Decay of Passively Acquired Maternal Antibodies against Measles, Mumps, and Rubella Viruses

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The decay of maternally derived antibodies to measles, mumps, and rubella viruses in Swiss infants was studied in order to determine the optimal time for vaccination. A total of 500 serum or plasma samples from infants up to 2 years of age were tested by enzyme-linked immunosorbent assay and fluorescent-antibody testing. The decline of antibody prevalence was slowest against the measles virus. By 9 to 12 months of age, only 5 of 58 (8.6%; 95% CI, 2.9 to 19.0) infants were antibody positive for the measles virus, and only 2 had levels above 200 mIU/ml. Mumps and rubella virus antibody seropositivity was lowest at 9 to 12 months of age with 3 of 58 (5.2%; 95% CI, 1.1 to 14.4) infants and at 12 to 15 months with 1 of 48 (2.1%; 95% CI, 0.1 to 11.1) infants, respectively. Concentrations of passively acquired antibodies decreased rapidly within the first 6 months of life. We observed no significant differences in antibody prevalence or concentration according to gender in any age group. In conclusion, MMR vaccination at 12 instead of 15 months of age could reduce the pool of susceptible subjects in infancy and support the efforts to eliminate these infections, particularly in combination with a second vaccine dose before school entry.

Vaccination of preschool children against measles and mumps for individual protection has been carried out in Switzerland since 1970, and selective vaccination of prepubertal girls was instituted in 1974 in order to eliminate congenital rubella (38). In 1985, the combined measles, mumps, and rubella vaccination (MMR vaccination) was introduced for all children between 15 to 24 months of age with the aim of interrupting the transmission of these viruses in the population. At present, it is recommended that children be vaccinated at the age of 15 months. Since measles has the highest transmission rate of these three infections, the MMR vaccination schedule is determined by this vaccine component (29). In order to eliminate measles, the proportion vaccinated should be greater than 90 to 95% at the age of 2 years (2). Vaccination rates below this critical proportion will shift the remaining virus circulation to older nonimmune individuals and increase the risk of age-dependent complications, such as the congenital rubella syndrome (2, 28).

Due to suboptimal implementation of the MMR vaccination campaign and some antivaccination activism, MMR vaccination rates among preschool-age children have levelled off at about 80% in Switzerland; accordingly, measles, mumps, and rubella have remained endemic throughout Switzerland, with 20 to 25% of measles cases occurring in children up to 4 years of age (13). Several countries around Switzerland face a similar situation (14, 22, 32, 33).

Active transplacental transfer of immunoglobulin G (IgG) begins at about 6 months of gestation and increases sharply thereafter. At the end of gestation, IgG concentrations in fetal serum exceed maternal levels by a ratio of 1.2 to 1.8.1. Passively acquired IgG is subjected to an exponential clearance rate with a half-life of 35 to 40 days (34). Only after antibody levels are low enough that vaccine virus can induce an immune response is live-virus vaccination feasible. The achievement of the goal of eliminating measles, mumps, and rubella is facilitated by vaccination at the earliest possible time after the clearance of maternal antibodies, in order to keep the number of susceptible subjects in the population as low as possible. This study was designed to determine the optimal age for vaccinating infants in Switzerland against measles, mumps, and rubella.

MATERIALS AND METHODS

Participants. A total of 500 serum or EDTA-plasma samples (208 from girls and 292 from boys) were used. A total of 317 samples (113 from girls and 204 from boys) were collected consecutively from all infants up to 24 months of age hospitalized at the Pediatric Clinic of the University of Bern, Switzerland, between January and November 1996. As well, 183 serum samples (95 from girls and 88 from boys) submitted in 1995 and 1996 to the Institute for Medical Microbiology, University of Bern, for diagnostic testing unrelated to measles, mumps, or rubella were included. Both institutions serve a similar mixed urban and rural population in west-central Switzerland. All samples were divided into 3-month age categories and were used in an unlinked anonymous manner to establish the age-stratified seroprevalence of antibodies to measles, mumps, and rubella viruses. If more than one sample was available from the same patient, we only included the earliest one. This study was approved by the Ethical Commission of the Medical Faculty at the University of Bern (no. 145/95).

Serology. Anti-measles and anti-mumps IgGs were detected by enzyme-linked immunosorbent assay (Human/RUWAG, Zurich, Switzerland) by procedures recommended by the manufacturer. Weakly reactive and negative samples (i.e., an optical density less than 120% of the cutoff) were examined by indirect immunofluorescence assay (IFAT) (slides were from Bios, Gräfelfing, Germany; anti-human IgG-fluorescein isothiocyanate was from Sanofi-Pasteur, Marnes-la-Coquette, France) (26). All samples with a typical reaction pattern at a sample dilution of 1:10 were considered positive.

A pool of 50 Swiss blood donor serum samples was calibrated with the Second International Standard for Anti-Measles Serum (National Institute for Biological Standards and Control, London, Great Britain) and used for the quantification of measles-specific IgG in milli-international units per milliliter. Two hundred milli-international units per milliliter was considered the threshold protective antibody concentration (19). One milliliter of the pool contained 5 IU of anti-measles IgG. Since no international standard is available for measuring mumps virus antibodies, we defined the blood donor serum pool as 100 arbitrary units (AU) per ml.

Anti-rubella IgG was detected by the ETI-RUBEK-G test (Sorin Biomedica, Saluggia, Italy) (26). Quantitative values were determined with the standards provided by the manufacturer. They were comparable to those obtained with the Second British Standard for Anti-Rubella Serum (National Institute for Biological Standards and Control) (7). A cutoff of 10 IU/ml was used, based on a panel of 93 serum samples from subjects whose susceptibility or immunity had been

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ascertained by the immune response to rubella vaccination (data not shown) (27).

Statistics. Descriptive and box plot analyses were done with the StatView program (SAS Institute). Exact confidence intervals (CI) were extracted by the procedures outlined by Diem and Lentner (12).

RESULTS

By the age of 0 to 0.5 months, almost all infants had detectable antibodies against measles, mumps, and rubella viruses, which decreased rapidly to less than 50% seroprevalence before the ninth month of life for the measles virus and before the sixth month of life for the mumps and rubella viruses. Between 9 and 15 months of age, the percentage of infants with detectable antibodies reached a nadir with 8 of 106 (7.5%; 95% CI, 3.3 to 14.5) infants positive for the measles virus, 7 of 106 (6.6%; 95% CI, 2.7 to 13.3) positive for the mumps virus, and 3 of 106 (2.8%; 95% CI, 0.6 to 8.12) positive for the rubella virus (Fig. 1). After the age of 12 to 15 months, seroprevalence started to increase. There were no significant differences between girls and boys in any age group.

The concentration of antibodies against measles, mumps, and rubella viruses decreased rapidly up to the 3- to 6-month age group (Fig. 2). The median concentration of anti-measles IgG was below the protective level of 200 mIU/ml (19) between 6 and 12 months: it was 118 mIU/ml at 6 to 9 months and <10 mIU/ml at 9 to 12 months. Between 9 and 15 months of age, only 4 of 106 children had concentrations of anti-measles IgG above 200 mIU/ml, which could interfere with successful vaccination, and 4 infants had anti-measles IgG levels <10 mIU/ml that were detectable only by IFAT. Measles-specific IgMs were undetectable by IFAT in these subjects. At no age was gender a significant risk factor for lower antibody levels.

The increasing seroprevalence of antibodies against measles, mumps, and rubella viruses after 15 months of age may reflect vaccination as well as a wild-type virus infection. While the increase was similar for antibodies against measles and rubella viruses, reaching about 75% by the age of 2 years, it was slower for antibodies against the mumps virus. This may be due to poor immunogenicity of the mumps vaccine component that has mainly been used in Switzerland (15, 24, 38).

DISCUSSION

These results are the first to document the decay of maternally derived antibodies against measles, mumps, and rubella viruses in a European population during infancy. Whereas the seroprevalence of mumps and rubella virus antibodies presents as a U-shaped curve, the curve for measles virus antibodies is V-shaped, which suggests a slower antibody decay. Therefore, the timing of MMR vaccination depends mainly on the level of antibodies to the measles virus, which offers the narrowest window of opportunity between the clearance of maternal antibodies and the transmission of virus to susceptible infants.

Vaccination rates in different regions of Switzerland as well as the prevalence of several infectious diseases show no considerable regional differences, and the demographic characteristics of the Swiss population are quite homogeneous (38). Although our serum samples were collected in the region of Bern, they may therefore be considered representative for Switzerland. Data from the Swiss Sentinel Surveillance Network give evidence for the continued endemicity of measles, mumps, and rubella throughout Switzerland since 1986, with 20 to 25% of measles cases occurring in children up to 4 years of age (13). As different countries around Switzerland, such as Germany, France, and Italy, have a similarly poor vaccine

FIG. 1. Percentage of IgG-positive infants according to age for measles (a), mumps (b), and rubella (c) viruses. Numbers (n) of samples available in each age group are given above panel a. Vertical lines indicate 95% confidence intervals.
coverage with persistently endemic measles, our data could be typical for west-central and southern Europe (14, 22, 32, 33).

Since MMR vaccination of infants was introduced in Switzerland after 1985 and vaccination against measles and mumps had previously only been offered on an individual basis (38), we expected that the mothers of infants tested in this study would predominantly have naturally acquired immunity against measles and mumps viruses, which would provide passive protection to their infants for a longer period than would vaccine-induced maternal immunity (4, 23, 30). Even if some mothers had been vaccinated, their antibody levels would have been boosted by the continuing circulation of wild-type viruses, a phenomenon which has been well documented (13). The selective immunization strategy used for rubella until 1985 and the slow uptake of MMR vaccination in infancy thereafter have provided ample opportunity for naturally acquired immunity against rubella as well (25). Nevertheless, we found a rapid loss of passively acquired antibodies. After the age of 6 months, the median antibody concentration against the measles virus was below the protective level of 200 mIU/ml (19); between 9 and 15 months of age, only 8 of 106 (7.5%; 95% CI, 3.3 to 14.5) infants had detectable measles virus antibodies. Thus, the currently recommended age for MMR vaccination leaves most infants unprotected for about half a year and provides a large susceptible population for wild-type virus circulation, which compromises the elimination of these infections.

With an increasing proportion of women with vaccine-acquired immunity, a further shift to the left of the seroprevalence curve in the infant population is expected to occur. As predicted by Wilkins and Wehrle (37), by the time most infants are born to vaccinated mothers, vaccination recommendations must be adapted, because of the premature loss of maternally derived antibodies (4, 18, 21, 23). Studies that have been conducted in Africa (8), Israel (9), and Turkey (1) have shown that most infants of well-vaccinated populations become susceptible to clinical measles after 6 months of age. The consequences of a shift from long-lasting passive immunity in infancy to early loss of maternally derived vaccine-induced antibodies are evident from investigations of an epidemic of measles in the United States in 1992 which showed that 22.2% of all cases were in infants aged less than 1 year (5).

The possibility of decreased seroconversion rates and weak responses to vaccine boosting has to be taken into account if infants are vaccinated at an earlier age (37). During a measles outbreak in Quebec in 1989, De Serres et al. (10) found a lower rate of vaccine effectiveness in children at 12 months of age (85%) than in older children vaccinated after 15 months of age (94%), but in 1996 they found a 96% rate of effectiveness of vaccination at 6 to 11 months of age during a measles outbreak in a population immunized exclusively by vaccination (11). In 1994, infants from mothers born in the United States after 1961 with low levels of passively acquired measles antibodies were vaccinated at the ages of 9, 12, and 15 months, and they seroconverted at high rates of 92, 97, and 99%, respectively (20). In addition, American infants of vaccinated mothers who received measles vaccine at 6 or 15 months developed neutralizing antibodies at rates of 74 and 100%, respectively, and revaccination at 15 months of age induced neutralizing antibodies in those vaccinated at 6 months. Thus, there was no depression of the immune response in infants vaccinated before 12 months of age (17). In Haitian infants, a seroconversion rate of 100% was found at 12 months of age (16).

The increasing pool of susceptible subjects accumulating before the currently recommended age of MMR vaccination in Switzerland as well as in other populations with similar epidemiologic characteristics carries the risk of outbreaks, mainly of measles with its associated morbidity and mortality, and serves to maintain wild-type virus circulation. Primary vaccination at the earliest possible time and revaccination of children, preferably before school entry, may therefore provide the highest degree of individual protection as well as herd immunity (35). A two-dose schedule can compensate for primary vaccine failures, and outbreaks in adolescence may thereby be prevented (3, 6). Such a schedule has been effective for the elimination of these infections in Finland (31) and has recently been established in Switzerland.

Recent outbreaks of measles in the United States have been due to genetically heterogeneous wild-type viruses that are circulating in Europe and Asia and were epidemiologically linked to importation. These data suggest the interruption of indigenous measles virus transmission after the epidemic in the United States from 1988 to 1992 and an increasing rate of cases imported from Europe (33, 36). Improving the control of endemic measles in Switzerland and other European countries by the vaccination of infants at an earlier age should be considered in the near future. This may also help to maintain the...
elimination of indigenous measles in the Americas and northern Europe.

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