Control of Influenza and Poliomyelitis with Killed Virus Vaccines

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Experiences over the last 40 years have increased our understanding of the immune response and of the requirements for inducing effective immunity against infectious diseases. We now know that the requirements include (i) stimulation with a sufficient quantity of antigen, (ii) use of a suitably specific antigen, and (iii) the induction of an appropriate immune response for the prevention of the pathological consequences of infection.

The first effective viral vaccines (for smallpox, rabies, and yellow fever) were made of attenuated, infectious viruses. Because adequate techniques for growing and purifying viruses were not available prior to the 1940's, it was necessary that the virus reproduce within the host in order to supply a sufficient quantity of suitably specific antigen to stimulate the immune mechanism. The effectiveness of toxoids (bacterial toxins treated with formaldehyde) for immunization against diphtheria and tetanus suggested that it might also be possible to inactivate viruses to produce vaccines against viral diseases. Technical advances allowed for the large-scale production of virus that could be concentrated, purified, and rendered noninfectious without destroying immunogenicity. More recent advances permit the splitting of viruses chemically and the selection of specific antigenic subunits for use in vaccine preparation (*1*).

Application of the principles of effective immunization against a particular disease requires an understanding of its etiologic agents and pathogenic mechanisms. In the case of diphtheria and tetanus, for example, an appropriate immune response is one that neutralizes the toxin produced in the course of infection. The prevention of infection is not essential for the prevention of pathology. A similar understanding is required for other diseases (*2*).

Evidence now suggests that "natural" infection with an attenuated (live) virus is not necessarily inherently superior to "artificial" immunization with an inactivated (killed) virus. Different problems are encountered with different methods. Live virus vaccines against influenza and paralytic poliomyelitis, for example, may in each instance produce the disease it is intended to prevent; the live virus vaccines against measles and mumps may produce such side effects as encephalitis. Both of these problems are due to the inherent difficulty of controlling live viruses in vivo. Killed virus vaccines against measles and the respiratory syncitial virus have caused undesirable hypersensitivity reactions in individuals subsequently exposed to natural infection. These reactions appear to be due to induction of an allergy to some antigenic component of the virus, an antigen which may not be essential for inducing immunity to disease (*3*, p. 139).

The study and application of the basic requirements for effective immunization, which might be called "vaccinology," requires an understanding of the etiologic agents, the pathogenic mechanisms, and the epidemiology of the individual diseases. In this article, we discuss poliomyelitis and influenza from this viewpoint, and demonstrate that they can be effectively controlled with killed virus vaccines. Many misconceptions about the relative effectiveness of killed and live viruses as immunizing agents still exist, particularly with regard to paralytic poliomyelitis. The present vaccines against influenza could be improved by using immunological adjuvants; and with adequate immunization of the population, influenza may be brought under control as effectively as smallpox and paralytic poliomyelitis.

Etiologic Agents

Poliomyelitis. There are three antigenic types of poliovirus (types I, II, and III), any one of which can cause paralytic disease. In contrast to the antigenic variability and instability of influenza viruses, variation among strains within each of the three types of poliovirus is of no practical importance.

Influenza. There are three types of influenza viruses (types A, B, and C). Influenza types A and B can cause epidemic disease of variable morbidity and mortality, and they have the capacity to change antigenic specificity (*4*). Influenza type C usually causes inapparent infections (*5*).

Two distinct kinds of antigenic variation have been demonstrated for influenza A: antigenic *shift* and antigenic *drift* (*4*). The first consists of major antigenic changes that occur periodically. Five subtypes of influenza A have been recognized and are classified according to the specificity of the hemagglutinin (H) and neuraminidase (N) antigens: $H_{sw}N1$ (1918), H0N1 (1928), H1N1 (1946), H2N2 (1957), and H3N2 (1968) (*6*). Antigenic drift consists of relatively minor changes that occur gradually within a subtype. Influenza B also shows antigenic drift, but has not exhibited antigenic shift (*6*).

The appearance and disappearance of different antigenic subtypes of influenza A (antigenic shift) may be related, in part, to the level of immunity of the population (*5*, *7*). As a greater proportion of the population is exposed to the epidemic strain and develops immunity, the segment of the population in which the virus can become established becomes smaller. As the immunity index of the population increases, this specific antigenic form of the virus is suppressed and apparently disappears until a new generation of susceptibles develops. At such time, this antigenic subtype can again become manifest epidemically (*6*).

Pathogenesis

Poliomyelitis. The incubation period for paralytic poliomyelitis is relatively long—approximately 10 to 14 days. After entering via the oropharynx, the virus establishes an essentially harmless primary infection in the digestive tract. It is then carried via the bloodstream to the spinal cord and medulla, where it establishes a potentially paralyzing secondary infection (*8*).

Influenza. The incubation period for influenza is short. In the experimentally induced disease in man it is as short as 12 hours, rarely longer than 24 to 48 hours. Under natural circumstances it may be

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slightly longer, presumably due to smaller infectious doses of virus. In poliovirus disease, the sites of initial infection and significant pathology are not the same, but in influenza the sites of infection and pathology are both at the portal of entry, the respiratory tract mucosa. Spread of virus to the lung parenchyma, associated with more severe clinical disease, takes place on the epithelial surface and not via the bloodstream (*2, 9*).

Epidemiology—Herd Effect

Transmission of poliovirus between humans can be via the fecal-oral route, but in countries where good sanitation is practiced, oral-oral spread of virus is more common (*10–12*). Transmission of influenza virus between humans is by droplet inhalation (*2*).

The most efficient control of a viral disease is achieved by decreasing the number of transmitters and reducing the spread of virus within the community. This diminishes the risk of infection for susceptible individuals, who are therefore less likely to become transmitters as well. If immunization interrupts viral dissemination, then the community as a whole will be protected. This is known as the herd effect. If there is no reservoir for the virus other than man, human immunization can result in eradication of the virus (*13*).

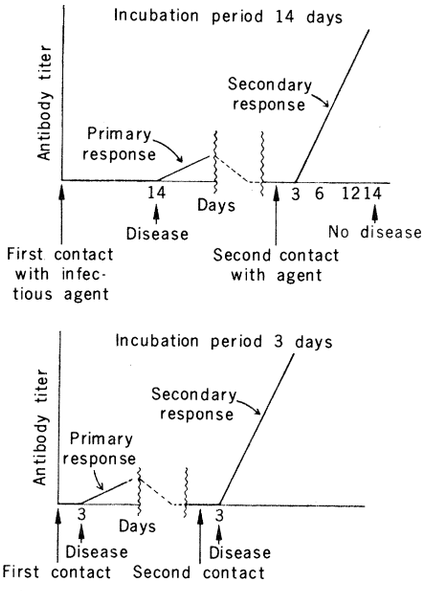


Fig. 1. The effect of the length of incubation period on the development of permanent immunity. Polio is an example of a disease with a long incubation period (upper graph), and influenza is an example of a disease with a short incubation period (lower graph). [From C. M. MacLeod (*29*); courtesy of Williams & Wilkins Co., Baltimore]

A herd effect is demonstrable with the use of both killed polio and influenza virus vaccines (*2; 3*, p. 136; *10–17; 18*, pp. 77–78). This is discussed below. Poliovirus can be eliminated from a population because humans appear to be the only natural host. The existence of animal reservoirs for type A influenza virus (*6, 19*) must be considered in developing effective control of human influenza.

Requirements for Effective Immunity

As previously discussed, an effective immune response must be both specific and appropriate. Having considered the etiologic agents and pathogenic mechanisms of poliomyelitis and influenza, it becomes apparent that there are somewhat different requirements for developing effective immunity to these diseases.

To provide immunity which will be specific for the infecting virus, it is necessary to include all antigenic types in a vaccine. This is not difficult for poliomyelitis because of the known number and antigenic stability of polioviruses. It is more difficult for influenza because the virus is antigenically variable, and the total number of subtypes is yet to be determined.

To provide appropriate immunity in the individual against paralytic poliomyelitis, it is necessary to block virus transmission to the central nervous system (CNS). The actual prevention of intestinal infection by inducing local production of immunoglobulin A (IgA) is not essential for protection against the significant pathologic features of this disease since "in the case of polioviruses the endpoint of virulence is obtained in the nervous system" (*20*). Viral invasion of the CNS, and resulting paralysis, is blocked by antibody in the bloodstream (*21*).

To provide appropriate immunity against influenza, it is necessary to block viral infection of the respiratory epithelium (*2*). The postulated importance of local secretory antibody (IgA) has not been demonstrated (*22*), and the question may well be academic in view of the known correlation between serum hemagglutination-inhibiting (H-I) antibody levels and effective immunity (*23–25; 26*, pp. 373–379). This correlation exists whether the circulating antibody is induced by natural infection or by artificial immunization (*23; 26*, p. 384–386; *27*) as will be discussed below. Antibody to neuraminidase reduces the severity of disease, but does not protect against infection (*17; 26*, p. 379–384; *28*).

Duration of immunity. MacLeod has discussed the relation of incubation period to duration of immunity, and has proposed a mechanism to account for the permanent immunity observed in diseases with a long incubation period (Fig. 1) (*29*). He postulates that the first contact with an infectious agent induces permanent immunologic sensitization, which results in an accelerated and heightened secondary-type antibody response when reexposure to the agent occurs.

For an infectious disease with a relatively long incubation period, such as poliomyelitis, this secondary response occurs rapidly enough to produce an antibody blockade against viremia and CNS invasion (Fig. 2). Persistent immunologic memory may be present without demonstrable levels of serum antibody (*30–33*). This would account for the lifelong immunity observed after naturally occurring poliovirus infection (*34*).

For influenza, however, MacLeod's proposed mechanism would be inoperative since the incubation period is shorter than the minimum time required for the secondary-type antibody response.

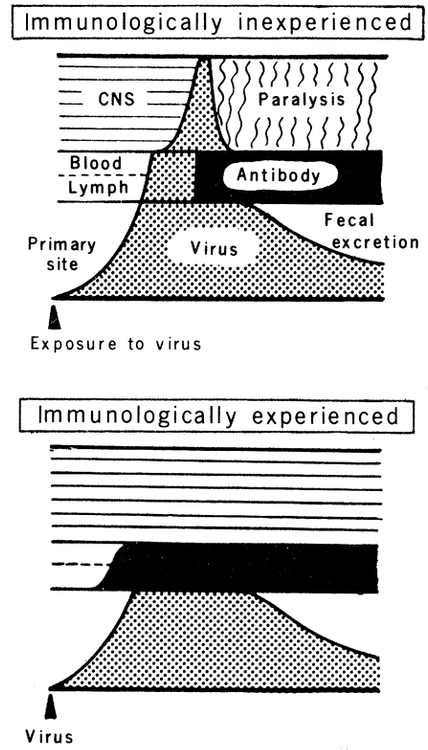


Fig. 2. Schematic representation of the influence of previous immunologic experience (infection or vaccination) on the prevention of paralysis from polio. In the immunologically experienced individual, the antibody response occurs sufficiently rapidly to block central nervous system invasion even without detectable antibody at the time of exposure. [From J. E. Salk (*31*); courtesy of the *American Journal of Public Health Association*]

Table 1. Cumulative number (in millions) of doses of poliovirus vaccine distributed in the United States, 1955 to 1971 (*116*).

Year	10^6 Poliovirus vaccine doses	
	Killed	Live*
1955–61	400	0
1962	415.3	33.1
1963	434.3	76.0
1964	443.3	124.9
1965	450.6	147.0
1966	456.1	172.4
1967	460.1	191.7
1968	462.8	216.1
1969	462.8	239.1
1970	462.8	265.2
1971	462.8	290.9

*Type I monovalent and trivalent.

Accordingly, immunity to influenza depends on the actual presence of antibody at a level sufficiently high at the time of exposure to prevent virus infection of the respiratory epithelium (*35*). Because antigenically different virus strains produce similar clinical disease, immunity to influenza appears to be of short duration. However the level of antibody against any specific strain of influenza virus is maintained longer than is generally appreciated. For example, antibody against the A/New Jersey/76 (swine-type) virus is generally not found in individuals under the age of 50 (*36*), and this implies that the antibody observed in older individuals resulted from initial exposure to a similar virus 50 or more years ago.

Effective immunization. The problems presented for effectively immunizing against influenza and poliomyelitis are different. In order to immunize against influenza, it is necessary to develop means for inducing immunity against multiple, variable subtypes and strains of influenza virus. In order to provide long-term immunity, it is necessary to develop means for inducing and maintaining adequate levels of circulating antibody. In the case of poliomyelitis, it is necessary only to induce persistent immunologic memory against three stable types of poliovirus.

Effectiveness of Killed Poliovirus Vaccine

Field experience. A sharp decline in the incidence of poliomyelitis in the United States followed the introduction of a killed virus vaccine (inactivated vaccine) in 1955 (Fig. 3). By the time a live virus vaccine (oral vaccine) was introduced in 1961–62, poliomyelitis was already being brought under control, particularly in the well-vaccinated, upper socioeconomic groups (*11*). The occurrence of a herd effect extended the protective effect of vaccination to nonvaccinated individuals (*3*, p. 136; *12–14*). After 1961–62, when the live poliovirus vaccine was introduced into the United States, it was not possible to evaluate the potential of a killed poliovirus vaccine for eradicating wild viruses from the population. However, experience in countries such as Sweden and Finland, where only a killed poliovirus vaccine has been used, has shown that it is possible to do so (*37–39*).

The decline of polio incidence in the United States after 1961 cannot be attributed solely to the introduction of the oral live poliovirus vaccine. The proportion of individuals under the influence of the killed virus vaccine was substantially greater than that under the influence of the live virus vaccine (Table 1). Moreover, the live virus vaccine was initially used largely by the segment of the population previously immunized with the killed virus vaccine, and the effect of the live virus vaccine was merely additive.

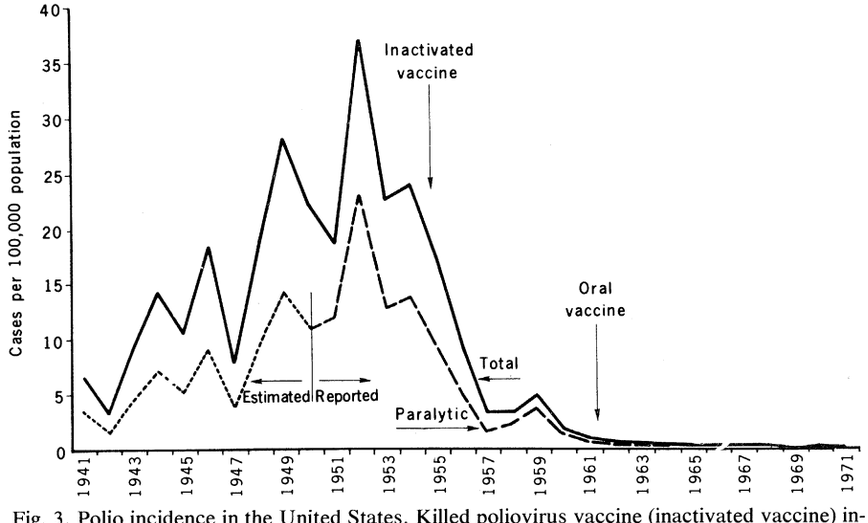


Fig. 3. Polio incidence in the United States. Killed poliovirus vaccine (inactivated vaccine) introduced in 1955, and live poliovirus vaccine (oral vaccine) introduced in 1961–62. Broken line, paralytic polio only. Solid line, both paralytic and nonparalytic polio. [Courtesy of the Center for Disease Control, Atlanta (*116*)]

Table 2. Search for poliovirus in Finland, April 1972 to December 1974 (*41*).

Source	Number	Poliovirus	Other viruses (%)
Patients	308	0	52
Aseptic meningitis and meningoencephalitis			
Healthy children	4878*	0	8 to 18
Preschool—40 fecal samples per week			
Helsinki sewage	132	0	65
One sample per week			

*Total number of samples from 4878 different children.

The pattern of polio decline in Finland is seen in Fig. 4, and similar data are available for Sweden (*40*). In these countries, where only the killed poliovirus vaccine has been used, the last domestic cases occurred in 1963 and 1964, respectively, and they "have not only eradicated poliomyelitis but have also eradicated the live virus" (*39*). Data soon to be published by Lapinleimu from intensive poliomyelitis surveillance in Finland (*41*) between April 1972 and December 1974 revealed no cases of poliomyelitis and no evidence of poliovirus (Table 2). Their experience indicates that the proper use of a killed virus vaccine can reduce poliovirus dissemination to the point of eradication of domestic wild virus.

Quantitative studies. The following factors were examined in the course of studies on vaccine effectiveness: quantity of antigen, number of doses, vaccine potency, and the use of immunologic adjuvants.

The effect of quantity of antigen on antibody induction was demonstrated by a titration carried out in human subjects with a reference vaccine (*42, 43*). Substantial levels of antibody could be induced consistently with a single dose of sufficient quantities of antigen (Table 3). A second dose of the same quantity of reference vaccine A was given 2 weeks later to each group, and 1 year later antibody determinations were made before and after a uniform third dose of vaccine (Table 4). These data reveal that even the smallest dose of reference vaccine A, when used for primary immunization, established a state of immunologic hyperreactivity as compared with the re-

sponse to vaccine J in the control group (no primary immunization).

The relation between the number of doses of vaccine and the rate of paralysis was studied in 1959 (*32*). An inverse linear relation was revealed (Fig. 5) when the logarithm of the attack rate (paralytic cases per 100,000 population) was plotted against the number of doses of vaccine administered. This suggests that with each succeeding dose the remaining susceptibles were reduced by the same proportion as by the first dose, and this indicates that a state of immunity to paralysis is induced by a single critical dose of vaccine, whether it is the first, second, or subsequent dose.

The number of doses required for inducing effective immunity is influenced by the concentration of antigen in the vaccine. Vaccine prepared commercially in the United States prior to mid-1955 conformed to the originally established potency requirements relative to reference vaccine A. When tested in human subjects, vaccines of such potency induced antibody formation in virtually all who had received two doses, given a month apart (*43*). For example, antibody response induced by six lots of commercially produced vaccine (three each from two manufacturers), which met original standards of potency, were compared with reference vaccine A. The two doses of reference vaccine A, given 1 month apart to 43 individuals, induced an immune response in 100 percent for types I, II, and III. The response rates for two doses of the commercial vaccines in 171 individuals were 95 percent for type I, 100 percent for type II, and 98 percent for type III.

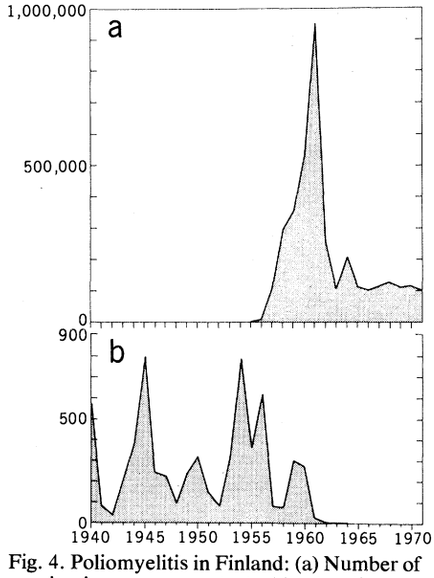


Fig. 4. Poliomyelitis in Finland: (a) Number of vaccinations per year (only killed poliovirus vaccine used); (b) number of cases per year. [From L. Noro (*38*); courtesy of S. Karger, Basel]

Table 3. Percentage of subjects with type I poliovirus antibody titers, at or above levels indicated, 2 weeks after a single intramuscular injection of killed poliovirus vaccine. Subjects were divided into groups which received different volumes of reference vaccine A. The pattern of response to poliovirus types II and III was similar (*42*).

Antibody titer*	Volume of reference vaccine A					
	2 ml	1 ml	1/2 ml	1/4 ml	1/8 ml	1/16 ml
≥ 4	100	100	96.2	93.4	87.2	77.2
≥ 8	100	100	80.9	73.4	65.7	57.2
≥ 16	94.2	88.3	61.7	50.1	37.6	40.1
≥ 32	64.8	58.9	38.7	16.8	15.8	11.6
≥ 64	32.5	17.8	8.0	10.2	6.5	0
≥ 128	12.0	6.1	0	0	0	
≥ 256	3.2	0				
≥ 512	0					
	Number of subjects					
	34	34	26	30	32	35

*Reciprocal of serum dilution capable of neutralizing 100 $TCID_{50}$ (tissue culture infective doses, 50 percent effective) type I virus.

Vaccines produced subsequently, however, including those whose performance is reflected in Fig. 5, were of lower potency. This occurred because the Division of Biologics Standards (of the Department of Health, Education, and Welfare) lowered potency requirements in order to permit the release of greater quantities of vaccine. This was done to permit vaccination of a larger number of individuals (*43*). Three doses of this lower potency vaccine reduced the attack rate by about 90 percent, and four doses by 96 percent (Fig. 5). The expected performance of vaccines of higher potency shows that fewer doses would immunize a higher proportion of individuals (Table 5).

In studies in human subjects, some of the experimental preparations of killed poliovirus vaccine were emulsified in mineral oil (incomplete Freund's adjuvant) in an effort to create a one-dose vaccine (*44*). The usefulness in humans of mineral oil as an immunologic adjuvant to increase the potency of killed virus vaccine had been demonstrated in the investigations on emulsified influenza vaccines (*45*), and is discussed below. The use of this adjuvant in polio vaccine was not pursued when questions were raised about possible side effects, and when satisfactory responses were induced with multiple doses of an aqueous vaccine. This method might again be pursued with the aim of more efficiently producing vaccines sufficiently potent to be effective in a single dose.

Duration of immunity. Many observations indicate that a potent killed poliovirus vaccine induces antibody response of long duration, with some observations extending over a 12-year period (*32, 33, 37, 38*). The degree of antibody persistence is dose-dependent (Table 6), as is the initial antibody response (Tables 3 and 4). A plateau in antibody level has been observed for at least 6 years after primary and booster vaccination as well as after primary vaccination alone (*32*). Such persistence can be attributed to vaccination, and not to restimulation by infection, because natural infection in a vaccinated individual would result in a characteristic secondary-type antibody response to the infecting poliovirus type but not to the other two (*31*). Böttiger has confirmed the observation that antibody titers "remain fairly stable after the first post-vaccination fall of titer has occurred during the year following the vaccination" (*46*). Antibody titers as low as 1 to 4 have been shown to be completely protective against paralysis in monkeys

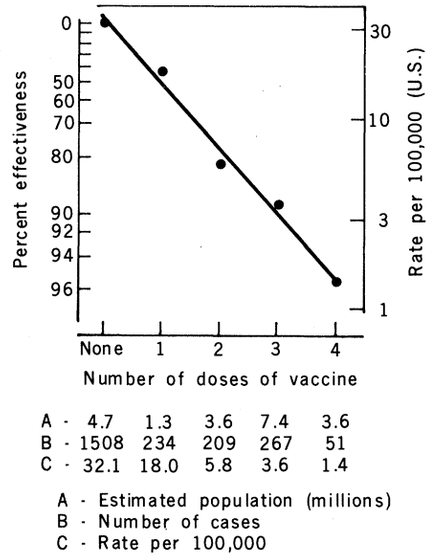


Fig. 5. Relation between killed poliovirus vaccination status and paralytic poliomyelitis attack rates in the 0- to 4-year-old age group in the United States in 1959. The vaccine used in the United States between 1955 and 1959 was of low potency. [Adapted from J. E. Salk (*32*); courtesy of *Lancet*]

challenged intravenously with poliovirus (*30*).

Persistent immunologic memory is associated with durable immunity to paralytic polio, as has been discussed above (*29, 31, 32*). The persistence of immunologic memory is revealed by a secondary-type antibody response even in the absence of demonstrable antibody (*32, 43*). Böttiger has confirmed this phenomenon 7 to 8 years after the last previous dose of killed poliovirus vaccine (*33*). Booster doses of vaccine reveal the presence of immunologic memory, but are not required to maintain it (*31–33*).

Live and Killed Poliovirus Vaccines

Although it has been shown in the foregoing section that a killed poliovirus vaccine can be fully effective for the control of poliomyelitis and for the eradication of poliovirus from a population, many misconceptions about the killed virus vaccine principle still persist, as revealed in continuing discussions regarding the use of live or killed poliovirus vaccine (*47*).

Prior to licensing for use in 1955, the killed poliovirus vaccine was subjected to a scientifically controlled field trial for safety and effectiveness (*48*). An attenuated live virus vaccine that could be administered orally was introduced into the United States in 1961–62 without a controlled field trial (*49*). Its approval was based on uncontrolled field studies in other countries, even though the occurrence of "post-vaccination poliomyelitis [was] not capable of being examined in as great detail as one would wish it to be" (*50*).

Several justifications were given in 1961 for the replacement of a proven safe and effective killed poliovirus vaccine with a live virus vaccine (*50*). One was that the live virus vaccine would provide more effective community protection by inducing "intestinal immunity"; another was that live virus vaccine would induce more persistent immunity; a third was that an oral vaccine would be easier to administer and would be more acceptable to the public than an injected vaccine; and finally, the advantage of a live virus vaccine in arresting outbreaks was pointed out. In addition, it was stated that the live virus vaccine could be administered "without the risk of paralysis" (*50*). Each of these is discussed below in light of our accumulated experience in 1976.

Community protection. When live virus vaccine was first introduced, it was stated that "although [killed poliovirus] vaccination can be expected to reduce greatly the relative risk of paralytic poliomyelitis among adequately vaccinated individuals, the procedure cannot be expected to have a great effect on the incidence of alimentary poliovirus infection among either vaccinated or unvaccinated individuals, and therefore the eradication of the disease as a community health problem" (*50*). This was a reflection of the belief that the principal mode of viral transmission was by the fecal-oral route. The live virus vaccine was preferred because it more effectively reduced the rate of fecal excretion of virus upon subsequent reinfection with attenuated viruses, and better induced the production of IgA in nasal and duodenal secretions (*51*). However, such "intestinal immunity" does not seem to be significant epidemiologically in view of the herd effect observed in areas where the killed virus vaccine has been widely used (*3*, p. 136; *14, 37, 38, 52, 53*). Apparently virus dissemination is reduced by the use of a killed poliovirus vaccine.

A mechanism for this effect is suggested by studies on the presence of pharyngeal poliovirus in individuals vaccinated with the killed poliovirus vaccine and exposed to either wild-type or attenuated poliovirus. Wehrle *et al.* (*54*) studied throat swabbings from individuals exposed to cases of paralytic polio. They found a lower incidence of positive tests for virus in individuals vaccinated with the killed poliovirus vaccine, but no difference in the frequency of positive tests for fecal virus in vaccinated or unvaccinated individuals. They have interpreted their data as suggesting that vaccination with killed poliovirus can have an effect on potential pharyngeal transmissibility, but would be less likely to have an effect on fecal transmissibility.

Similarly, tests for pharyngeal virus were uniformly negative after large amounts of attenuated strains were fed to children previously vaccinated with a killed virus vaccine, although tests for pharyngeal virus were positive in 80 per-

Table 4. Percentage of subjects with type I poliovirus antibody titers at or above levels indicated before (pre) and 2 weeks after (post) a third dose of killed poliovirus vaccine. Primary immunization administered 1 year earlier with two equal doses (2 weeks apart) of reference vaccine A. Subjects were divided into groups which received different volumes of reference vaccine A per dose. The third dose consisted of 1 ml of vaccine J for all groups (*43, 44*).

Antibody titer*	Percentages after a primary immunizing dose of:													
	2 ml		1 ml		1/2 ml		1/4 ml		1/8 ml		1/16 ml		None	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
≥ 4	92.0		84.7		60.0		72.8		45.2		35.3		0	78.8
≥ 8	84.0		61.7		40.0		45.6		29.1		14.8			51.6
≥ 16	68.0		42.5		30.0	100.0	22.9		13.0	100.0	6.0	100.0		33.5
≥ 32	24.0		11.8		15.0	96.2	9.3		3.4	93.4	3.1	96.2		6.3
≥ 64	8.0		8.0		0	92.4	0	100.0	0	80.1	0	80.9		3.3
≥ 128	0	100.0	0			80.9		96.3		56.8		34.8		0
≥ 256		95.9		100.0		73.3		70.4		33.5		15.6		
≥ 512		91.8		95.3		69.5		40.8		16.9		4.1		
≥ 1024		83.5		85.8		46.5		29.7		10.3		4.1		
≥ 2048		75.2		52.5		19.6		14.9		7.0		0		
≥ 4096		54.4		28.7		15.8		11.2		3.7				
≥ 8192		25.3		14.5		12.0		7.5		0				
≥ 16,000		8.7		9.8		4.4		7.5						
≥ 32,000		4.6		5.1		0		3.8						
≥ 64,000		0		0				0						
Subjects (No.)†	26	24	26	21	21	26	22	27	31	30	24	26	33	33

*Reciprocal of serum dilution capable of neutralizing 100 $TCID_{50}$ type I virus. †Number from whom serum samples were available.

cent or more of unvaccinated controls. In commenting on these results, Sabin (*55*) states that this "strongly suggests that antibody produced by a killed virus vaccine can interfere with the localization and multiplication of poliovirus in the throat. . . ." He also points out "that under natural conditions of infection with 'viraemic' strains [virus that is carried in the blood] the high incidence of pharyngeal virus in patients with the clinical disease is more readily explained on the basis of secondary localization from the blood than on primary localization of ingested virus." He adds that "on this basis one would expect that even minimal amounts of antibody in the blood engendered by killed virus vaccine would be sufficient to block the secondary localization of 'viraemic' poliovirus in the throat." This is equivalent to the prevention of paralysis by blocking the secondary localization of "viraemic" poliovirus in the CNS, and it has been observed that the killed poliovirus vaccine reduces community spread to the same degree that it reduces the risk of paralysis for individuals (*10, 11, 13*).

In addition, it is known that the period of highest communicability of naturally occurring paralytic poliomyelitis is more closely related to the presence of virus in the pharynx (*56*) than to the excretion of virus in the feces (*10*). These findings suggest the importance of the oral-oral route of viral dissemination, especially when sanitation conditions are generally good.

Persistence of immunity. When live poliovirus vaccine was first introduced, it was stated that "the persistence of immunity induced by the oral poliovirus vaccine may be of much longer duration than is the case with [killed poliovirus] vaccine . . ." (*50*).

Data demonstrating the persistence of immunity induced with killed poliovirus vaccine have already been presented and discussed. The impression that immunity induced by the killed virus vaccine was not of long duration arose as a result of the lowering of the original potency requirements by the Division of Biologics Standards in 1955. To compensate for the less potent vaccine then produced, a *supplementary* dose was recommended (*43, 57*). This detail in the early history of the killed poliovirus vaccine is, in large part, the basis for claims of the imperfect immunizing power of the killed virus vaccine and the assumption that there was a need for repeated booster doses. The impression of imperfect immunizing capacity of killed poliovirus vaccine was also created by the low levels of protection achieved with the use of two doses of intradermally administered vaccine of poor potency in the initial mass immunization campaigns in some European countries (*58*).

As the technology of virus cultivation improved, more potent vaccine became available in the late 1950's, and the level of potency originally required for vaccine release in the United States was restored in 1968. Vaccines now being produced are above this level (*59, 60*), and induce persistent immunologic memory reliably with two to four doses (*32, 33*). In Finland and Sweden (*37, 38*), for example, two primary doses are given a month apart, starting at 5 and 9 months of age, respectively; a third dose is given at about 18 to 24 months, and a supplementary fourth dose at about 6 to 7 years.

Studies on persistence of immunity subsequent to the use of live poliovirus vaccine have been reported and discussed (*61*). At present four or five doses of live poliovirus vaccine are recommended in the United States: three primary doses at 2, 4, and 6 months, with supplementary doses at 18 months and on entering school (*62, 63*).

Vaccine utilization. It was also felt in 1962 that a vaccine given by mouth would be more readily accepted and used than a vaccine given by injection. However, available data do not support this belief. The 1974 utilization rates of

Table 5. Calculation of expected effectiveness rates for killed poliovirus vaccines of different hypothetical potencies, based on data and relationships shown in Fig. 5. The potency of vaccine shown in Fig. 5 is approximately 0.55. The potency of vaccine currently available (*59, 60*) is greater than 0.8.

Vaccine potency*	Effectiveness rate† after each dose				Doses required for desired effectiveness	
	First	Second	Third	Fourth	≥ 90%	≥ 95%
1.0	100				1	1
0.9	90	99	99.9		1	2
0.8	80	96	99.2		2	2
0.7	70	91	97.4	99.2	2	3
0.6	60	84	93.6	97.6	3	4
0.5	50	75	87.5	93.8	4	‡
0.4	40	64	78.4	85.4	‡	‡
0.3	30	51	64.7	75.3	‡	‡

*Single-dose effectiveness rate divided by 100 percent. †Expressed as cumulative percent of vaccinated individuals expected to be effectively immunized against paralysis. ‡Impractical.

Table 6. Persistence of demonstrable antibody after immunization with killed poliovirus vaccine in the groups referred to in Table 4. The percentage of subjects with antibody titers at or above the levels indicated at yearly intervals after booster dose. In each of the two groups there were 43 subjects who were followed throughout the study (*32*). The primary immunization consisted of two doses 2 weeks apart of reference vaccine A in quantities indicated. The booster dose was a single 1-ml dose of vaccine J 1 year later.

Antibody titer*	Response to immunization with:					
	2, 1, or 1/2 ml			1/4, 1/8, or 1/16 ml		
	Year 1†	Year 2†	Year 3†	Year 1†	Year 2†	Year 3†
			Type I			
≥ 4	100	100	100	88.4	79.1	72.1
≥ 8	97.7	100	97.7	65.1	46.5	51.2
≥ 16	95.3	93	93.0	37.2	27.9	23.3
≥ 32	93.0	93	99.4	25.6	20.9	18.6
≥ 64	93.0	93	96.0	11.6	11.6	13.9
			Type II			
≥ 4	100	100	100	100	100	100
≥ 8	100	100	100	100	100	100
≥ 16	100	100	100	100	100	95.3
≥ 32	100	100	100	100	100	93.0
≥ 64	100	100	100	100	95.3	93.0
			Type III			
≥ 4	100	100	100	95.3	90.7	95.3
≥ 8	100	100	90.7	74.4	74.4	74.4
≥ 16	97.7	95.3	86.0	55.8	51.2	48.8
≥ 32	90.7	86.0	76.7	39.5	30.2	27.9
≥ 64	83.7	79.1	72.1	32.6	18.6	16.3

*Reciprocal of serum dilution capable of neutralizing 100 $TCID_{50}$ virus. †Time interval after booster dose.

diphtheria-tetanus-pertussis (DTP) vaccine and of live poliovirus vaccine in the United States show a higher rate for three or more doses of DTP given by injection as compared with three or more doses of live poliovirus vaccine given by mouth (Table 7). A useful advantage of a killed poliovirus vaccine is that it can be effectively combined with other vaccines to simplify programs of routine immunization. Combined DT-polio and DTP-polio vaccines are used in Canada, Holland, Denmark, France, and other countries (*3*, p. 139; *59, 64*).

The ease of administering an oral vaccine which is effective in a single dose would be an advantage in immunization programs, especially in underdeveloped countries. However, multiple doses of live poliovirus vaccine are needed to induce immunity reliably. In particular, studies in countries with warm climates (where most polio cases now occur) have demonstrated that the live virus vaccine is less effective that had been expected (*65*). Immunity in the individual is not reliably established because vaccine virus implantation is blocked by the presence of unexplained inhibitors in the intestinal tract. There is the further problem of loss of vaccine potency due to the need to maintain the live virus vaccine in the frozen state, and at low temperatures during routine use. These problems can be solved by the use of the killed virus vaccine (*66*) which does not require intestinal infection, which maintains potency with normal refrigeration, and which is more stable during routine use in warm climates.

It is possible to adjust killed virus vaccine potency so as to induce immunity with fewer doses (Tables 3 and 5). The advantage in economy and efficiency of a poliovirus vaccine requiring only one or two doses given by injection might offset any present advantages in cost associated with the use of the live poliovirus vaccine given orally in three or more doses. In addition, recent improvements in technology have reduced the cost of killed poliovirus vaccine production (*3*, p. 137; *67*). The possibility of further improvement exists by using diploid cell cultures or cultures of continuously propagating cells (*68*), by using viral subunits free of nucleic acid and cell constituents (*1*), and by using immunological adjuvants.

Control of outbreaks. The live poliovirus vaccine is distinctly advantageous during an outbreak, when widespread administration of a single dose can compete with the wild virus prevalent in the community. An established attenuated virus infection in the alimentary tract interferes with subsequent wild virus infection and exerts a protective effect prior to the development of any antibody response. Such an effect is not produced by the killed virus vaccine.

Safety. Poliomyelitis has disappeared in Sweden and Finland with the use of a killed virus vaccine alone; but in the United States cases of poliomyelitis have continued to occur. This comparison is statistically significant even when the difference in population size is taken into consideration (*69*). Norway is similar to Sweden and Finland, both socially and demographically. In Norway the live virus vaccine is used alone, and the attenuated vaccine virus is the only source of domestically arising cases of paralytic poliomyelitis (*70*). In the United States, after 1972, wild-type virus activity appears to have ceased (*71*), and, except for occasional imported cases, the live virus vaccine is now the principal cause of polio in the United States (*72*) and in other countries (*73*).

Between 1961 and 1976, 148 cases associated with live virus vaccine were reported (Table 8). The reason for the decrease in number of cases in recipients after 1965 is that the live virus vaccine was no longer recommended for adults (*74*). More children than adults had previously received the killed virus vaccine, and were therefore protected against the paralytic effect of the live poliovirus vaccine (*75*). The number of contact cases increased after 1965 because adults were no longer being immunized (the killed poliovirus vaccine was unavailable in the United States between 1968 and 1975), but the adults were still being exposed to vaccine virus (live) shed by vaccinated children (*74*).

The risk in the United States of paralytic disease for individuals vaccinated with live poliovirus and their contacts is estimated to be 1 per 3 to 4 million doses of vaccine distributed (see Table 8). Calculation of the actual risk to susceptible individuals is difficult, both because most of the 25 million doses of vaccine distributed annually are administered to those already immunized at least once, and because the number of susceptible individuals in contact with vaccinated persons cannot be estimated. The risk of paralytic disease associated with use of the same vaccine in Norway was estimated to be 1 case per 1 million doses distributed, or 1 case per 300,000 vaccinated children (*70*).

The actual number of cases of vaccine-associated disease is more meaningful than the estimated risk based on the number of doses of vaccine distributed. A comparison of the actual number with the number of cases of naturally occurring wild-type poliovirus infection is a more appropriate measure of risk associated with the use of the live poliovirus vaccine. In 1973, all 13 of the domestically arising cases of paralytic poliomyelitis in the United States were associated with the use of the live virus vaccine (*72*). In all cases there was significant to severe residual paralysis, and there were three deaths—the latter in immunodeficient children. There were nine recipient cases (ages 4 months to 6 years) and four contact cases (ages 17 months to 36 years). Between January 1973 and September 1976, 36 cases of

Table 7. Comparison of utilization of diphtheria-tetanus-pertussis (DTP) and oral live poliovirus vaccine (OPV) in the United States (1974). The data are shown as percentages of the age groups that received three doses of DTP by injection and the percentage that received three doses of OPV by mouth (*117*).

Age group	U.S. total		Inner city areas	
	DTP	OPV	DTP	OPV
< 1	33%	21%	29%	22%
1– 4	74	63	70	60
5– 9	85	74	83	71
10–13	86	70*	83	68*

*Age group of 10 to 14 years.

Table 8. The number of cases of live virus vaccine-associated paralytic poliomyelitis for known recipients and contacts, in the United States, 1961 through September 1976 (*74, 118*). In the period 1961 to 1964, approximately 100 million doses each of monovalent types I, II, and III and approximately 28 million doses of trivalent were distributed. In the period 1965 to 1976, approximately 7 million doses each of monovalent types I, II, and III were distributed and approximately 280 million doses of trivalent.

Cases	1961–64	1965–76	1961–76
Recipient	63	32	95
Contact	3	50	53
Total	66	82	148

Table 9. Summary of cases of paralytic poliomyelitis: United States, January 1973 to September 1976 (*72, 118*).

Total	Source	Type	No.
6	Imported		
30	Domestic	Vaccine-associated (16 recipients)* (11 contacts)	27
		"Endemic"	3†

*Eleven immunodeficient children. †Two "vaccinelike" or "intermediate" viruses, and one wild-type virus isolated (see text for details).

polio have been reported (Table 9). Of the 30 domestically arising cases 27 (90 percent) were reported as associated with the live poliovirus vaccine. Three cases were officially reported as "endemic—not vaccine associated" although the two samples of type III virus isolated from two cases were classified as "vaccine-like" and "intermediate" with respect to their genetic markers. A type I virus isolated in the third case did not have the genetic markers of the vaccine virus. However, it is known that these markers can be lost as the attenuated virus multiplies in the intestinal tract, and virus without the genetic markers of the vaccine strain are found in fecal samples from vaccine recipients and from known vaccine-associated paralytic cases (*63*, pp. 8–9; *76*). Hence, it would appear that the live virus vaccine was the source of virus in two of the "endemic" cases, and, in the third case, the source of virus cannot be definitely identified: it may or may not have been the live virus vaccine.

In 1961, the spread of attenuated poliovirus from vaccinated to unvaccinated individuals was thought desirable to increase community protection by "spreading immunity." This mechanism is difficult to control since the attenuated virus is not completely without virulence, and it can produce disease in normal as well as immunodeficient individuals (*72*). Vaccine virus-induced disease has been observed in persons without known contact with a vaccinated individual (*77*). The original belief that the live poliovirus vaccine could be administered without risk of paralysis has not been supported by experience (*74*, *78*).

Effectiveness of Killed Influenza Virus Vaccines

Studies beginning in the mid-1930's demonstrated that the incidence of influenza could be reduced by inoculation with inactivated viruses (*15*, *79*). Many subsequent reports have confirmed these observations (*18*, *23–26*). For the purpose of discussion of the principles involved, we briefly present data from field studies (*80*) in 1943, 1945, and 1947 (*81–83*).

In these early studies, a significant degree of protection was observed when there was a close match between one of the viral antigens contained in the vaccine and the virus causing the epidemic (*23*, *81*, *82*, *84*). The incidence of influenza A in 1943 was reduced by 70 percent (7.5 percent incidence of disease in the controls and 2.2 percent in the vaccinated) (*81*). The incidence of influenza B in 1945 was reduced by 92 percent (11.2 percent incidence of disease in the controls and 0.9 percent in the vaccinated) (*82*). The greater effect observed in 1945 may have been due, in part, to a herd effect since separate totally vaccinated and unvaccinated groups were compared; the 1943 study involved an equal number of vaccinated and control subjects intermingled within the same limited population.

Table 10. Incidence of influenza among individuals with different serum antibody titers (*23*).

Antibody titers*	Percent of population		Disease incidence (percent)	
	Control (N = 888)	Vaccinated (N = 888)	Control (N = 72)	Vaccinated (N = 20)
<8	13.4		26.1	
8	12.2	2.4†	14.8	20†
16	22.0		7.7	
32	29.3	9.9	3.5	3.4
64	14.2	19.5	2.4	2.9
128	6.9	30.5	1.6	2.2
256	2.0	20.7	0	1.0
512		7.3		0
1024		8.5		0
2048		1.2		0

*Reciprocal of initial serum dilution capable of inhibiting four hemagglutinating units of Weiss strain of type A virus. †Percentage combined for antibody levels of ≤ 16.

The importance of vaccine virus specificity was evident from the experience in 1943. In May of that year, an influenza A virus was isolated from a localized outbreak (*85*). Since there was discernible antigenic drift between the 1934 PR-8 strain and the 1943 isolate (Weiss strain), both were included in a vaccine to be tested the following winter. The expected epidemic began in late October, and in nine study groups comprising 6211 controls and 6263 vaccinated, the incidence was reduced by 70 percent, as noted above (*81*). The incidence of illness requiring admission to the infirmary was inversely proportional to the level of antibody when antibody titer was assayed with a strain closely related to the strain causing the outbreak (Fig. 6). This inverse relationship was more obvious with the 1943 isolate than with the 1934 strain (*13*, *23*). Failure to protect in 1947 (*83*) (only 9 percent reduction in vaccinated as compared to controls) was due to the first appearance of the type A_1 variant, not represented in the vaccine. The explanation of the failure was evident in that the antibody response to the vaccine strains was high, while response to the type A_1 strain was insignificant, except in approximately 1 out of 20 persons.

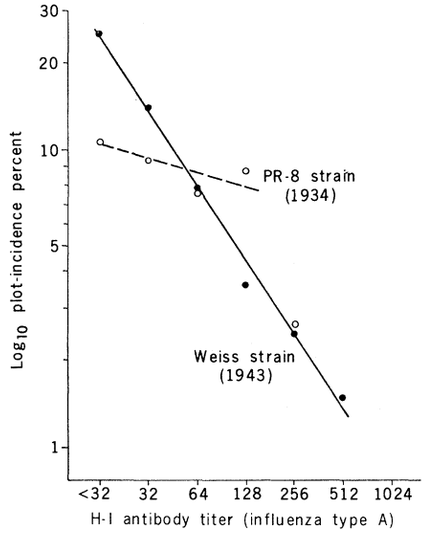


Fig. 6. Relation between hemagglutination-inhibiting (H-I) antibody titer and illness rate in unvaccinated individuals with naturally acquired antibody (influenza A, 1943). Antibody titers are expressed as the reciprocal of the serum dilution inhibiting 4 hemagglutinating units of virus. To conform to the present method of expressing antibody levels in terms of initial rather than final serum dilutions, divide by 4. The point for the PR-8 antibody titer of 256 is based on very small numbers since only 6.3 percent of the population had antibody titers at or above this level. [From J. E. Salk (*13*); courtesy of the University of Toronto Press]

The incidence of disease in both vaccinated and unvaccinated groups in 1943 was observed to be inversely related to the level of serum H-I antibody (Table 10). The similarity of disease incidence at equivalent antibody titers for vaccinated and unvaccinated groups indicates that serum H-I antibody was equally well correlated with protection whether induced by prior natural infection or by vaccination. The incidence of disease was 2.3 percent in the vaccinated and 8.6 percent in the control group, a reduction of 72 percent. The degree of protection is directly correlated with the distribution of antibody levels in each population. Other investigators have reported similar

Table 11. Incidence of febrile reactions (≥ 100°F or 38°C) following the injection of different doses of aqueous influenza virus vaccine (*88*).

Dose (CCA units)	Subjects (No.)	Fever (%)
4100*	25	80
1875†	15	52
1710‡	15	33
1140‡	20	25
1025*	40	48
855‡	30	33
570‡	30	16
410*	39	15
285‡	30	10
100*	40	0
20*	40	0
Vaccine§	30	16

*Twice-centrifuged, batch 7 (2050 CCA units per milligram of protein). †Twice-centrifuged, batch 8 (1150 CCA units per milligram of protein). ‡Once-centrifuged, lot No. 4981 (1140 CCA units per milligram of protein). §Vaccine used in 1943 field trial (approximately 500 CCA units per dose).

observations on the relation between antibody level and susceptibility to disease (*24–26*).

During the epidemic of 1943–44, onset of immunity was observed 8 to 9 days after vaccination (*81, 86*), and persistence of immunity from vaccination 1 year previously was also observed (*15*). The latter observations were made in an institution in which approximately 40 percent of the population in some living units had been vaccinated the year before, and in other units the population was essentially unvaccinated. The total incidence of clinical disease in 1319 members of the unvaccinated groups was 12.4 percent; among the 1916 in the partially vaccinated groups the incidence was 1.9 percent. The incidence of disease in the partially (40 percent) vaccinated groups was 85 percent less than in the unvaccinated groups. These results indicate that vaccination continued to exert a protective effect after a year, and that vaccination of 40 percent of a population induced a herd effect. Other investigators subsequently reported persistence of immunity for 3 years after vaccination (*18*, pp. 281 and 285; *87*), and also the existence of a herd effect (*16–18*).

The actual duration of immunity to any specific influenza virus is obscured by antigenic drift and antigenic shift. New antigenic subtypes or strains may cause varying degrees of clinical illness even in the presence of antibody which is fully protective against the previously prevalent virus (*18*).

An attempt was made to enhance influenza virus vaccine effectiveness by increasing its antigen content. Graded doses of purified concentrated killed virus preparations were studied in 1944 (*88*). Although antibody response was enhanced, the immunological benefit was nullified by an increase in rate of febrile reactions (≥ 100°F or 38°C) accompanied by chills, headache, and malaise (Table 11). This has also been observed by others (*89*).

The vaccine used in the 1943 field trial was included for comparison, and the number of febrile reactions appeared to be proportional to its virus content when compared with the purified virus preparations. This suggested that the reactions observed with the field trial vaccine were due to the virus itself and not to allantoic fluid or to chicken red blood cell components contained in the vaccine. The virus was grown in developing chick embryos and concentrated crudely by adsorption with chick embryo red cells and eluted into a smaller volume (*90*).

Recent technical developments allow for the preparation of purified antigenic material with fewer febrile reactions: the use of continuous flow zonal centrifugation (*18, 25, 91*), the disruption of virus particles (*92*), the isolation of highly purified envelope proteins, and even the preparation of crystalline hemagglutinin (*93*).

The development of an effective means of immunization against the influenza viruses, which vary unpredictably, depends partly on the answer to the theoretical question of whether their antigenic variation is finite or infinite (*5, 7*). If antigenic variation is finite, and if influenzas A and B are represented by a limited number of subtypes, then it might be possible to develop a vaccine that contains antigens for all human pathogenic strains. If antigenic variation is infinite, it would be necessary to rely on a good surveillance system, rapid decision-making, and an adequate production capability when new antigens appear.

There is serologic evidence that the subtypes designated H2N2 (Asian 1957) and H3N2 (Hong Kong 1968) were prevalent in 1889 and 1900, respectively (*6*). The reappearance of these subtypes after many decades might mean that major antigenic variation (shift) is cyclic (Table 12). This would be compatible with the idea of a finite number of subtypes, but does not prove it. Only future studies will reveal the validity of these hypotheses.

It may be easier to control human influenza than has been generally believed. The available data indicating the occurrence of a herd effect suggest that the prevalence of influenza virus in a human population can be influenced by appropriate immunization programs.

Table 12. Periodic variation in prevalent subtype of influenza A resulting from antigenic shift. [Adapted from E. D. Kilbourne (*6*)]

Subtype designation		Initial year of cycles of prevalence	
Present	Former		
H0N1	A_0		1928
H1N1	A_1 (A prime)		1946
H2N2	A_2 (Asian)	1889	1957
H3N2	HK (Hong Kong)	1900	1968
$H_{sw}N1$	Swine	1918	

The epidemiologic relation between the proportion of the population with antibody and the natural suppression of virus strains (*5, 7*), together with the relation between antibody titer and reduction of incidence of disease (Fig. 6) indicate that the long interval between periods of prevalence of each subtype could conceivably be extended indefinitely by effective immunization.

At present, the strategy for control of human influenza is to anticipate future strains and to change the strain composition of the current vaccine as needed (*18*). This requires vaccination for each anticipated strain change, as was being done (in late 1976) for the A/New Jersey/76 (swine-type) influenza. However, it would be expected that by increasing the immunity index of the population against all known antigenic varieties, it would be possible to suppress the development of future outbreaks of these strains. The fundamental question in the development of effective influenza control is therefore the feasibility of developing a single immunizing preparation against all of the known antigenic variations of influenza virus which can cause human disease. This would permit immunization early in life (*18, 94*), routinely before entrance into school, for example; and reimmunization only if long-term studies indicate the need, or if a new, unknown antigenic strain were to appear. It may be possible to develop such a vaccine by using a potent immunologic adjuvant (*18*).

Immunologic Adjuvants

In view of the febrile reactions associated with the use of increasing quantities of influenza virus antigen (*88*), studies were undertaken in 1950 with immunologic adjuvants (*95*). Mineral salts are commonly used for this purpose, as in adsorbed diphtheria and tetanus toxoid vaccines. When calcium phosphate–precipitated influenza virus was tested, minimal potentiation of the immune response occurred (*96*). Since Friedewald (*97*) and

Henle and Henle (*98*) had previously shown the enhancing effect of Freund's adjuvant (*99, 100*) on the antibody response to influenza virus, such studies were again undertaken. Freund's adjuvant consists of a water-in-mineral oil emulsion, with or without mycobacteria (*99*).

Undesirable local inflammatory reactions were encountered in early investigations in animals by Friedewald (*97*) using complete Freund's adjuvant (with mycobacteria), and in humans by Henle and Henle (*98*) using incomplete Freund's adjuvant (without mycobacteria). These local inflammatory reactions can be reduced, however, by using an incomplete Freund's adjuvant which contains emulsifying reagents less tissue-damaging than those used by Henle and Henle, and by dispersing the inoculum via the intramuscular rather than the subcutaneous route (*101*).

Studies with emulsified influenza virus vaccine in monkeys resulted in high, sustained levels of antibody even when the dose of antigen was reduced by several orders of magnitude (*102*). Data from human studies with emulsified vaccines, which are presented below, reveal the increased efficiency of antigen utilization for inducing and maintaining high levels of antibody (*45*).

The rise in antibody levels is more striking after inoculation with emulsified (adjuvant) vaccine, than after inoculation with aqueous (saline) vaccine (Fig. 7). The antibody titers 6 weeks after vaccination in both groups tend to persist for a year, with some decline at the highest levels. This decline of antibody titer does not continue (Fig. 8). It can be seen that antibody titers induced by virus emulsified in mineral oil continue to rise over a longer period and persist at a higher level than those induced by virus in saline. Stuart-Harris and Smith *et al.* (*103*) have reported similar findings, and Bell *et al.* (*104*) have reported persistence of antibody for 9 years.

Antibody response is directly related to quantity of antigen in both aqueous and adjuvant vaccines (Fig. 9). In this population, which had previous exposure to this strain of influenza virus, equivalent responses were evoked with 320 CCA (chicken cell agglutinating) units per dose in an aqueous vaccine and with 1.0 CCA unit per dose in an emulsified vaccine. An emulsified vaccine containing 10 CCA units per dose induced a higher level of response than did an aqueous preparation containing 320 CCA units. These data also suggest little advantage, in terms of antibody response, in increasing the amount of this particular strain of virus much beyond 10 CCA units per dose in an emulsified vaccine in this population. When the volume of emulsion was increased, however, and the antigen content was kept constant (in this instance, at 32 CCA units per dose), a significantly greater response occurred.

Equivalent quantities of antigen of different influenza virus strains induce different levels of antibody response (Table 13). The superiority of adjuvant vaccine is again seen.

Previous natural exposure to specific virus strains, as evidenced by antibody

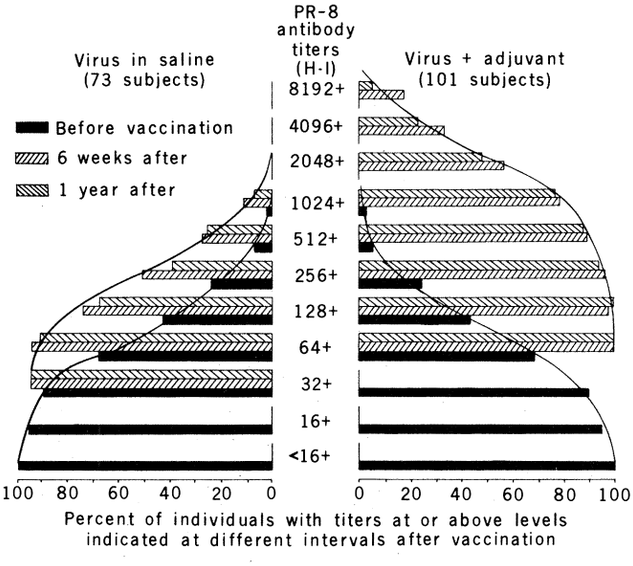
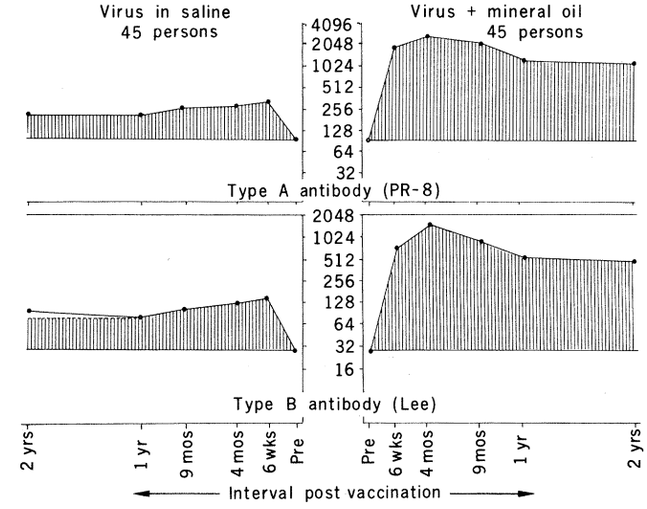


Fig. 7 (upper left). Comparison of antibody response and persistence in human subjects inoculated with influenza virus in aqueous (saline) or emulsified (adjuvant) vaccines. [From J. E. Salk (*45*); courtesy of the *Journal of the American Medical Association*] Fig. 8 (upper right). Geometric mean antibody titers at intervals up to 2 years after vaccination with influenza virus in aqueous (saline) or emulsified (mineral oil) vaccines. The slight rise in type B geometric mean antibody titer between the first and second year was due to the natural occurrence of influenza B in the interim. [From J. E. Salk *et al.* (*45*); courtesy of the *Journal of the American Medical Association*] Fig. 9 (lower left). Antibody response to diminishing quantities of influenza virus in aqueous (saline) or emulsified (adjuvant) vaccines. Each point represents the mean value of type B Lee antibody titer rise for a group of about 50 young adults. The vaccines used contained equal parts of PR-8 (type A), Cuppett (type A_1), and Lee (type B) strains. The standard aqueous vaccine then in use contained 500 CCA units per 1.0-ml dose. [From J. E. Salk *et al.* (*45*); courtesy of the *Journal of the American Medical Association*]



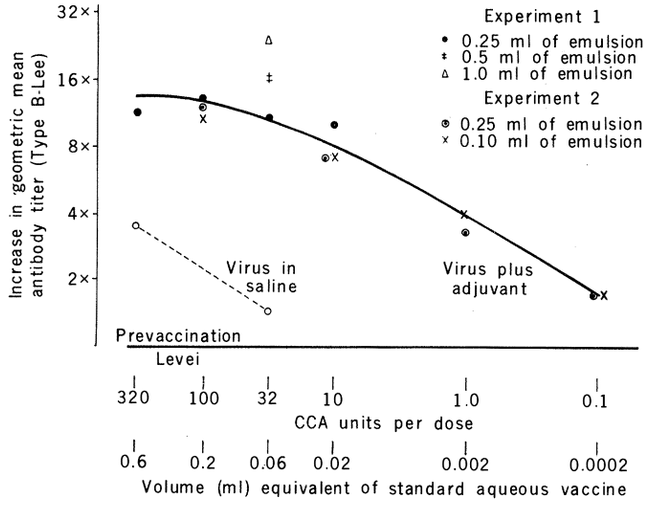


Table 13. Specific antibody responses in 36 subjects given aqueous influenza virus vaccine and 36 given adjuvant vaccine. Each vaccine contained equal proportions of PR-8, FM1, and Cuppett strains in a final concentration of 125 CCA units per dose (0.5 ml inoculum). It did not contain strain 283 (*45*).

Antigen used in serologic test	Vaccine	Antibody titers			
		Before vaccination*	After vaccination*		
			2 weeks	6 weeks	12 weeks
PR-8 (1934) (type A)	Aqueous	42	333	243	218
	Adjuvant	58	256	1843	3277
FM1 (1947) (type A_1)	Aqueous	38	109	122	102
	Adjuvant	26	166	1536	1843
Cuppett (1950) (type A_1)	Aqueous	16	27	32	26
	Adjuvant	16	48	870	1331
Strain 283 (1951 F.D.) (type A_1)	Aqueous	16	27	27	22
	Adjuvant	16	42	384	480

*Geometric mean of reciprocal of serum dilution capable of inhibiting four hemagglutinating units of antigen.

titers prior to vaccination, influences the degree of antibody response to vaccination (Table 14). Studies have shown that a second dose of vaccine induces the same kind of enhanced antibody response as that seen after primary vaccination of individuals who have been previously sensitized by natural infection (*105*). Thus, two suitably spaced doses used for primary immunization would more uniformly induce higher initial antibody titers than a single dose in previously unsensitized individuals; subsequent doses would act as antibody boosters for that specific antigen.

Emulsification reduces the tendency toward febrile reactions, in part because of the smaller amounts of antigen required with the adjuvant, and in part because of the slower release of antigen. As was already noted, febrile reactions were not observed with aqueous vaccines which contained less than 100 to 200 CCA units of virus (Table 11).

The only undesirable side effect of mineral oil adjuvants which was observed was the occasional occurrence of a nodule or cyst at the inoculation site. Some of these reactions were due to free oleic acid in certain batches of the emulsifying agent, Arlacel A (mannide monooleate). After this was corrected, such local reactions occurred less frequently and were believed to be due to inadvertent subcutaneous rather than intramuscular deposition of the inoculum, or to insufficient purification of the antigen (*45, 106, 107*). The occurrence of infrequent local reactions in those inoculated in large-scale programs in Britain (*108*) has discouraged the use of such vaccines, except in persons with a high risk of death from influenza. Davenport (*106*) expressed the view that these reactions are ". . . unimportant in comparison to the tens of thousands of excess deaths that generally accompany each visitation of epidemic influenza." Nevertheless, it would be advantageous to eliminate them by further investigation into their causes. Hilleman has reviewed the results of his studies on influenza vaccines emulsified in peanut oil (*109, 110*). It is likely that the use of split-virus preparations, viral subunits, or the use of different adjuvant substances will eliminate the few local reactions that have been associated with the use of emulsified vaccines.

The question has been raised concerning a possible delayed tumorigenic effect of emulsified vaccines. Beebe *et al.* (*111*) conducted a 10-year follow-up (since then updated to 18 years) (*112*) of the records of 18,000 men given mineral oil adjuvant influenza vaccine, of 4,000 given aqueous vaccine, and of 22,000 given formalinized saline placebo control in 1951–53. "The vaccine groups have been compared with respect to all diagnoses listed on the death certificates, autopsy protocols, and terminal hospital records. The findings are essentially negative with respect to malignant neoplasms, allergic diseases, and collagen diseases" (*112*, p. 337). Sufficient time has elapsed for a 23- to 25-year follow-up.

Tests have been subsequently conducted in mice to measure the safety of mineral oil adjuvant and its components

Table 14. Antibody response to aqueous and adjuvant influenza virus vaccines in groups with different prevaccination antibody titers. Figures indicate percent of subjects with antibody titers at or above the levels indicated before and 12 weeks after vaccination. Horizontal lines mark postvaccination antibody levels reached by 95 percent or more of those given adjuvant vaccine. Each vaccine contained equal proportions of PR-8, Cuppett, and Lee strains in a final concentration of 500 CCA units per dose; it did not contain strain 283. The aqueous vaccine was given in a 1-ml inoculum and the adjuvant vaccine was given in 0.25 ml of inoculum (*45*).

Antibody titers*	Percent of subjects at or above titer indicated before and after vaccinations											
	PR-8 (type A) (1934)			Lee (type B) (1940)			Cuppett (type A_1) (1950)			Strain 283 (type A_1) (1951)		
	Before	After		Before	After		Before	After		Before	After	
	Before (N = 198)	Aqueous (N = 97)	Adjuvant (N = 101)	Before (N = 143)	Aqueous (N = 44)	Adjuvant (N = 99)	Before (N = 198)	Aqueous (N = 97)	Adjuvant (N = 101)	Before (N = 198)	Aqueous (N = 97)	Adjuvant (N = 101)
≤ 8	100			100			100	100	100	100	100	100
16	85			60	100		40	82	99	18	51	95
32	71	100		22	93	100	8	39	97	3	20	75
64	50	98		11	75	99	2	26	91	1	14	64
128	26	77	100	4	55	96	1	10	80	0	8	41
256	7	52	97	1	29	88	0	4	60		2	27
512	4	29	89	0	18	70		2	42		2	11
1024	1	10	80		9	41		1	22		1	4
2048	1	4	56		9	15		1	7		0	0
4096	0	0	20		0	6		0	0			
8192			7			0						

*Reciprocal of serum dilution capable of inhibiting four hemagglutinating units of virus.

(*113*). Sporadic tumors that were not considered significant were observed in low incidence at the injection site in BALB/c and C57B1 mice of both sexes, and in female Swiss mice. A significant incidence of tumor formation was observed at the injection site in male Swiss mice.

Hilleman *et al.* (*109*) have questioned the meaning of these findings and their relevance to man in view of the controlled observations made in their laboratory, and in view of the findings of Beebe *et al.* (*112*). Hilleman *et al.* state that in their opinion, "the minor theoretical risk raised by the tests in these particular male Swiss mice seems small when compared to our need for an effective influenza vaccine." (*109*, p. 482).

Davenport has reviewed the results of continuing studies on vaccines emulsified in mineral oil (*106*). In summarizing 17 years of experience with the mineral oil adjuvant, Davenport proposed (*106*, p. 292):

> . . . that the wealth of animal, chemical and clinical data available now urges adoption of the mineral oil adjuvant influenza virus vaccine for widespread use in the United States. That decision takes into consideration the probability that a new pandemic strain is expected to emerge shortly, and that the use of mineral oil adjuvant vaccines affords the greatest promise for coping with such a potential disaster.

Conclusion

The basic requirements for effective immunization include stimulation with a sufficient quantity of a suitably specific antigen to induce an immune response that is appropriate to protect against the pathological consequences of infection. An understanding of these requirements and the use of quantitative immunologic methods have shown that the nature of the problem of immunization against poliomyelitis, and the extent to which it remains unsolved, is entirely different from that of immunization against influenza. For influenza, a killed virus vaccine exists which is in need of improvement. For poliomyelitis, there are two vaccines: one made of killed viruses and the other made of attenuated live viruses.

Contrary to previously held beliefs about poliovirus vaccines, evidence now exists that (i) the live virus vaccine cannot be administered without risk of inducing paralysis, (ii) the killed virus vaccine does suppress virus spread and can eradicate poliovirus from a population, (iii) booster doses of killed poliovirus vaccine are no more necessary than booster doses of live poliovirus vaccine, and (iv) an orally administered live poliovirus vaccine is not necessarily more effective or more acceptable for poliomyelitis immunization than a killed poliovirus vaccine administered by injection.

A killed poliovirus vaccine is safe and effective under all circumstances when properly prepared (*58, 114*). The live poliovirus vaccine carries a small, inherent risk of inducing paralytic poliomyelitis in vaccinated individuals or their contacts. Where paralytic poliomyelitis is prevalent, this risk is relatively less than that of the natural disease; but where naturally occurring poliomyelitis has been suppressed or eradicated, the risk from live poliovirus vaccine is greater than that from the natural disease. This is similar to the present situation with smallpox vaccine.

The live poliovirus vaccine has been the predominant cause of domestically arising cases of paralytic poliomyelitis in the United States since 1972. To avoid the occurrence of such cases, it would be necessary to discontinue the routine use of live poliovirus vaccine. Since poliomyelitis is still prevalent in many parts of the world, however, discontinuation of programs of routine vaccination would be unwise at this time. A killed poliovirus vaccine is available (*115*) both to maintain population immunity in areas of low poliovirus prevalence, such as the United States, and to eradicate poliovirus from areas of the world where poliomyelitis continues to be prevalent. The live virus vaccine should be used in the event of outbreaks of poliomyelitis in areas where unprotected individuals are at high risk.

A single vaccine against all known strains of influenza virus cannot be achieved with an aqueous preparation of killed viruses which can contain only a few strains because of the large quantity of each which is needed to stimulate immunity. It might possibly be achieved by a suitable combination of killed viruses or their purified antigens which is potentiated by an immunologic adjuvant. Water-in-oil emulsified vaccines more effectively evoke and maintain higher antibody titers than either aqueous vaccines or infection (*95*). More strains can be included in an adjuvant vaccine because smaller quantities of each antigen are required. Further enhancement is possible by choosing the most potent antigenic strains available to induce the broadest degree of antigenic cross-reactions.

If a new pandemic strain appears, the use of a potent immunologic adjuvant would permit more rapid and more economical production of large quantities of a monovalent influenza virus vaccine, because of the relatively small amounts of antigen needed. Use of an adjuvant would also permit the preparation of a polyvalent influenza vaccine which would allow routine immunization programs to be developed.

Only by raising and maintaining the immunity index of the population against all antigenic variants that are pathogenic in humans will we be able to control influenza effectively. We will gain further understanding of the requirements for controlling influenza only by continued basic research and by epidemiological studies in the course of attempting to prevent outbreaks. As Kilbourne has said, "one approaches the prospect of 'eradication' in biology with temerity, but it is not an impossible goal" (*6*, p. 538). With what is now known about the immune response, the influenza viruses, and immunologic adjuvants, we may well be able to do so.

Summary

The requirements for inducing immunity against an infectious disease are outlined, and the application of these requirements to the development of effective vaccines (vaccinology) is discussed. Influenza and poliomyelitis are examined from this viewpoint, and data are presented that demonstrate the effectiveness of killed virus vaccines against these diseases. A comparison between live and killed poliovirus vaccines suggests the desirability of returning to the use of a killed virus vaccine for the eradication of polio. The natural history of influenza and experience with vaccination suggest that influenza might be brought under effective control by routine immunization in childhood with a polyvalent killed virus vaccine potentiated by an immunologic adjuvant.

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Interpreting Cancer Survival Rates

The available data on survival are not a sensitive measure of progress in cancer control.

James E. Enstrom and Donald F. Austin

Recently there has been much discussion about the progress or lack of progress in cancer research and control in the United States during the last 25 years. Various authors (*1–4*) have employed cancer survival rates to support their opinions. For instance, Greenberg says (*2*):

> The lay press is unduly gullible in reporting "progress" in cancer treatment. The basis for this contention [is] that cancer survival rates, as reported by the National Cancer Institute, have shown little improvement over the past two decades or so, and that the frequent claims of markedly improved survival rates ignore or blur the fact that most of the changes occurred before 1950, and can probably be attributed to lower mortality from operations. . . .

Statisticians at the National Cancer Institute respond (*3*):

> The picture is neither as dull nor as bright as some have claimed. The improvement in patient survival observed during the 1940's and 1950's has generally slowed since then. However, continuing improvement in survival rates took place during the 1960's and is continuing into the 1970's for a substantial segment of cancers. In fact, prognosis for more than half of all patients with cancer is better now than it was 10 years ago. The recent upward trend is less dramatic, but it is nonetheless real and consequential.

One oncologist concludes (*4*):

> One measure of the very real and increasing progress that has occurred in applied and basic cancer research has been the controversy that it has engendered.

The purpose of this article is to put this discussion in perspective by pointing out the many limitations and qualifications in the interpretation of survival rates and their trends. This is not meant to be a comprehensive review of cancer survival rates, but rather a summary of several points necessary for understanding their meaning and their use.

Any discussion of "progress" must first state the goals toward which progress is to be measured. The National Cancer Act of 1971 created the National Cancer Program, for which the goals are specifically detailed in a National Cancer Plan (*5–7*). In general, the overall goal is "to develop the means to reduce the incidence, morbidity, and mortality of cancer in humans" (*5*). More specifically, it is to reduce the burden of cancer in the population by intervening in all of the following effects of cancer: premature death, presence of disease, persistent disability, somatic discomfort, subjective dissatisfaction, and social disruption. Thus any judgment regarding progress or lack of it must be based upon a measurement of change in one or more of these effects. Whether survival rates and their trends can be used to measure progress against any of the effects of cancer in the population is at issue.

A consideration of cancer survival rates and their trends should begin with an explanation of what these rates measure. Basically, they give the probability of a person's remaining alive for a specified period after being diagnosed as having cancer. The rates are expressed as the percentage of patients still alive at some specified time after the diagnosis. Thus, for any individual patient, survival is equivalent to a period of observation, the start being the point of diagnosis and the end being death or the completion of a specified number of years. Survival rates are most often used to evaluate the effectiveness of therapy in curing cancer, cure being usually defined as survival for at least 5 years. It is common to use relative survival rates, which adjust for the probability of dying from other causes.

Factors Influencing Survival Rates

A number of factors enter into the determination of survival rates. For the patient destined to terminate observation through death due to cancer, survival can be lengthened in either of two ways: first, the endpoint (death) can be displaced distally in time; second, the starting point (diagnosis) can be displaced proximally in time. For instance, every patient could be under observation 1 year longer if the diagnosis could be made 1 year earlier in the course of the disease. This would have the effect of creating a 5-year survival rate equivalent

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