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Follow-Up Surveillance for Antibody in Human Subjects following Live Attenuated Measles, Mumps, and Rubella Virus Vaccines (40675)

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The value of live attenuated measles, mumps, and rubella virus vaccines is necessarily dependent on the continued presence of circulating antibodies which, in turn, are the basis for immunity. The present report describes the findings in follow-up studies to measure the levels of antibody following vaccination with monovalent live virus vaccines: 10 years after measles vaccines (Enders' Edmonston, Moraten line (Attenuvax), and Schwarz line); nearly 12 years after Jeryl Lynn strain mumps vaccine (Mumpsvax); and 9 and 9.5 years after duck cell modified HPV-77 rubella vaccine (Meruvax) in adult women and children, respectively. These vaccines were licensed for general use in the USA between 1963 and 1969: Enders' original (Edmonston) measles 1963; Moraten line measles (Attenuvax) 1968; Jeryl Lynn strain mumps vaccine (Mumpsvax) 1967; and HPV-77 duck rubella vaccine (Meruvax) 1969.

Materials and methods. Previous reports (1–18) gave detailed descriptions of the vaccines and the clinical trials in which they were investigated. The methods for surveillance were also presented (1, 3, 5, 7). The late bleedings required to carry out the present investigations were obtained with informed written consent and in compliance with the Investigative New Drug laws. The serum samples were tested using procedures described previously (1–18). In the tests, the last previous serum sample was reassayed in the same test with the new serum sample employing the same test procedure throughout. The close agreements in the values obtained provided assurance that differences in serum titer were not being introduced by the test itself. The parents, guardians, or older children were queried at the time of the late bleedings as to whether they had been revaccinated or had experienced the illness in the intervening period following vaccination. None of the children was revaccinated and none developed the corresponding illness since the time of inoculation.

Results. Measles virus vaccine. During May and June, 1967 (3), 256, 273, and 248 children who resided in suburban Philadelphia and who were seronegative for measles were given, respectively, Enders' original Edmonston measles vaccine or the Moraten or Schwarz lines of more attenuated measles virus vaccine. A portion of the children were followed at 1- to 2-year intervals to determine the titers of their measles hemagglutination-inhibiting (HI) antibodies. The parents and children reported no natural measles and no administration of additional measles virus vaccine. The serologic findings in the tests performed on serum samples taken 1 month and at 10 years after vaccination are given in Fig. 1. Decreases and increases in antibody were evident. Importantly, the antibody level of only one person fell to less than detectable level (Enders' Edmonston). Only the Enders' Edmonston group showed significant decline ($P < 0.01$) in mean antibody titer (63%) during the 10 years following vaccination at which time it was at a level similar to that of the Moraten and Schwarz line vaccine recipients. The least decline in mean antibody titer (24%) was seen with the Moraten line vaccine (Attenuvax), (cf. Schwarz, 31%).

Mumps virus vaccine. A controlled field study of mumps virus vaccine was initiated in the fall of 1965 in family and school populations in the Havertown–Springfield suburb of Philadelphia (4–6). Twenty-two children who were vaccinated in the study, as well as 24 unvaccinated control children in whom natural mumps developed shortly after the time that the vaccine was given, were bled periodically for up to 141 months after vac-

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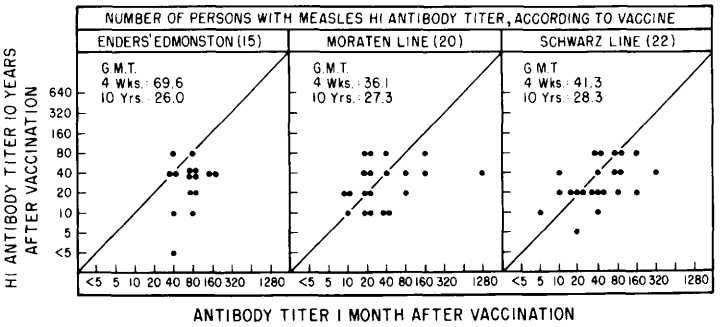

FIG. 1. Retention of measles HI antibody 10 years after vaccination with Enders' Edmonston, Moraten Line, or Schwarz Line measles vaccine (Study 97).

cination or onset of natural mumps and the serum samples were titrated for mumps neutralizing antibody. There was no readministration of mumps vaccine and no reported occurrence of natural mumps in the vaccinated persons. The antibody titers are given in Fig. 2. The initial level of neutralizing antibody reached after vaccination was usually considerably less than that following natural infection. However, a mumps neutralizing antibody titer of 1:1 or greater, in all but rare instances, conferred solid immunity against natural mumps (6). The levels of antibody among persons who had been vaccinated were just as great as among those whose antibody was the result of infection in nature. The mean titers following vaccination fell only 27% in nearly 12 years while those following the natural infection fell 80% during the approximately same time period to nearly the same level (mean 11.5) as following vaccination (mean 9.1). Subclinical natural reinfection might have occurred more frequently in the vaccinees than in those whose first experience with the virus had resulted from infection in nature.

Rubella virus vaccine. Children. The first large-scale clinical studies of HPV-77 duck cell modified rubella virus vaccine were initated in the Havertown–Springfield suburb of Philadelphia during September 1967 (7, 8). Fifty initially seronegative children who were vaccinated in 1967 were selected at random and bled 5.5, 7.5, and 9.5 years after vaccination. The serum samples were tested for rubella HI antibody and the results are shown in Fig. 3. The parents and children reported no natural disease and no administration of additional rubella vaccine. There was an expected initial decline in mean antibody titer at 2.5 years (mean 34.5) (18) with only slight reduction thereafter. One vaccinee was without detectable rubella antibody 9.5 years after vaccination. One of the two vaccinees who were without detectable rubella HI antibody (titer <1:8), after 7.5 years demonstrated an antibody titer of 1:8 9.5 years following vaccination. This difference might have been due to subclinical reinfection in nature during the intervening time period.

Adults. Sixteen initially seronegative adult women who were given HPV-77 rubella vaccine in 1968 (9) were bled again 5 and 9 years later and their sera were tested for rubella HI antibody. Fig. 4 shows that there were both decreases and increases in antibody. There was a greater than twofold increase in mean HI antibody titer at 5 years (94.5 versus 43.3) and this fell only slightly by the end of 9 years. None of the women became seronegative. Thus, the antibody level was retained. Some of the subjects presented serologic evidence for subclinical reinfection in nature.

Discussion. Measles, mumps, and rubella vaccines have been in widespread, routine use for several years, principally as single-dose combined vaccines. Protective efficacy has been very high and the continued presence of antibody has been remarkable, resembling that occurring after natural infections. It was of interest that, while highest homologous antibody levels were achieved following less attenuated measles vaccine (Enders' Edmonston) and following natural mumps compared with Moraten measles and mumps vaccine, respectively, this differential was lost with time. The mean titers 10 years after vaccination with measles vaccine were nearly

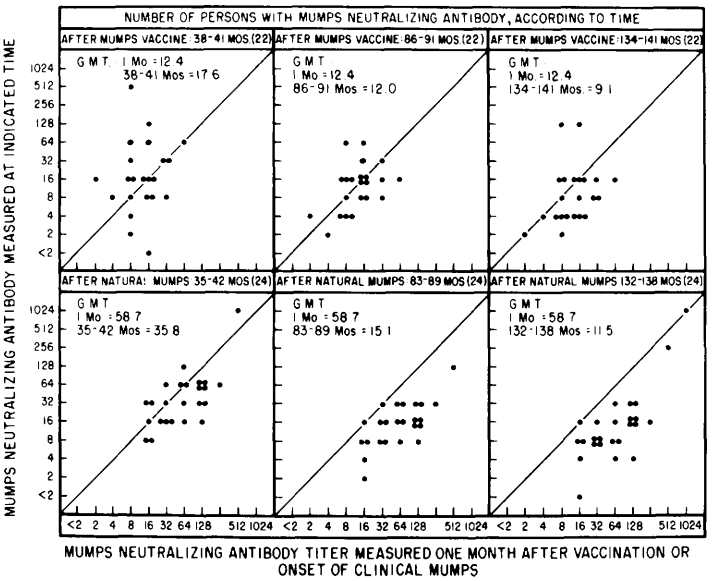

FIG. 2. Duration of neutralizing antibody following Jeryl Lynn strain live attenuated mumps virus vaccine compared with that following natural mumps (Study 71).

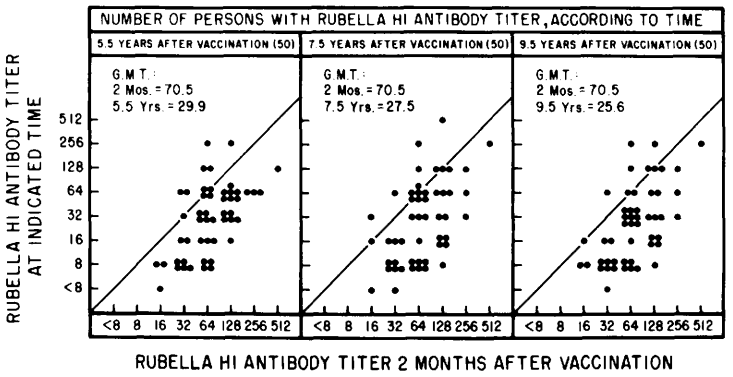

FIG. 3. Persistence of rubella HI antibody in children after administration of HPV-77 duck rubella vaccine (Study 153).

the same following all three measles vaccines (Enders' Edmonston, Moraten (Attenuvax), and Schwarz) and the mean titers nearly 12 years after natural mumps or Jeryl Lynn mumps virus vaccine were nearly the same. It may be that immunity following vaccination was more permissive of subclinical reinfection in nature than after natural disease with consequent boost in titer. Whatever the reason, it was of some importance that there was no apparent advantage, immunologically, of natural infection compared with vaccination.

The occurrence, in recent years, of clinical measles among persons who were vaccinated (19–26) has been explained on several bases: (a) use of killed virus vaccine that affords only short-term immunity, (b) the usual and expected failure of serologic response in 2 to 5% of persons who were given the vaccine under proper conditions, (c) the use of live measles vaccine of low or no potency owing to improper handling, storage temperature, overexposure to light, etc., (d) administration of the vaccine concomitantly with human immune globulin as originally carried out routinely with Enders' original vaccine or was improperly done with the more attenuated

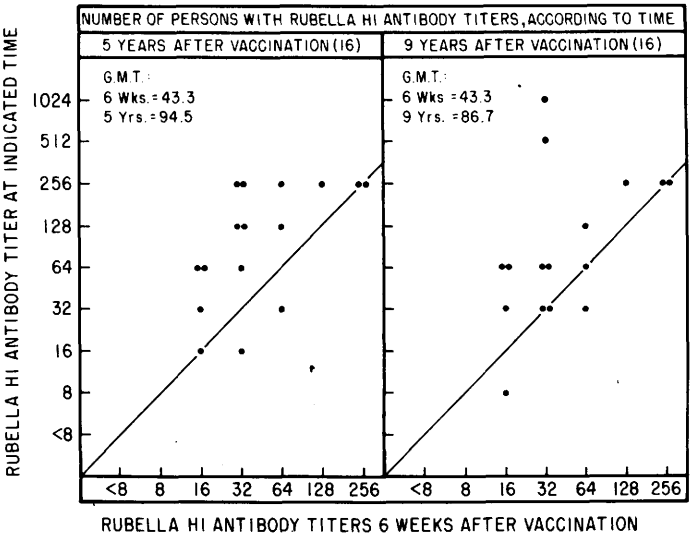

FIG. 4. Persistence of rubella HI antibody in adult women after administration of HPV-77 duck rubella vaccine (Study 169).

measles virus vaccines, and (e) neutralization of live virus in the vaccine by maternal measles antibody in infants less than 15 months of age. Validity for the conclusions relating to reduced takes when the vaccine is given after 12 months, but before 15 months, of age is currently disputed (27).

Whatever minor deficiencies may have been found, live attenuated measles, mumps, and rubella virus vaccines have performed exceptionally well (27–30) and continue to appear likely to provide lifelong protection against clinical disease. The findings in these studies of excellent persistence of antibodies against rubella virus following HPV-77 duck cell vaccine given in children and adult women 9.5 or 9 years earlier are in accord with the findings recorded earlier by Meyer *et al.* (31) and by Hermann *et al.* (32). They are at variance with the declines in antibody reported by Horstmann (33) and by Balfour *et al.* (34) in studies with the same vaccine.

Summary. Hemagglutination-inhibiting antibodies were present at comparable levels 10 years after vaccination with Enders' original Edmonston and more attenuated Moraten (Attenuvax) and Schwarz line measles vaccines. There was no substantial decline in neutralizing antibody titer for nearly 12 years after administration of Jeryl Lynn strain mumps virus vaccine (Mumpsvax). Hemagglutination-inhibiting antibodies were present without important decline in amount for at least 9.5 and 9 years, respectively, in children and adult women after administration of HPV-77 duck cell modified rubella vaccine (Meruvax). Higher homologous antibody titers were achieved initially following less attenuated Enders' Edmonston measles vaccine compared with more attenuated Moraten line vaccine and following natural mumps compared with mumps vaccine. Approximately 10 years later, however, the mean titers were roughly the same in each instance, indicating no apparent advantage of more virulent vaccine virus or natural infection in providing immunity. In our opinion, the relatively small number of purported measles virus vaccination failures reported in recent years were due mostly to mishandling or misadministration of the vaccine and not to deficiencies in measles vaccine itself.

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