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Original Article

An Investigation into a Measles Outbreak in Southeast Iran

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SUMMARY: In 2009 and 2010 a series of measles outbreaks, involving different age groups, occurred in rural areas of the Chabahar district in southeast Iran. These outbreaks raised questions regarding the effectiveness of immunization programs in these areas. To determine the most important factors leading to these outbreaks, and to determine the effectiveness of the measles vaccination program, the present study analyzed surveillance data and performed a case-control study. The total number of reported cases during the study period was 126. The estimated vaccine effectiveness, based on the adjusted odds ratio of the case-control study, was 74.2% (95% CI, 10.2–92.6). On two occasions, both primary and secondary cases of the outbreaks were vaccinated school children. In total, 42% of all cases were aged above 7 years, and 6.3% were above 20 years. With regard to the important role of schools as the foci of contact between uninfected and infected children, supplementary immunization of children before starting in school could be effective in preventing measles outbreaks. In addition, implementation of supplementary immunization every 5–10 years in older age groups might be effective in preventing future outbreaks.

INTRODUCTION

Measles is one of the most contagious diseases known to man and often occurs in explosive epidemics. It usually does not kill children directly; however, as a result of its associated immunosuppression, measles can lead to lethal complications, such as pneumonia, croup, and diarrhea. Measles can also lead to lifelong disabilities, including blindness, brain damage, and deafness (1,2).

In May 2003, the World Health Assembly endorsed a resolution urging its member states to achieve the goal adopted by the United Nations General Assembly Special Session on Children, which was to halve global measles deaths by the end of 2005 (compared to 1999 estimates) (3). Between 1999 and 2004, improvements in routine measles vaccination coverage and the implementation of supplementary immunization activities (SIAs) in prioritized countries resulted in a 48% decrease in the estimated number of global measles deaths. Although Iran is not among prioritized countries in the measles campaign, it is in close proximity to at least three of those countries, with two of them yet to implement any SIAs (i.e., Pakistan and India) (3).

During May and June 2009, the physicians in charge of Uraki and Pirsohrab Rural Health Centers of Chabahar district reported a measles outbreak in their catchment areas. Chabahar district is located in the coastal region of the Sistan-va-Baluichestan province in southeast Iran and has a subtropical climate. It has a population of approximately 214,000 (33% living in Chabahar Port and the remaining in rural regions) and has experienced rapid development within the past two decades (4). However, in the inland rural areas, villagers still retained traditional lifestyle, with their economy being mostly based on subsistence agriculture, animal breeding, working on large fishing boats, and illegal fuel smuggling to Pakistan. The urban areas, composed almost exclusively of Chabahar Port, contains a mixed population of the original residents of Chabahar, along with those who have recently immigrated from the other parts of Iran for work, trade, and as civil servants. In addition, the ever-growing illegal Paki and Afghan immigrant populations, who mostly live in the outskirts of Chabahar Port, are included in the above-mentioned subpopulations.

Similar to other parts of Iran, the health system in Chabahar has a stepwise structure. In the rural areas, health houses are the first providers of healthcare services. Each health house has a catchment area that includes the village in which they are located and some nearby villages (usually within a 5-km range), which encompasses an overall population of approximately 2000–5000. In each health house, two healthcare workers cover Primary Health Care (PHC) services, including routine immunizations. All important health-related information in the households, including the vaccination status of children, is recorded in logbooks. In addition, every child in the catchment area is required to have a ''health card,'' in which records of his/her vaccination status are maintained. Every 4–5 health houses are under the supervision of a Rural Health Center. All health services, including PHC and the surveillance of disease in each area, are managed and supervised by the physician in charge of the Rural Health Center. All Rural Health Centers in a particular district report to the District Health Center, which in turn, is under the supervision of the Provincial Health Center, which fi-

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nally reports to the Center for Disease Management at the Ministry level.

Based on the National Immunization Schedule of Iran, by the end of the second year of life, all children should receive at least 2 doses of measles vaccine, scheduled at 12 and 18 months. This schedule has been changed several times during the past few years. Before the nationwide catch-up campaign of December 2003, in which all people who were 5–25 years of age were vaccinated for measles and rubella, the measles vaccine was prescribed at 9 and 15 months of age. After the campaign, the measles vaccine, together with mumps and rubella vaccines, was prescribed as MMR (measles-mumps-rubella) at 12 months, and again at 4–6 years of age. However, since mid-2008, the time schedule for MMR vaccinations was changed to 12 and 18 months to enhance immunity at lower ages. According to official reports, since 2001, the coverage of measles containing vaccine (MCV) throughout Iran was greater than 90% of the population, and during 2008 and 2009, it was approximately 99% (5).

After the nationwide catch-up campaign of 2003 and the exhaustive efforts taken in recent years for controlling measles in Iran, the occurrence of outbreaks in two consecutive years was a shock to the health sector and had the potential to seriously undermine confidence in the immunization program. Thus, the main purpose of this study was to determine the effectiveness of anti-measles vaccinations and to restore confidence in vaccination programs as a feasible method for elimination of measles.

MATERIALS AND METHODS

We first analyzed data gathered by the surveillance system and then performed a case-control study in order to develop our understanding of causative factors that lead to the accumulation of susceptible individuals into foci.

Study population: The study population was composed of the inhabitants of the Chabahar district villages involved in the measles outbreaks. The total study population was approximately 14,600, from 23 villages that ranged in size from 130 to 2,060 inhabitants. The cases of the ''case-control'' part of the study were selected randomly from cases that had been confirmed serologically by the beginning of the study. For each case, two age-matched controls (age ± 2 years) were selected from the general population of the same village. This way the cases and controls were matched individually for both age and place of residence. There was no national, ethnic, or religious precondition for inclusion in the study.

Study period: Surveillance data were analyzed from all reported cases since the beginning of the first outbreak on April 29, 2009, until the end of the second outbreak on August 3, 2010. However, the case-control study began on May 25, 2010 and enrollment of the controls continued until June 3, 2010. Patients and their matched controls were interviewed (by questionnaire) approximately 1 to 2 months after the appearance of disease symptoms.

Routine surveillance activities: After a suspected case of measles was reported to the District Health Center, an investigation team composed of a health expert, a general practitioner, and a lab technician, filled out a detailed surveillance form. The data gathered in these forms included demographic and vaccination history, summary of clinical signs and symptoms, history of travel and contact with other suspicious cases, the clinical course, outcomes, and date of blood sampling. The results of lab tests, along with the final categorization of the case (positive serologic or epidemiologic confirmation of measles versus a negative diagnosis), were added to the form later.

Individuals were considered to be vaccinated only if vaccination was documented in their vaccination cards or their log files. Children who had lost their vaccination cards or who had no record of vaccination, either in cards or logbooks, were considered to be unvaccinated. However, it should be kept in mind that vaccines received during the supplementary vaccination campaigns were not recorded, either in the vaccination cards or in logbooks, and this could be an important cause of misclassification. In the measles surveillance system, every patient with fever, maculopapular rash, and cough, coryza, or conjunctivitis, was considered to be a suspected measles case. However, even mere suspicions of clinicians (either healthcare workers or physicians) were considered to be sufficient for identification of suspected cases. Such cases had to be reported as soon as possible, no later than 24 h after the appearance of the rash. The basis for laboratory confirmation of measles infection was the presence of measles-specific IgM antibodies in serum from cases sampled 5–28 days after the appearance of the rash (6–9). All laboratory tests were performed in the National Reference Laboratory of Measles, Tehran University of Medical Sciences, Tehran, Iran. Confirmed cases were considered to be those that were either confirmed serologically, or which met Center for Disease Management standard clinical criteria for case definition, and which were linked epidemiologically to another case that had been confirmed serologically (10).

Case-control study: Fifty confirmed measles cases were selected from those reported to the Center for Disease Management from 2009–2010. As mentioned above, only subjects that were positive for IgM antibodies in their serum were selected as cases. For each case, two individually matched controls were selected, as described above.

A questionnaire specifically designed for the case-control part of the study was completed during an interview. The interview was conducted in the local language and with the subjects' parents, mostly mothers, present. Interviews of each pair of cases and controls were performed mostly on the same day. In addition to demographic information and history of exanthematous disease from 2009–2010, a full vaccination history based on records from vaccination cards and logbooks was included in the questionnaire. Controls with a history of any type of exanthematous disease since the beginning of 2009 were excluded from the study and replaced with other appropriate controls. Other important variables recorded were as follows: history of traveling and destinations during the previous 20 days (or for the cases, during the 20 days before symptoms were apparent), history of contact with any kind of exanthematous case, including confirmed measles cases, within the past 20 days (or for the cases, during the 20 days before symptoms were apparent), education level and occupation of the parents, and other economic indices, such as household size and number of rooms, possession and availability of furniture (such as air conditioners, refrigerators, mobile and fixed phones, ovens, televisions, washing machines, vacuum cleaners, and computers), internet availability, and possession of motorcycle, or any other kind of vehicle.

Analysis: A computerized data bank was produced based on completed questionnaires and the data were analyzed using SPSS (Statistical Package for Social Scientists, version 15; SPSS, Chicago, Ill., USA) and STATA (version 9.0; STATA Corp., College Station, Tex., USA). We used descriptive tables and charts, χ^2 tests, and odds ratio (OR) statistics for data analysis. For multivariate analysis, we used conditional logistic regression modeling and calculated the adjusted OR and 95% confidence interval (CI). To select a model, the backward elimination procedure was used, starting with a complex model and successively taking out terms. At each stage, the term in the model that had the greatest P value was eliminated, and it was checked whether its parameters were equal to zero. The maximum likelihood estimation was calculated using the likelihood ratio test. Asymptotic standard error values were used to find the CI for the parameters in the model (11). The criteria for accepting a statistically significant relationship was a type-one error value of less than 0.05. Vaccine effectiveness was derived from the cumulative incidence during the outbreak and was calculated according to the following formula (12–14):

$$\text{Vaccine Effectiveness (\%)} = [(\text{ARU} - \text{ARI})/\text{ARU}] \times 100 = (1 - \text{RR}) \times 100$$

where ARU, ARI, and RR stand for "attack rate in the unimmunized population," "attack rate in the immunized population," and "relative risk," respectively. For the case-control part of the study, vaccine effectiveness was estimated by subtracting the exposure OR for vaccinated cases versus vaccinated controls from 1 (i.e., 1–OR) (10). As occurrence of measles was rare in the children of the study population (approximately 2%), the adjusted OR was used as an approximation to the risk ratio to calculate vaccine effectiveness.

RESULTS

On April 29, 2009, the first exanthematous case (later confirmed serologically as measles) was reported to the District Health Center of Chabahar. The patient was an 8.4-year-old primary school student that was living in Kalsekan village, approximately 50 km north of Chabahar Port. Within 12–16 days of the primary case being reported, 4 secondary cases occurred in the same school. The fifth secondary case was a 39.5-year-old woman. The primary case and 3 of the secondary cases had histories of 2 prior measles vaccination. Within a time interval of 8–13 days from the secondary cases, 17 tertiary cases appeared, with 6 of them being school children, 9 being preschool children (aged 1–5 years), and 2 adult females (aged 27.6 and 31 years). All of the above-mentioned cases were later confirmed serologically. Until the end of the first outbreak, on June 21, 2009, 10 more cases were reported from Kalsekan and 2 nearby villages, bringing the total number of cases in 2009 to 33 (23 of which were confirmed serologically, 6 were confirmed epidemiologically, 2 were clinically compatible but had no blood testing, and 2 were excluded) (Fig. 1).

The second outbreak began on January 20, 2010 in Negor, a village approximately 50 km southeast of Kalsekan, and was stopped within 5 days. All 6 cases in this outbreak were 7–10-year-old schoolchildren. All cases were serologically confirmed, and all but the youngest case had histories of receiving at least 1 measles vaccination (1 case had received 2 vaccinations). The time interval between the appearance of the first and the last cases was 6 days. However, the primary case of this outbreak remained unidentified.

Approximately 4 weeks later, the next outbreak began. This time, the cases were widely distributed throughout the district and defining a logical pattern or chain of transmission was almost impossible. Cases that were from different age groups were reported simultaneously in villages that were 20–60 km apart. On this occasion, in order to control the epidemic, all children in the Chabahar district (both in urban and rural regions) between 9 months and 12 years of age were immunized with a supplementary dose of MMR. This out-

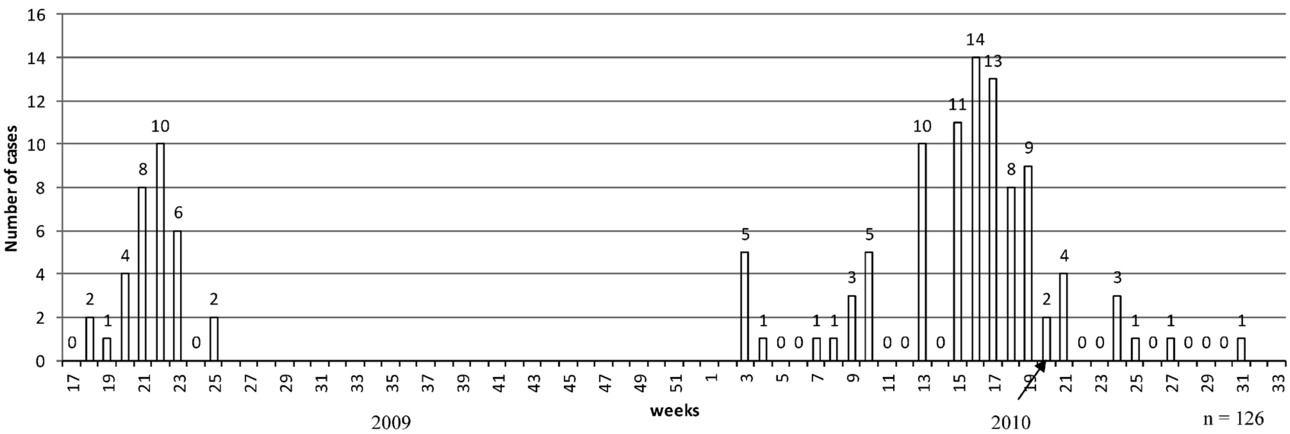

Fig. 1. Time trend of occurrence of the cases in 2009 and 2010 measles outbreaks in Chabahar district, southeast Iran. Arrow indicates the outbreak-response immunization activities. Total number of cases = 126.

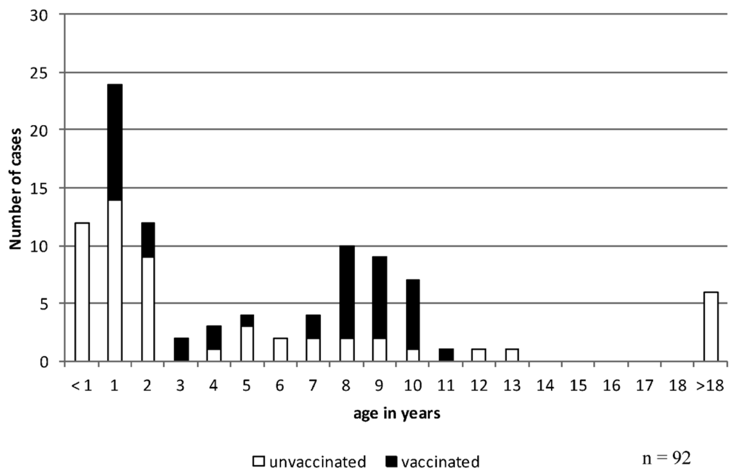

Fig. 2. Age specific vaccination coverage of the confirmed measles cases, Chabahar district, Iran, the outbreaks of 2009 and 2010 (total number of cases = 92).

break-response immunization program began on May 18, 2010 and ended on May 25, 2010. However, occurrence of cases continued for a few more weeks, and the last case was reported on August 3, 2010 (Fig. 1). The second part of the epidemic curve depicted in Fig. 1 is very similar to a self-restricting outbreak, which usually ends merely due to a lack of susceptible individuals for continuing the chain of transmission. Presumably, the above-mentioned supplementary vaccinations hastened this trend. We did not consider these supplementary vaccination in our analysis of vaccine effectiveness or in the case-control part of the study. During the 2010 outbreaks, 67 cases were finally categorized as confirmed cases (56 serologically and 11 epidemiologically) from a total of 93 suspected cases. The total number of reported cases in these outbreaks was 126 (33 from the first outbreak and 93 from the second).

Approximately 47% of confirmed cases in 2009 and 37% in 2010 were older than 7 years, 6 of the confirmed cases were above 20 years (20.5–39.5 years old, 3 confirmed serologically) and 6 were below 6 months old (5 confirmed serologically). Figure 2 shows the age distribution of the 92 confirmed cases by vaccination status (the vaccination histories of 4 cases were not reliable and were not used). Below the age of 14 years, a bimodal pattern in age distribution is clearly recognizable, while in cases older than 3 years, most had a positive immunization history against measles (29 out of 50 cases).

Even though 22 of the suspected cases were admitted to hospital (6 in 2009 and 16 in 2010), there were no severe complications or deaths, and all were discharged within 2–4 days. Most hospitalized cases were admitted to provide sufficient time for sample collection or confirmation of diagnosis by a pediatrician.

Table 1 shows the descriptive characteristics of the participants in the case-control part of the study, and Table 2 shows the results of the univariate and multivariate conditional logistic regression analyses. Since by multivariate analysis, there was a positive correlation between the number of measles vaccines received and age (Spearman's rho = 0.2080, $P = 0.01$), neither of these variables could be employed in the same regression model. Therefore, the values for ''the number of received vaccines'' were used from another model that includes number of vaccines received, contact history, and father's education as predictors. Vaccine effectiveness, based on the calculated OR for measles vaccination given twice versus no vaccination, was approximately 74.2% (95% CI, 10.2–92.6).

There were no statistically significant associations between history of vaccination (as the response variable) and other variables, such as parent(s) education level, living conditions, or financial status (number of rooms, possession of vehicle or phone lines or house furniture

Table 1. Characteristics of the participants in the case-control part of the study, 2009 and 2010 measles outbreaks of chabahar, Iran

Variable	Case No. (%)	Control No. (%)
Gender		
Female	23 (46.9)	42 (42.9)
Male	26 (53.1)	56 (57.1)
Age group (y)		
≤ 3	19 (38.8)	27 (27.6)
>3–6	9 (18.4)	27 (27.6)
>6–9	5 (10.2)	16 (16.3)
>9	16 (32.7)	28 (28.6)
Vaccination time		
No vaccination	15 (30.6)	19 (19.4)
Only 1 time	8 (16.3)	11 (11.2)
2 times	26 (53.1)	68 (69.4)
Travel history		
Positive	10 (21.7)	23 (23.7)
Negative	36 (78.3)	74 (76.3)
Contact history		
Positive	38 (77.6)	41 (41.8)
Negative	11 (22.4)	57 (58.2)
Father education (years of successful education)		
Illiterate	33 (68.8)	49 (50.0)
1 to 5 years	5 (10.4)	25 (25.5)
More than 5 years	10 (20.8)	24 (24.5)
Mother education (years of successful education)		
Illiterate	44 (91.7)	81 (82.7)
1 to 5 years	4 (8.3)	13 (13.3)
More than 5 years	0 (0.0)	4 (4.1)

Table 2. Adjusted odds ratios, 95% confidence intervals, and *P*-values of the factors found to be associated with measles on conditional logistic regression analyses, 2009–2010 measles outbreaks of Chabahar, Iran

Variable	Univariate analysis matched OR (95% CI)[1)]	Adjusted OR (95% CI)[2)]	*P* (adjusted analysis)
Contact history[3)] (yes/no)	10.93 (3.24–36.90)	13.73 (3.34–56.43)	0.000
Father education (educated vs. illiterate)	0.30 (0.12–0.79)	0.18 (0.05–0.67)	0.010
Age group			
>18 to 36 mo vs. Birth to 18 mo	0.36 (0.08–1.52)	0.15 (0.02–1.06)	0.058
>36 to 72 mo vs. Birth to 18 mo	0.16 (0.03–0.82)	0.07 (0.01- 0.70)	0.024
>72 mo vs. birth to 18 mo	0.12 (0.01–1.21)	0.04 (0.002–0.69)	0.026
No. of received measles vaccines[4)]			
1 dose vs. no vaccination	0.74 (0.20–2.71)	0.72 (0.16, 3.31)	0.675
2 doses vs. no vaccination	0.31 (0.10–0.92)	0.26 (0.07, 0.90)	0.033

1): Single conditional logistic regression.
2): Multivariate conditional logistic regression.
3): Within the previous 20 days of the onset of the disease for cases and within the past 20 days of interview for controls.
4): Number of received measles vaccines has been reported from another model containing 'contact history', 'father education' and 'number of received vaccines' as cofactors. See the results section for further explanation.

such as type and number of air conditioners or refrigerator and so on). The lack of distinct differences between cases and controls with regard to these variables was partly because cases and controls were matched, not only for age, but also for place of residence.

DISCUSSION

This study was conducted in response to concerns that anti-measles vaccination programs were ineffective and were failing to protect the community against measles outbreaks. The results showed that, despite the outbreak, vaccine effectiveness was acceptably high. It appears that the main reason underlying the outbreaks, or at least their initiation, was the formation of susceptible foci among school children. One of the reasons for these children becoming susceptible, despite having been immunized against measles at young ages, may be attenuation of their immunity over the years since their vaccination. Such a phenomenon would presumably be exaggerated by measles elimination programs that prevent the immune-enhancing influence of repeated exposure of vaccinated children to the wild-type measles virus (15–17). Although it is generally thought that vaccine-induced immunity against measles persists for life and is almost comparable to that induced by wild-type virus, there are many reports, including this one, that question this belief (15–20). This trend of loss of immunity with time can be observed in Fig. 2, showing that the proportion of measles cases in subjects that had been previously vaccinated increases with age. This trend appears to be especially true for 6–12-year-old children, although it might not be proven statistically unless enough background data are available to conduct separate risk calculations for each age group (15,16,18,20). Another issue arising from the data shown in Fig. 2 is the occurrence of measles in 1- and 3-year-old children who, based on the measles vaccination schedule, had been immunized within the previous few months. In this group of children, the time interval from vaccination to infection was too short to be accounted for by loss of immunity. One explanation for this could be that errors occurred during preparation and administration of the vaccine that violated cold chain regulations, thereby decreasing vaccine efficacy. Similarly, although highly unlikely, problems with vaccine manufacture cannot be overlooked. On the basis of previous observations, even high levels of measles vaccination coverage have not always prevented subsequent outbreaks of the disease that is spread by airborne transmission. It has also been suggested that a large inoculum can increase the risk of vaccine failure. Furthermore, total protection against measles might not be attainable, even among revaccinees, when children are confronted with intense exposure to the virus (16,19,20).

Further evidence for attenuation of vaccine-induced immunity in older age groups comes from the observation that 6 of the cases examined in this study were above 20 years of age and 6 were less than 6 months of age. The occurrence of cases below 6 months of age is extremely rare, and it has been suggested that vaccinating infants before, or at, the age of 6 months often fails to induce seroconversion due to immaturity of the immune system as well as the presence of neutralizing maternal antibodies (17). During a large epidemic in Dade County, Florida, 22% of cases occurred in infants aged 6–11 months (10). It is generally presumed that the effects of neutralizing maternal antibodies do not cease before 6 months of age; however, several factors could influence this expectation in either direction (e.g., exposure to natural disease versus vaccination, prematurity, and parity) (17,21). Considering all these factors, we hypothesize that a gradual attenuation of immunity against measles, due to cessation of maternal exposure to the natural booster effects of wild-type virus, leads to lower antibody levels in the mother's serum, and consequently, earlier disappearance of passive immunity transferred from mother to child.

Based on results from the case-control part of our study, only subjects who had been vaccinated twice had a significantly lower chance of acquiring measles, when compared to unvaccinated cases (Table 2). As mentioned earlier, based on these results, vaccine effectiveness (for 2-dose vaccination) is approximately 74.2%. However, there may be some disagreement with these calculations. In the case-control part of the study, judgments on vaccination status were merely on the basis of the vaccination card or logbook records from health houses. This approach could result in an underestimation of vaccine effectiveness due to misclassification of vaccinated subjects who had lost their cards or who had no records in the log files (either due to ignorance of the health workers, immigration of the vaccinated subjects from another catchment area, or other similar reasons). Such misclassifications could lead to a lower estimation of vaccination coverage, higher estimation of the attack rate in the vaccinated group, lower attack rate in the unvaccinated group, and lower estimation of vaccine effectiveness. Furthermore, this problem could be further exaggerated if the effect of the vaccine dose administered during the outbreak-response immunization is ignored. Considering these points, the calculated effectiveness of vaccination seems acceptable and in a good range. Field studies of vaccine effectiveness in similar settings in other countries have provided estimates of approximately 85% protection. Low effectiveness levels, generally below 80%, could indicate problems in either production of the vaccine or in the cold chain (8,22).

In Table 2, modeling of the variables (by conditional logistic regression analysis), revealed that there was collinearity between age and the number of vaccines received (Spearman's rho = 0.2080, $P = 0.01$), and therefore, these two variables could not be reported in the same model. It is worth of noting that, since controls were matched with cases for age (age ± 24 months), we did not expect to find any significant associations with age. However, the fact that this variable shows significant association with disease risk indicates that the matching range was too wide and a residual effect remained. Table 2 also shows the results of univariate analysis, which for almost all variables, were similar to those of multivariate analysis.

There was a strong relationship between paternal education level and the chances of acquiring measles (OR = 0.18; 95% CI, 0.05–0.67). In other words, when the father was less well educated, there was a greater than 5-fold chance of his child acquiring measles during an outbreak. Usually, in urban societies, education is interpreted as an index of financial status; however, in rural settings, such as the one in which this study was performed, education level rarely implies a better financial situation and should rather be interpreted as a knowledge indicator. Furthermore, the most powerful relationship was observed for ''contact history,'' which is not surprising given that the virus has a secondary attack rate of more than 90% among susceptible individuals (3,8).

An interesting point regarding each of these outbreaks was that they were initiated in schools and were subsequently transmitted to the community through families. This pattern of infection propagation, first within schools, and then from schools to families and the community, has been reported in several previous studies, and emphasizes the importance of boosting the immunity of schoolchildren against measles (15,16, 18–20).

Boosting the immunization status of schoolchildren seems to be essential for controlling and preventing measles outbreaks. In addition, to prevent the accumulation of susceptible individuals and the formation of susceptible foci, implementation of measles SIA every 5–10 years should be seriously considered, at least in provinces that share a common border with high-risk countries. In addition, the fact that 12 out of 96 confirmed cases were younger than 12 months should lead us to reconsider the age at which the first measles vaccine is administered. Returning to a scheme where the first dose of vaccine is administered at 9 months of age may be a logical approach to immunization in such high-risk areas.

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Conflict of interest None to declare.

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