Measles Outbreak in a Northern Pakistani Village: Epidemiology and Vaccine Effectiveness

Megan Murray and Zeba Rasmussen

In the spring of 1990, local community health workers reported a measles outbreak in several partially vaccinated villages in the Punal Valley in northern Pakistan. The authors conducted an investigation in one of these villages to assess vaccine coverage and vaccine efficacy and to describe the patterns of measles outbreaks that prevailed in this community. The results of a survey of the entire village revealed two major gaps in vaccine coverage: the small minority Sunni community and children over 3 years of age. Vaccine efficacy was estimated to range from 73 to 90% but was markedly reduced in children who were vaccinated under 12 months of age. The occurrence of such an outbreak in a community in which a relatively new vaccination program is primarily directed at younger children has been predicted by theoretical models of measles dynamics and is consistent with the experience of other vaccination programs in the developing world. These observations suggest that, in some areas of the developing world, the age groups targeted to receive measles vaccinations may need to be broadened to ensure adequate coverage to prevent recurrent outbreaks. Am J Epidemiol 2000; 151:811-19.

immunization; infection; measles

The ongoing evaluation of vaccine programs is a strategy essential to ensuring their success. Such evaluation involves the assessment of vaccine coverage, surveillance to measure disease incidence, and the evaluation of vaccine effectiveness in the field (1). These measures are meant to differentiate among failure to vaccinate, vaccine failure, and problems such as persistent susceptibility of older children after the initiation of a vaccine program directed toward the very young, that is, the posthoneymoon phenomenon (2). Such postlicensure vaccine evaluation can only be performed by conducting observational studies, studies which are vulnerable to bias under the most controlled circumstances. Nonetheless, it is often in those areas where such studies are most difficult to conduct that they are most needed.

Although many methodological studies have been published (3-5) outlining potential sources of bias in observational studies of vaccine efficacy under difficult field conditions, few field studies have addressed these biases by conducting sensitivity analyses around estimates of vaccine efficacy (6). This report documents an investigation we conducted of a measles outbreak in a northern Pakistani village in which a vaccination program was well established. We assess vaccine coverage and vaccine efficacy and describe the pattern of measles outbreaks that prevailed in this community. We consider the problems of misclassification and missing data commonly encountered in observational vaccine studies in the developing world and present a range of effect measures based on different methods to adjust for them. Finally, we note that our observations are consistent with the disease patterns predicted by mathematical models of partially vaccinated populations (7, 8) as well as the findings from other studies of measles outbreaks in areas with active vaccination programs in developing countries.

MATERIALS AND METHODS

Study setting

In the spring of 1990, local community health workers reported a measles outbreak in several small villages in northern Pakistan. These villages were among many in the area that had been receiving routine immunizations from the Expanded Program on Immunization administered by the nongovernmental organization, the Aga Khan Health Service, Pakistan (AKHSP). At the time of the outbreak, the immunization program had been in place for more than 3 years, and local health workers believed that vaccine cover-
age in the villages was high. The outbreak caused great concern to both the community and the AKHSP, not only because of the immediate morbidity and mortality it caused, but also because it had the potential to seriously undermine confidence in the program.

The village of Hassis was chosen for this study as representative of the communities affected by the outbreak. This village consists of 132 households located in a sparsely populated region in the Karakorum mountain range of central Asia. Villagers are subsistence farmers, the majority of whom belong to the Ismaili branch of Islam and a small minority of whom are Sunni. Health indicators in the area are comparable with those in other rural areas of Pakistan. Based on an unpublished AKHSP survey, the 1988 annual birth rate was estimated at 44.2/1,000, the annual death rate at 14.4/1,000, and the infant mortality at 158/1,000.

The AKHSP provided immunizations in the context of a primary health care initiative that includes antenatal care, growth monitoring of children, health education, and the training of birth attendants and community health workers. Although many of the villages targeted by the program had no permanent health facilities at that time, outreach immunization sessions were held at monthly intervals. In accordance with Expanded Program on Immunization recommendations, children were vaccinated with a single dose of heat-stable Schwartz live measles vaccine after 9 months of age (9). Although the program primarily targeted children under 2 years of age, vaccination was available to any child in the village.

Risk factor and outcome assessment

The measles outbreak occurred over an 8-week period in April 1990; no further cases were identified in the village over the subsequent 6 weeks. Two weeks after the measles outbreak, we conducted a door-to-door household survey of the entire population of the village of Hassis to identify measles cases and to determine the vaccination status of cases and noncases. All households were visited by a survey team that included a medical student (M. M.), an outreach nurse, and the local community health worker assigned to the village. We conducted interviews with at least one parent of all resident children younger than 14 years. Interviews were conducted in the local language with the community health worker functioning as a translator. Informed consent was obtained from the parents of the children participating in the study, and the protocol was approved by the AKHSP Regional Health Board for Punial/Ishkomen, Northern Areas, Pakistan.

Parents were asked for Road to Health cards for each of their children. We classified children as vaccinated only if vaccination was documented on the card. Birth date and age at measles vaccination were calculated for each child from the information on the card. Where records were not available, we used available documentation, such as birth certificates and school entry cards, as well as parental reports to estimate the child's age or birthdate. We classified children without documents as unvaccinated if their parents reported that they had never received measles vaccination. If parents did not know a child’s vaccination history or believed the child was vaccinated but did not have documentation, we listed vaccination status as unknown. We further subdivided the category of those with unknown vaccine status into those whose parents believed their children to have been vaccinated and those who did not.

A history of measles was based on the parental report except in the few cases in which the diagnosis could still be substantiated by clinical examination. We based the case definition on World Health Organization guidelines: an illness with a generalized rash of 3 or more days' duration, fever, and any one of the following: cough, coryza, or conjunctivitis (10). Measles history was classified as measles prior to the outbreak, measles during the outbreak, or no known history of measles. For children with a prior history of measles, we recorded age at infection and/or year of infection. Cases of measles that had occurred in the month prior to the survey were considered part of the outbreak.

Analysis

We estimated vaccine coverage by age, sex, and religious group. The data on previous history of infection are expressed as a percentage of children under 14 years who were alive in that calendar year and present in the cohort under investigation in 1990. We further characterized previous infection into cases that occurred during an epidemic year and those that occurred sporadically. Epidemic years were defined as those in which more cases occurred than expected. Since the baseline annual incidence of measles in the population was less than 5 percent of the population of children alive and susceptible at that time, years in which more than 5 percent of these children were affected were classified as epidemic years. Vaccine efficacy was derived from cumulative incidence during the outbreak and calculated according to the formula (11):

$$\text{Vaccine efficacy} = \frac{\text{attack rate in unvaccinated} - \text{attack rate in the vaccinated}}{\text{attack rate in the unvaccinated}}$$
Since attack rates were high for all age groups up to 13, the analysis of vaccine efficacy included all children aged from 9 months to 13 years. We calculated both crude vaccine efficacy and a Mantel-Haenszel summary statistic for analyses stratified on religious group and age.

To adjust for potential sources of misclassification, we calculated attack proportions under several different assumptions about susceptibility. We calculated crude vaccine efficacy (A) by including all children under 14 years regardless of previous measles history. We then obtained several estimates of vaccine efficacy by excluding children considered nonsusceptible. We first considered vaccine efficacy (B) by excluding all children whose parents reported a history of measles prior to the outbreak under investigation. We then excluded only those children who reported disease during the year of a known outbreak, based on the assumption that sporadic cases may have been other viral exanthems misclassified as measles (C). To adjust for potential misclassification of vaccination status, we repeated the analysis excluding those without a Road to Health card (D). Finally, to control for differential exposure, we calculated the secondary attack proportion in vaccinated and unvaccinated children from households in which there were two or more cases that occurred no less than 9 days and no more than 18 days apart. The first case in a household was considered the primary case, subsequent cases that occurred before the 9-day incubation period had passed were considered co-primary cases, and those that occurred at least 9 days later than the first were classified as secondary cases (12). For this analysis, we again report three measures of effect based on including or excluding susceptibles as described above.

We analyzed the data, assuming that the missing data occurred at random. To explore the possibility that missingness was associated with the outcome, we also performed the analysis while weighting the observed data by the inverse probability of having been observed, given the measured covariates (13). Since the estimates of vaccine efficacy obtained using these methods were essentially identical, we report only the results based on the premise that the process generating the missing data is random. To further assess the potential impact of the missing data on our results, we reanalyzed the data under the assumption that children whose parents believed them to be vaccinated were vaccinated.

Statistical analyses were performed using SAS (SAS Institute, Cary, North Carolina) and Epi-Info (Centers for Disease Control and Prevention, Atlanta, Georgia) software.

### RESULTS

We surveyed 132 households and found 601 children under 14 years of age, of whom 563 were older than 9 months and therefore eligible for vaccination. Of these, 192 (34 percent) had a documented history of vaccination, and 189 (34 percent) reported no previous measles vaccination. Among those reportedly unvaccinated, only 57 (30 percent) had a Road to Health card with no documentation of measles immunization. Vaccine status for the remaining 182 children (32 percent) was unknown. Of these, 101 (55 percent) of the children's parents believed that they had been vaccinated. Table 1 presents these data by religious affiliation. Among the Ismaili community, vaccine coverage for children aged from 9 months to 13 years was 38 percent, whereas within the small Sunni community, coverage was only 5 percent. Figure 1 shows that age-specific vaccination coverage was highest for children aged from 9 months to 3 years and then fell off gradually for older children.

A total of 139 children (25 percent) reported a history of measles prior to the 1990 outbreak. Most of these cases reportedly occurred in two epidemic years, 1982 (when 44 percent of the susceptible population surveyed was affected) and 1978 (when 14 percent of the susceptible population surveyed was affected). Another 31 cases reportedly occurred sporadically during nonoutbreak years. None of the children who reported a prior history of measles became infected during the 1990 outbreak.

Of the 563 children younger than 14 years, 104 (18 percent) met the case definition for measles during the 1990 outbreak. Age-specific attack proportions were highest among children under 15 months; however, attack proportions of about 20 percent were found among all age groups of children from 2 to 8 years, that is, those who had not been exposed during the 1982 outbreak (figure 2). Five of the 38 children under 9 months (13 percent) were infected. None of the children who were under 9 months at the time of the outbreak had been vaccinated.

Reported complications of measles included pneumonia, diarrhea, otitis media, and mouth sores; at least

### TABLE 1. Vaccination status of children aged from 9 months to 13 years by religious affiliation, Hassis, Pakistan, 1990

<table>
<thead>
<tr>
<th>Vaccine status</th>
<th>Ismaili community</th>
<th>Sunni community</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>Vaccinated</td>
<td>189</td>
<td>37.6</td>
<td>3</td>
</tr>
<tr>
<td>Unknown</td>
<td>177</td>
<td>35.3</td>
<td>5</td>
</tr>
<tr>
<td>Unvaccinated</td>
<td>136</td>
<td>27.1</td>
<td>53</td>
</tr>
<tr>
<td>Total</td>
<td>492</td>
<td>71</td>
<td></td>
</tr>
</tbody>
</table>
one complication occurred in 94 percent of cases. There were no significant differences in either the number or severity of complications reported in vaccinated and unvaccinated children with measles. Complications were more frequently reported in Sunni children and in those who were considered secondarily infected in contrast to primary or co-primary cases. Three deaths occurred, giving a short-term case fatality of 3 percent; all of these occurred in unvaccinated Sunni children over 1 year of age.

The crude vaccine efficacy was 75 percent. Excluding children with a previous history of measles from the study population led to an increase in the estimate to 84 percent. Excluding only those with a history of measles during an epidemic year gave an estimate of 82 percent, and restriction of the analysis to those with Road to Health cards gave an estimate of 89 percent. When we attempted to control for exposure by using the secondary attack rate among household contacts of cases, we found that the estimates of vaccine efficacy increased by about 5 percent (table 2). Mantel-Haenszel estimates after stratification by religious affiliation and age group were very similar. Estimates of vaccine efficacy decreased by 6–11 percent, depending on the exclusion criteria chosen, when children whose parents thought they had been vaccinated but had no documentation were classified as vaccinated (data not shown). Although absence of vaccination and previous infection were the strongest predictors of disease, younger age and minority religious affiliation were also associated with an increased risk of measles (table 3).

To explore potential causes of vaccine failure, we estimated vaccine efficacy by age at vaccination. In the crude analysis, vaccine given to children under 9 months was only 40 percent effective, and children vaccinated at 9–11 months and 12–14 months were less well protected than children vaccinated at 15 months or later. To control for the effects of religious group and age, we repeated the analysis including only Ismaili children under 8 years of age. In this stratum, vaccine efficacy was found to be even lower, especially in those children vaccinated before 1 year of age.
Although confidence intervals for these results were wide, a chi-square test for linear trend across age groups was highly significant. We also noted that none of the 15 vaccinated children with measles was vaccinated on the same day or during the same outreach visit.

**TABLE 2.** Estimates of measles vaccine efficacy based on varying inclusion criteria, Hassais, Pakistan, 1990

<table>
<thead>
<tr>
<th>Method*</th>
<th>Attack rate</th>
<th>No. whose vaccination status unknown</th>
<th>Vaccine efficacy</th>
<th>Vaccine efficacy MH†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vaccinated</td>
<td>Unvaccinated</td>
<td></td>
<td>%</td>
</tr>
<tr>
<td></td>
<td>No. of cases</td>
<td>No. vaccinated</td>
<td>No. cases</td>
<td>No. unvaccinated</td>
</tr>
<tr>
<td>1A</td>
<td>15</td>
<td>192</td>
<td>59</td>
<td>189</td>
</tr>
<tr>
<td>1B</td>
<td>15</td>
<td>172</td>
<td>59</td>
<td>106</td>
</tr>
<tr>
<td>1C</td>
<td>15</td>
<td>179</td>
<td>59</td>
<td>125</td>
</tr>
<tr>
<td>1D</td>
<td>15</td>
<td>192</td>
<td>40</td>
<td>57</td>
</tr>
<tr>
<td>2A</td>
<td>5</td>
<td>73</td>
<td>28</td>
<td>79</td>
</tr>
<tr>
<td>2B</td>
<td>5</td>
<td>63</td>
<td>28</td>
<td>41</td>
</tr>
<tr>
<td>2C</td>
<td>5</td>
<td>65</td>
<td>28</td>
<td>47</td>
</tr>
<tr>
<td>2D</td>
<td>5</td>
<td>73</td>
<td>19</td>
<td>24</td>
</tr>
</tbody>
</table>

* Method 1 uses subsets of the population of children from 9 months to 13 years; method 2 uses subsets of children from 9 months to 13 years who are household contacts of cases. Subsets: A, no exclusions based on history; B, children with a previous history of measles excluded; C, children with a previous history of measles during an epidemic year excluded; D, children without vaccination cards excluded even if unvaccinated.
† MH, Mantel-Haenszel estimate after stratification on religious group and age (<8 or 28 years); CI, confidence interval.
TABLE 3. Risk factors for measles among children, Hassis, Pakistan, 1990

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Measles (no.)</th>
<th>Crude RR*</th>
<th>95% CI*</th>
<th>Adjusted† RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>47</td>
<td>271</td>
<td>Ref.</td>
<td></td>
<td>Ref.</td>
</tr>
<tr>
<td>Females</td>
<td>57</td>
<td>226</td>
<td>1.36</td>
<td>0.96, 1.94</td>
<td>1.18</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;8</td>
<td>84</td>
<td>293</td>
<td>Ref.</td>
<td></td>
<td>Ref.</td>
</tr>
<tr>
<td>≥8</td>
<td>20</td>
<td>204</td>
<td>0.40</td>
<td>0.25, 0.63</td>
<td>0.59</td>
</tr>
<tr>
<td>Religious group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ismaili</td>
<td>77</td>
<td>453</td>
<td>Ref.</td>
<td></td>
<td>Ref.</td>
</tr>
<tr>
<td>Sunni</td>
<td>27</td>
<td>44</td>
<td>2.62</td>
<td>1.82, 3.76</td>
<td>1.5</td>
</tr>
</tbody>
</table>

* RR, relative risk; CI, confidence interval.
† Adjusted for vaccine status and measles history as well as for the other risk factors in the table.

DISCUSSION

We conducted this survey in response to concern that the existing vaccination outreach program had failed to protect the community from a measles outbreak. This study showed that, despite the outbreak, the program had achieved moderate coverage of younger children and high vaccine effectiveness. We found that this outbreak fit the pattern of measles epidemics predicted by mathematical models of partially vaccinated populations; a long interepidemic period allowed the accumulation of older unvaccinated children who provided a significant pool of susceptibles in which an outbreak could take place.

Although total vaccine coverage for children under 14 years was only 34 percent, documented coverage for children aged 3 years and under was 64 percent. Since some of the children with missing Road to Health cards are likely to have been vaccinated, this figure is probably an underestimate of the true level of coverage. Coverage among older children who were not specifically targeted by the vaccination program was substantially lower. Most vaccination programs in developing countries broadly target their efforts to younger children, because the average age of measles cases in these areas is under 3 years. This reflects the fact that measles epidemics occur every 1–2 years in large urban populations in developing countries, and most children are exposed early in life (14). Our data suggest that there had been a period between 1982 and 1990 during which there had been no measles outbreak. At the time of the 1990 outbreak, there were many children over age 3 who had been neither exposed to measles nor immunized against it. This large cohort of susceptibles represented the major gap in vaccine coverage in Hassis, one which was not addressed by the existing policy of focusing vaccination efforts on the very young.

Another gap in vaccine coverage occurred among children in the small minority Sunni population of

TABLE 4. Vaccine efficacy by age at vaccination (atv), Hassis, Pakistan, 1990

<table>
<thead>
<tr>
<th>Age at vaccination</th>
<th>No. of cases</th>
<th>Total no.</th>
<th>Vaccine efficacy by atv†</th>
<th>No. of cases</th>
<th>Total no.</th>
<th>Vaccine efficacy by atv§</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;9 months</td>
<td>2</td>
<td>6</td>
<td>40 0.809</td>
<td>2</td>
<td>6</td>
<td>21.8 0.755</td>
</tr>
<tr>
<td>9–11 months</td>
<td>6</td>
<td>44</td>
<td>75.5 47.5, 88.6</td>
<td>6</td>
<td>44</td>
<td>67.9 30.0, 85.4</td>
</tr>
<tr>
<td>12–14 months</td>
<td>4</td>
<td>55</td>
<td>86.9 65.9, 94.9</td>
<td>4</td>
<td>55</td>
<td>82.7 54.3, 93.6</td>
</tr>
<tr>
<td>≥15 months</td>
<td>3</td>
<td>67</td>
<td>92 73.4, 97.4</td>
<td>3</td>
<td>53</td>
<td>86.7 41.3, 95.7</td>
</tr>
<tr>
<td>All vaccinated</td>
<td>15</td>
<td>172</td>
<td></td>
<td>15</td>
<td>158</td>
<td></td>
</tr>
<tr>
<td>Unvaccinated</td>
<td>54</td>
<td>106</td>
<td></td>
<td>31</td>
<td>73</td>
<td></td>
</tr>
</tbody>
</table>

* Crude rates based on population of all children from 9 months to 13 years.
† Stratum-specific rates based on Ismaili children from 9 months to 7 years.
‡ p value based on chi-square test for linear trend = 0.0152.
§ p value based on chi-square test for linear trend = 0.0378.
¶ CI, confidence interval.
whom less than 5 percent had been vaccinated. The first cases of measles reported in this village occurred among Sunni children, suggesting that this pocket of susceptibles may have been the source of the epidemic. The Sunni community was both spatially distinct from the Ismaili community and had larger households. The rate of contact between Sunni children would thus be expected to be higher than the contact rate between Sunni and Ismaili children, leading to an increased probability of spread within this group. Furthermore, the relative isolation of this group from their vaccinated Ismaili counterparts meant that these children received less benefit from the herd immunity provided by children who were immune. The clustering of unvaccinated children among minority groups with heterogeneous mixing is an important problem of vaccination programs throughout the world. Fine and others have pointed out that such clustering is one of the principal causes of continued measles epidemics in highly vaccinated populations (3).

The outbreak eventually involved 104 children, 17 percent of all children under 14 years and 23 percent of those without a previous reported history of measles. The acute case fatality proportion of 3 percent is consistent with that reported from outbreaks in other developing countries. Many previous studies have shown marked late fatality, depending on the age group examined (15–17). As this study was primarily concerned with an evaluation of the vaccine program, we did not examine mortality after the immediate outbreak. The figure of 3 percent may therefore represent a sizable underestimate of the ultimate impact of the outbreak in this community. All three children who died belonged to the Sunni community, and two were over 8 years of age. This is in contrast to the findings of most measles outbreak studies in which very young children have had the highest mortality.

Complications were common and were reported with similar frequency in both vaccinated and unvaccinated measles cases. Thus, our small study does not add support to the hypothesis that vaccination results in milder disease in the case of vaccine failures (18). The number of complications was associated with both secondary infection and membership in the Sunni community. Although these data are consistent with the observation of Aaby and others (19–21) that intensity of exposure predicts severity of disease, we note that our study was not designed to evaluate risk factors for this outcome.

Depending on assumptions about susceptibility, estimates of vaccine efficacy ranged from 73 to 90 percent, compared with the vaccine efficacy of 90–98 percent reported in controlled clinical trials (22). We considered several potential sources of vaccine failure. Given the difficult field conditions in the region, our prior belief was that there had been a breakdown in the cold chain or the inactivation of some batch of vaccine. We found no temporal pattern in the administration of the vaccinations that failed and therefore consider this cause unlikely. We also considered the possibility that children were vaccinated too early, before maternal antibody had waned, and did not mount a full immune response to the vaccine. Vaccine efficacy was found to be markedly lower for children vaccinated before 9 months and intermediate for children vaccinated between the ages of 9 and 15 months, a trend which was highly significant and compatible with theoretical expectations and previous reports (23, 24).

We noted that age less than 8 years and membership in the Sunni community were risk factors for measles independent of vaccine status. Although the explanation for these associations is not clear, they are likely to reflect demographic features that affect the contact rates among the infected. When the analysis was restricted to children who were secondarily exposed, there was no association between Sunni affiliation and measles occurrence. Moreover, in this subset of the population the correlation between age and measles was even more pronounced. A potential explanation of this latter finding is that older immune children are more likely to be misclassified as susceptible than the young, since distant histories of measles are less certain than recent ones.

The major potential source of bias in this study is misclassification of susceptibility. We classified children as susceptible if they had no reported history of measles prior to the outbreak in 1990. We approached the problem of potential misclassification of susceptibility by calculating several measures of vaccine efficacy as a sensitivity analysis. There was little difference between the two estimates that excluded children with a history of previous disease, but vaccine efficacy fell considerably when the 25 percent of children considered immune were included in the analysis. A further source of bias in this approach is the exclusion of children who had been vaccinated prior to their previous infection with measles. As discussed by Haber et al. (5), this effectively removes previous vaccine failures from the analysis while retaining those who did not fail. To estimate the potential impact of this bias in our estimates, we identified children with a previous history of measles whose infection reportedly occurred after vaccination. We found only three previous cases whose disease had occurred in the interim between vaccination and the current outbreak. Even if these cases were included in the attack rate in the vaccinated without making a comparable adjustment in the attack.
rate in the unvaccinated, vaccine efficacy would fall by only 3–4 percent.

A second potential source of bias was misclassification of vaccination status. Children were classified as vaccinated only if they had documentation of vaccination; however, we relied on parental report in the case of the unvaccinated, since relatively few unvaccinated children had Road to Health cards. To assess the impact of this potential misclassification, we conducted a sensitivity analysis by evaluating vaccine efficacy under various scenarios, a strategy previously described by Chen et al. (6). We thus repeated the analysis considering only those with Road to Health cards but without vaccination as unvaccinated. An additional advantage of this approach is that it may reduce the likelihood that the vaccinated and unvaccinated differ on unmeasured confounders. Since the AKHSP program involves primary health care including mostly education and prevention, children with a Road to Health card may be similar to those vaccinated in their utilization of available health services in contrast to children who have not participated in preventive care. This restriction resulted in higher estimates of vaccine efficacy, raising the possibility that some substantial proportion of children in the unrestricted population who were classified as unvaccinated may truly have been vaccinated. This result also suggests that the observed effect of the vaccine was not confounded by use of preventive services or other socioeconomic factors for which health care use may be a reasonable proxy.

Another methodological problem in studies of infectious disease is the possibility of differential exposure to the infection in the risk groups under investigation. Thus, it is not unreasonable to assume that, for a variety of social and demographic reasons, unvaccinated children tend to be more heavily exposed to communicable diseases than their vaccinated counterparts. We repeated our analyses including only household contacts of cases who had not developed measles before a latent period of 9 days had passed. This restriction ensures that all of the children in the study population have some baseline exposure but does not adjust for the intensity of that exposure. Fine and Zell (3) have pointed out that this method may lead to underestimates of vaccine efficacy, since it confines the investigation to those subgroups of the population most likely to fail vaccination. In this study, however, vaccine efficacy increased slightly in each exclusion category.

Another methodological problem relates to the missing data in our survey. Parents were unable to provide information on vaccination status in about a third of the children surveyed. We considered possible mechanisms by which vaccination status data could be missing to try to determine whether the probability of observation of vaccine status was associated with vaccination status. Although the true but unknown vaccination status would be expected to be correlated with observation in a crude analysis, we believe that the most likely mechanisms of this association are accounted for by the measured confounders in this study. For example, recently vaccinated children may be more likely to have available documentation of vaccination and may also be younger than previously or never vaccinated children. Since younger children in Hassis were more likely to be vaccinated than their older counterparts, there will be a positive association between observation and vaccination; children with missing data would tend not to have been vaccinated. This association would disappear, however, after stratification by age. Conversely, Sunni families rarely used the Aga Khan Health Service health services. They were therefore unlikely to be vaccinated but likely to be aware of their unvaccinated status and thus counted among the observed. Following this logic, we might anticipate an apparent inverse association between observation and vaccination that would, nevertheless, be removed by controlling for religious affiliation. Although we did not measure other socioeconomic variables that may impact both vaccination and observation status, we believe that the consistency of our effect measures across a variety of exclusion criteria suggests that, after stratification on religious group, residual confounding by socioeconomic status is minimal. We also found that vaccine efficacy did not change substantially when we used parents’ beliefs about their children’s vaccination history as a proxy for vaccine status. Although such data are probably too unreliable to be used to estimate vaccine efficacy, they again support our contention that these estimates are robust to the missing data on vaccine status.

Finally, we note that our estimates of vaccine efficacy, like all those obtained from observational studies in partially vaccinated communities, may not be comparable to estimates obtained from small clinical trials of vaccines. The probability of infection in a community is directly proportional to the number of infected contacts to which a person is exposed. Since the effect of mass vaccination is to lower disease rates in the community, the attack rate in the unvaccinated reflects the indirect benefit of the vaccine (25).

In conclusion, this study showed that the measles outbreak in Hassis occurred despite reasonable vaccine effectiveness in those children to whom vaccine had been administered after 12 months of age. Our findings revealed several major gaps in vaccine coverage including the small minority Sunni community and older children who were not specifically targeted by
the program and who had not yet been exposed to a measles outbreak. We also found that evaluation of the vaccination program was hampered by a lack of data on the vaccination status of the children participating in the program. Vaccination programs in developing countries may benefit from more rigorous and innovative methods of record keeping as well as a systematic attempt to include minority groups and older children who may constitute residual pockets of susceptibility to vaccine-preventable infections.

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