had significantly lower measles case fatality than the unvaccinated cases (p = 0.038). There was a higher proportion of vaccinated cases in the second period (RR = 1.41, 95 percent CI 1.00–1.98). During the second period the proportion of vaccinated cases tended to increase with intensity of exposure, being higher among secondary cases in the hut than among secondary case in the compound or in the household (RR = 1.25, 95 percent CI 1.00–1.98).

We evaluated whether the immunization status of the index case was important for outcome of infection in the secondary cases. Although the difference was not statistically significant, vaccinated cases tended to

### Table 1. Measles case fatality ratio according to period and place of contamination, Niakhar, Senegal, 1983–1990

<table>
<thead>
<tr>
<th>Period and age (years)</th>
<th>Outside study area</th>
<th>Health center</th>
<th>Index in village</th>
<th>Secondary not in same hut</th>
<th>Secondary in same hut</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1983–1986</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–2</td>
<td>9 (10/110)</td>
<td>23 (3/13)</td>
<td>8 (7/84)</td>
<td>12 (20/165)</td>
<td>17 (18/108)</td>
<td>12 (68/480)</td>
</tr>
<tr>
<td>3–4</td>
<td>0 (0/27)</td>
<td>0 (0/3)</td>
<td>0 (0/67)</td>
<td>5 (7/314)</td>
<td>10 (9/90)</td>
<td>5 (16/321)</td>
</tr>
<tr>
<td>5–9</td>
<td>0 (0/36)</td>
<td>0 (0/3)</td>
<td>0 (0/126)</td>
<td>2 (2/133)</td>
<td>3 (3/109)</td>
<td>1 (5/407)</td>
</tr>
<tr>
<td>≥10</td>
<td>0 (0/35)</td>
<td>–</td>
<td>0 (0/24)</td>
<td>0 (0/34)</td>
<td>0 (0/127)</td>
<td>0 (0/127)</td>
</tr>
<tr>
<td>Total</td>
<td>5 (13/247)</td>
<td>20 (5/25)</td>
<td>8 (3/320)</td>
<td>7 (34/514)</td>
<td>10 (38/394)</td>
<td>6.5 (98/1,500)</td>
</tr>
<tr>
<td>1987–1990</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1</td>
<td>0 (0/11)</td>
<td>–</td>
<td>0 (0/4)</td>
<td>0 (0/11)</td>
<td>6 (1/17)</td>
<td>2 (1/43)</td>
</tr>
<tr>
<td>1–2</td>
<td>4 (1/25)</td>
<td>0 (0/2)</td>
<td>0 (0/7)</td>
<td>0 (0/24)</td>
<td>14 (4/29)</td>
<td>6 (5/87)</td>
</tr>
<tr>
<td>3–4</td>
<td>0 (0/8)</td>
<td>–</td>
<td>0 (0/13)</td>
<td>0 (0/17)</td>
<td>0 (0/25)</td>
<td>0 (0/83)</td>
</tr>
<tr>
<td>5–9</td>
<td>4 (1/26)</td>
<td>–</td>
<td>1 (1/79)</td>
<td>0 (0/73)</td>
<td>1 (1/73)</td>
<td>1 (3/251)</td>
</tr>
<tr>
<td>≥10</td>
<td>0 (0/45)</td>
<td>0 (0/3)</td>
<td>0 (0/49)</td>
<td>0 (0/43)</td>
<td>1 (1/46)</td>
<td>1 (1/166)</td>
</tr>
<tr>
<td>Total</td>
<td>2 (2/115)</td>
<td>0 (0/5)</td>
<td>1 (1/152)</td>
<td>0 (0/168)</td>
<td>4 (7/190)</td>
<td>1.6 (10/630)</td>
</tr>
</tbody>
</table>

### Table 2. Measles case fatality ratio and percent infected outside Niakhar according to epidemic period, Niakhar, Senegal, 1983–1990

<table>
<thead>
<tr>
<th>Epidemic period</th>
<th>Case fatality ratio (%) (no. of cases)</th>
<th>% Infected outside Niakhar (no. Infected outside area/no. of cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td>March 1983–Nov. 1983</td>
<td>38 (21)</td>
<td>15 (41)</td>
</tr>
<tr>
<td>Dec. 1983–Sept. 1984</td>
<td>10 (42)</td>
<td>12 (113)</td>
</tr>
<tr>
<td>Oct. 1984–July 1985</td>
<td>12 (42)</td>
<td>15 (150)</td>
</tr>
<tr>
<td>Aug. 1985–Dec. 1986</td>
<td>3 (50)</td>
<td>8 (178)</td>
</tr>
<tr>
<td>July 1987–July 1989</td>
<td>0 (18)</td>
<td>0 (42)</td>
</tr>
<tr>
<td>Aug. 1989–May 1990</td>
<td>4 (23)</td>
<td>12 (42)</td>
</tr>
<tr>
<td>June 1990–Dec. 1990</td>
<td>0 (2)</td>
<td>0 (3)</td>
</tr>
</tbody>
</table>

* RR, relative risk adjusted for age; CI, confidence interval.

provide milder infection as none of the secondary cases infected by a vaccinated index case died ($p = 0.104$). Vaccinated index cases produced fewer secondary cases on average (1.2) than unvaccinated index cases (2.8) ($p < 0.001$, likelihood ratio test) though there was the same number of contacts under 15 years of age in compounds with vaccinated and unvaccinated cases.

**Decline in severity: changes in exposure**

As previously described for the period 1983–1986 (6), during the 1987–1990 period, secondary cases in the hut had a higher case fatality ratio than index cases ($RR = 4.17, 95\% CI 0.35–49.12$) and other types of secondary cases ($RR$ undefined, $p = 0.038$) (table 1). There was no reduction in the proportion of secondary cases relative to all cases in the second period ($RR = 0.98, 95\% CI 0.91–1.07$). Changes in the proportion of secondary cases did not therefore contribute to the decline in case fatality.

Changes in severity of infecting cases could be important as we have previously found that the case fatality ratio of secondary cases depended on the severity of respiratory symptoms in the index case (2). It was only in the period from 1987–1990 when clinical examinations were performed that we had sufficient information on respiratory complications to evaluate this possibility. The severity of the transmitting case had a clear impact on severity of the secondary cases (table 3). After adjusting for age, secondary cases infected by another case with respiratory problems were 1.60 times (95\% CI 1.08–2.37) more likely to develop respiratory complications than those infected by someone without respiratory problems. The relative risk for development of severe respiratory complications was even more pronounced ($RR = 3.11, 95\% CI 1.06–9.14$) among the secondary cases infected by another case with respiratory complications compared with secondary cases infected by someone without respiratory problems.

**Decline in severity: changes in age at infection**

In both periods (table 1), the case fatality ratio was much higher for children under 3 years of age compared with the older children ($RR = 4.94, 95\% CI 3.17–7.69$). Mean age at infection increased from 4.1 to 7.2 years between the two periods ($p < 0.0001$, Mann-Whitney). Standardized for age and place of infection, the relative mortality risk ($RR$) between the two periods was 0.42 (95\% CI 0.21–0.84). Most of the change occurred in the group with many deaths, i.e., the secondary cases ($RR = 0.39, 95\% CI 0.18–0.85$). There was no significant decrease for the children who contracted infection outside the study area ($RR = 0.56, 95\% CI 0.11–2.76$) or index cases infected in the village ($RR = 0.86, 95\% CI 0.05–13.84$).

**DISCUSSION**

The overall comparison of the two periods indicated a fourfold reduction in the case fatality ratio simultaneously with the reduction in measles incidence. However, the interpretation of this result from an observational longitudinal study has to take account of other changes in the study area, including the identification of measles cases, age structure, nutritional factors and medical care. In both periods, the identification of measles cases relied on reports from parents rather than identification at a health center. However, during the second period the home visits conducted by the project physician may have contributed to earlier detection of cases. Assessed by seroconversion, the predictive value of medical diagnosis was of the order of 95–99\% (8), somewhat higher for secondary cases than for index cases. A positive parental history of previous measles has been found to have a similar predictive value (6, 12). Parental reports of measles were also collected in the second period. If anything, one would expect the diagnostic specificity to have been higher during the second period thus producing a higher case fatality ratio as no similar infection has higher case fatality ratio than measles. Hence, it is unlikely that differences in ascertainment of measles infection in the two periods can have contributed to the trend towards lower case fatality ratio in 1987–1990.

The case fatality ratio in measles has been related to age at infection, state of nutrition, type of exposure (6), vaccination status (17), respiratory complications of the infecting case (2), type of complications, and medical care (18). We therefore tried to assess whether

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**TABLE 3. Risk of respiratory complications during second week of disease according to respiratory infection of Infecting case, Niachar, Senegal, 1983–1990**

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>% of secondary cases with respiratory complications</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Infecting case without respiratory complications</td>
</tr>
<tr>
<td>&lt;1</td>
<td>26 (4/11)/18</td>
</tr>
<tr>
<td>1-2</td>
<td>50 (17)/34</td>
</tr>
<tr>
<td>3-4</td>
<td>27 (7)/26</td>
</tr>
<tr>
<td>5-9</td>
<td>18 (131)/71</td>
</tr>
<tr>
<td>≥10</td>
<td>16 (7/45)</td>
</tr>
<tr>
<td>Total</td>
<td>25 (48/192)</td>
</tr>
</tbody>
</table>

* No. of cases with severe respiratory complications.
changes in these factors could explain the decline in case fatality ratio.

Given the dramatic change in mean age at infection from 4 to 7 years from the first period to the second, it is clear that changes in age distribution were important. Taking other factors into consideration, changes in age structure accounted for 20 percent of the decline. The nutritional surveys carried out for other purposes did not suggest any improvement in the state of nutrition from 1983–1986 to 1987–1990, weight-for-age z-scores for children aged 22–45 months being, respectively, −1.23 in 1984–1985 (10) and −1.31 in 1990 (15).

Intensive exposure continued to be an important risk factor for the case fatality ratio and a reduced frequency of secondary cases could therefore be instrumental in producing a case fatality decline. Although the number of generations was reduced (data not shown), there was no reduction in the proportion of all cases being secondary cases. Hence, changes in the pattern of exposure was not a major cause of the change in measles case fatality ratio.

The change in case fatality ratio seems to have started after the introduction of the accelerated immunization program (figure 1). The reduced severity of vaccinated measles cases and the higher proportion of vaccinated cases in the second period suggest that this could be an important mechanism for reduced case fatality ratio in measles (17). Previous studies from developed countries have also suggested that vaccinated cases have milder measles infection (19, 20).

Other studies have suggested that severe index cases generate severe secondary cases and mild cases generate mild secondary cases (2, 4). This suggestion was supported by the present study since vaccinated index cases tended to produce lower case fatality ratio in secondary cases and index cases without respiratory complications produced less pneumonia. This aspect could not be formally compared between the two periods because we have no information on respiratory complications from 1983–1986. However, the mechanism of mild cases generating mild cases may have contributed to the decline in case fatality ratio in measles (17). Previous studies from developed countries have also suggested that vaccinated cases have milder measles infection (19, 20).

It is difficult to plan general improvement in health or in the availability of medical care for everyone in the developing countries. However, it may be possible even with the limited resources of an immunization program to consider how to get the optimal impact from transforming the transmission pattern. In Niakhar, there was a strong temporal association between the national immunization campaign and a decline in the measles case fatality ratio. In Niakhar, routine vaccination in connection with the high-tier trial (7, 15) maintained a high coverage for measles vaccine after the initial national campaign. However, in some parts of Senegal, routine immunizations were not maintained (22) and measles returned as it also did in Niakhar in 1990. A new national campaign 2–3 years after the initial campaign would probably have avoided the outbreak or kept the case fatality ratio at an even lower level. Further studies of the impact of

transmission patterns on severity and how to modify
transmission dynamics seem warranted. Specifically,
there are reasons to examine how campaigns can be
used to control epidemics and the case fatality ratios in
areas with limited capacity to maintain a high cover-
age through routine immunizations (22).

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