

AMERICAN ACADEMY OF PEDIATRICS

Committee on Infectious Diseases

Age for Routine Administration of the Second Dose of Measles–Mumps–Rubella Vaccine

ABSTRACT. The purpose of this statement is to inform physicians of a modification in the recommendation of the appropriate age for routine administration of the second dose of measles–mumps–rubella (MMR) vaccine. The implementation of the two-dose measles vaccine schedule has improved the control of measles, but some outbreaks continue to occur in school children, although $\geq 95\%$ of children in school have received one dose of vaccine. Because most measles vaccine failures are attributable to failure to respond to the first dose, that all children receive two doses of measles-containing vaccine is essential for the control of measles. Routine administration of the second dose of MMR vaccine at school entry (4 to 6 years of age) will help prevent school-based outbreaks. Physicians should continue to review the records of all children 11 to 12 years of age to be certain that they have received two doses of MMR vaccine after their first birthday. Documenting that all school children have received two doses of measles-containing vaccine by the year 2001 will help ensure the elimination of measles in the United States and contribute to the global effort to control and possibly eradicate measles.

ABBREVIATIONS. AAP, American Academy of Pediatrics; MMR, measles–mumps–rubella; ACIP, Advisory Committee on Immunization Practices; CDC, Centers for Disease Control and Prevention; IgM, immunoglobulin M.

BACKGROUND

1989 Recommendation for a Two-dose Measles Vaccine Policy

In 1989, the American Academy of Pediatrics (AAP) recommended that two doses of measles-containing vaccine be given to all children after their first birthday.¹ Under routine circumstances, the AAP recommended that for both doses, measles–mumps–rubella (MMR) vaccine be used and that the first dose be given at 15 months of age (which was subsequently revised to 12 to 15 months) and the second dose be given at ~11 to 12 years of age. During 1989, more than 17 800 measles cases were reported—the largest number reported since 1978.² Although the incidence of measles had increased in all age groups, a dramatic increase in persons 15 to 19 years of age was seen. In addition, numerous outbreaks of measles occurred in schools despite immunization rates of $\geq 96\%$.³ From 1985 to 1989, 65%

of school children (5 to 19 years of age) with measles had received a single dose of measles-containing vaccine after their first birthday; this was in contrast to children < 5 years of age with measles, of whom only 8% had been appropriately vaccinated.⁴ The AAP recommendation was targeted to have the most immediate impact by preventing disease in children attending middle (or junior high) school and high school.

In 1989, the Advisory Committee on Immunization Practices (ACIP) of the US Public Health Service also recommended the use of a second dose of measles-containing vaccine, but in 4- to 6-year-old (school entry-age) children.⁵ The primary reason for choosing this age group was accessibility; revaccination of children at school entry was believed to be more feasible than the revaccination of older children.

RECOMMENDED CHILDHOOD IMMUNIZATION SCHEDULE

Since 1995, the AAP, ACIP, and the American Academy of Family Physicians have published jointly the Recommended Childhood Immunization Schedule, which allows for the second dose of MMR to be administered at 4 to 6 years of age or at 11 to 12 years of age. Policies for implementing the two-dose strategy have varied by state; some states require the second dose for entry into elementary school, whereas other states require the second dose of measles-containing vaccine for entry into middle school. For the 1996 to 1997 school year, only six states had no second-dose requirement (Centers for Disease Control and Prevention, [CDC], unpublished data). The AAP has advised health care providers for children of the need to comply with state school law requirements;⁶ however, differences in age cohort implementation have created some confusion and frustration among physicians, school officials, and parents.

MEASLES EPIDEMIOLOGY SINCE 1989

From 1989 through 1991, more than 55 000 cases and 147 measles-related deaths were reported.⁷ Most cases occurred in children ≤ 5 years of age who had not received measles immunizations, although the number of cases in school children also increased substantially.

Improved vaccine coverage in preschool children, particularly in large urban centers, has led to a decline in measles disease incidence, with < 1000 cases reported annually since 1992 and only 309 cases re-

The recommendations in this statement do not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

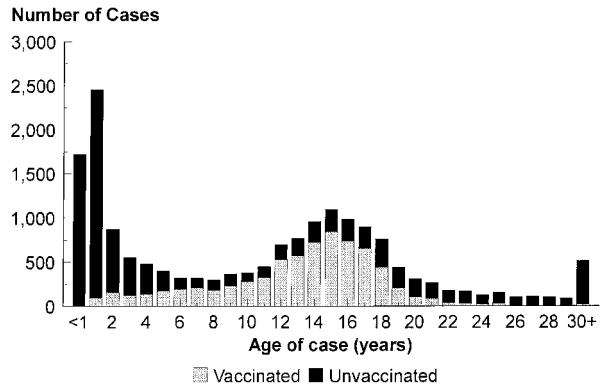
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ported in 1995 (the smallest number of cases ever reported).^{8,9}

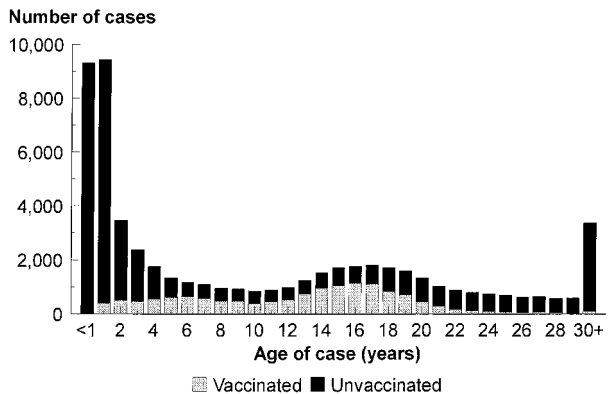
The vaccination status of measles cases by age at onset of rash for the 10-year period between 1985 and 1994 is shown in the Figure. Children ≤ 2 years of age constituted the largest proportion of cases reported; $>90\%$ of these children were unvaccinated. From

1985 through 1991, most of the 12- to 19-year-old children in whom measles developed had received a single dose of measles-containing vaccine, and most vaccine failures were in this age group. From 1992 through 1994, the incidence of measles disease declined in all age groups, and most children in whom measles developed were unvaccinated. Although

A
Vaccination status of measles cases, by age at rash onset, U.S., 1985--1988



B
Vaccination status of measles cases by age at rash onset, U.S., 1989--1991



C
Vaccination status of measles cases by age at rash onset, U.S., 1992--1994

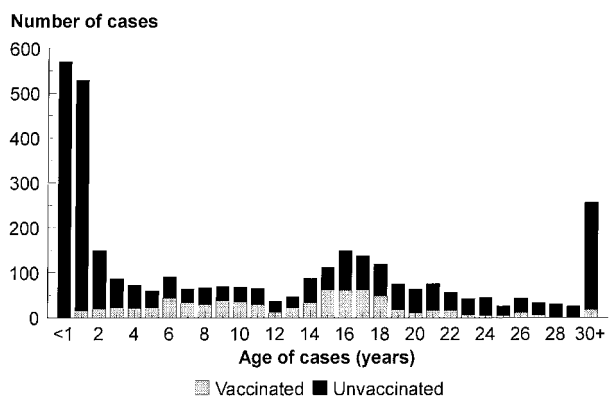


Figure. Vaccination status of measles cases by age at rash onset, 1985 to 1994 (reprinted with permission from the Centers for Disease Control and Prevention).

measles has continued to occur in vaccinated children, the proportion of cases occurring in elementary school children has increased over the proportion of cases occurring in middle and high school students.

Transmission of measles was likely interrupted in the United States beginning in the fall of 1993, when for 3 consecutive weeks, no indigenously acquired measles cases were reported.¹⁰ Subsequent genomic analysis of measles viruses isolated in 1994 indicated that those strains were similar to isolates from Europe and other areas of the world, but different from strains of measles that had been circulating in the United States from the late 1980s through 1992.¹¹

In 1993, the Childhood Immunization Initiative was announced by the CDC, calling for the elimination of indigenous transmission of six diseases, including measles and rubella, from the United States.⁷ In 1994, the Pan American Health Organization set a goal to eliminate measles throughout the Americas by the year 2000.¹² All countries of the Americas except the United States and some Canadian provinces have initiated national campaigns in which all children 1 to 14 years of age receive a supplemental dose of measles-containing vaccine regardless of measles vaccination status or disease history.¹² Improvements also have been made in routine vaccination services and surveillance systems in many of these countries. Canada has recently adopted a two-dose measles vaccine policy and a catch-up program has been implemented in school children in most provinces to ensure high levels of immunity. These elimination efforts in the Americas have resulted in a marked decrease in the importation of measles into the United States in recent years.

In a recent conference sponsored by the CDC, the Pan American Health Organization, and the World Health Organization, it was concluded that worldwide eradication of measles is feasible, but that a two-dose strategy is required as part of a routine immunization schedule or through supplemental vaccination campaigns. Until measles is eradicated worldwide, however, sporadic importations of measles will continue to occur in the United States each year. Maintaining high levels of immunity in preschool and school children will be the best defense against another resurgence of measles disease in this country.

MEASLES VACCINE FAILURES

Measles vaccination induces humoral and cellular immune responses.¹³ The measurement of cell-mediated immunity is impractical for large scale studies; therefore, the response to measles-containing vaccine usually is determined by measuring humoral immunity. In 1989, primary vaccine failure, a failure to seroconvert after vaccination, and secondary vaccine failure, loss of immunity over time, seemed to contribute to the outbreaks of measles. Failure to respond to an initial dose of measles-containing vaccine has been associated with vaccination at too early an age when maternal antibody is still present,¹⁴ to technical problems such as improper vaccine storage, or to administration and receipt of immune globulin.^{4,6} These and other unknown factors result in fail-

ure to develop measles-neutralizing antibody in 2% to 5% of vaccinated children despite age-appropriate first-dose measles vaccination.^{6,15,16}

In 1989, information about secondary vaccine failure was limited, but some documented cases of measles in previously immune children had been reported.¹⁷ Although isolated reports of secondary vaccine failure continue to occur,¹⁸ a recent metaanalysis of published studies indicates that most measles vaccine failures in the United States are primary vaccine failures and that the role of secondary vaccine failures in measles outbreaks seems to be very small.¹⁹ The higher incidence of measles in older school children (12 to 18 years old) compared with younger school children in the past (Figure) was most likely the result of increased contact between small cohorts of susceptible children in middle and high school settings rather than of increasing susceptibility with increased time since vaccination.

IMPACT OF SECOND-DOSE MEASLES VACCINE

A second dose of measles-containing vaccine, regardless of the age when given, is highly effective in inducing immunity in children who did not have a response to the first dose (provided the interval between doses is ≥ 1 month). In a recent study of measles revaccination among school entry-age children by Watson et al,¹⁵ 37 (5.4%) of 679 children who had received a measles-containing vaccine between 15 and 17 months of age were found to be seronegative for measles antibody at school entry. Of the 37 seronegative children, 36 seroconverted after revaccination, and 33 produced an immunoglobulin M (IgM) response measured by a sensitive antibody capture technique.²⁰ Although an IgM serologic response in previously immunized children with measles may not represent only primary vaccine failure,²¹ the results of Watson and associates are similar to results published by Erdman and colleagues²² and suggest that primary vaccine failure was the cause of seronegativity in almost all the children. Johnson and colleagues²³ evaluated responses to the second dose of MMR vaccine in 4- to 6-year-old versus 11- to 13-year-old children, all of whom had received their first dose of MMR when they were ≥ 15 months. The IgM response to the second dose of vaccine was similar in both groups, and 100% of children became seropositive after revaccination. The CDC also has evaluated responses to the second dose of measles vaccine in three studies with 1426 subjects ≥ 4 years of age. More than 96% of initially seronegative children responded to revaccination (CDC, unpublished data).

The antibody response to a second dose of measles-containing vaccine in children who do not respond to the first dose of vaccine (primary vaccine failure) has been demonstrated to be sustained for long periods.²⁴ In a small number of children, however, detectable, but low, antibody titers develop after primary vaccination, and the children have only transient rises in antibody titer after revaccination.^{24,25} The implications of these findings are unclear, because we do not know whether exposure to natural measles will result in clinical disease in these children.

Vaccination in the presence of maternal antibody

can result in the development of low antibody titers to measles and a reduced immune response to subsequent revaccination that may not be sustained.^{24,26} Because MMR vaccine is routinely given at or after 12 months of age, concern about a lack of a sustained immune response to a second dose of measles-containing vaccine should be minimal. Infants who receive measles vaccine before 12 months of age should receive two subsequent doses of MMR vaccine beginning at or after 12 months of age.

The rate of adverse reactions associated with revaccination of immune persons is lower than the rate observed in persons who are not immune.⁶ Serologic (antibody) screening of children before administration of the second dose of MMR is not warranted and may pose a barrier to reimmunization. Because immunity develops in almost all children who receive two doses of measles-containing vaccine, antibody screening after revaccination is not indicated.

MUMPS AND RUBELLA

As with measles, most mumps and rubella vaccine failures seem to be primary vaccine failures.^{27,28} Asymptomatic reinfection has occurred in persons who received only one dose of rubella vaccine, and mumps has occurred in highly immunized populations, raising concern about the protection induced by a single mumps vaccination.^{29,30} Johnson et al,²³ evaluated the antibody responses to the second dose of mumps and rubella vaccines (given as MMR) in 4- to 6-year-old and 11- to 13-year-old children. The mumps geometric mean antibody titers were somewhat, but not significantly, lower before and after revaccination in 11- to 13-year-old children compared with the 4- to 6-year-olds. Compared with the 11- to 13-year-olds, a statistically significant greater percentage of 4- to 6-year-old children had evidence of enzyme-linked immunosorbent assay antibody and neutralizing antibody to rubella before revaccination.²³ In both groups, 100% of children were seropositive for rubella and mumps antibody 3 to 4 weeks after revaccination.

Although the question of secondary rubella vaccine failures has been raised during follow-up intervals of up to 16 years, almost all patients had detectable antibody when more sensitive assays were used.²⁸ No data are available on the persistence of antibody for >10 years in children who have received two doses of mumps or rubella vaccine. The overall decrease of rubella cases in the United States in recent years and the absence of outbreaks in older vaccinated populations suggest that the issue of secondary vaccine failures may not be clinically relevant.

MMR REVACCINATION: SPECIAL CIRCUMSTANCES

Timing of the Second Dose

The second dose of MMR vaccine can be administered at any time ≥ 1 month after the child has received his or her first dose of vaccine, provided the first dose was administered at or after 12 months of age. However, the large number of injections in the current schedule for the first 2 years, the ease of implementation of vaccine recommendations at school

entry, and the current epidemiology of measles in the United States support the administration of the second dose at 4 to 6 years of age. There are specific, individual circumstances in which the interval between doses could be as short as 1 month, such as for children entering school without documentation of having received any measles vaccination and to control measles outbreaks in child care settings.⁶ Administration of a second dose of MMR vaccine to healthy or mildly symptomatic HIV-infected children as soon as 1 month after receiving their first dose to optimize the likelihood of an immune response to this vaccine is advised.³¹ Additional information on the use of measles-containing vaccine in HIV-infected children will be forthcoming in a statement from the AAP.

Adolescents

The AAP, ACIP, American Academy of Family Physicians, and the American Medical Association have published recommendations on the immunization of adolescents with an emphasis on establishing a routine health care visit for immunizations at 11 to 12 years of age.^{32,33} Health care professionals are strongly encouraged to ensure that all 11- to 12-year-old children have received two doses of MMR, that a tetanus and diphtheria toxoid booster is administered, and that the three-dose schedule for hepatitis B vaccine has been initiated if not completed. The physician also should ensure that the child has had varicella or has received the varicella vaccine. If indicated, other vaccines, including influenza and pneumococcal vaccines, should be provided, as should other preventive services.

Older adolescents should have their vaccination status assessed at each visit to their health care provider, and any deficiencies should be corrected. Health care professionals should be particularly aware to ensure that older, healthy, nonpregnant adolescents and young adults have received two doses of MMR vaccine.

FINANCIAL IMPACT

This revision in the age for routinely administering the second dose of MMR will not have a substantial effect on the overall cost of immunizing children. In some states, however, children will receive the second dose sooner than they might have previously. Therefore, this revision will result in a temporary increase in expenditures in those states. However, the earlier administration of the second dose should help prevent measles outbreaks and result in cost savings to schools, local and state health departments, and parents.

RECOMMENDATIONS

1. All children should receive two doses of measles-containing vaccine after their first birthday, unless the vaccine is contraindicated. MMR vaccine should be administered for both doses.
2. The first dose of MMR vaccine should be administered routinely at 12 to 15 months of age. Children who receive measles-containing vaccine before 12 months of age should receive additional doses of MMR when they are 12 to 15 months of age and at 4 to 6 years of age.

3. The second dose of MMR should be administered routinely at school entry (age 4 to 6 years), but can be given as early as 1 month after the first dose if the dose was administered at or after 12 months of age.
4. Records of all school children, particularly those 11 to 12 years of age, should be evaluated to be certain that they have received two doses of MMR vaccine after their first birthday.
5. The AAP supports the public health goal to assure that all school children have received two doses of measles-containing vaccine by the year 2001.

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