CLINICAL MICROBIOLOGY REVIEWS, Apr. 1995, p. 260–267 Vol. 8, No. 2
0893-8512/95/$04.00+0
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Measles Control in the United States: Problems of the Past and Challenges for the Future

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INTRODUCTION

It is useful to review what has happened since the licensing of measles vaccine in 1963, both to assess the progress in eliminating the disease and to identify what remains to be done. Before the introduction of the measles vaccine in 1963, 400,000 to 500,000 cases were reported and an estimated 5 million cases of measles occurred in the United States annually (Fig. 1). By 1979, 16 years after the introduction of the measles vaccine, the incidence of measles had declined 93% (75). At that time, the federal government initiated a campaign to eliminate indigenous measles from the United States by 1982. The strategy consisted of achieving and maintaining high coverage with a single dose of measles vaccine at 15 months of age, careful surveillance by public health departments, and aggressive outbreak control. In addition, during the 1970s, all states passed laws mandating documentation of immunization against measles and other childhood diseases for entry into school.

By the early 1980s, high immunization rates were achieved for school-age children; more than 95% of children were completely immunized by the time of school entry. In 1983, reported measles cases fell to a record low at that time of 1,497 (an incidence of 0.6/100,000 population) (31). Immunization efforts during the 1980s, however, failed to eradicate indigenous measles, and the number of reported cases averaged 3,700/year until 1989 (9, 21, 58). During the 1980s, measles cases continued to occur both in epidemics and during interepidemic periods (46).

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MEASLES IN HIGHLY VACCINATED POPULATIONS: EARLY IN THE MEASLES EPIDEMIC OF 1989 TO 1991

During the 1970s and 1980s, measles outbreaks in school-age children accounted for the majority of reported measles cases (Table 1) (9). From 1985 to 1988 there were a median of 47 outbreaks among school-age populations and only 8 outbreaks among preschool populations; 42% of the affected children had been appropriately vaccinated for measles (9, 19, 41). In 1989, the number of outbreaks among school-age children swelled to 170 and the number of total reported measles cases increased to more than 18,000, with 41 deaths. The epidemic continued unabated through 1990, when 27,786 cases were reported, with more than 60 deaths (Fig. 1) (24). The overall incidence rate in 1990 surged to 11.2/100,000 population, compared with a low of 0.6/100,000 in 1983. In 1989, the majority of reported cases were in school-age or college-age individuals and a minority were in preschool children (Fig. 2). Outbreaks among school-age children compared with preschool children were both more numerous (n = 101) and larger (median, 25 cases) (77). Approximately 80% of the affected school-age children were appropriately vaccinated.

Studies have documented that epidemics of measles can be sustained in school-age populations despite their having very high vaccination rates. For example, an outbreak of measles was sustained in two Texas schools when only 4.2% of the students were seronegative before the epidemic (42, 65). Typical of outbreaks among highly vaccinated populations, attack rates are low, on the order of 1 to 4%. Although Texas had laws requiring documented immunizations for school entry, 20% of the patients with measles in the 1985 Texas outbreak had not been immunized. There are four explanations for the increased rates of measles among highly vaccinated populations: (i) primary vaccine failure, (ii) secondary vaccine failure or waning immunity, (iii) nonrandom mixing patterns among school-age populations, and (iv) failure to enforce school entry immunization laws.

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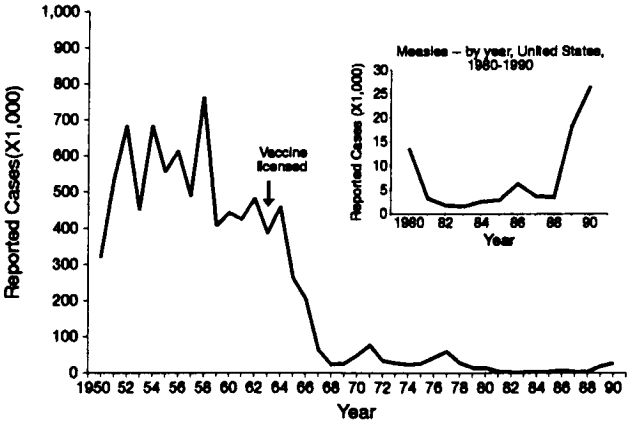

FIG. 1. Reported measles cases in the United States from 1960 through 1990. Reprinted from reference 24 with permission.

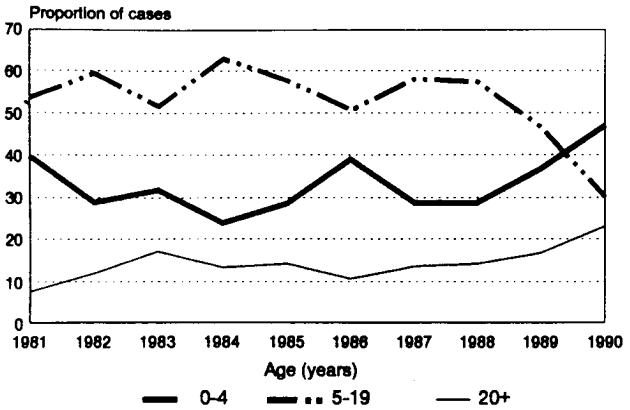

FIG. 2. Age distribution of patients with measles in the United States from 1981 through 1990. Reprinted from reference 41 with permission.

Primary Vaccine Failure

By using serologic surveys and outbreak investigation data, the efficacy of the current measles vaccine (measles, mumps, rubella [MMR]) has been estimated at between 93 and 98% (34, 42, 52, 59, 76). Most of these studies were conducted with patients immunized during the 1960s and 1970s. More-recent studies of the measles vaccine administered in the 1980s have found seroconversion rates of 98.3 to 100%, for an overall failure rate of only 1% (14, 17, 18, 59, 71). There is some evidence that the efficacy of the current measles vaccine may be overestimated because of the underreporting of "vaccine-modified" measles (35). From the recent epidemic in California, the effectiveness of the vaccine was calculated at 95% (95% confidence interval, 89 to 97%) (52). Therefore, vaccine efficacy in the 1980s and 1990s appears to continue to be between 95 and 98%.

Several factors may contribute to an increased risk of primary vaccine failure. First, children younger than 12 months who received the measles vaccine in the 1970s had a higher primary failure rate and increased attack rates during epidemics (29, 83). Another possible reason for vaccine failure is faulty handling of the vaccine. Improper cold storage has been associated with vaccine failure (53, 92). Importantly, improper handling practices may be more common than was previously thought. Bishai et al. (11) found that the majority of private pediatricians practiced many improper vaccine storage techniques, such as having refrigerators at temperatures higher than recommended for vaccine integrity or leaving temperature-sensitive vaccine out at room temperature for hours at a time. Lastly, studies have shown that children receiving vaccine before 1979 had higher attack rates of measles than did children receiving the vaccine after 1979 (22, 23, 49, 63). The addition of a new heat stabilizer to measles vaccine in 1979 may be responsible for the better performance of the vaccine since 1979 (66).

Secondary Vaccine Failure and Waning Immunity

A second possible reason for epidemics of measles among highly vaccinated populations is the waning of immunity with time. Results of studies examining the relationship between time since vaccination and vaccine efficacy have been conflicting (49, 59, 65, 80). In these studies, the time since vaccination may be confounded by the age of the individual at the time of the vaccination (<15 months) or the effect of vaccinations performed before the improvement in the MMR vaccine in 1979. Other studies have found that while a slight decline in measles antibody does occur over time, the protective effect seems to be lifelong, as demonstrated by no increase in attack rates (34, 42, 49, 59, 74). In an outbreak among Blackfeet Indians, no association between attack rate and length of time since immunization was found, if immunization occurred after the child was 15 months of age (34). In an outbreak in a highly vaccinated high school population, only students who were seronegative at the beginning of the epidemic contracted measles (42). The most disconcerting observation is perhaps a report that measles occurred in children who had been demonstrated to be seropositive following receipt of measles vaccine (64). This observation has not been confirmed by others and may have been related to a false-positive serologic test. Serologic testing for measles has been problematic and has been fraught with false-positive and false-negative results (15).

Nonrandom Mixing Patterns among School-Age Populations

Models of measles transmission predict that rates of immunity among target populations of between 93.5 and 96% will

TABLE 1. Measles outbreaks in the United States, 1985 to 1988, 1989, and 1990[a]

Year	Preschool children			School-age children		
	No. of outbreaks/yr	No. of outbreaks with ≥100 cases	% of total cases reported from outbreaks	No. of outbreaks/yr	No. of outbreaks with ≥100 cases	% of total cases reported from outbreaks
1985–1988	8	1	20	47	6	51
1989	56	9	45	170	16	32
1990	106	20	72	70	6	10

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eliminate measles transmission (6, 45). These models assume random mixing of populations and average contact rates of infectious and susceptible individuals. In school-age populations, increased levels of contact are common, violating the assumptions of the common models of measles transmission. School-age children attend assemblies and sporting events and are in common large groups for classes most of the day. In addition, students frequently mix with each other after school. In a study of a sustained outbreak in a highly vaccinated Indian population, a primary risk factor for contracting measles was attendance at basketball games, a setting in which there is a high contact rate (34). Given the high, nonrandom contact rates among schoolchildren, epidemics can be sustained even in populations with positive seroprevalence rates of 95% or more (42). In addition, persons who have elected not to receive immunizations for religious reasons may cluster together, thus increasing the chance of contact between an infected child and a group of susceptible children. In proposing target rates for immunization, it is essential to include the elimination of pockets of susceptible people, such as those that might occur in the inner cities, religious groups, or school populations (25).

Failure To Enforce School Entry Immunization Laws

Despite laws in all states requiring students to document immunization against measles before entry into school, some schools are lax in enforcing these laws. In 1989, 350 California schools reviewed pupil records for documentation of measles immunization. Of 280,000 children, 6,000 (2.1%) lacked documentation of measles immunization (33). Factors contributing to errors in documentation include high turnover of students in schools, lost records by parents, and difficulty in acquiring written documentation from providers. Ideally, schools should require immunization for entry into each grade. Required proof of immunization only at entry into kindergarten or first grade may permit entry of older unimmunized susceptible children from foreign countries or from other school districts that have been lax in enforcing immunization laws.

Immunization Strategy for School-Age Children: the Two-Dose Measles Immunization Recommendation

To address the failure of the measles immunization policy to eradicate measles from the school-age population, two policy options were considered: (i) a selective policy of revaccination with MMR vaccine and (ii) universal revaccination of children with a second dose of MMR vaccine. Under the selective revaccination policy, children who had received measles vaccination before 1980 or at less than 15 months of age would be vaccinated again. Advocates for a selective vaccination strategy cited the improved efficacy of the MMR vaccine during the 1980s and the increased cost-effectiveness of a selective immunization strategy (63).

Opponents of selective revaccination cited the difficulties in identifying students who had been immunized before 1980 or before 15 months of age. Moreover, under this strategy, assuming the most optimistic estimates of primary failure, at least 1% of each age cohort (approximately 40,000 children) would be added to the pool of susceptible children each year. Outbreaks could still occur if measles were again introduced into the population. Lastly, proponents of universal revaccination pointed out that universal administration of two doses of measles vaccine has been effective at dramatically reducing measles cases in a number of European countries and among U.S. military recruits (28, 36).

TABLE 2. Incidence of reported measles cases by age group in the United States, 1980 to 1988, 1989, and 1990[a]

Age group (yr)	Incidence of measles cases[b]		
	1980–1988[c]	1989	1990
<1	5.6	50.5	119.3
1–4	4.7	31.7	59.3
5–9	1.8	9.7	14.9
10–14	3.5	13.1	13.4
15–19	4.5	24.8	17.4
20–24	1.0	8.5	13.3
≥25	0.1	1.0	2.3
Total	1.4	7.3	11.2

[a] Reprinted from reference 9 with permission.
[b] Cases per 100,000 population. Rates calculated for all reported patients of known age (18,107 [99.5%] in 1989, 27,678 [99.6%] in 1990), and an extrapolated proportion of patients of unknown age, using census estimates.
[c] Median rate, 1980 to 1988.

In 1989, after New York State initiated a program for universal administration of two doses of MMR vaccine, both the Advisory Committee on Immunization Practices and the American Academy of Pediatrics published the same recommendations (4, 23). The American Academy of Pediatrics recommended that the second dose be given at entrance to middle or junior high school (11 or 12 years of age), as this age precedes the highest risk period for outbreaks. However, a large proportion of adolescent children receive only episodic health care. Adolescents average only one physician or clinic visit per year, and many adolescents, particularly in inner-city areas, are seen by physicians less frequently than that (72). Many visits by adolescents are for episodes of acute illness in settings such as emergency rooms, where immunizations are not routinely administered. Thus, many authorities believe that administering a second measles immunization to this population would be difficult (72).

The Advisory Committee on Immunization Practices has recommended that the second MMR vaccine dose be given at the time that a 5-year-old child has a school entry health care visit, along with other required childhood immunizations due at that time (diphtheria-pertussis-tetanus vaccine and oral polio vaccine). The economic and practical considerations of administering MMR vaccine at the time of school entry, especially for the public clinics, outweighed the 5- to 10-year delay in reducing outbreaks in junior and senior high school populations. In addition, giving MMR vaccine at school entry would protect preteens against mumps and rubella. Recently, these two recommendations have been combined, and a second dose of MMR vaccine is recommended sometime between 5 and 6 years of age or between 11 and 12 years of age.

MEASLES IN UNVACCINATED PRESCHOOL CHILDREN: LATER IN THE MEASLES EPIDEMIC OF 1989 TO 1991

During the 1989 to 1991 measles epidemic, the epidemiology shifted dramatically from school-age children to preschool children. In 1990, attack rates among all age groups increased. They were highest for children less than 1 year of age (119/100,000) and for children 1 to 4 years of age (59/100,000) (Table 2). In contrast to the outbreaks of measles in vaccinated schoolchildren, the epidemic among preschool children was largely among unvaccinated children. Of the 13,323 cases among preschool children, 4,700 occurred among children less

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than 15 months old and not yet eligible for vaccination. Among children 15 months to 4 years old, of whom 56% were unimmunized, 8,617 cases occurred. Eighty-one percent of all preschool children with measles were unimmunized, and more than 17,000 of the 27,000 cases of measles during 1990 could have been prevented with the currently available vaccine (73).

The measles epidemic among preschool children was concentrated in urban African American and Hispanic children, with incidence rates of 87/100,000 for African American preschool children and 164/100,000 for Hispanic preschool children compared with 23/100,000 for non-Hispanic white preschool children (9, 20, 33). While complication and death rates were no higher for minority children, complication rates of 21% and death rates of 3.2/1,000 cases were the highest for measles in the past 30 years (33). Sixty percent of measles-related deaths occurred among preschool children. Nineteen percent of all reported persons with measles required hospitalization for a total of 31,000 hospital days at a cost of over 150 million dollars (9).

The National Vaccine Advisory Committee concluded that the primary cause of the 1989 to 1991 measles epidemic was widespread transmission of measles among unimmunized preschool and minority urban populations (33, 73). Retrospective surveys of school records of first graders in 10 urban areas demonstrated that the median proportion of children up-to-date for diphtheria-pertussis-tetanus vaccine, oral polio vaccine, and MMR vaccine at 24 months of age in 1987 was 43% (range, 12 to 46%). The median proportion of children who had received MMR vaccine at 24 months was 70% (range, 51 to 79%). An inverse relationship between the mean incidence of measles and measles vaccine coverage levels by the second birthday was observed in metropolitan areas (25).

The reasons for low rates of immunization among preschool children are described in a number of recent studies (43, 90); they include (i) missed opportunities for administering vaccines, (ii) barriers to immunization in the health care delivery system, (iii) inadequate general access to care, and (iv) incomplete public awareness and lack of public request for immunizations (73).

A missed opportunity to vaccinate is defined as the failure to provide children with the immunizations for which they are due at a health care visit. Studies show that missed opportunities occur frequently, at 20 to 70% of child health care visits (38, 48, 86). Missed opportunities occur at well-child visits, visits for sickness, and visits to subspecialists (78), and they may occur more frequently at public clinics (38, 86, 90). The failure of the health care system to immunize children during office visits may be the largest contributing factor to underimmunization of preschool children.

Other health system barriers to child immunization services include the fees and long waits for immunization services and inconvenient clinic hours (89). More general barriers to adequate care, such as lack of health insurance or lack of a regular provider of health care, also impede access to medical services that are likely to provide needed immunizations (2, 5–7, 13, 87). Fewer than half of private indemnity insurance plans cover immunizations, resulting in high out-of-pocket costs for parents and an increasing tendency for private physicians to refer patients to the public health clinics for immunizations (8).

Several population characteristics have also been associated with low immunization rates, including lower parental education and knowledge, larger family size, and poverty (5, 12, 56, 61). Moreover, in some studies, children in Latino families, families with low English language capability, and families with undocumented immigration status also have lower immunization rates (37, 85, 88).

STRATEGIES FOR INCREASING IMMUNIZATION LEVELS AMONG PRESCHOOL CHILDREN

A number of national efforts are under way to remove barriers to immunizations for preschool-age children. First, the payment system for immunizations is being changed dramatically. Many states are passing laws requiring all private insurance policies to cover immunizations. Second, the President's Immunization Initiative will make free vaccines available to children who are uninsured or on Medicaid and children whose insurance does not cover immunizations if seen at a federally qualified health center (81). In addition, state savings from the bulk purchase program may be used to increase the administration fees paid to providers for administering vaccinations, increasing providers' financial incentive to deliver immunizations.

The President's Immunization Initiative is also aimed at reducing missed opportunities at health visits for young children. A new set of immunization delivery standards has been promulgated to educate providers on optimal immunization practices. These standards are as follows:

(i) immunization services are readily available;
(ii) there are no barriers or unnecessary prerequisites to the receipt of vaccines;
(iii) immunization services are available free or for a minimal fee;
(iv) providers utilize all clinical encounters to screen and, when indicated, immunize children;
(v) providers educate parents and guardians about immunization in general terms;
(vi) providers question parents or guardians about contraindications and, before immunizing a child, inform them in specific terms about the risks and benefits of the immunizations their child is to receive;
(vii) providers follow only true contraindications;
(viii) providers administer simultaneously all vaccine doses for which a child is eligible at the time of each visit;
(ix) providers use accurate and complete recording procedures;
(x) providers coschedule immunization appointments in conjunction with appointments for other child health services;
(xi) providers report adverse events following immunization promptly, accurately, and completely;
(xii) providers operate a tracking system;
(xiii) providers adhere to appropriate procedures for vaccine management;
(xiv) providers conduct semiannual audits to assess immunization coverage levels and to review immunization records in the patient population they serve;
(xv) providers maintain up-to-date, easily retrievable medical protocols at all locations where vaccines are administered;
(xvi) providers operate with patient-oriented and community-based approaches;
(xvii) vaccines are administered by properly trained individuals; and
(xviii) providers receive ongoing education and training on current immunization recommendations (2a).

Public health departments have received increased allocations of federal funds to increase immunization services, increase outreach, and monitor immunization delivery in public clinics and in other health care provider networks such as health maintenance organizations and large health groups. Immunization registries to track immunization levels for all children from birth through adulthood are planned. Immunization

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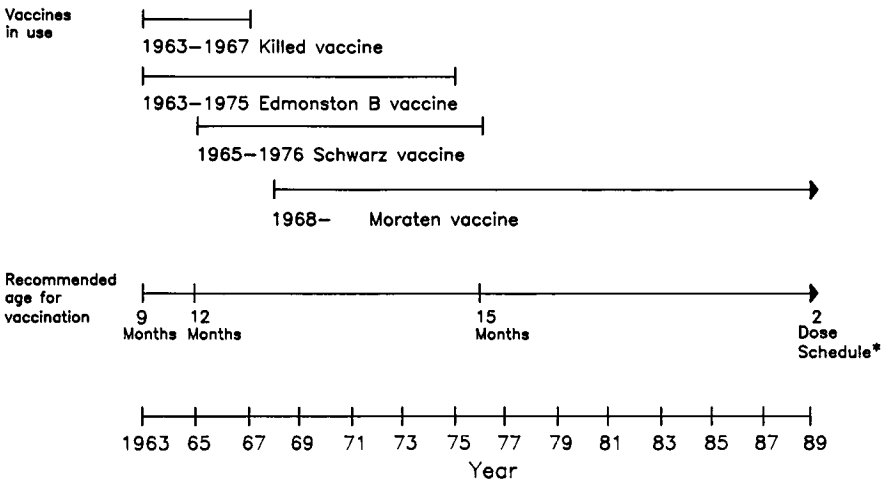

FIG. 3. Recommended ages for measles vaccination and vaccines in use in the United States. *, In 1989, both the Advisory Committee on Immunization Practices and the American Academy of Pediatrics recommended a two-dose schedule for the MMR vaccine. The Advisory Committee on Immunization Practices and the American Academy of Pediatrics recommends that the second dose of vaccine be administered at 5 to 6 years of age or 11 to 12 years of age. Reprinted from reference 58 with permission.

registries will be used to monitor community immunization levels, identify high-risk areas and populations, and target them for more-intensive outreach and education. These immunization registries will take several years to develop and implement.

Lowering the Age of MMR Administration

It has been observed that in the United States, compliance with immunization is highest in the first 6 months of life and drops off thereafter (84). Therefore, reducing the age at immunization for the MMR vaccine may be effective in increasing the uptake or immunization rate. The American Academy of Pediatrics already has recommended that the first dose of MMR vaccine be given at 12 to 15 months of age.

Studies in the late 1970s suggested a decreased seroconversion rate for vaccinees immunized between 12 and 14 months rather than at 15 months. This was believed to be due to the presence of maternally acquired antibodies, which has been associated with vaccine failure (3, 62, 76). These reports prompted a raising of the recommended age of routine MMR immunization to 15 months. Unfortunately, this change may have contributed to the epidemic of 1989 to 1991 by leaving the group of 12- to 14-month-old children unprotected; in 1990, it contributed 2,551 cases, or >11% of the cases in the epidemic (all cases, all ages) (24). More importantly, the delay in immunization from 12 to 15 months probably resulted in fewer preschool children receiving measles vaccine and resulted in a larger number of susceptible children in this age group who subsequently acquired measles.

At the time these studies were conducted, most mothers had acquired antibodies through natural measles rather than measles vaccine. Thus, they endowed their fetuses with high measles antibody levels (76). Currently, most women of childbearing age (15 to 35 years of age) have had the measles vaccine and have lower antibody levels than women who had natural measles infection (57). As a result of these lower antibody levels, their infants are born with lower titers of measles antibody, which they lose earlier than the infants of mothers who had natural measles (50, 54). Thus, MMR vaccine may now be as efficacious at 12 months as at 15 months (27, 58, 79). Trials are under way to evaluate the efficacy of administering the current measles vaccine at 9 months of age in the United States, as is recommended by the World Health Organization in developing countries (30, 82). It is hoped that reducing the age for the first dose of MMR vaccine will increase the proportion of preschoolers immunized and thus will decrease the transmission of measles from older siblings to infants less than 9 months old (32, 51).

Development of New Measles Vaccines

Development of new, more potent vaccines that would be effective earlier than 12 months of age would be helpful. The current measles vaccine used in the United States is prepared from the Moraten strain, an attenuated strain developed from the Edmonston B strain of measles virus through multiple passages in chicken embryo cells (47). Figure 3 shows the various vaccines used over a time line from 1963 to 1989. Figure 4 diagrams the derivations of the various measles vaccines that have been or are in use. The Moraten strain produces fewer side effects than does the original vaccine derived from the Edmonston B strain. According to studies performed in the 1970s, it is not sufficiently immunogenic in children under 9 months of age; however, as discussed above, those studies may not apply to children born in the 1990s (68, 69). Several studies have demonstrated that the Edmonston-

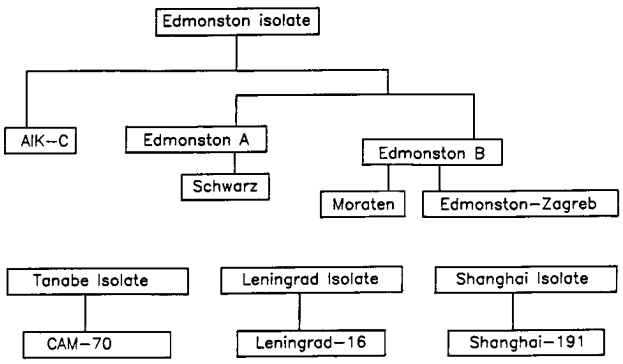

FIG. 4. Origin of selected strains of measles vaccine. Reprinted from reference 58 with permission.

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Zagreb (E-Z) vaccine administered to children at 4 to 6 months of age induces seroconversion rates equal to or greater than those achieved by a standard dose of Schwartz or Moraten vaccines administered at 9 months of age (55, 60). The reasons for the increased immunogenicity of the Edmonston-Zagreb vaccine is not known. In addition, a Schwartz vaccine with increased potency has been tested for infants at 4 to 6 months of age and has been shown to be effective (1, 40, 55, 60).

The increased-potency vaccines were recommended for children 6 months or older in areas of the world where measles is endemic and where attack rates are high for infants 4 to 12 months of age (91). During the 1989 to 1991 epidemic, the attack rate for children under 1 year of age in urban communities reached 119/100,000, the highest of any age group (24). In addition, the morbidity and mortality were highest among this age group. Therefore, a vaccine effective in preventing measles in infants less than 1 year of age is greatly needed worldwide (30). Development of such a vaccine and distribution to developing countries would decrease measles in those countries and decrease the likelihood of importation of measles cases to the United States (70). The United States epidemic of 1989 to 1991 occurred shortly after a major epidemic of measles in Mexico, and Mexican immigrants were believed to be the source of outbreaks in Washington state (23).

The momentum toward using the existing high-titer vaccines to immunize children at 6 or 9 months of age was halted by reports of increased mortality among preschool children 6 months to 2 years after receiving high-titer Edmonson-Zagreb or Schwartz vaccines at 6 months (39, 40). Increased mortality months to years following natural measles infection has also been documented, presumably because of prolonged suppression of cell-mediated immunity (67). This phenomenon has been observed only in underdeveloped countries. The late mortality following administration of the high-titer measles vaccines was observed in three underdeveloped countries in which child mortality rates were already high (1, 40). The deaths were not necessarily related to measles and appeared to be restricted to girls. It is believed that, similar to natural measles infection, the high-titer measles vaccine may have caused immunosuppression in these children; however, no satisfactory explanation has been identified for this sex-specific mortality (44). Although the interpretation of these findings is controversial (1), an expert panel considered it prudent to recommend that high-titer measles vaccines no longer be used in field trials or in the international Expanded Program of Immunization (36). Because of these findings, the Centers for Disease Control and Prevention National Immunization Program has halted further study of the Edmonston-Zagreb vaccine in the United States (10). It is essential that the data leading to the cessation of trials and development of high-titer measles vaccines be reexamined to determine when these studies can be resumed.

CONCLUSIONS

Measles, which was targeted for elimination from the United States in 1979, persisted at low incidence until 1989, when an epidemic swept the country. Cases occurred among appropriately vaccinated school-age populations and among unimmunized, inner-city preschool children. In response to the epidemic, measles immunization recommendations have been modified. To prevent spread among school-age populations, a second dose of MMR vaccine is recommended at 5 to 6 or 11 to 12 years of age. To increase immunization coverage among inner-city preschool populations, a number of activities have been undertaken to improve the immunization delivery system, including the following: (i) the recommended age for the first dose of measles vaccine has been lowered to 12 to 15 months; (ii) the federal government has dramatically expanded the distribution of free vaccine to both public and private providers; (iii) increasingly, states are mandating private insurance plans to cover childhood immunizations; and (iv) federal programs are increasing outreach to high-risk groups and monitoring vaccination coverage nationally and in high-risk inner-city areas.

In 1993, the numbers of measles cases reported reached a new low of 277 cases (26). In the face of these current statistics, it is tempting to become complacent or turn our efforts to more pressing problems. However, our ability to prevent the next measles epidemic will depend on how effective we are in preventing an accumulation of new susceptible people by ensuring that all children are immunized during this interepidemic period.

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