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Measles Vaccine: Do We Need New Vaccines or New Programs?

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Three converging factors have rekindled interest in measles virus, measles vaccine research, and public health policies directed toward the control and eventual elimination of measles. First, after 23 years of relative obscurity, measles re-emerged as a public health issue in the United States when focal outbreaks between 1989 and 1991 resulted in more than 55,000 reported cases. Second, on the international scene, the World Health Organization (WHO) formally resolved to intensify vaccination efforts in order to reduce by 95% the number of measles-related deaths and by 90% the number of measles cases before 1995. A third factor was the adverse experience encountered in several developing nations when measles vaccines containing elevated titers of attenuated virus (see below) were administered to 4- to 6-month-old infants in an attempt to overcome the maternally conferred immunity that normally prevents successful vaccination at that early age.

In the United States, measles had been a ubiquitous childhood illness so communicable that by their early teens more than 95% of each annual birth cohort (3 to 4 million) had been infected. After licensure in 1963 of live attenuated measles virus vaccine and funding of federal programs initiated in 1966, there was such a striking reduction in the number of cases that the U.S. Public Health Service targeted 1982 as the year of measles elimination (*1*). Although this goal has yet to be achieved, there were only 277 cases reported in 1993, a remarkable all-time low.

Prior to 1989, many of the small clusters of measles cases that persisted in the United States occurred among high school and college students. These cases reflected the accumulation of measles-susceptible individuals resulting from the 5% failure rate of infant immunization, as well as some cases of waning immunity. In response, both the Advisory Committee on Immunization Practices (ACIP) and the American Academy of Pediatrics (AAP) recommended administration of second doses of measles vaccine to be given at varying ages. By contrast, the measles outbreaks occurring between 1989 and 1991 showed a new and surprising shift in age prevalence—namely, there were increased numbers of cases in preschoolers and infants less than 15 months old, the usual time when primary measles immunization has been recommended. At least two factors were responsible for this shift. First, many of the cases occurred in urban-dwelling infants from poverty areas where multiple socioeconomic factors rendered these children less likely to have the recommended immunizations until school entry. Second, the widespread use since 1963 of measles vaccines in the United States had resulted in a population of young mothers who had vaccine-conferred immunity rather than immunity conferred by natural disease. The antibody levels induced by measles vaccination are generally lower than those induced by measles itself, and the measles-specific antibodies (immunoglobulin G) supplied transplacentally by these mothers diminished more rapidly in the infants. As a result, babies 6 to 12 months of age no longer had passive protection, creating a 3- to 9-month window of susceptibility before the customary administration of vaccines at 15 months of age (*2*).

In an attempt to control these outbreaks, it was recommended that vaccine

A successful vaccination campaign. Licensure of the measles vaccine in 1963 and funding of federal programs initiated in 1966 were highly effective in reducing the number of measles cases in the United States. In this 1976 photograph, schoolchildren in Highland Park, Illinois, line up for the vaccine. [Photo by Thomas S. England, Photo Researchers, Inc.]

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be given at 6 to 12 months of age in those areas where infant cases were occurring. To ensure effective, enduring immunization, a repeat vaccination was recommended after the first birthday. This increased attention to protection of younger children preceded the highly favorable 1993 data.

On the international scene, however, the situation is more complex. For reasons not fully understood, infants in developing nations are measles-susceptible at an even younger age than infants elsewhere—up to one-third of measles cases can occur in infants under 9 months of age. The fatality rate among such children is very high, but paradoxically the attenuated measles virus vaccines have been ineffective in the first 6 months of life. Under WHO's Expanded Program on Immunization, vaccine is administered at 9 months of age. WHO estimates that 78% of children throughout the world have now received measles vaccine and that deaths from this infection have been reduced to about 1 million annually, versus 8 million annually prior to vaccine availability. Eleven percent of infant deaths throughout the world are still attributable to measles, and one-half of these deaths occur in children less than 12 months of age.

In a well-intentioned attempt to overcome maternally conferred immunity in the early months of life, measles vaccines containing 10 to 50 times the usual titer of virus were administered to infants between 4 and 6 months of age in several developing countries. Initial results of studies conducted in Gambia, Guinea-Bissau, Senegal, Togo, Sudan, Haiti, Mexico, and Peru were encouraging; the infants showed good serologic responses and apparent protection against measles (3). Two problems arose subsequently. It was difficult and costly to produce such high-titered vaccine in large amounts. Far more troublesome, however, was the incipient awareness between 1990 and 1991 that these high-titered vaccines appeared to be associated with an increased infant mortality, caused not by measles but by other infections (4). Even more perplexing was the finding that female infants had a higher mortality rate than male infants (5). Although these correlations were not consistently observed in all countries, they were documented in four studies, a sufficient number to discourage further use of these formulations.

With the widespread success of the measles vaccine programs that began in the mid-1960s, interest in measles virus research has waned in most laboratories throughout the world. This complacency has coincided with a diminished flow of funds for basic virologic and immunologic research. Optimism that measles would come eventually under full control was tempered only by the realization that, in those parts of the world where morbidity and mortality were most serious, the funding and the public health infrastructure for vaccine delivery were absent or desperately inadequate. However, the success of smallpox eradication (1977) has provided continued incentive to those leading the measles elimination programs. Most recent efforts have focused on strengthening the public health capability for measles virus control. Thus, when the problems of the early 1990s first became apparent, there was no critical mass of measles investigators to explore their etiology. Only a handful of laboratories had persisted in basic research; there was no cadre of young molecular virologists or immunologists available to address the "new" measles problem (6).

Although the 15.9-kb RNA genome of measles virus has been completely sequenced, the molecular basis for virulence and attenuation remains to be determined. Measles virus infection results in lifelong immunity, but it also produces a period of immunosuppression of varying duration, first documented at the turn of the century by the loss of tuberculin skin sensitivity after the illness. The $CD4^+$ cytotoxic T lymphocytes and cytokine-secreting lymphocytes observed during measles virus infection may be important in this immunosuppression. The role of mucosal immunity in protection against reinfection has not yet been fully elaborated. There is still uncertainty about persistent measles virus infections, other than the rare occurrence of subacute sclerosing panencephalitis, where the virus is sequestered in neurons and glial cells.

From the perspective of clinical immunity and epidemiology, measles virus has remained stable, in contrast to other viruses whose rapidly shifting antigenic determinants have produced new strains that escape neutralization by antisera to their progenitors. Recent studies have demonstrated some genetic variability among circulating measles viruses (7), but it has been of insufficient magnitude to alter the protection afforded by previous illness or vaccination. As in the past, clinical and epidemiological experience predicts long-term (lifelong?) immunity, but continued surveillance of the virus's genetic variability will be critical.

Increasing awareness of the postnatal development of the infant's immune system, and the dilemma posed by maternal antibodies blocking the infectivity of attenuated measles virus vaccines in the early months of life, continue to challenge attempts to immunize earlier in populations where measles is common in the first 6 months. Trials of aerosolized vaccine administered by the respiratory tract have produced generally unsatisfactory results. Analysis of the six major proteins of measles virus has suggested that the fusion (F), hemagglutinin (H), and nucleoprotein (N) may be the dominant antigens in the stimulation of lasting immunity. A brief experience between 1963 and 1967 revealed that inactivated measles virus vaccines did not provide enduring protection. Furthermore, these vaccines appeared to sensitize recipients so that later contact with circulating measles virus resulted in a severe atypical measles illness. This unexpected result was attributed to denaturation of the F protein during the formalin inactivation process. As a result of this unfortunate past history, progress with inactivated measles vaccines has been slow and cautious.

Current technology has been exploited to prepare purified measles virus proteins with the hope of using them as antigens that might escape neutralization by maternal antibody. Early immunization with such antigens might be followed by a reinforcing dose of live attenuated virus. A number of developing countries have demonstrated in model programs that WHO's 1995 goal for control can be met by a single dose of current vaccine given at age 9 months (8), while others have successfully employed mass vaccination campaigns to halt measles transmission (9).

What is contemplated and what should be done? A recent conference of experts under the aegis of the Children's Vaccine Initiative met in Bellagio to discuss strategies for measles control in the coming years. Their recommendations included a reemphasis on the basic science of measles, the establishment of animal models in which to study pathogenesis, a continuation of clinical studies and field research with current vaccine, an exploration of alternative routes of vaccine administration, and finally, a search for new vaccine candidates that, ideally, would evade maternal antibody, remain thermostable, and confer at least as much protection as the current vaccines.

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