Invited Commentary: Vaccine Failure or Failure to Vaccinate?

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Despite the availability of safe and effective measles vaccines since 1963, measles still accounts for approximately 10 percent of global mortality from all causes among children aged <5 years—an estimated 36.5 million cases and 1 million deaths in 1996 (1). Worldwide in 1996, routine coverage with one dose of measles vaccine was 81 percent; the African Region of the World Health Organization continues to report the lowest coverage (56 percent) and the largest proportion of measles cases and deaths (2). For these reasons, the work of Dr. Badara Cisse and colleagues is particularly relevant. We agree that there is an urgent need to strengthen measles control and to conduct research on the most effective ways to achieve this, especially in areas such as West Africa. However, we do not agree that the data presented in the paper by Cisse et al. (3) demonstrate that the 1995 outbreak in Niakhar, Senegal, was due primarily to waning of vaccine-induced immunity among school-age children. Therefore, we do not think waning immunity can be used as the justification for introducing a multidose vaccination schedule (e.g., administering a second dose of measles vaccine prior to school enrollment) as a priority strategy for improving measles control in developing countries.

Our opinion is based mainly on three arguments. Firstly, the data presented in the paper suggest that low vaccination coverage with the first dose of measles vaccine (64 percent among children aged 1–14 years) was the major reason for the outbreak. This coverage estimate was for 1995, and the outbreak occurred between October 1994 and June 1995. Coverage immediately prior to the start of the outbreak may have been even lower, especially if vaccination activities were increased as part of outbreak control. Among the 207 cases of measles documented in the outbreak, 83 (40 percent) were in children who had been vaccinated; this suggests that the majority of cases (up to 60 percent) occurred among persons who had never been vaccinated. According to the investigators’ assessment, among secondary measles cases aged <15 years, 54 of 104 (52 percent) case children were unvaccinated (3). Empirical and theoretical evidence suggests that achieving and maintaining ≥90 percent vaccination coverage with one dose of measles vaccine results in a substantial reduction in measles morbidity and mortality (4).

Secondly, Cisse et al.’s estimates of vaccine efficacy in the schools and in the compounds may be biased downward and are not generalizable to other settings. There were several potential sources of bias in the estimates of vaccine efficacy: 1) a nonspecific case definition was used (laboratory confirmation was not available for any cases; children who had onset of symptoms within 2 weeks of measles vaccination could have been experiencing vaccine reactions and should not have been included in the analysis as unvaccinated cases; and secondary cases were defined imprecisely as “developing measles more than 6 days after another case in the same compound”); 2) there was misclassification of vaccination status (the proportion of children with a written record of their vaccination history was not reported, nor was the proportion whose vaccination status was obtained retrospectively by maternal interview, and it was not clear whether children without such information were included in the analysis); and 3) investigators relied on verbal histories obtained from mothers or guardians for information on measles disease in the years prior to the outbreak. The low vaccine efficacy in the study appears to have been the result of a low attack rate (7 percent) among “unvaccinated” children, as might be seen if exposure to measles did not occur or if some of these children had undocumented prior measles or measles vaccination. Because nondifferential misclassification (e.g., use of a nonspecific case definition) would result in a “bias toward the null” (5, 6), the vaccine efficacy estimates presented in the article are likely to be biased downward.

If waning immunity was a major cause of susceptibility to measles, the vaccine efficacy should have been lower in older age groups. However, the data presented in the article indicate only a slight difference in
vaccine efficacy between children aged <5 years and children aged 10–14 years, with 95 percent confidence intervals that overlap widely. As Cisse et al. explained, measles vaccine efficacy was lower among children aged 5–9 years than among children aged <5 years or ≥10 years because many of the children aged 5–9 years had taken part in a measles vaccine trial with high-titer vaccines. Reduced vaccine efficacy in this age group may be explained by differences in seroconversion by vaccine strain and/or titer. An additional reason for poor seroconversion in this age group is that approximately 25 percent of vaccinated children received measles vaccine at <6 months of age. Therefore, the lower vaccine efficacy estimates for children aged 5–9 years may be due to failure to seroconvert rather than waning of vaccine-induced immunity. In addition, because high-titer vaccination at 6 months of age is no longer recommended by the World Health Organization, the findings are not generalizable to many other developing countries.

Thirdly, the authors argue that because school-related cases occurred at the beginning of the outbreak and played a role in the general propagation of the outbreak, it is necessary to require vaccination prior to school entry. However, it appears that the outbreak was ongoing for 3 months (October—December 1994) before the first cases were detected in the schools in January 1995. Furthermore, the report does not provide clear criteria that would enable the reader to determine how measles cases were classified as being either school-related or acquired from exposure in the home. The data presented indicate that the most important source of measles infection for both index cases and secondary cases was neighbors in the community—56 percent and 55 percent, respectively (3). School was the likely source of infection for 24 percent of index cases and 36 percent of secondary cases. Indeed, the authors point out that attack rates in the schools were significantly lower than the rates found in the community. Although school transmission clearly played a role in transmission, it does not necessarily follow that outbreak control in the schools or vaccination prior to school entry would have prevented the outbreak.

In our opinion, the immediate objective of any measles control program should be to provide a first dose of measles vaccine to unvaccinated children. Because measles is most severe and carries the highest risk of complications and death among children under 5 years of age in developing countries (4), increasing routine first-dose coverage among infants to >90 percent has the greatest impact on reducing morbidity and mortality and should be the first priority. If susceptibility exists among older children, additional strategies such as "catch-up" vaccination campaigns (7) or strictly enforced school entry requirements can be implemented. ("Catch-up" vaccination is defined by the Pan American Health Organization as a one-time vaccination in which all children aged 9 months to 14 years receive one dose of measles vaccine regardless of history of measles or previous vaccination status.) A policy of administering measles vaccine at school entry relies on a high proportion of children attending school, a condition that may not be fulfilled in many developing countries. Multidose schedules that may distract measles vaccination programs from delivery of the first dose to the most vulnerable children are unlikely to result in effective measles control.

REFERENCES