Building an Immunity Fence against Measles

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(See the article by McQuillan et al., on pages 1459–64.)

In “Mending Wall,” Robert Frost quotes his neighbor as saying “Good fences make good neighbors” [1]. Since 1966, the United States has been building fences of immunity against measles to stop the spread of the virus within and between communities and to prevent introduction of the virus from other countries, with re-establishment of indigenous transmission [2, 3]. The building blocks in this fence are each susceptible individual rendered immune through vaccination with measles vaccines, which were first licensed in 1963 [4]. The health burden of measles in the United States prior to vaccine licensure was substantial. Over 500,000 cases were reported annually, there were probably ~4 million cases that occurred each year, and these cases were associated with 48,000 hospitalizations, 4000 cases of encephalitis, and 500 deaths [5]. Measles vaccines offered the opportunity to eliminate this burden.

The declaration, in 2000, that measles was no longer an endemic disease in the United States represents the achievement of a 34-year effort, characterized by several cycles of marked reduction of disease that were the result of vaccination followed by a resurgence of outbreaks [6, 7]. To respond to the outbreaks with specific solutions that addressed their causes, the national immunization program was strengthened. This program now regularly achieves high levels of immunization coverage and record or near-record low levels of most vaccine-preventable diseases. Some of the key components of the modern immunization program that grew out of the efforts to eliminate measles are the enactment and enforcement of school and day-care immunization laws in each state, a comprehensive immunization coverage-assessment system to measure progress, and, through the Vaccines for Children Program, the removal of financial barriers to access for some of our poorest children [7]. In addition, the recognition that measles transmission could persist among children in schools who had previously received the single recommended dose led to implementation of a 2-dose schedule [8, 9].

There were 4 components to the measles-elimination strategy: (1) routine vaccination of young preschool children, (2) catchup vaccination of those who were unvaccinated at school entry, (3) surveillance, and (4) response to cases [10]. The underpinning of the effort was the need to achieve high levels of population immunity as a result of vaccination. Multiple lines of evidence have been used to support the elimination of indigenous measles in the United States. These are summarized in a prior supplement of the Journal [11].

The study by McQuillan et al., in the current issue of the Journal, provides strong support to the concept that measles is no longer endemic in the United States [12]. Overall seropositivity among persons 6–49 years of age who were sampled during 1999–2004 was 95.9%. Whether this represents the immunity level in the population is unclear. Plaque reduction neutralization (PRNT) assays are considered the gold standard for assessing immunity to measles. Chen et al. have shown that 8 of 9 college students with titers <1:120 (<200 mIU/mL) immediately preceding a measles outbreak developed disease, compared with 0 of 71 with titers ≥1:120 [13]. Studies using some commercial EIAs have shown the tests to be less sensitive than PRNT but highly specific [14, 15]. It is unclear how well antibody levels measured by the EIA used in the McQuillan et al. study correlate with protective levels of antibody as they are defined by the PRNT. EIA was used to test sera at a 1:200 dilution, and appropriate negative controls were used in defining a positive test; thus, it is likely that, if anything, the EIA data may under-
estimate the true level of population immunity.

Most mathematical models for measles calculate an \( R_0 \) value (i.e., the average number of secondary cases following a single introduction into a fully susceptible population) of 12–18 [16]. This translates into the need for herd-immunity thresholds to be 92%–94% in order to interrupt transmission. The serologic data presented by McQuillan et al. suggest that the immunity levels achieved in the United States are compatible with these herd-immunity thresholds. Although some groups, such as persons born during 1967–1976, had statistically significant lower levels of seroprevalence, all groups had seroprevalences >89%, suggesting that these differences were probably not important from a public-health perspective [12]. Transmission of measles is dependent on a number of variables, including susceptibility within the population and contact rates between those who are susceptible. Although precise measurement of the number of effective contacts by age group, during which transmission can take place, are not available, some mathematical models suggest that the rate of contact between children, particularly teenagers, are likely to be substantially higher than those between adults [17]. Thus, the highest levels of immunity necessary to prevent transmission would be needed among teenagers. In contrast, transmission within other populations may cease at lower levels of immunity [18]. Persons 31–40 years of age—that is, those born between 1967 and 1976—would likely not have the same degree of contact with others as would school-age children.

The high levels of overall population immunity in the United States are compatible with the absence of indigenous transmission of the virus and with the failure to reestablish indigenous transmission despite multiple importations. Since 2000, measles incidence has consistently been <1/1,000,000 [6, 19], and most cases can be traced to international importations or limited spread from them. There is no endemic measles genotype in the United States [20].

But the high seroprevalence reported by McQuillan et al. does not mean that measles outbreaks will not occur. In fact, outbreaks have been reported among subpopulations who refuse vaccination [21, 22]. Such small groups are unlikely to be detected in a major national survey. Thus, how can the United States protect itself from the continuing threat of measles? First, because 11,000 additional susceptible individuals are born each day in the United States, the fence must be continuously rebuilt. Thus, there is a need to continue to achieve high levels of coverage in all communities, with both the first dose of measles vaccine, recommended at 12–15 months of age, and with the second dose of vaccine, recommended at 4–6 years of age [23]. But, because 100% immunity can never be obtained, and because some groups do not get vaccinated, the fence being built will always have some holes. Therefore, the other major means of protection against measles is to decrease importations—and that means that measles transmission must be reduced globally.

Measles meets biologic criteria for eradication [24]. Humans are essential for continuing transmission, accurate diagnostic tests are available, and an effective intervention—namely, measles vaccine—can interrupt transmission. In fact, measles appears not to have been endemic in the Americas since November 2002 [25]. The strategy used to eliminate measles transmission in the developing world involves 4 components: (1) routine immunization, usually at 9 months of age, with a single dose of measles vaccine; (2) providing a “second opportunity” for immunization to all children, regardless of prior vaccination status; (3) case-based surveillance with laboratory testing of suspected measles cases; and (4) improved case management [26]. (The “second opportunity” cited above is usually provided through a mass-vaccination campaign—e.g., in countries with moderate to low routine immunization coverage—but may be delivered through routine services as a second dose if high immunization coverage can be achieved and sustained. The purpose of the second opportunity is to protect children who were not previously vaccinated, as well as those who were vaccinated but failed to respond.) The World Health Organization (WHO) now recommends a second-opportunity strategy throughout the developing world, to reduce measles-related mortality [27]. Efforts during the early part of this decade reduced measles-related deaths from 873,000 in 1999 to 345,000 in 2005, a 60% reduction [28]. The next global goal is to reduce by 90% the 2000 level of measles-related mortality. Regional elimination goals have been set by 4 of the 6 WHO regions [28]. Although measles eradication is not now a global goal, efforts to achieve elimination in many of the WHO regions and to reduce measles mortality in all regions should decrease importations of measles into the United States and decrease the likelihood that our fence of immunity will be breached.

As long as measles virus circulates in the world, it will remain essential that we maintain our fence and minimize its gaps and holes. Evaluating the effectiveness of the fence involves both careful surveillance to detect cases and outbreaks and monitoring of immunization coverage. Serosurveys can help in validating the coverage information and in identifying any decrease in immunity, should there be significant waning in protection with increasing time since vaccination and with the absence of natural boosts from exposure to wild virus.

References