PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE 164, 435–438 (1980)

Persistence of Pneumococcal Antibodies in Human Subjects following Vaccination (40891)

PHILIP P. VELLA,* ARLENE A. McLEAN,* ALLEN F. WOODHOUR,* ROBERT E. WEIBEL,† AND MAURICE R. HILLEMAN*

Division of Virus & Cell Biology Research, Merck Institute for Therapeutic Research, West Point, Pennsylvania 19486, and †Department of Pediatrics, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania 19104

Abstract. Adult persons who were given a pneumococcal polysaccharide vaccine containing 50 μg each of 12 serotypes showed an average 10-fold increase in amount of antibody to the 12 antigens (range 6- to 20-fold) 1 month after vaccination and there was an approximate average 50% decline in antibody 3½ years later. Children who were 2 to 12 years old at the time of vaccination showed about the same antibody response to the vaccine but this was less persistent and there was about a 55% decline, on the average, after only 21 months. The findings are discussed in the light of need for revaccination and of the nature of antibody responses to polysaccharide antigens.

Polyvalent pneumococcal capsular polysaccharide vaccine (1–5) was first licensed for general use in the USA in 1977 and has been used extensively in persons who are at high risk to illnesses caused by infections with pneumococci. About 4.2 million doses of vaccine were distributed in the USA by the end of 1979. The introduction of new vaccines leaves several questions that are the subject of continuing research and one of these relates to the persistence of antibody following vaccination. The present report gives the findings in clinical trials that measured the persistence of antibody in adults and children from 20 months to 3½ years after the vaccine was given.

Materials and methods. Clinical studies. Study 384. Nineteen adult persons who were employees of the Overbrook School for the Blind in Philadelphia, Pennsylvania, were given 0.5 ml of lot 561 12-valent pneumococcal polysaccharide vaccine on April 23, 1974 (5). The vaccine contained 50 μg of each pneumococcal polysaccharide shown in Fig. 1. The subjects ranged in age from 23 to 65 years (mean 46.9 years). Blood samples were taken prior to and 1, 20, and 42 months after the vaccine was given. The sera were assayed by the RIA procedure (6) for content of homologous pneumococcal antibodies.

Study 482. Twenty-eight children aged 2 to 12 years (mean 6.2 years) who resided in the Philadelphia area were immunized on August 9, 1975 with 0.5-ml amounts of the same vaccine described above (5). Blood samples for antibody assay were taken prior to vaccination and 1 and 21 months after vaccination. All studies were carried out with informed written consent and in compliance with the Investigational New Drug regulations.

Results. Study 384 in adults. Figure 1 shows homologous pneumococcal antibody titers in 19 adult persons given pneumococcal vaccine and bled prior to, 1, 20, and 42 months after vaccination. There was substantial increase in antibody 1 month after vaccination, ranging from 6- to 20-fold (average 10-fold). As seen in the figure, the arithmetic average of these increases had declined from 10- to 6-fold by 20 months and to 5-fold by 42 months. The rate for decline was far greater during the first 19 months than during the latter 22 months. From 58 to 100% of the subjects still had at least twice as much antibody against the 12 serotypes 42 months after vaccination as they did prior to vaccination, and 42 to 94% of persons had at least four times as much antibody.

Study 482 in children. The homologous pneumococcal antibody titers in 28 children given pneumococcal vaccine and bled prior to and 1 and 21 months after vaccination are

0037-9727/80/080435-04$01.00/0

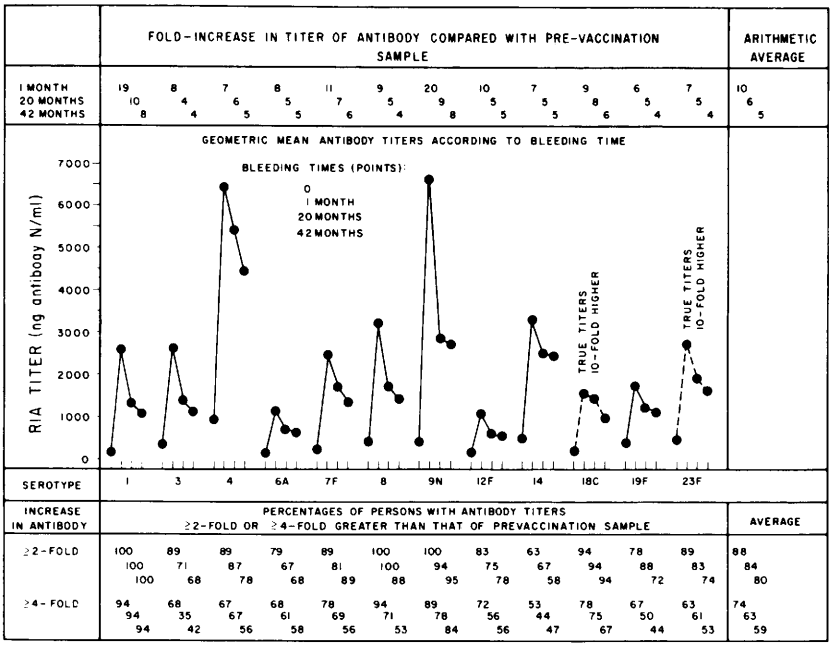

FIG. 1. Patterns of antibody persistence among 19 adult persons who received a single dose of 12-valent pneumococcal polysaccharide vaccine containing 50 μg of each polysaccharide type (study 384).

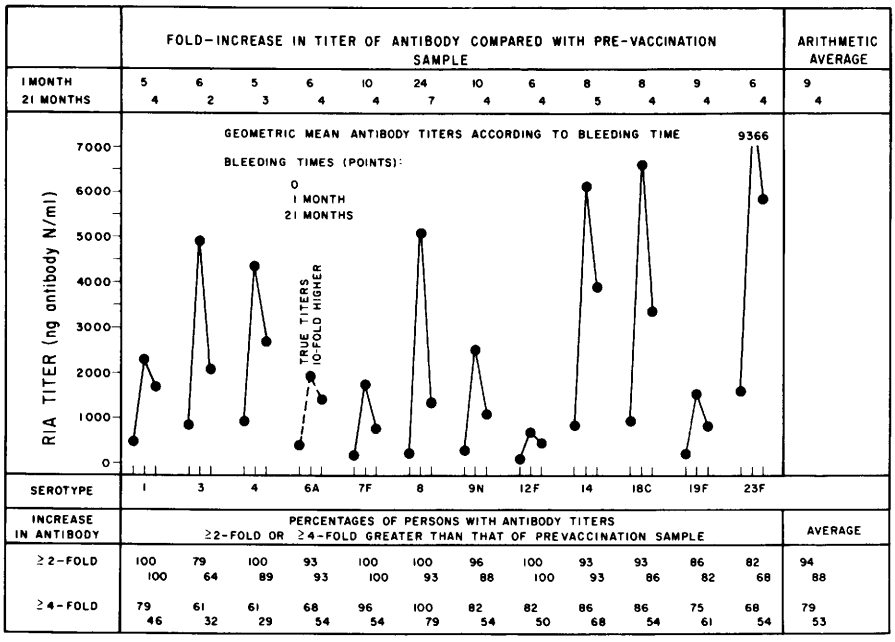

FIG. 2. Patterns of antibody persistence among 28 children 2 to 12 years of age who received a single dose of 12-valent pneumococcal polysaccharide vaccine containing 50 μg of each polysaccharide type (study 482).

presented in Fig. 2. As for adults, there was a substantial increase in antibody level against all serotypes in the vaccine ranging from 5- to 24-fold (average 9-fold). The decline in the arithmetic average of the fold increases 21 months after vaccination was greater in the children than in the adults, decreasing from 9- to 4-fold. The average of the percentages of children who showed a 2-fold or greater increase in titer, compared with their prevaccination titers, was reduced from 94 to 88% by 21 months and the 4-fold increases in titer were reduced from 79 to 53%.

No pneumococcal pneumonia was diagnosed among the adults or the children during the time periods of the observations in the studies described above.

Discussions. One of the unanswered questions relating to the use of pneumococcal vaccine is whether and when revaccination should be carried out. Studies reported by Heidelberger *et al.* (7) in 1950 employing a 6-valent vaccine revealed that 1/5 to more than ½ the maximum antibody titers induced by vaccination were still present in most persons 3 years after the vaccine was given. In some individuals, abundant residual antibody persisted 8 years after vaccination. Reinjection of vaccine in persons from whom antibody had disappeared or remained in only small quantity usually caused the antibody to reappear or to increase but most often not to the original maximal level. Previous studies in our laboratories (3, 8) revealed very small decline in antibody, if any, in adults 1 to 1½ years after vaccination compared with the titer achieved soon following vaccination and there was no meaningful increase in amount of antibody after the vaccine was given again. There was, however, substantially greater local reaction in adults at the injection site than after the first dose of vaccine. The reaction after initial injection was usually limited to mild soreness at the site that lasted up to 3 days. In contrast, nearly all persons given the second dose 1 year after the initial dose displayed induration with erythema in addition to soreness and this finding persisted for a slightly longer time period in some individuals. Mild fever was somewhat more frequent on revaccination (3). This clinical response appeared due to local reaction between the injected antigen and circulating antibody at the site in which the vaccine was given and resembled an Arthus-like reaction. Support for the Arthus concept was provided (3) by the observation that persons with a large total amount of antipneumococcal antibody showed a greater chance of having a more severe reaction than did those with a smaller amount of antibody. Reduction of dose of antigen on revaccination also brought about a decrease in local reaction on revaccination (8).

The findings in adults in the present studies showed retention of a substantial amount of antibody, about half on the average, for at least 3½ years after the vaccine was given. Eighty percent of individuals, on the average, still showed a 2-fold or greater amount of antibody in their circulation than they had prior to vaccination. It would appear, therefore, that these subjects would not be in need of revaccination after this period of time, though the level of antibody required for protection is not known.

The children in the present study, who were 2 to 12 years of age, showed a mean antibody response that was as great as that for adult persons. However, the antibody did not persist as well as in adults and studies are in progress to determine if and when children will need to be revaccinated. Such loss of antibody is associated with the observed phenomenon that children, especially those who are very young, respond poorly to many pneumococcal serotypes and to meningococcal and *Haemophilus influenzae* polysaccharide vaccines (3, 9–13) as well. The observed difference between adults and children might be due, in part at least, to the less extensive prior experience of children with natural infections with bacteria containing these same polysaccharides. In our studies (3), infants given vaccine at 3–5 months of age responded well to only a few of the pneumococcal serotypes in the vaccine and this antibody usually fell to low level 5 months later. Revaccination at that time usually did no more than to restore the titers to their previous postvaccination levels. Very substantial increase in antibody to all pneumococcal

serotypes was obtained when revaccination was made 21 months after the initial dose of vaccine. This may have been due, in part, to immunologic maturation, to increased experience in nature with bacteria containing polysaccharide antigens, and possibly also to prior sensitization to the polysaccharide vaccine. Beuvery *et al.* (14, 15) have postulated that the responses to polysaccharide antigens, in the absence of protein, are primarily the IgM type that are of short duration. Antibody of IgG class, that is persistent, is obtained only following vaccination with polysaccharides that are coupled or otherwise associated with proteins as in whole bacteria. Once such sensitization has been made, then booster responses to polysaccharide alone can be achieved. He postulated that the increased responsiveness to polysaccharides with protein was due to the stimulation of T-cell-helper responses that are not evoked when the experience is limited to polysaccharide alone.

The authors are indebted to the administrators of the Overbrook School for the Blind, to G. Starkweather, M. D., to K. Campbell, B. S., R. N., and C. Rothenberger, R.N., V. Holmes, B.S., V. Ioli, B.A., and J. Staub, B.S. gave valuable technical assistance. The data were tabulated and analyzed by T. Saboe, M.P.H.

1. Austrian, R., *in* "The Role of Immunological Factors in Infectious, Allergic, and Autoimmune Processes" (R. F. Beers, Jr. and E. G. Bassett, eds.), p. 79. Raven Press, New York (1976).
2. Austrian, R., Douglas, R. M., Schiffman, G., Coetzee, A. M., Koornhof, H. J., Hayden-Smith, S., and Reid, R. D. W., Trans. Assoc. Amer. Phys. **89**, 184 (1976).
3. Borgono, J. M., McLean, A. A., Vella, P. P., Woodhour, A. F., Canepa, I., Davidson, W. L., and Hilleman, M. R., Proc. Soc. Exp. Biol. Med. **157**, 148 (1978).
4. Smit, P., Oberholzer, D., Hayden-Smith, S., Koornhof, H. J., and Hilleman, M. R., J. Amer. Med. Assoc. **238**, 2613 (1977).
5. Weibel, R. E., Vella, P. P., McLean, A. A., Woodhour, A. F., Davidson, W. L., and Hilleman, M. R., Proc. Soc. Exp. Biol. Med. **156**, 144 (1977).
6. Schiffman, G., and Austrian, R., Fed. Proc., Fed. Amer. Soc. Exp. Biol. **30**, 658 (1971).
7. Heidelberger, M., Dilapi, M. M., Siegel, M., and Walter, A. W., J. Immunol. **65**, 535 (1950).
8. Carlson, A. J., Davidson, W. L., McLean, A. A., Vella, P. P., Weibel, R. E., Woodhour, A. F., and Hilleman, M. R., Proc. Soc. Exp. Biol. Med. **161**, 558 (1979).
9. Gold, R., Lepow, M. L., Goldschneider, I., and Gotschlich, E. C., J. Infec. Dis. **136**, S31 (1977).
10. Parke, J. C., Jr., Schneerson, R., Robbins, J. B., and Schlesselman, J. J., J. Infec. Dis. **136**, S51 (1977).
11. Mäkelä, P. H., Peltola, I., Käyhty, H., Jousimies, H., Pettay, O., Ruoslahti, E., Sivonen, A., and Renkonen, O. V., J. Infec. Dis. **136**, S43 (1977).
12. Gold, R., Lepow, M. L., Goldschneider, I., Draper, T. F., and Gotschlich, E. C., J. Infec. Dis. **138**, 731 (1978).
13. Gold, R., Lepow, M. L., Goldschneider, I., Draper, T. F., and Gotschlich, E. C., J. Infec. Dis. **140**, 690 (1979).
14. Beuvery, E. C., and van Delft, R. W., "WHO Third International Conference on Immunity and Immunization in Cerebrospinal Meningitis," Abstract 13. Marburg, Germany (1979).
15. Beuvery, E. C., and van Rossum, F., "WHO Third International Conference on Immunity and Immunization in Cerebrospinal Meningitis," Abstract 26. Marburg, Germany (1979).

Received March 17, 1980. P.S.E.B.M. 1980, Vol. 164.