

## One-Dose Immunization Against Paralytic Poliomyelitis Using a Noninfectious Vaccine

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Recent advances in production and standardization of noninfectious poliovirus vaccine now make it feasible to induce durable immunity against paralytic poliomyelitis with one dose of a suitably standardized vaccine. A single dose of a vaccine containing 40, 8, and 32 D-antigen units of type 1, 2, and 3, respectively, administered to six-month-old infants, was observed to induce antibody levels of  $\geq 1:4$  in  $>90\%$  and immunologic memory in all. Since protection against paralysis is associated with the presence of either type-specific serum antibody or type-specific immunologic memory, and since immunologic memory once induced is irreversible, then lifelong immunity to paralytic poliomyelitis can be induced with a single dose of a suitably standardized vaccine administered at five to seven months of age. In areas of the world where exposure to poliovirus can occur before this age, vaccine should be administered earlier. Until the influence of age and/or maternal antibody has been further studied, infants immunized before the age of six months should receive a second dose after six months of age.

An ideal vaccine is one that induces lifelong protection uniformly after a single administration. The theoretical possibility that such an immunizing agent could be developed for poliomyelitis was suggested by observations made in the early years of use of a noninfectious poliovirus vaccine [1, 2]. However, its practical realization had to await the advances that have recently been made in cell-culture technology, in methods for purification and concentration of virus, and in methods for vaccine standardization [3-5]. These developments now make realizable a one-dose procedure for immunization against paralytic poliomyelitis.

For the development of strategies for use of vaccines, it is necessary to establish criteria by which to determine that immunity to paralysis has been induced. For this there are two criteria for recognizing the existence of such a state: (1) the presence of specific virus-neutralizing antibody in the serum and (2) the presence of immunologic memory recognizable by a type-specific hyperactive antibody response to antigenic challenge either by an injection of a noninfectious vaccine or by natural infection.

### Immunologic Memory

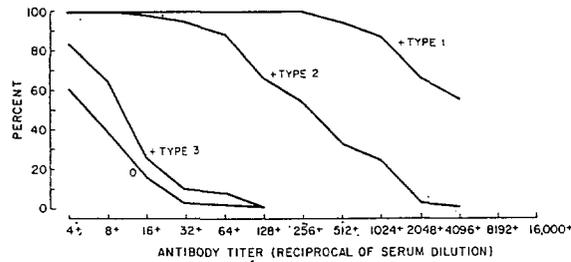
The presence of either serum antibody alone or of immunologic memory alone is associated with immunity to paralysis (table 1). Antibody alone, without immunologic memory, is seen in infants with passively acquired maternal antibody or in those to whom  $\gamma$ -globulin is administered. Immunologic memory alone, in the absence of detectable serum antibody, is seen in individuals who exhibit a secondary-type antibody response to antigenic stimulation following vaccination or infection. The latter is seen in individuals with only type 2 antibody, as a result of natural type 2 poliovirus infection, who exhibit a secondary-type antibody response to type 1 as well as to type 2 antigenic stimulation. Such individuals are immune to paralysis due to type 1 as well as to type 2 virus [6, 7]. Since type 1 virus is not neutralized by type 2 antibody, the immunity to type 1 paralysis cannot be explained by the presence of type 2 antibody but could be explained by the presence of type 1 immunologic memory. The type 1 immunologic memory induced by type 2 natural infection is due to the presence of type 1 antigens in naturally occurring type 2 virus that are not present in type 3 virus [8, 9]. In figure 1, the degree of type 1 immunologic memory induced by type 2 natural infection is compared with the degree of immunologic memory induced by a natural type 1 infection. This is revealed by the comparative type 1

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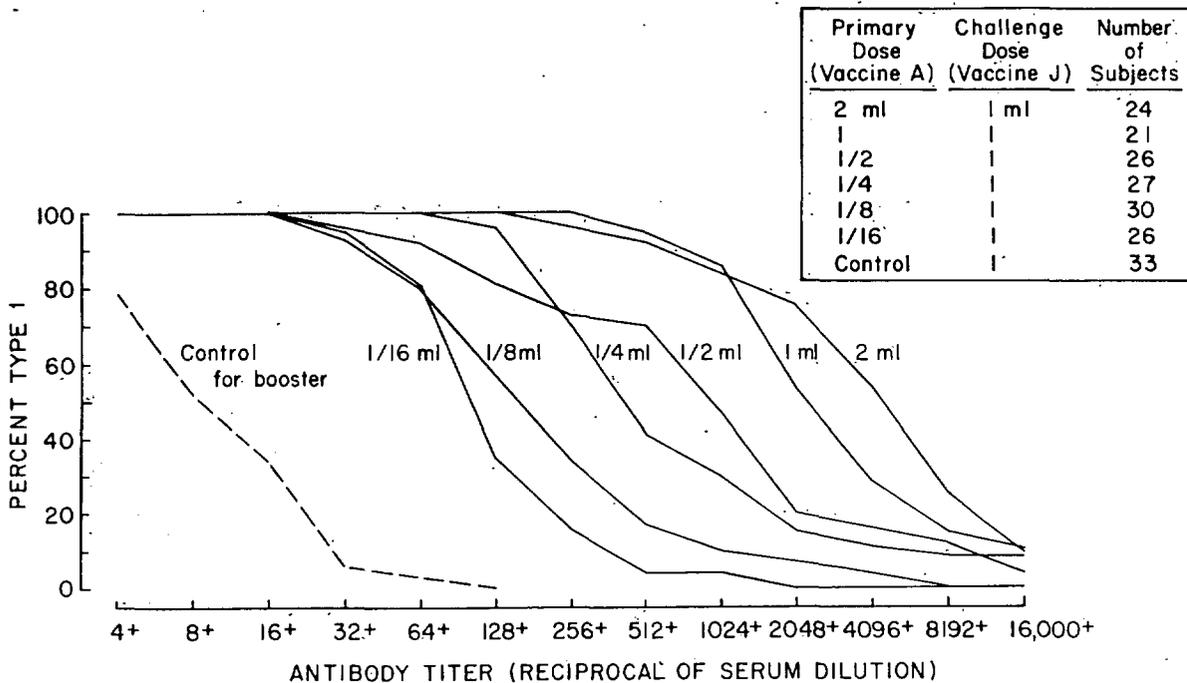
**Table 1.** Relationship between presence of protection against paralysis and presence or absence of serum antibody and immunologic memory.

Naturally acquired immunity	Presence of serum antibody	Presence of immunologic memory	Protection against paralysis
Infection-induced	Yes	Yes	Yes
Infection-induced	No	Yes	Yes
Maternal	Yes	No	Yes
None	No	No	No

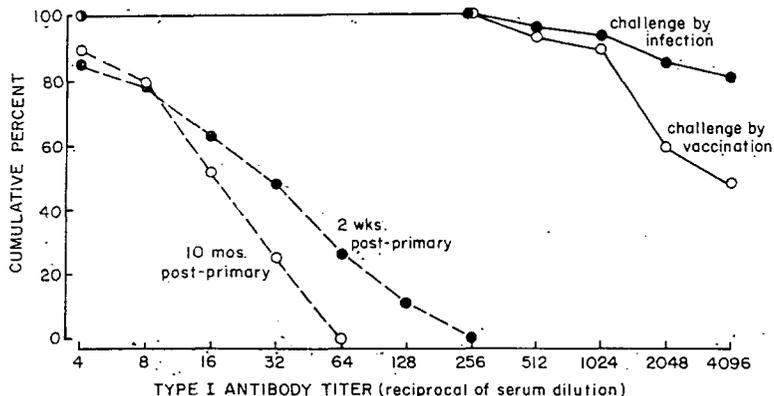
antibody response to type 1 antigen in groups of individuals who have prevaccination antibody either to type 1, type 2, or type 3 or who have no antibody to any of the three types. The comparison of responses shown in figure 1 reveals the similarity between the two groups who have either no antibody to any of the three types or have antibody only to type 3 and between the two groups who have either type 1 or type 2 antibody before vaccination.



**Figure 1.** The degree of antibody response following a single dose of vaccine is shown for groups of children with different prevaccination antibody patterns: 0 = no detectable antibody before vaccination; + = positive for antibody at a titer of  $\geq 1:4$ . Number of subjects per group: + type 1 = 62; + type 2 = 41; + type 3 = 44; and 0 = 88. The percentage of individuals with antibody titers at or above the indicated levels is plotted against antibody titer. This illustrates the presence of type 1 immunologic memory in individuals who have type 1 or type 2 antibody only in their serum as a result of prior type 1 or type 2 natural infection and reveals the absence of type 1 immunologic memory in those who have type 3 antibody only in their serum as the result of prior type 3 infection or have no antibody to any of the three types [7].



**Figure 2.** Degree of immunologic memory induced by vaccination. Data are expressed in terms of percentage of individuals with titers of type 1 antibody at or above the indicated levels two weeks after a uniform challenge dose of vaccine J given one year after a two-dose primary series (two-week interval) in groups given different quantities of reference vaccine A for primary immunization. (Reprinted with permission from S. Karger, Basel [1].)



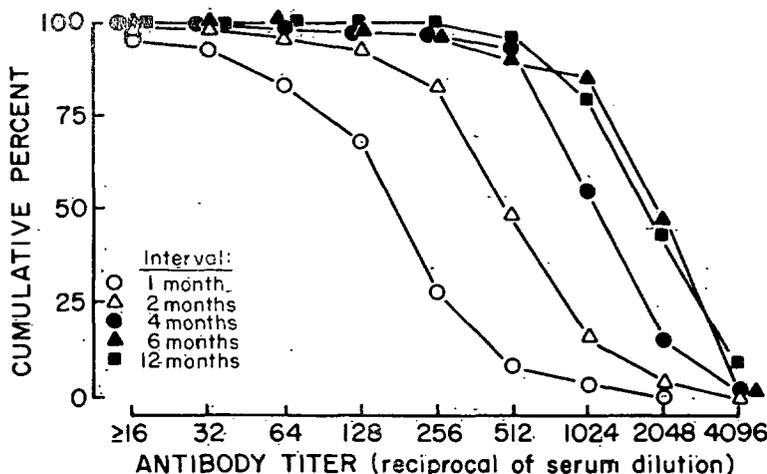
**Figure 3:** Comparison of titers of type 1 antibody at or above the indicated levels in response to challenge by vaccination or by infection in children who had previously received primary immunization with two doses of vaccine two weeks apart; prechallenge (---) and postchallenge (—) distribution of antibody in subjects challenged by infection (●; *n* = 27) and in subjects challenged by vaccination (○; *n* = 61). These titers reveal the hyperactive response to infection as well as to vaccination in individuals in whom immunologic memory is induced by vaccination [12].

The degree of immunologic memory induced by a noninfectious poliovirus vaccine depends on the mass of antigen used for primary immunization (figure 2) [2, 11]. A comparison of figures 1 and 2 reveals that, depending on antigen content, primary immunization with a noninfectious vaccine (figure 2) induces immunologic memory of a degree comparable to that induced by natural infection (figure 1); the larger doses of antigen induce a degree of immunologic memory equivalent to that of a homotypic (type 1) infection, and smaller doses induce a degree of memory corresponding to that of a heterotypic (type 2) infection. Since immunologic memory induced by poliovirus antigen is irreversible, then immunity to paralysis induced with a noninfectious vaccine as well as by infection could be expected to be durable for life [1].

Figure 3 shows that, in individuals who had

previously received primary immunization only, type 1 antibody response to challenge either by natural infection or by vaccination was similar [12]. This finding suggests that the presence of immunologic memory—revealed by the character of the response to a challenge dose of vaccine—may be interpreted as indicating the presence of immunity to paralysis, even in the absence of serum antibody.

The time required for the development of a maximum response to a challenge dose following primary immunization was observed in a group of infants who had received a single dose of triple vaccine for primary immunization at six months of age. This group was divided into smaller groups, which were then challenged 1, 2, 4, 6, or 12 months later (K. Lapinleimu, unpublished observations). The type 1 antibody responses, shown in figure 4, reveal the progressive increase in the level of the



**Figure 4.** Results of study of killed poliovirus vaccine in Finland. Titers of type 1 antibody at or above the indicated levels after the second dose of vaccine showing the effect of varying the interval between the first and second dose. The vaccine used was prepared at the Rijks Instituut voor de Volksgezondheid and contained 80 D-antigen units of type 1 virus per dose. (Reprinted with permission from *Behring Institute Mitteilungen* [13].)

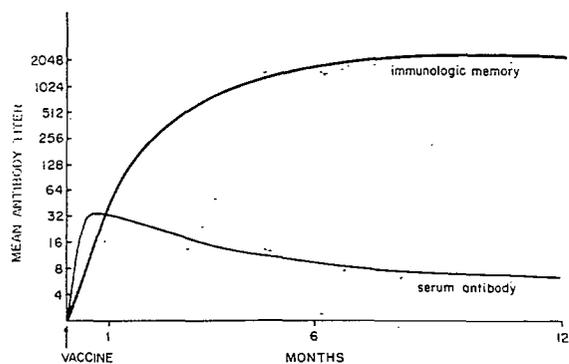


Figure 5. Development and persistence of serum antibody and immunologic memory following one dose of noninfectious poliovirus vaccine.

secondary-type response up to six months after primary vaccination with no further change in the ensuing six months. As shown schematically in figure 5, this increase contrasts with the course of serum antibody development, which reaches a maximum in two to three weeks. Thus, the course of development of immunologic memory and of serum antibody are not the same. Seen from an evolutionary point of view, it is as if serum antibody serves a short-term need and memory serves a long-term need.

**Minimum Number of Doses of Vaccine Required to Induce Immunity to Paralysis**

The minimum number of doses of vaccine required to induce immunity to paralysis was revealed in an analysis of the incidence of paralytic poliomyelitis in vaccinated and unvaccinated individuals in the epidemic that occurred in the United States in 1959 [1]. An inverse linear rela-

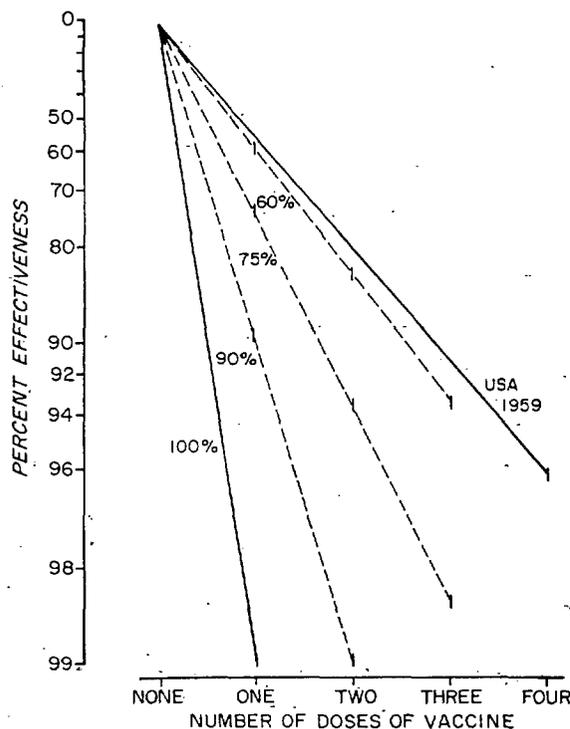
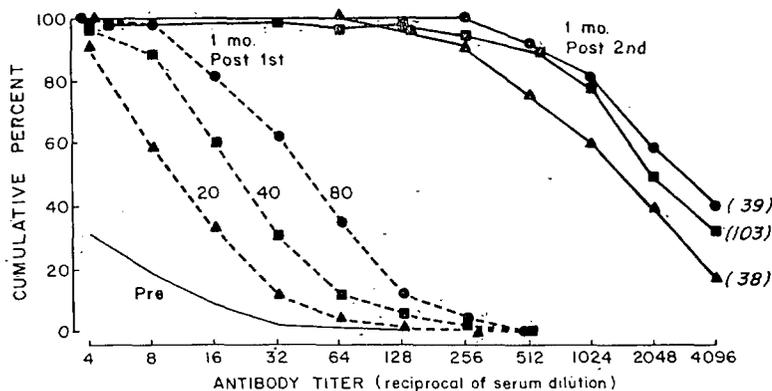
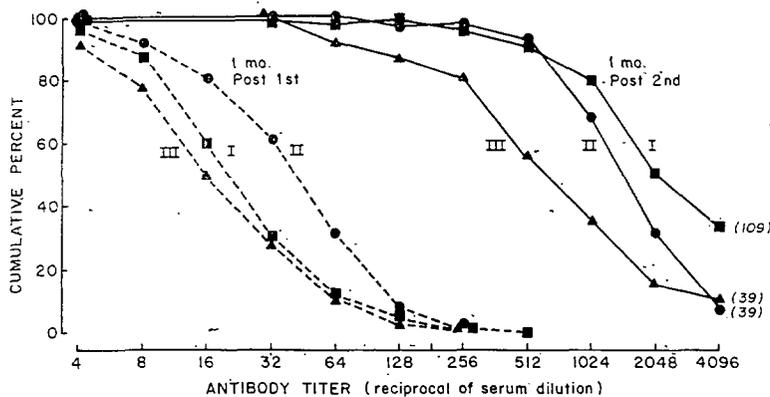


Figure 6. Percent effectiveness in the prevention of paralysis that was observed in the poliomyelitis epidemic of 1959 in the United States among those who had received one or more doses of vaccine. The dashed lines indicate the theoretical effect of vaccines of greater one-dose effectiveness in comparison to a vaccine that would be fully effective with a single dose. (Adapted from [1].)

tionship was observed between the paralytic rate and the number of doses of the vaccine of relatively low potency that was available between 1955 and 1959. The data suggest that immunity to paralysis could be conferred by a single dose of suitably potent vaccine (figure 6).

Figure 7. Titers of poliovirus antibody at or above the levels indicated one month after a first dose and one month after a second dose (administered six months after the first dose) of vaccines containing 20, 40, or 80 D-antigen units for type 1. (Reprinted with permission from *Annals of Clinical Research* [15].)





**Figure 8.** Titers of types-1, 2, and 3 antibody at or above the levels indicated after a first and challenge dose (administered six-months apart) of 40, 8, and 32 D-antigen units per dose for the three respective types. Numbers in parentheses indicate number of subjects per group. (Reprinted with permission from *Behring Institute Mitteilungen* [13].)

**Antigen Content for a One-Dose Vaccine**

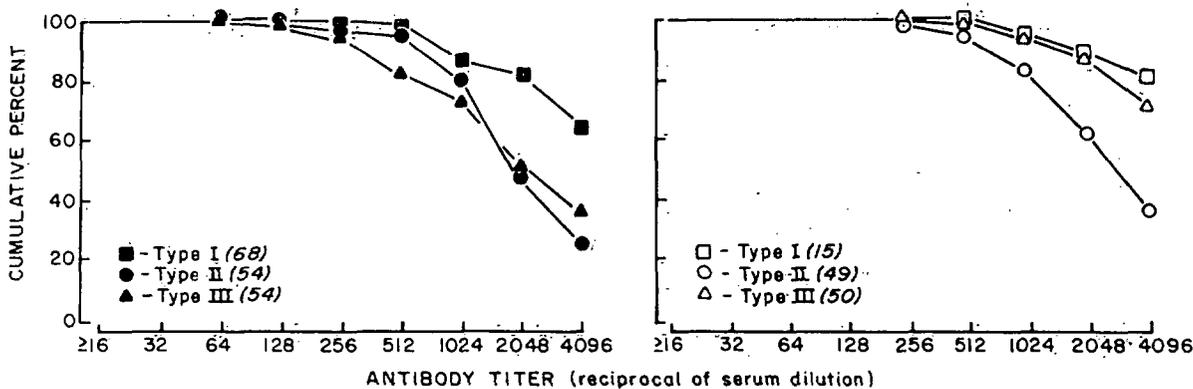
In view of the foregoing, a series of studies was undertaken beginning in 1977 to establish the antigen content of a noninfectious poliovirus vaccine that would induce immunologic memory uniformly with a single dose [10, 14, 15]. The trivalent vaccines employed were prepared by van Wézél et al. [4], at the Rijks Instituut voor de Volksgezondheid (RIV), The Netherlands, from monovalent vaccine pools that have been stored for use as future reference vaccines and standardized in human subjects:

Figure 7 shows the dosage-response relationships for the type 1 component of the trivalent vaccines containing 20, 40, and 80 type 1 D-antigen units per dose in terms of serum antibody measurements after primary and challenge doses administered six months apart; the primary dose

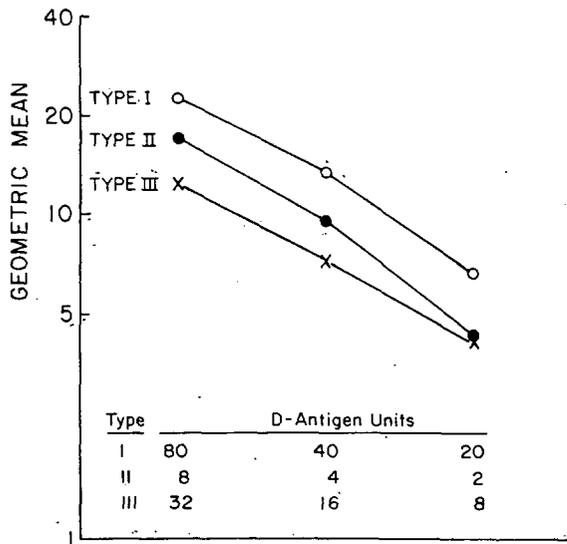
was administered at six months of age [15]. Figure 8 shows the types 1, 2, and 3 antibody responses to primary and challenge doses of 40, 8, 32 D-antigen units per dose for the respective types [15]. Figure 9 shows the post-challenge antibody response six months after primary immunization with a 40, 8, 32 D-antigen unit vaccine administered once or twice (one month apart); the first dose was administered at seven to nine months of age (M. Böttiger, unpublished data). The levels of antibody induced after a challenge dose in these studies (figures 8 and 9) reveal the regularity with which one dose of sufficiently potent vaccine induces immunologic memory in infants of six months and seven to nine months of age, respectively.

**A Reference Standard Vaccine**

The relationship between the D-antigen unit con-

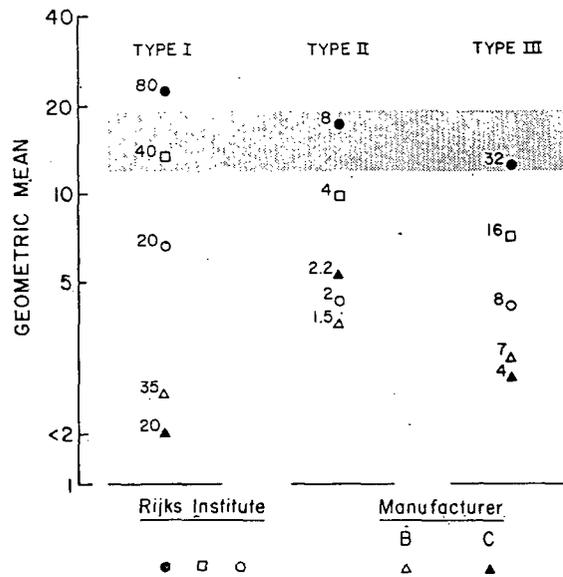


**Figure 9.** Titers of types 1, 2, and 3 antibody at or above the levels indicated after a challenge dose administered six months after a first dose in two groups given either one or two doses (one month apart) for primary immunization. Numbers in parentheses indicate number of subjects per group.



**Figure 10:** Geometric mean titers of types 1, 2, and 3 antibody induced by a single dose of each of three vaccines prepared by the Rijks Instituut voor de Volksgezondheid containing the indicated number of D-antigen units per dose. (Reprinted with permission from S. Karger, Basel [10].)

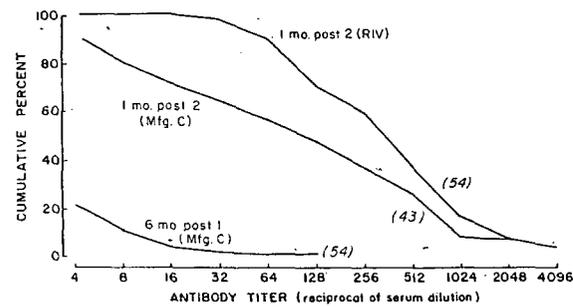
tent [5] and the geometric mean antibody titer induced by a single dose of the vaccines used in these studies is shown in figure 10 [10]. This figure shows the characteristics of the dose-response relationship for the three different types relative to the D-antigen content of the vaccine made according to the methods used at RIV. Figure 11 reveals that the 40, 8, 32 D-antigen formulation induced similar geometric mean antibody responses to the three types following a single dose. The antibody response induced by the type 1 component of the vaccines prepared by manufacturers B and C was less than expected from the D-antigen unit content as compared with the response to vaccine prepared by RIV. However, the antibody response induced by the types 2 and 3 components corresponded to the D-antigen unit content of the RIV vaccine. (The likely explanation for this is in the nature of the virus particles contained in the vaccine [16], which may induce memory following a first dose and higher levels after a second [figure 12]. [15].) These differences are also detectable in an in vivo assay for immunogenic potency in rats. The D-antigen unit serves as a guide in manufacturing and also for standardizing the trivalent vaccine prior to assay in animals.



**Figure 11:** Geometric mean antibody titers induced by a single dose of vaccines of different D-antigen unit content prepared by the Rijks Instituut voor de Volksgezondheid and by manufacturers B and C. (Reprinted with permission from S. Karger, Basel [10].)

**Strategy for Use of a Noninfectious Poliovirus Vaccine**

A single dose of poliovirus vaccine prepared according to the methods of RIV and appropriately standardized can be expected to induce durable (lifelong) immunity when administered at six to seven months of age. In areas of the world where exposure to poliovirus can occur before this age,



**Figure 12:** Titers of type 1 antibody at or above the levels indicated six months after a first dose of vaccine of manufacturer C and one month after a second dose of the same vaccine or a second dose of vaccine prepared by Rijks Instituut voor de Volksgezondheid (40 D-antigen units type 1) [15]. Numbers in parentheses indicate number of subjects per group.

vaccine should be administered earlier. Until the influence of maternal antibody has been further studied, a second dose should be given after six months of age.

This strategy corresponds to that recommended for measles vaccination. Where increased risk of exposure to measles exists, vaccine is administered as early as necessary, even at an age when maternal antibody may be present; it is then followed by a second dose after 15 months of age, when any effect of maternal antibody is no longer evident.

In demonstration zones in Senegal and Upper Volta, diphtheria-tetanus-pertussis (DTP)-poliomyelitis vaccine is first administered to infants three to six months of age and is followed by a second dose four to six months later [17].

Where noninfectious poliovirus vaccine has been widely used, a herd effect has been observed [18, 19], and viruses have been eliminated from the population [2].

Noninfectious poliovirus vaccine is now being made on a large scale from virus cultivated in continuously propagating cells [20], with an increase in economy in vaccine production. This, together with the economy resulting from a reduction in the number of doses required and the combination with DTP, makes this strategy applicable to regions of the world where costs are a limiting factor in the adoption of vaccination programs.

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