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Assessment of the Epidemiology and Burden of Measles in Southern Mozambique

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Abstract. Measles has been a major killer among vaccine-preventable diseases in children < 5 years of age in developing countries. Despite progress in global efforts to reduce mortality, measles remains a public health problem. Hospital-based measles surveillance was conducted in Manhica, Mozambique (July 2001–September 2004). Suspected cases and community-based controls were enrolled, and blood was collected for immunoglobulin M (IgM) confirmation. Two hundred fifty-three suspected cases and 477 controls were enrolled, with 85% (216 of 253) cases reported during a measles outbreak. Measles-IgM confirmation was 30% among suspected cases and 5% in controls. Fifty-eight percent (14 of 24) of laboratory-confirmed cases had records indicating previous measles vaccination. Mortality was 3% (8 of 246) among cases and 1% among controls (6 of 426). Forty-five percent (33 of 74) of cases were < 24 months of age and 22% occurred in infants < 9 months of age and were associated with a high case-fatality rate (25%). Our data suggest that improved diagnostics, new tools to protect infants < 9 months of age, and a supplemental dose of measles vaccine could assist measles control.

INTRODUCTION

Measles has been one of the major killers among vaccine-preventable diseases in children < 5 years of age, particularly in developing countries.[1,2] An ongoing global effort committed to diminish the measles mortality burden has made significant progress.[3–5] However, despite the remarkable reduction in mortality achieved,[4] measles epidemics continue to occur and affect both children and young adults, including vaccinated individuals.[6–8] Moreover, the sizable proportion of infants below vaccination age (i.e., < 9 months of age) who remain susceptible to the infection when their maternally derived antibodies wane[9–11] are prone to develop severe disease accompanied by a high case fatality; this is particularly true among human immunodeficiency virus (HIV)-infected subjects.[12,13]

In Mozambique, a single dose of measles vaccine is administered at 9 months of age through the Expanded Program of Immunization (EPI).[14] In addition to routine infant vaccine administration through the EPI, mass measles vaccination campaigns implemented since 1997 have succeeded in reaching many children < 5 years of age. The measles supplemental immunization campaigns have been conducted every 3 to 4 years and in 2005 included ~8.2 million children from 9 months to 14 years of age.[15] Despite a reported high vaccine coverage, epidemics continue to occur in Mozambique with the most recent having taken place in 2003.[14,16] In addition, recent serosurveys have shown that almost one-third of infants < 9 months of age are susceptible to infection, particularly during the "window of vulnerability" (~4–8 months of age) when maternal antibodies have fallen to non-protective levels and infants have not yet been vaccinated.[17,18]

Mozambique has a high HIV prevalence with an estimated 13% of the population (≥ 15 years of age) infected in 2007.[19] Maternal HIV infection has various effects on the infant including a decrease in the placental transfer of measles protective antibody.[20,21] The HIV infection is also considered to be an important factor contributing to primary and secondary measles vaccine failure.[22,23] Thus, there is a need to characterize the local epidemiology of measles in regions with a growing HIV prevalence, to design new control strategies to protect children before the age of vaccination, and to overcome vaccine failure.[12]

Monitoring for measles in Mozambique is conducted through a hospital-based Weekly Information Bulletin System (Boletim Epidemiológico Semanal – BES) notification from health facilities.[18] Laboratory case-based investigation has been running since 2006 in the Central Laboratory of the National Institute of Health (INS). However, despite continuous monitoring, few studies have been designed to address the burden of measles disease in Mozambique in the current situation of elevated measles vaccine coverage and high HIV prevalence. In the study described herein, we aimed to elucidate the epidemiology and burden of measles disease and associated mortality in the Manhiça district of southern Mozambique.

MATERIALS AND METHODS

Study area and population. This study was conducted in the Manhiça District, a rural area of Maputo Province, in Southern Mozambique. The district has an estimated population of 150,000 inhabitants,[24] and the characteristics of the area have been described in detail elsewhere.[25] Briefly, the climate is subtropical with two distinct seasons: a warm, rainy season between November and April and a generally cool and dry season during the rest of the year. Since 1996, in this area, the "Centro de Investigação em Saúde da Manhiça – CISM" has maintained a demographic surveillance system (DSS) of a population that includes ~84,000 people.[26] The CISM is adjacent to an urban Health Center and District Hospital (MDH), a 110-bed health facility. The hospital and CISM have jointly operated a round-the-clock surveillance of all pediatric visits at the outpatient department and admission to the hospital wards since 1997. According to Ministry of Health administrative data, measles vaccine coverage during the study period was > 98%.[27]

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Measles surveillance and sample collection. Between July 2001 and September 2004, we conducted a hospital-based measles' surveillance through the ongoing morbidity platform at the MDH, and all other health facilities within the District including "Hospital Rural de Xinavane." Cases clinically suspected to be measles were reported by clinicians (doctors or medical officers in peripheral health posts) to the investigators, and cases were visited by a trained field worker. Notification of cases to the investigators was done either by direct contact for cases reported to the MDH, which is adjacent to the CISM, or by telephone for cases reported to the peripheral health facilities. Additionally, on a weekly basis, a field worker visited all peripheral sentinel health facilities to capture possible new cases. After obtaining informed consent from the mother or caretaker, the field worker completed a brief questionnaire collecting demographic and clinical information and measles vaccination status (recorded when a vaccination card was available). The child's weight, height, and median upper arm circumference were also measured. For each case, at least one community controls matched by age (within 2 months for infants and within 6 months for older subjects), sex, and neighborhood was enrolled, after obtaining informed consent. A list of potential controls was generated from the DSS database and the households were visited by a field worker. Both cases and controls were seen at Months 1, 3, 6, and 12, when demographic, clinical, and outcome information was collected. The geographic coordinates of the household identified by GPS (Garmin Etrex Legend, Taiwan) were recorded.

One milliliter (mL) of blood was collected from both cases and controls by finger prick and placed in an EDTA microtainer for serologic confirmation by detecting measles immunoglobulin M (IgM) antibodies in the plasma. Samples were transported to the CISM laboratory and after centrifugation; plasma was stored at –20°C until shipment to the Center for Vaccine Development (CVD), University of Maryland School of Medicine for measurement of IgM or IgG measles antibodies. This study was approved by the Mozambican Ethics Committee, the Hospital Clínic of Barcelona Institutional Review Board (IRB), and the IRB of the University of Maryland, School of Medicine (Baltimore, MD).

Measles laboratory confirmation. Measles IgM antibodies were measured by enzyme-linked immunosorbent assay (ELISA). Immulon II plates (ThermoLabsystems, Franklin, MA) were coated for 3 h at 37°C with 5 μg/mL of measles lysate (Advanced Biotechnologies Inc., Columbia, MD) in carbonate buffer (pH 9.0). Plates were washed with phosphate buffered saline (PBS) containing 0.05% Tween 20 (PBST) and blocked overnight at 4°C with 10% dried milk (Nestle USA Inc., Glendale, CA) in PBS. Samples were added in serial 2-fold dilutions in PBS-Tween containing 10% nonfat dry milk (PBSTM) and plates incubated for 1 h at 37°C. Horseradish peroxidase-labeled goat anti-human IgM (Jackson, West Grove, PA) diluted in PBSTM was used as conjugate and TMB (KPL, Inc., Gaithersburg, MD) as substrate. The reaction was stopped after 15 min incubation by addition of 100 μL of 1 M H_3PO_4 and absorbance values at 450 nm was measured. Samples were run in duplicate along with positive and negative controls. Measles IgG antibodies were measured as previously described.[9]

Definitions. Clinical measles was defined as the presence of fever, rash, and one or more of the following signs: cough, coryza, or conjunctivitis. A primary case was defined as a measles case with no evidence of household or community contact with measles in the previous 3 weeks. Laboratory confirmation of measles was defined as a measles IgM antibody titer ≥ 117.2 EU/mL. This cutoff was established as the mean titer + 3 SD from 103 serum samples obtained from healthy adult individuals from a non-endemic area. The IgM negative samples (when enough volume was available) were tested for measles IgG and a titer equal or > 200 mIU/mL was considered as positive. Measles-vaccination status was recorded from vaccination cards, when available. Nutritional status was assessed by weight for age (WAZ) and height for age (HAZ) Z-score. Mild malnutrition was defined as a WAZ or HAZ between –2 and –1; moderate malnutrition was between –3 and –2; and severe malnutrition was < –3.

Data management and statistical analysis. Epidemiological and clinical data were double entered into a FoxPro database using visual FoxPro version 2.6 (Microsoft Corporation, Redmond, WA). Laboratory data were entered in Excel and transferred to Stata software by stat transfer version 7.0 (Stata Corp., College Station, TX). The two entries were compared and discrepancies were resolved by referring to the original forms. The statistical analysis was performed using Stata software version 9.0 (Stata Corp.). Student's *t* test or Wilcoxon rank sum test were conducted for continuous variables and χ^2 or Fisher's exact tests for categorical variables. A P value ≤ 0.05 was considered as significant.

RESULTS

Measles by clinical and laboratory definitions. During the study period (July 2001 to September 2004), 253 suspected measles cases and 477 matched controls were enrolled into the study. The clinical definition of measles was applied for clinical management of patients. Both the clinically suspect cases and IgM serology-confirmed cases were assessed in this study. Table 1 summarizes the study population according to clinical and laboratory-confirmed definitions of measles. Among clinically suspect cases, only 29% (74 of 253) were positive for measles IgM, compared with 5% (22 of 477) of controls.

TABLE 1
Description of study population according to clinical and IgM laboratory definition of measles

		Clinical definition		Laboratory IgM definition	
		N = 253		*N* = 74	
		n	%	n	%
Gender	Male	132	52	34	46
Age	< 9 months	23	9	16	22
	9–23 months	31	12	17	23
	23–59 months	52	21	7	10
	5–9 yrs	86	34	12	16
	10–14 yrs	38	15	9	12
	≥ 15 yrs	23	9	13	18
Primary cases		218	86	63	85
Complications*	Yes	105	42	47	64
Mortality†		8	3	6	8
Measles vaccination‡	Yes	116	88	14	58

*Complications in Clinical definition (N = 251), and in immunoglobulin M (IgM) laboratory definition (N = 74).
†Mortality in Clinical definition (N = 246).
‡Vaccination status was assessed among study population ≥ 9 months presenting vaccination cards. In Clinical definition (N = 132), in IgM laboratory definition (N = 24).

Among the clinically suspect measles cases, 21% were infants and toddlers < 24 months of age and 9% were infants < 9 months of age. Eighty-six percent of the cases were primary cases, and 42% presented complications. Among the laboratory-confirmed cases, a greater proportion were children < 24 months of age (45%; 33 of 74) and 22% were infants < 9 months of age. Notably, 64% (47 of 74) of the laboratory-confirmed cases reported complications.

Among IgM-negative samples from clinically suspect cases, 61 had a sufficient volume of plasma remaining for measles IgG to be measured and 98% (60 of 61) had ELISA titers ≥ 200 mIU/mL; ~50% of these individuals had not been immunized against measles nor had an unknown vaccination status.

Measles outbreak during surveillance. Of the total clinical cases reported in this study, almost 85% (216 of 253) were identified during the measles outbreak that occurred in Mozambique between June and December 2003. The proportion of IgM-confirmed cases during the outbreak and other times was similar (29%; 63 of 216 versus 30%; 11 of 37, respectively, $P = 1$). Table 2 describes the characteristics of clinically suspect measles cases and laboratory-confirmed cases during the outbreak period.

Exploratory analysis of measles during the outbreak period according to whether they were from peripheral (Ilha Josina and 3 de Fevereiro) or referral (Manhiça and Maragra) health facilities showed that 55% (119 of 216) of clinical cases reported within the outbreak period were from Ilha Josina and 3 de Fevereiro communities compared with 45% from Manhiça and Maragra areas. The proportion of laboratory-confirmed measles cases was lower among cases reported from peripheral health facilities (12%, 15 of 121) versus cases reported from the referral health facilities (45%, 59 of 132), ($P < 0.001$). Among laboratory-confirmed cases, the proportion < 24 months of age was significantly lower in cases from Ilha Josina and 3 de Fevereiro communities (1 of 15, 7%) compared with those from the Maragra and Manhiça area (24 of 48, 50%) ($P = 0.02$). In contrast, the proportion of IgM confirmed cases among children 5–9 years of age was higher from Ilha Josina and 3 de Fevereiro communities as compared with Maragra and Manhiça areas (40%; 6 of 15 versus 8%; 4 of 48, respectively, $P = 0.008$).

When looking at the geographic distribution of cases not occurring during the outbreak period, 35 of 37 (95%) clinical cases were from Manhiça, with the majority (16 of 35; 46%) being children < 24 months of age and 17% (6 of 35) being infants < 9 months of age.

Measles in previously vaccinated children. Measles vaccination status was recorded when vaccination cards were available, and analysis was restricted to children 9 months of age or older. Approximately 55% of clinical measles cases (126 of 230) had vaccination cards of which 110 cases (87%) had a record of having received measles vaccine. The remaining 16 children (13%) had no record of having received the measles vaccine. Tables 1 shows stratification by vaccine status according to clinical or IgM laboratory definitions of measles. Among all patients (Table 1), the proportion of measles cases who were previously vaccinated was over 58% (95% confidence interval [CI]: 41–81), regardless of whether they were only clinically suspect cases or laboratory-confirmed cases. However, among those in the outbreak, there was a significant difference in the apparent proportion of measles cases who were previously vaccinated if analysis was performed using clinically suspect cases or laboratory-confirmed measles cases (91% versus 59%, respectively). In 10 of the 14 cases among previously immunized individuals (71%), sufficient time had elapsed to generate an antibody response with a median of 1,036 days (range: 155–1,535 days) between vaccination and disease onset.

Clinical presentation and outcome. Overall, 105 cases presented cough as the most frequent sign or symptom, followed by fever. Table 2 presents the most frequently reported clinical presentations among clinically suspect and laboratory-confirmed cases. With the exception of difficulty of breathing, which was more frequent during the outbreak period by clinical definition, there was no significant difference in the clinical presentation of cases presenting within or outside the outbreak.

Among clinically suspect cases, unvaccinated individuals were likely to have more complications than vaccinated children (60%; 6 of 15 versus 33%; 38 of 116, respectively, $P = 0.04$). This difference was not significant when analysis was performed using laboratory-confirmed cases (70%; 7 of 10 versus 57%; 8 of 14, $P = 0.5$).

There were 14 deaths during the study period, of which 8 of 246 (3%) were among clinically defined cases and 6 of 426 (1%) among controls. Seven out of eight deaths among clinically defined cases were children < 24 months of age; notably, five of the deaths occurred among infants < 9 months of age, i.e., before the age of vaccination. The case fatality rate among laboratory-confirmed cases, was 8% (6 of 74); all in children < 24 months of age, including four infants < 9 months of age.

According to WAZ and HAZ definitions, there was no evidence of long-term poor outcome (malnutrition or growth) caused by measles infection among cases, as shown in Table 3.

TABLE 2
Clinical complication of measles cases within and outside outbreaks according to clinical and laboratory definition*

	Overall		Within outbreak			Overall		Within outbreak		
	Clinical definition ($N = 105$)		Clinical definition ($N = 97$)			Laboratory definition (IgM +)		Laboratory definition (IgM +)		
	n	%	n	%	P value†	n	%	n	%	P value‡
Fever	88	84	82	84	0.5	36	49	33	79	0.4
Cough	102	97	94	97	0.6	46	62	41	98	0.7
Diarrhea	38	36	35	36	0.9	22	30	20	48	0.7
Increased respiratory rate	26	25	23	24	0.4	9	12	8	19	0.9
Difficulty in breathing	18	17	13	13	< 0.001	7	10	5	12	0.09
Vomiting	20	19	20	20	0.3	13	18	13	31	0.1
No stimulus response	23	22	23	23	0.1	3	4	3	7	0.5

* IgM = immunoglobulin M.
† Comparison of clinical presentation within and outside outbreak by clinical definition.
‡ Comparison of clinical presentation within and outside outbreak by IgM laboratory.

TABLE 3
Comparison of measles outcome (malnutrition and growth) between cases and controls during the follow-up period*

		Cases	Controls	
		Median (IQR)	Median (IQR)	*P* value
1 month				
	WAZ	–1.07 (–1.77; –0.21)	–1.04 (–1.8; –0.25)	0.9
	HAZ	6.9 (5.3; 12.1)	7.2 (5.2; 12.4)	0.8
3 months				
	WAZ	–1.08 (–1.77; –0.34)	–1.04 (–1.83; –0.31)	0.7
	HAZ	6.9 (5.2; 11.4)	7.1 (5.1; 12.0)	0.9
6 months				
	WAZ	–1.19 (–1.80; –0.34)	–1.00 (–1.77; –0.31)	0.4
	HAZ	6.5 (5.2; 11.2)	6.6 (5.1; 11.5)	0.9
12 months				
	WAZ	–0.98 (–1.68; –0.20)	–0.99 (–1.81; –0.31)	0.3
	HAZ	6.1 (5.1; 10.3)	6.1 (5.1; 10.6)	0.8

* IQR = interquartile range; WAZ = weight for age; HAZ = height for age.

DISCUSSION

Although a significant measles mortality reduction has been shown during recent years, particularly in Africa,[3] sporadic cases and epidemics continue to occur.[8,28] Since January 2010, Malawi, a neighboring country of Mozambique, has been experiencing the largest measles outbreak with 77,000 cases reported and 195 deaths.[29] Data reported in this study, obtained in Manhiça District during 2004 shows a high number of measles cases occurring in children with a record of prior measles vaccination, and among infants before the age of vaccination. Furthermore, measles was associated with complications and a high case fatality rate among young infants before the age of vaccination. Our results also point to a significant discrepancy between clinical and laboratory diagnosis of measles cases, particularly in peripheral health posts where misdiagnosis of cases was high, especially for infants and toddlers < 24 months of age. Although these data were collected in 2004, vaccine policies and measles diagnosis tools have not significantly changed in Mozambique over the past 6 years. Although the current number of cases may be different, the distribution and presentation of cases is likely to be similar.

Measles in infants below vaccination age may reflect less protection by maternally transferred measles antibodies than was seen in decades past. This could arise in infants born to vaccinated or non-immune mothers. There is growing evidence that measles vaccine-induced antibody levels are lower than wild virus-elicited antibody levels and that they wane over time. Thus, less maternal passive immunity is available to be transferred during pregnancy when vaccinated women reach childbearing years.[30,31] In this study, it is likely that the infants' mothers were born after the introduction of measles vaccine in Mozambique in 1981.[32] Between 1981 and 2004, the probability that the mother was vaccinated was high, because the measles vaccine was well established in the EPI program. Infants born to vaccinated mothers may therefore receive less maternal measles antibody and be vulnerable to the infection and associated clinical disease.[9,30,31,33,34] Unfortunately, information on age and vaccination status of the mothers was not available to test this hypothesis in our study. There is also evidence that HIV infection may lower the level of placental transferred antibodies from the mother to her child.[20,21,35] Although not assessed in this study, HIV prevalence is increasing among women attending antenatal clinics in this community[36,37] and was ~23% in 2004 in women attending the Manhiça antenatal clinic.[37] At that time, the rate of transmission mother-to-child transmission during the first year of life was ~25% in the Manhiça district.[38] It is, however, difficult to estimate the HIV prevalence in infants, which would have been likely higher for those < 2 years of age, during a time when combined antiretroviral treatment was not available.

This study found that 22% of IgM-confirmed measles cases were infants < 9 months of age, and they had a case fatality rate of 25%. This corroborates many previous reports from sub-Saharan Africa noting a high case fatality of measles in the young infant host; it also shows that high case fatality with measles is still occurring in Africa. Other factors associated with high case fatality in African infants with measles include malnutrition and HIV status of both infants and their mothers. Maternal HIV infection has been suggested to be associated with increasing risk of child death regardless of the infants HIV status.[37]

The finding that only 30% of clinically suspect measles cases were serologically confirmed should be interpreted with caution. This result may be partially explained by clinical misdiagnosis caused by the lack of qualified, adequately trained health staff, particularly in peripheral health post facilities such as Ilha Josina and 3 Fevereiro. The referral Manhiça district hospital is adjacent to the CISM where there are more medical doctors providing technical assistance and this is likely to increase the quality of clinical diagnosis. A proportion of the measles cases could thus have been misdiagnoses of rubella and other febrile exanthematous infections. Indeed, a large proportion of the infants had rubella IgM (data not shown).

Another factor contributing to a generally low serological confirmation of clinical measles in this population could be related to the timing of sample collection with respect to onset of clinical measles, which is considered to be an important factor in interpreting IgM results. This is also true for samples collected more than 2 weeks after vaccination, which are also difficult to interpret.[38] In this regard, 50% of individuals who tested negative for IgM and showed an IgG titer ≥ 200 mIU/mL (N = 60) had no history of having been vaccinated or their vaccination status was unknown. We hypothesize that many of these were in fact measles cases that may have been properly confirmed with the IgM antibody test if specimens had been collected at an earlier time point. This may be supported by the fact that few measles cases from the most remote rural areas seek health care at the hospital or arrive late in the course of disease if they do come. Other rural patients do not seek care at the hospital because of the distance to be traveled or because of the cultural "taboo" that "children with measles should not cross the road."[39] These observations can help explain the low laboratory confirmation rates encountered in our study.

We cannot accurately assess the time of sample collection with respect to the onset of clinical measles. However, it should be noted that the laboratory confirmation of one-third of the clinical cases reported in this study is significantly higher than the 11% IgM confirmation found in Mozambique at the national level in 2009.[40] One explanation for the 5% of controls with measles IgM is that some (particularly during the outbreak) represent subjects that experienced clinically mild or asymptomatic measles.

The high proportion of vaccinated individuals with laboratory-confirmed measles may be partially explained by immunity waning over time or vaccine failure, which is well

documented,[30,31,41] and the cold chain required to preserve measles vaccine, which is difficult to monitor in many rural areas of Mozambique, although it may only be relevant for peripheral health posts. Although our data of vaccine failure is based on a small number of laboratory-confirmed cases, a large proportion of cases previously immunized had sufficient time to generate an antibody response as shown in the results.

Our study provides insightful data on the local epidemiology of measles in one area of Mozambique that is a setting of high measles vaccine coverage accompanied by growing HIV prevalence. Limitations of our study include small sample size with respect to cases in infants younger than 9 months of age and previously vaccinated individuals. However, these epidemiological patterns are important in the context of measles elimination efforts and stress the need for continued monitoring.

Data from the national epidemiological surveillance show a decrease of measles cases.[40] However, the patterns reported in our work appear to occur also in the urban setting in Mozambique. Jani and others[10] have recently reported that maternal antibody wanes by 6 months of age, in ~82% of infants and that one-third of 9-month-old children in Maputo city have evidence of contact with measles wild-type virus before vaccination.

Our epidemiologic data encourage the development of new strategies to protect infants < 9 months of age,[42] particularly in this setting of high HIV prevalence. Furthermore, the clinical diagnosis of measles should be strengthened to monitor measles in rural areas that do not have access to laboratory confirmation. In addition, our study and others support intensifying measles elimination efforts through supplemental mass immunization campaigns and a second dose of measles vaccine. Further study of the role of HIV infection in the burden of measles disease and mortality among infants and children < 2 years of age should also be pursued.

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