Case-Fatality Rate during a Measles Outbreak in Eastern Niger in 2003

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Background. The World Health Organization (WHO) estimates that the case-fatality rate (CFR) for measles in West Africa is 4%–6%. In Niger, 50,138 measles cases and 201 deaths (CFR, 0.4%) were reported in 2003. We conducted an investigation to determine the epidemiology and the true CFR of measles in the Mirriah district in Niger.

Methods. Twenty-two villages from the Mirriah district that reported measles cases in 2003 were included in the investigation. A comprehensive household search for measles cases and deaths was conducted, and serum samples from 12 villages were collected for laboratory confirmation. A measles case was defined as illness characterized by fever, rash, and either cough, coryza, or conjunctivitis, with rash onset during the period from 1 January 2003 to 15 April 2003. Deaths occurring within 30 days after rash onset were attributed to measles unless they were obviously due to other causes.

Results. Measles was confirmed serologically in all villages from which samples were collected. Of 945 case patients identified, 900 (95.2%) were aged <15 years, 114 (12.3%) were vaccinated, and 789 (83.5%) sought treatment at a health care facility. A total of 92 deaths were attributed to measles (CFR, 9.7%; 95% confidence interval, 7.9%–11.5%). The CFR was highest in infants aged <1 year (15.6%). Households with ≥2 case patients had a higher CFR (10.8%) than that of households with only 1 case patient (6.0%). Households consisting of ≥8 members had a CFR of 12.8%, whereas the CFR of smaller households was 7.1%.

Conclusions. This investigation suggests that the measles CFR in the Mirriah district may be 2-fold higher than the WHO regional estimate and 20-fold higher than the estimate derived from routine surveillance. Reducing measles mortality in Niger will require wide-age-range vaccination campaigns, improvement in routine immunization services, and periodic “follow-up” campaigns.
children aged <5 years has suggested that the WHO may be overestimating measles deaths worldwide [20, 21].

Accurate and current estimates of measles CFRs are critical for calculating the global burden of measles. In turn, accurate measles burden estimates are important for appropriately prioritizing measles-control programs among other public health interventions.

BACKGROUND

Niger, a sub-Saharan African country with a population of ~12.5 million persons, is among the poorest countries in the world (gross national income per capita, US$170). The Expanded Program on Immunization in Niger was established in 1987 and includes measles vaccination for children aged 9 months. Over the past decade, estimates of the national measles vaccine coverage ranged from 25% to 91%; in 2003, coverage was estimated to be 64% [22].

Measles outbreaks occur annually in Niger, with the reported number of cases ranging from 11,385 to 69,101 (figure 1) and measles CFR ranging from 0.42% to 2.91% since 1991. In 2003, the Ministry of Health received reports of 58,118 measles cases and 243 measles-associated deaths, which yields a CFR of 0.42%. This rate is much lower than that reported from previous community-based investigations in Niger and other parts of West Africa [23–26].

Most of the cases in 2003 were reported from eastern Niger, with the Maradi (14,401 cases) and Zinder (26,511 cases) regions accounting for ~70% of all cases. Of the 6 districts in the Zinder region, the Mirriah district, comprising a predominantly rural population of 677,885, reported the highest number of cases (n = 8817). The Mirriah district, located ~1000 km east of the capital, Niamey, is economically underprivileged, with subsistence farming as the main source of livelihood. The rate of measles vaccination coverage in the district was 39% in 2002 and 48% in 2003, according to district immunization records.

In response to this outbreak, some of the district’s 22 health care centers conducted outreach vaccination services in their areas, although the extent of these efforts was not well documented. To better understand the epidemiology of measles and to estimate the measles CFR, we conducted an outbreak investigation in the Mirriah district.

METHODS

A retrospective, community-based investigation of the outcome of measles cases was conducted from 24 May to 28 June 2003 in the Mirriah district. A measles case was defined as illness characterized by fever, rash, and either cough, coryza, or conjunctivitis, with rash onset in the period from 1 January to 15 April 2003, in a resident of the Mirriah district. This period encompassed the “high season” for measles transmission in Niger and ensured that there were at least 30 days between rash onset and interview date, so that outcome at 30 days after rash onset could be determined. A measles-associated death was defined as a death occurring within 30 days after rash onset in a measles case patient for whom unrelated causes of death (e.g., trauma) had been ruled out [27]. A household was defined as all persons living and eating together from 1 January to 15 April 2003. A survey questionnaire was developed that included questions on demographic characteristics, details of the illness, and outcome. Survey questionnaires were translated from English into French and Hausa and were back-translated and pretested prior to use. Local survey workers attended a 2-day workshop, during which they received training on conducting a community-based survey and on appropriate interviewing techniques.

Villages to be surveyed were selected using a 2-step procedure. Weekly surveillance data were used to select the 5 health care centers reporting the highest number of cases. Health care workers at these centers then generated a list of villages reporting measles cases. From these lists, 4–6 villages were selected on the basis of the number of reported cases and the presence of recent measles cases, to facilitate the laboratory confirmation of the outbreak.

A house-to-house search for measles case patients was conducted in each selected village. In the larger villages and towns, areas were divided into equal sections. One or more sections were then randomly selected by the survey team, and a comprehensive search for cases was conducted. All households were visited and were asked whether any household members had had measles. In households in which a measles case patient was identified, a household census was completed, and all measles case patients were enumerated. Case patients (or guardians, in the case of young children) were interviewed after verbal consent was obtained, and a questionnaire was completed for each case patient identified. A local calendar of events was used to ascertain dates accurately.

To confirm the cause of the outbreak, in every village, serum
samples were collected from 5–10 patients who experienced rash onset <30 days before our investigation [28]. These patients were not included in the investigation, because their outcome at 30 days after rash onset could not be ascertained without additional follow-up visits. These patients were provided therapeutic doses of vitamin A and were advised to seek treatment if they developed measles-related complications. Serum samples were tested for measles IgM by commercially available ELISA kits (Enzygnost Anti-Measles virus/IgM assay; Dade Behring). Samples that tested negative for measles IgM were tested for rubella IgM by commercially available ELISA kits (Enzygnost Anti-Rubella virus/IgM assay; Dade Behring). Nasopharyngeal swab specimens for virus isolation and genotyping were collected from measles case patients seen within 5 days after rash onset.

Data were entered into an EpilInfo 2002 database, version 3.3.2 (Centers for Disease Control and Prevention). Analysis was performed using EpilInfo 2002 and SAS, version 8.02 (SAS Institute). Categorical variables were analyzed with the $\chi^2$ or Fisher’s exact test, as appropriate. A multivariate model was constructed that included potential risk factors for mortality: age, sex, household size, number of case patients in household, order in which illness was experienced within household, treatment at health care facilities, distance to health care center, and receipt of vitamin A supplementation (either before or during the illness). A backward selection process was done by beginning with a full model and subsequently removing 1 variable at a time until the final model was attained. A significance of <0.10 was used as an inclusion criterion for the final model. A forward selection process was also done, to confirm the final model. A separate model was used that was limited to case patients aged <5 years, because this age group is targeted for vitamin A supplementation during Polio National Immunization Days. Clustering at the village level was controlled for by use of SUDAAN, version 8.0 (Research Triangle Institute).

**RESULTS**

**Descriptive epidemiology.** A total of 945 cases of measles from 451 households in 22 villages were investigated during this survey. The mean family size was 7.3 persons (median, 6 persons; range, 2–35 persons), and the average number of case patients per household was 2.1 (median, 2 case patients; range, 1–11 case patients). Cases were evenly distributed by sex: 50.4% male and 49.6% female. The age of the case patients ranged from 3 months to 32 years (mean, 4.5 years; median, 3 years) (figure 2). Infants aged <1 year accounted for ~10% of all cases. Two-thirds of case patients were aged <5 years, and 90% were aged <10 years.

Of surveyed case patients, 114 (12%) reported having been vaccinated for measles. Of these, 26 (23%) could not recall the date of vaccination, and 16 (14%) were vaccinated after the onset of rash. Only 37 (4%) of the case patients reported being vaccinated >18 days before rash onset, the time required to achieve an adequate immune response. The remaining 35 case patients (4%) reported being vaccinated during the incubation period for measles (<18 days before rash onset) and may have been infected with the measles virus prior to vaccination. All data on vaccination status were based on respondent recall; written documentation of vaccination history was not available for most case patients.

More than 83% of case patients sought treatment at a health care center after the onset of illness. Distance to the health care center (median, 5 km; range, 1–20 km) had minimal effect on whether case patients sought treatment. Among case patients living within 5 km of a health care center, 83.4% sought treatment, whereas 79.8% of those living within 5–15 km sought care. A total of 16 (1.7%) of the case patients were hospitalized during their illness; the range of duration of admission was 1–32 days (mean, 5.5 days; median, 2 days).

Of all case patients, 59% reported receiving vitamin A capsules as part of treatment for their illness; 69% of patients who
Table 1. Risk factors for mortality among measles case patients in the Mirriah district, Niger, 2003.

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of case patients</th>
<th>No. of deaths</th>
<th>Mortality, %</th>
<th>Univariate analysis RR (95% CI)</th>
<th>Multivariate analysis RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>All case patients</td>
<td>Case patients aged &lt;5 years</td>
</tr>
<tr>
<td>Age, months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;12</td>
<td>83</td>
<td>13</td>
<td>15.7</td>
<td>Referent</td>
<td>Referent</td>
</tr>
<tr>
<td>12–59</td>
<td>558</td>
<td>64</td>
<td>11.5</td>
<td>0.73 (0.42–1.27)</td>
<td>0.73 (0.37–1.42)</td>
</tr>
<tr>
<td>60–179</td>
<td>259</td>
<td>14</td>
<td>5.4</td>
<td>0.35 (0.17–0.70)</td>
<td>0.30 (0.10–0.96)</td>
</tr>
<tr>
<td>&gt;180</td>
<td>45</td>
<td>1</td>
<td>2.2</td>
<td>0.14 (0.02–1.05)</td>
<td>0.12 (0.02–0.56)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>476</td>
<td>49</td>
<td>10.3</td>
<td>1.14 (0.77–1.68)</td>
<td>NI</td>
</tr>
<tr>
<td>Female</td>
<td>468</td>
<td>43</td>
<td>9.2</td>
<td>…</td>
<td>…</td>
</tr>
<tr>
<td>Household size, no. of persons</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥8</td>
<td>436</td>
<td>56</td>
<td>12.8</td>
<td>1.79 (1.19–2.63)</td>
<td>1.83 (1.12–2.99)</td>
</tr>
<tr>
<td>&lt;8</td>
<td>509</td>
<td>36</td>
<td>7.1</td>
<td>NI</td>
<td>2.00 (1.25–3.23)</td>
</tr>
<tr>
<td>No. of case patients per household</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥2</td>
<td>741</td>
<td>80</td>
<td>10.8</td>
<td>1.80 (1.00–3.23)</td>
<td>1.70 (0.95–3.04)</td>
</tr>
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<td>1</td>
<td>200</td>
<td>12</td>
<td>6.0</td>
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<tr>
<td>Distance to health care center, km</td>
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<td></td>
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<td></td>
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<tr>
<td>≤5</td>
<td>584</td>
<td>68</td>
<td>11.6</td>
<td>1.75 (1.12–2.74)</td>
<td>NI</td>
</tr>
<tr>
<td>&gt;5</td>
<td>361</td>
<td>24</td>
<td>6.7</td>
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<td>…</td>
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<td>Place in order of case patients within household</td>
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<tr>
<td>≥2</td>
<td>485</td>
<td>55</td>
<td>11.5</td>
<td>1.41 (0.95–2.10)</td>
<td>NI</td>
</tr>
<tr>
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<td>460</td>
<td>37</td>
<td>8.0</td>
<td>…</td>
<td>…</td>
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<tr>
<td>Treatment at health care center</td>
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<td></td>
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<tr>
<td>Yes</td>
<td>789</td>
<td>77</td>
<td>9.8</td>
<td>1.02 (0.60–1.72)</td>
<td>NI</td>
</tr>
<tr>
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<td>156</td>
<td>15</td>
<td>9.6</td>
<td>…</td>
<td>…</td>
</tr>
<tr>
<td>Vitamin A supplementation before illness</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>470</td>
<td>52</td>
<td>11.1</td>
<td>0.77 (0.49–1.22)</td>
<td>NI</td>
</tr>
<tr>
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<td>23</td>
<td>14.3</td>
<td>…</td>
<td>…</td>
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<td>Vitamin A supplementation during illness</td>
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<td></td>
</tr>
<tr>
<td>Yes</td>
<td>550</td>
<td>58</td>
<td>10.6</td>
<td>1.29 (0.83–1.88)</td>
<td>NI</td>
</tr>
<tr>
<td>No</td>
<td>377</td>
<td>31</td>
<td>8.2</td>
<td>…</td>
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</tr>
</tbody>
</table>

**NOTE.** NI, not included in the final model; RR, relative risk.

* Case patients within a household were ordered according to the time at which illness was experienced, from first to last place (i.e., 1, first; 2, second; etc.).
* For children aged <5 years.

visited a health care center received such treatment. Because data regarding vitamin A therapy were obtained by maternal recall, the dose and frequency of vitamin A administration was not accurately ascertained. Receipt of vitamin A capsules was associated with proximity to a health care center. Of patients living within 5 km of a health care center, 64% reported receiving vitamin A, whereas 51% of those living ≥5 km (P < .001) from a health care center reported receiving such therapy.

Of the 22 villages surveyed, only 12 had measles cases with rash onset ≤30 days prior to our investigation and therefore amenable to laboratory confirmation by detection of measles IgM. All villages with measles case patients from whom blood specimens were collected had at least 1 measles-positive specimen. The remaining 10 villages were in close proximity to villages with serologically confirmed measles cases and are likely to have been affected by the same outbreak. All samples that tested negative for measles IgM also tested negative for rubella IgM. The measles virus was isolated from nasopharyngeal swab specimens and was genotyped as group B3, a genotype previously found in West Africa [29].

**Mortality.** A total of 92 of the 945 case patients died within 30 days after rash onset, corresponding to an overall CFR of 9.7% (95% CI, 7.9%–11.5%). Most deaths occurred soon after rash onset, with nearly 75% occurring in the first 2 weeks and only 5% occurring during the fourth week (figure 3). Median time from rash onset to death was 10 days. Mortality was in-
versely associated with the age of the case patients (table 1). The highest CFR was among infants (15.7%), and CFR decreased with increasing age ($P = .0006$, by $x^2$ test for trend). The CFR for children aged 5–14 years was 5.4%. No significant difference by sex was observed for CFR.

Mortality was associated with proximity to a health care center, the size of the household, and the number of case patients within the household (table 1). Although most case patients sought treatment at a health care center during their illness, those seeking treatment had a similar CFR (9.8%) to that of patients who did not (9.6%). Vitamin A, administered as a treatment for measles, was not associated with a lower measles CFR.

In the multivariate analysis, younger age of the case patient and larger family size were significant risk factors for death, whereas the number of case patients in the household was only marginally significant ($P = .07$). Proximity to a health care center was not significant in the final model that was controlled for age. When restricted to children aged <5 years, both larger household size and households with >1 case per household were significant risk factors.

**DISCUSSION**

This investigation represents one of the few recent efforts to examine measles-associated mortality in a poor, rural West African population with low vaccine coverage. Almost 20 years after the introduction of measles vaccine in Niger and the demonstration by Barclay et al. [30] that treatment of measles cases with vitamin A supplementation can reduce measles-associated mortality, Niger continues to experience large measles outbreaks with unacceptably high mortality. Our investigation revealed that $\sim$10% of measles case patients died within 30 days after rash onset. The CFR that we observed in Zinder was lower than the 15.3% found in rural Niger in 1993 [23] and the 15.7% observed in rural Ghana in 1996 [26]. It was, however, higher than the 4.8% observed in rural West Africa in 1983 [5] and the 6.5% observed in Senegal in 1989 [25].

Nearly 1 in 6 children aged <1 year who contracted measles subsequently died. Although the mortality rate decreased with increasing age, it remained high among older children. Our data suggest that, in areas like Mirriah, measles vaccination campaigns that include older children would not only prevent deaths in infants who would have acquired measles from older children but also prevent deaths in this older age group.

We found a higher risk of death among case patients living in households with multiple measles cases, which might have resulted from higher intensity of exposure to the virus [31, 32]. Similarly, a higher risk of death was observed in larger households, which is likely associated with overcrowding and increased opportunities for exposure to secondary infections [33, 34]. Large households may indicate low socioeconomic status and poor nutritional status, both of which may be associated with increased measles mortality [35].

Although most patients sought treatment at a health care center during their illness, seeking medical care did not decrease a patient’s risk for mortality. However, case management at the health care centers was not evaluated; therefore, these data remain inconclusive. Furthermore, health care facility visits also could serve as a marker of more severe illness.

The reported vitamin A supplementation of measles cases was not protective in this study. This contradicts other studies that have demonstrated a 30%–40% decrease in measles mortality associated with 2 doses of vitamin A administered 24 h apart [36]. However, information on frequency or dose of vitamin A supplementation was not obtained during our study.

Potential risk factors for measles mortality that we could not assess were nutritional status and HIV infection. Malnutrition has been shown to be associated with higher measles mortality in some studies [37]. In 2000, 14% of children aged 6–59 months in Niger experienced wasting (weight for height, $<2$ SDs from the median of the National Center for Health Statistics (NCHS)/WHO standard), and 40% were stunted (height for age, $<2$ SDs from the median of the NCHS/WHO standard). Wasting and stunting in children aged <5 years in the Zinder region occur at even higher rates (17% and 47%, respectively) [38]. These figures are higher than those reported in other countries in the region and during many humanitarian emergencies and could have contributed to the high measles CFR in Mirriah.

HIV infection is less likely to have played a major role in measles mortality in Niger. HIV seroprevalence is still low in Niger, with The Joint United Nations Programme on HIV/AIDS (UNAIDS) data showing a prevalence of $\sim$0.7%–2.3% in 2003 [39]. If a mother-to-child transmission rate of 30% is assumed, this translates to an HIV prevalence of $<1\%$ in infants who become infected through this type of transmission. Most of these deaths would occur in the first few years of life; therefore, some of the deaths recorded in the younger age groups might be attributable to underlying HIV infection. However, the number of such cases would be small and would have minimal impact on overall CFR.

Measles-associated deaths were less likely to be reported through Niger’s routine surveillance system than were measles cases; the CFR found in our investigation was 20-fold higher than that reported through routine surveillance. Niger, like many developing countries, lacks systems for registration of death. We observed that most measles-associated deaths occurred at home and therefore were not reported. In addition, most measles-associated deaths are caused by complications (e.g., pneumonia and diarrhea), which often occur after the
rash has subsided [17]; these deaths might therefore not be attributed to measles.

Our investigation is subject to some limitations. First, because a comprehensive list of all measles cases in the district was not available, a representative sample could not be obtained. Instead, villages with reported measles cases were chosen for inclusion, and house-to-house searches were conducted. Second, recall bias may have occurred, because this investigation relied on the informants’ ability to retrospectively identify measles cases and deaths. Attempts were made to limit this bias by use of a short recall period and by provision of a local calendar of events. Third, some rash and fever illnesses may have been misclassified as measles. The potential for such misclassification was limited by the use of a specific case definition and serologic confirmation of measles in the areas investigated. In addition, local health care workers and the general population are very familiar with measles, because it is a common disease in the community. In similar settings, validation of verbal autopsy results have shown high sensitivity and specificity in accurately identifying measles cases [40].

Our investigation did not identify specific risk factors for measles mortality that are amenable to public health intervention. Decreasing the number of measles deaths in Niger will require prevention of measles transmission through increased vaccine coverage. Vaccine coverage can be increased in the short term through a “catch-up” campaign targeting a broad age range of infants and children. However, to maintain the gains of such a campaign, it will be necessary to improve routine immunization coverage and to conduct “follow-up” campaigns, targeting children aged 9 months to 5 years, every 2–4 years, depending on the routine coverage obtained.

This investigation highlights the high burden of measles mortality in Niger during annual measles outbreaks. Unlike other major illnesses that kill large numbers of young children, measles can be prevented through use of a safe, highly effective, and inexpensive vaccine. Unfortunately, in many of the poorest areas of the world, large numbers of children remain unvaccinated. Increased efforts are needed to insure that children in developing countries receive measles vaccine.

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