Measles Vaccine and Measles Control

MARTHA L. LEPOW, MD

Twenty-seven years have elapsed since the first measles vaccine was licensed for use in the United States. The thrust of vaccine development had been to produce a live attenuated vaccine that would stimulate long-lasting immunity comparable to the natural disease without eliciting significant symptoms and with interruption of transmission.

EFFECT OF VACCINATION ON THE EPIDEMIOLOGY OF MEASLES

It is estimated that measles immunization has been associated with a 98% reduction in the disease. The incidence has decreased from 400,000 cases per year before 1963 to 1500 in 1983, the lowest incidence in the 1980s (Figure). Since 1983 there has been a gradual rise in incidence; in 1989 over 14,000 cases were reported. It was previously anticipated that global eradication of measles was feasible and 1982 was the target date for eliminating measles in the United States, but that has not happened. Measles is highly contagious and prior to immunization programs, nearly everyone in the population had had the disease by adolescence and almost all cases were clinically overt. Inapparent infection was rare. The positive outcome of immunization has been an estimated savings of $7.5 billion dollars from prevention of complications requiring hospitalization and extended care, such as pneumonia and encephalitis.

In this article, the history of immunization policies in the United States is presented and the factors operating against total eradication of measles are explored. This review is followed by the rationale for and the implementation of a revaccination program.

HISTORY OF MEASLES VACCINES SINCE 1963

There have been several types of virus vaccines produced and marketed since 1963 (Table 1). The first vaccine was an attenuated virus designated as

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Edmonston B that was associated with a high rate of fever or rash (about 50%). In an attempt to modify the symptoms, a schedule of simultaneous administration of a small dose of gamma globulin of known titer was developed, which decreased reactions significantly. This vaccine was in use from 1963 to 1975 and approximately 18 million doses were given.

Concurrently, formalin-inactivated vaccine was derived from the Edmonston B virus and was used until 1967. The schedule was three doses 1 month apart or two doses of inactivated vaccine followed by one dose of live-attenuated vaccine. This vaccine was withdrawn, however, because of short-lived immunity and reports of atypical severe measles occurring in inactivated vaccine recipients when exposed to natural measles or when they received live attenuated vaccine.

In 1965, the first of two other attenuated vaccines, the Schwarz strain, was licensed, followed by a similar Moraten strain, which is currently in use in the United States. The Moraten vaccine is distributed as measles-mumps-rubella (MMR) produced in chick embryo tissue culture. Although strains have been adapted for intranasal administration, vaccines in use in the United States are administered subcutaneously.

**MEASURES OF PROTECTION INDUCED BY MEASLES VACCINE**

Two different measures of vaccine-induced immunity have been used. The first is serologic, and the second is clinical outcome, with vaccinees challenged by either natural disease or revaccination with currently used vaccines. The majority of data indicate a 95% initial seroconversion rate, and the epidemiologic data show a parallel 95% to 98% reduction in the incidence of disease.

**Factors Influencing Immune Response**

One of the factors that influences immune response is variability or loss of potency of live virus vaccine due to handling and storage. This was a problem until 1979, when a stabilizer was added.

Among host factors is the age at vaccination, especially with persistence of maternal antibody following the natural disease until 11 months of age. Because of this, the age of vaccination, originally 9 months, was raised to 12 months. In 1976, the age was raised to 15 months because of the better antibody response at that age and decreased infection during outbreaks (efficacy of 95% or greater). At that time, reimmunization was recommended for all who had received the vaccine before 12 months of age.

The cost-benefit ratio did not justify reimmunization for those who received the vaccine between 12 and 14 months of age.

Another factor that is believed to influence immune response is interferon, which is produced from intercurrent respiratory disease and may adversely affect response for measles vaccine.

**PERSISTENCE OF IMMUNITY**

Several measures are available for determining the persistence of immunity, including antibody persistence as measured in samples of different populations and the effects of vaccine challenge and attack rates in vaccinees exposed to disease as a function of time after vaccination.

**Studies in Institutionalized Children**

Studies by Krugman of antibody persistence at 16 years postvaccination in institutionalized children indicate that compared with children who had natural disease, the titer of antibody achieved by vaccinees was slightly lower 1 month postimmunization and the mean antibody titer was also lower 16 years later. Thirteen percent of the vaccinees had no detectable antibody at that time, but some of the
TABLE 1

<table>
<thead>
<tr>
<th>Type</th>
<th>Strain</th>
<th>Age at 1st Dose</th>
<th>Years in Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Live, attenuated</td>
<td>Edmonston B</td>
<td>9 months</td>
<td>1963–1975</td>
</tr>
<tr>
<td>Inactivated</td>
<td>Edmonston B</td>
<td>3 months</td>
<td>1963–1967</td>
</tr>
<tr>
<td>Live, further</td>
<td>Moraten*</td>
<td>12 months</td>
<td>1965–1976</td>
</tr>
<tr>
<td>attenuated</td>
<td></td>
<td>15 months</td>
<td>1968–present</td>
</tr>
<tr>
<td>Measles-mumps-rubella</td>
<td>Moraten</td>
<td>15 months</td>
<td>1971–present</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(6–9 months in epidemics)</td>
<td></td>
</tr>
</tbody>
</table>

*Produced in chick embryo tissue culture

Evidence of Measles in Vaccinees: Does Immunity Wane?
Several studies in the United States have demonstrated 95% seroconversion postvaccination; the occurrence of secondary vaccine failure has been found to be between 2% and 5%. These reports indicate a continuing low rate of disease in vaccinees. Although incidence in vaccinees of school age increased slightly in 1986 and 1988, the increase in high school students was not so great as to indicate waning immunity.

Several epidemiologic studies during measles outbreaks in which all vaccinees received their immunization at 15 months or older have reported attack rates between 1% and 4%.^4^ There are still issues that need to be addressed based on these data, including whether vaccine failures are primary or secondary and whether repeated exposure to wild-type virus is necessary for maintenance of immunity. The epidemiologic significance of "waning immunity" is yet to be determined and whether vaccinated persons would have milder disease if exposed or would transmit the virus to others is still not known.

SAFETY OF MEASLES VACCINE
Measles vaccine is safe and noncommunicable, although 5% to 15% of vaccinees may develop a fever of 103°F or greater 5 to 12 days postvaccination and 5% may develop a concurrent transient rash. Central nervous system complications, such as encephalitis or encephalopathy, are also reported but with a frequency of less than 1 per million doses administered,^1^ compared with a frequency of 1 per 1000 in cases of natural measles. The incidence of measles vaccine-associated encephalitis is lower than the background rate of encephalitis of unknown etiology in the United States.^3^ Most convulsions following a measles vaccine are simple febrile seizures and are not associated with any known risk factors in the patient or family member. Subacute sclerosing panencephalitis has virtually disappeared since the advent of the measles vaccination.^6^ In AIDS patients, the vaccine is safe but its effectiveness is unknown.

RECENT EPIDEMIOLOGIC OBSERVATIONS
In recent years, there have been two major types of outbreaks of measles:
1. Preschoolers in inner city areas where there are significant numbers of unimmunized children, including those younger than the recommended age of vaccination (less than 15 months).^7^
2. Vaccinated adolescents, college students, and personnel on college campuses.^8^

This latter phenomenon is in contrast to the age incidence in the prevaccination era when a high percentage of cases occurred in children less than 10 years of age (Table 2).^1^ Although most individuals who develop measles on college campuses and were born after 1956 give a history of measles immunization, documentation is lacking as to whether primary or secondary failure has occurred.

CHANGES IN THE MEASLES VACCINATION POLICY IN THE UNITED STATES
Although we have a very effective vaccine, measles has not yet been eliminated. The preschool reservoir of unimmunized children must be reached at 15 months of age by whatever means necessary.

Decreased Titers in Cord Blood Samples
Additional serologic data indicate that titers in the umbilical cord blood of infants, whose mothers have measles antibodies as a result of immunization, are lower than cord blood samples in babies whose mothers were born before 1956 and are likely to have had natural measles.^9^ These observations have implied...
MEASLES VACCINE AND CONTROL

Scheduling

Several years ago, the US Public Health Service's Advisory Committee on Immunization Practices (ACIP) and the American Academy of Pediatrics (AAP) Committee on Infectious Diseases recommended lowering the age of vaccine to 6 or 9 months with a univalent measles vaccine when exposure to natural measles seemed likely, such as during outbreaks in urban areas (Table 3). Reimmunization of children who might not have received the vaccine under 1 year of age should be carried out at 15 months. It appears necessary to immunize every child during urban outbreaks due to the extreme communicability of the virus.

RECENT CHANGES IN IMMUNIZATION SCHEDULE

Universal Second Dose

Today, the epidemiology of the disease is in marked contrast to the age-specific attack rates before 1963. The highest age-specific attack rates beyond 6 months of age in recent outbreaks have been in 5 to 19 year olds, with 80% occurring in children under 16 years of age. Many outbreaks have occurred in schools where immunization rates are believed to be greater than 95%, with attack rates of 1% to 5%. Particularly disruptive and expensive outbreaks have been seen on college campuses. Recognition of the index case is often delayed, and preventive interventions are frequently inefficient and costly. In 1989, the Immunization Practices Advisory Committee and the American Academy of Pediatrics both recommended that a second dose of vaccine be given to all children (Table 4). The additional dose should reduce the pool of susceptible children who did not have an adequate response to primary immunization, who were never immunized, or were among the small percentage of children who experienced waning immunity.

Timing of Second Dose

The ACIP, whose recommendations are followed by local health departments, and the AAP differ in their recommendations for the timing of the second doses (Table 4). The AAP recommends two doses of measles vaccine for all children after their first birthday. The first dose will usually be given as MMR at 15 months and the second dose at entrance into middle or junior high school (approximate age 11 to 12 years).

The reasoning behind this recommendation is the rapid impact the second dose will have on the continued from page 545 cations for lowering the age of vaccination to 1 year of age or even lower in the future. It is likely that preventing measles in a group not now protected until 15 months of age.

Lower Age of Vaccination in Areas of High Prevalence

Several years ago, the US Public Health Service's Advisory Committee on Immunization Practices (ACIP) and the American Academy of Pediatrics (AAP) Committee on Infectious Diseases recommended lowering the age of vaccine to 6 or 9 months with a univalent measles vaccine when exposure to natural measles seemed likely, such as during outbreaks in urban areas (Table 3). Reimmunization of children who might not have received the vaccine under 1 year of age should be carried out at 15 months. It appears necessary to immunize every child during urban outbreaks due to the extreme communicability of the virus.

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TABLE 2
Age Distribution and Mean Annual Incidence of Reported Measles Cases by Age Group—Four Reporting Areas,† 1960-1964, and Total United States, 1984-1985

<table>
<thead>
<tr>
<th>Age Group (Years)</th>
<th>1960-1964††</th>
<th>1984-1985**</th>
<th>%Decline in Incidence 1960-1985</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% Total</td>
<td>Cases/100 000</td>
<td>% Total</td>
</tr>
<tr>
<td>0-4</td>
<td>37.2</td>
<td>766.0</td>
<td>26.8</td>
</tr>
<tr>
<td>5-9</td>
<td>52.8</td>
<td>1236.9</td>
<td>9.9</td>
</tr>
<tr>
<td>10-14</td>
<td>6.5</td>
<td>169.1</td>
<td>21.8</td>
</tr>
<tr>
<td>≥15</td>
<td>3.4</td>
<td>10.0</td>
<td>41.5</td>
</tr>
</tbody>
</table>

†Yearly average for each interval
††Represents prevaccine years
**Incidence rates are extrapolated from age data of cases with known ages.

incidence of disease, which rises substantially after 12 years of age. There should be a boost of immunity as a result, and this recommendation can be carried out as part of the recommended health maintenance program of the AAP.

The ACIP and many states are mandating that the second dose, administered as MMR, be given at school entry (5 years of age). This is concordant with existing health maintenance programs provided by local health departments in a number of states. All physicians will need to conform to local requirements. Pediatricians can also offer the vaccine to older children and adolescents when they are seen for health supervision. A third dose is not necessary for those receiving two doses at least 1 month apart after 12 months of age.

Of special importance is the reimmunization of students at the time of college entry, as well as health professionals born after 1956 and hospital workers in areas of increased prevalence of measles. No significant adverse effects are to be expected with the second dose.

The Use of MMR with Revaccination

MMR is recommended to provide additional immunity to mumps and rubella. Although evidence for waning immunity to rubella is scant, there has been an increased incidence of mumps in individuals who have been previously vaccinated.

During outbreaks in schools, day care sites, and medical facilities (Table 3), or when international travel is planned, revaccination is recommended for persons born after 1956 who have not received a second dose. Those born before 1957 do not need a second dose (revaccination). In general, quarantine is not effective. Passive immunity through administration of immunoglobulin is indicated only for exposed infants less than 12 months of age and exposed immunocompromised patients, especially those with HIV infection. Others should receive attenuated vaccine within 72 hours of exposure for maximum effect.

CONTRAINDICATIONS TO MEASLES IMMUNIZATION

A history of anaphylactic reaction to eggs is a contraindication unless the patient can be tested according to a protocol developed by Herman,12 which involves a skin test with a 1:10 dilution of the vaccine. If no reaction is apparent, a 1:100 dilution is given intradermally (0.1 cc). If no reaction occurs, the full dose of 0.5 cc can be given subcutaneously and the patient observed for 20 to 30 minutes. A history of an anaphylactic reaction to neomycin constitutes an additional contraindication. Other forms of "allergies" to eggs (rash, upset stomach) are not a contraindication to receiving measles vaccine. Pregnancy and immunosuppression (except for patients with HIV infection) are also contraindications. The data available indicate that HIV-infected children, with or without symptoms, do not have an increase in reactions or development of illness when given MMR.13

REPORTING ADVERSE EVENTS

The National Childhood Vaccine Injury Act of 1986 was implemented in October 1988.13 Under this statute, physicians and other health care providers who administer vaccines must keep adequate records and report any adverse events specified in the act to the US Department of Health and Human Services. For vaccine supplied by the "public sector" reports should be made to the local health department and ultimately to the Centers for Disease Control. If the vaccine was purchased privately, reports should be made to the Food and Drug Administration.

FUTURE DIRECTIONS

Global eradication of measles is the goal. To accomplish this, we must continuously reassess our
**TABLE 3**

**Recommendations for Measles Immunization in High-Risk Areas* and for Outbreak Control**

<table>
<thead>
<tr>
<th>High-risk areas</th>
<th>2 doses with 1st dose at 12 months and the second according to AAP or ACIP guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outbreaks in schools, day care centers, and colleges</td>
<td>Revaccination (2nd dose) of all students, siblings, and school personnel born after 1957</td>
</tr>
<tr>
<td>Outbreaks in medical facilities</td>
<td>Revaccination of all workers involved in direct patient care and other personnel born after 1957 unless they have serologic proof of immunity</td>
</tr>
</tbody>
</table>

*Note: A high-risk area is a county with more than five cases of measles among preschoolers during each of the last 5 years; a county with recent outbreak among preschool children; or a county with a large inner city population.

**TABLE 4**

**Recommendations for Measles Vaccination: Routine Childhood Immunization**

<table>
<thead>
<tr>
<th>American Academy of Pediatrics*</th>
<th>Advisory Committee on Immunization Practices*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two doses (MMR)</td>
<td>Two doses (MMR)</td>
</tr>
<tr>
<td>1st dose at 15 months</td>
<td>1st dose at 15 months</td>
</tr>
<tr>
<td>2nd dose at least 1 month after the 1st</td>
<td>2nd dose at 4-6 years</td>
</tr>
<tr>
<td>Preferably at entrance to middle school or junior high school, or at 11-12 years of age.</td>
<td>(upon entry to kindergarten or 1st grade)</td>
</tr>
<tr>
<td>May be given at school entry (age 5 years), especially if required by statute; or at the time of health department scheduled maintenance visits between 5 and 18 years of age.</td>
<td></td>
</tr>
</tbody>
</table>

*Both recommend revaccination for college entrants and health care workers born after 1957.

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Current strategies and modify them as indicated. It is the responsibility of physicians who recognize a patient with measles to report the case to the local health department so that appropriate control measures can be effected.

**REFERENCES**
