Epidemiological Reviews
Vol. 21, No. 1

Printed in U.S.A.

Francis Field Trial of Inactivated Poliomyelitis Vaccine: Background and Lessons for Today

Arnold S. Monto

INTRODUCTION

The modern era of vaccine evaluation began with the landmark field trial of inactivated poliomyelitis vaccine conducted during 1954–1955 under the overall direction of Thomas Francis, Jr. The trial set the standard for the future by establishing the need for double-blind controlled assessment of vaccine efficacy. Other characteristics of the trial, such as definition of clear primary and secondary endpoints as ways to assess specified outcomes, also began the process culminating in currently accepted procedures. However, the trial also had features more similar to the then current laboratory investigations than to modern clinical trials, including evaluation of relative immunogenicity of different lots of vaccine. The fact that the trial was not conducted in a vacuum but, rather, under extreme levels of public scrutiny, also places the trial squarely at the start of the modern era. In particular, the choice of designs is illustrative of the conflict between the scientific requirement for randomization and the need to involve as many voluntary participants as possible in the evaluation of the vaccine under circumstances that were then deemed currently acceptable to them and to society. Obviously, the statistical analysis reflected the time; if the trial were conducted today, it would be analyzed differently and almost certainly would not be so large. The involvement of close to a million voluntary participants makes it unique in size alone. The regulatory climate at the time of the trial was totally different from that under which we currently operate, but the beginning of strict government oversight was an indirect result of the aftermath of the evaluation.

Received for publication October 19, 1998, and accepted for publication March 9, 1999.

Abbreviations: CDC, Communicable Disease Center; IBM, International Business Machines; ITT, intention to treat; OPV, oral poliomyelitis vaccine.

From the Department of Epidemiology, School of Public Health, University of Michigan, Ann Arbor, MI.

Reprint requests to Dr. Arnold S. Monto, School of Public Health, University of Michigan, 109 S. Observatory Street, Ann Arbor, MI 48109-2029.

Before reviewing details of the development of the vaccine and the changing distribution and characteristics of poliomyelitis leading up to the trial, it is useful to examine all of the various circumstances that came together in 1954. The first element was public awareness and anxiety, which not only established the priority attached to control of poliomyelitis but also the funding mechanism. From our current perspective, it is surprising that support for the trial itself, and much of the research leading up to it, did not come from government agencies or pharmaceutical manufacturers but, rather, from a voluntary organization, the National Foundation for Infantile Paralysis. This foundation was successful in raising funds for its activities not only because of the high visibility of the residual paralytic effects of the disease in its founder, President Franklin D. Roosevelt, but also because of the fear and apprehension which outbreaks of the disease caused in the general public. The emergence of the infection as an epidemic disease during the first half of the twentieth century is, then, the first part of the story.

The second element involves the laboratory developments which had moved from the very early demonstration of viral etiology in 1909 to use of animal models, and the later recognition that there were three immunologically distinct types of poliomyelitis. Inactivation was long established for production of a vaccine, and the first attempts at protection by vaccination actually occurred in the 1930s. However, it was the development of cell culture following the Nobel Prize winning work of Weller, Enders, and Robbins that lead to the ability to produce the virus safely and in sufficient quantity.

A third element, less well defined, is the early stages of development of the organizational and data management ability to conduct a large-scale trial. This will not be discussed to the same extent as the first two elements, but it was equally important in the success of the endeavor.

The causative agent and its epidemiology will first be reviewed as background to the trial. As a major public health problem, there is an extensive literature, composed of scientific papers, reviews, and meeting

reports on these subjects and which cover them in greater detail than will be done in this review. Epidemiology and virology will be discussed in parallel, since full understanding of one of these aspects is dependent on the other.

HISTORY OF POLIOMYELITIS AS AN EMERGING DISEASE

While poliomyelitis was not recognized as an epidemic disease in northern Europe until the late nineteenth century, it, like many infections termed emerging, is not new; rather, changes in characteristics of society, and in particular practices of sanitation, were responsible for its emergence as a major problem. Studies of Egyptian mummies have identified shortening of a lower limb, a characteristic of the late effect of poliomyelitis disease in a still-growing child (1). This and other evidence suggest that the virus was being transmitted during ancient times. At that time, it probably displayed the pattern of occurrence more recently recognized in developing countries before beginning the transition to industrialization, that is, occasional paralytic cases occurring sporadically in the few individuals who were not infected in early life, mainly in the upper classes. It is the upper class whose bodies would later be entombed in a recoverable form in Egypt. Most of the population would be infected in the first years of life, without producing the paralysis characteristic of the disease (2–4). We now know that this phenomenon was a result of an increased likelihood of infection being asymptomatic in young individuals, and maternal antibodies attenuating the infection, both factors contributing in debatable proportion (5). More recently, in countries such as Ghana and India, even though outbreaks were not reported, the residual paralysis typical of prior infection with poliomyelitis could be demonstrated in what has been termed lameness surveys. This brings us back to the method used to identify poliomyelitis occurrence in the Egyptian mummies (6–8).

Because of the dramatic and characteristic features of poliomyelitis, it is possible to identify historically the time of transition in the now developed world when the disease ceased to only be sporadic and began to occur in epidemics. Epidemics began to take place first in those countries in the forefront of development of hygienic standards, an apparent paradox to those not familiar with the transmission characteristics (9). Norway led the way in 1868, followed shortly thereafter by Sweden. Epidemics occurred for the first time in many parts of Western Europe in the 1880s and 1890s, while simultaneous outbreaks began in cities of the northeastern United States. The developing countries lagged far behind; evidence of such transmission was clearly documented in World War II when troops of young adults stationed in these developing countries experienced outbreaks of the paralytic form while no apparent illness was recognized in the local population (10, 11).

Because of the inability to identify the virus or antibodies to the virus in a convenient way, there was a good deal of speculation about how the agent was transmitted. The reason there was reluctance in some quarters to accept what is now considered obvious, a predominant fecal-oral mechanism, is that transmission did not follow the more familiar common source patterns, i.e., occurrence of milk and waterborne diseases such as those exhibited at that time by agents that cause such diseases as typhoid; also secondary cases followed the distribution more commonly associated with respiratory spread. It is now understood that agents, for example rotavirus, can be transmitted by the fecal-oral route and be characterized not by producing common source outbreaks but more by person to person transmission (12). The immune status of the population, the result of the high frequency of inapparent infection (not recognized at this time) was also responsible; the situation with hepatitis A is very similar, including the frequency of inapparent infection (6) in the very young (13).

The clinical presentation of poliomyelitis was so characteristic, with typical flaccid paralysis, that it was relatively easy to identify and quantify typical cases when epidemic behavior emerged. Thus, key epidemiologic features were documented during this early period. One curious observation was that once outbreaks began at the start of the century, they were extremely varied in intensity from year to year, but it was difficult to determine that a secular increase in incidence was truly taking place. In fact, in some cities outbreaks in the early part of the twentieth century were far larger than any occurring for some years thereafter (14). There was, however, a clear urban-rural differential at this early point, with far more cases occurring in urban areas. This was thought to be related to crowding which was extreme in the urban slums of the time. The disease was mainly one of young, often very young, children, thus the appropriateness of the name infantile paralysis. Seasonality in the regions experiencing outbreaks was pronounced, especially since all were in areas with distinct winter seasons (15). The summer predominance was used in the debate about spread to support the theory of fecal-oral transmission because of the similar seasonal occurrence of many enteric infections.

IDENTIFICATION OF THE POLIOVIRUS AND THE PROTECTIVE ANTIBODY

The agent of poliomyelitis was identified at a very early time relative to other viruses because of the abil-

ity to define the illness clinically, especially in the epidemic setting, and the ability to use an animal model in which disease could be produced. The first demonstration of the viral etiology of poliomyelitis virus was actually reported in 1909 by Lansteiner, who produced the disease in monkeys inoculated with human spinal cord (16). Thus, these early experiments demonstrated that the virus was found in neurologic tissue (17); another animal model, other than the nonhuman primate, was not identified for many years (18). In spite of obvious limitations, use of this model allowed further development of the understanding of the occurrence of poliomyelitis and its transmission. The later adaptation to the cotton rat and mouse was a great advance in the ability to propagate the virus, but for many purposes could not replace reliance on primates, even to show that virus was present (18). These limitations did not prevent experimental work on a vaccine to be attempted on two separate occasions in the 1930s (19, 20). The procedure was to inactivate the virus-containing animal material with formalin; the duration of formalization was felt to be critical as to whether the material for inoculation would remain immunogenic. However, it was complicated by the presence of large amounts of foreign proteins contained in the preparation, derived as it was from neurologic tissue. This led to the danger that in trying to retain immunogenicity, all virus would not be inactivated. First it was demonstrated that antibodies could be induced in rhesus monkeys without production of disease. Thereafter, "field studies" were conducted in children who were inoculated, and initially they were reported not to have experienced side effects aside from occasional reaction at the site of vaccination (20). In comparison with an uninoculated "control group," there was not only production of antibody in the thousands of children inoculated, but also protection from clinical disease. However, cases of poliomyelitis, apparently a result of the inoculation, began to be recognized after large numbers of individuals had been vaccinated, which put an end to this early attempt at immunization and indicated the importance of understanding and controlling the formalin inactivation process. However, it also did suggest that the inoculation of inactivated virus was a feasible way to induce antibodies, but that much more work in animals should be carried out before going back to humans.

Even with the cumbersome need for rhesus and other monkeys, it was learned from experiments in which the monkeys were inoculated first with a dose of a standard preparation calculated to produce antibodies, but not disease, and then with different challenge viruses calculated to produce disease, that sometimes monkeys were protected and sometimes they were not (21). Thus, it was hypothesized that there might be strains of virus which were different from others and that cross protection did not occur. Such observations go back as far as Burnet and Macnamara in 1931 (22). For a long period, viral isolates were given names with which they were identified, and thus there were many different strains. Order was restored by the observation in monkey experiments that there were three distinct types, each identified by a prototype strain, Brunhilde (type I), Lansing (type II), and Leon (type III) (23). This explained much that had previously been confusing and inexplicable and finally indicated that lack of protection in past experiments could have been a result of differences among types. However, at the same time it demonstrated that each of the three types would have to be represented in any vaccine.

POLIOMYELITIS EPIDEMIOLOGY IN THE PERIOD LEADING UP TO THE VACCINE FIELD TRIAL

Much of the understanding of the epidemiology of poliomyelitis in the period before the vaccine evaluations began was related to the laboratory developments described above. Increased availability of monkeys, and demonstration that infection in the chimpanzee was closest to the human, especially in terms of being infected by oral inoculation, allowed recognition of the dynamics of transmission of the virus and its pathogenesis (24). This increased availability of monkeys, still necessary at this point, was made possible by increased support from the National Foundation for Infantile Paralysis. Monkey inoculation of material collected from cases indicated that the virus was present not only in neural tissue of humans, but also in stools, throat swabs, and blood, demonstrating its widespread distribution in the body (25–27). As testing sera for the presence and rise in antibody titer became increasingly possible, the high frequency of asymptomatic infection became apparent, which, in turn, explained previous observations which had suggested that the disease was not communicable from person to person (28). The ability to carry out antibody studies also explained the occurrence of "virgin soil" outbreaks, such as on islands and in the arctic (29). Here, with the lack of introduction of the viruses for a considerable period of time there was broad absence of immunity; illness and transmission, when it occurred, was not restricted to younger individuals.

There continued to be vigorous debate about whether respiratory transmission occurred based on recovery of virus from the pharynx, but all were agreed that fecal-oral transmission was important, especially in less developed countries (30). Recovery of virus from stools and sewage, and demonstration that flies might also be involved in transmission, strengthened

the acceptance of the paramount role of ingestion of virus as had been documented in the chimpanzee model (31, 32).

The populations mainly affected by clinical disease were changing in the period leading up to the vaccine trial. This distribution had a direct effect on eventual planning of the trial once the inactivated vaccine was ready for evaluation. Comparisons of disease incidence in various groups over time are often fraught with difficulty, because changes in diagnostic criteria often occur which are not reflected in accompanying descriptions of methods. Some of the better data coming from areas with known consistency of reporting and definition were reported in a review presented by Sabin at the First International Poliomyelitis Conference held in 1948 in New York, under the sponsorship of the National Foundation for Infantile Paralysis (14). Two issues of interest related to transmission mechanisms and also to acquisition of immunity. These issues were examined with knowledge of the existence of asymptomatic and nonparalytic infection, but not with precise understanding of their relative frequency, given the limitations then existing in infection detection. One assumption used in the transmission discussion was that the previously documented urban-rural differential, as the disease became epidemic in the developed countries, had disappeared or very much lessened (33). This was thought to be related to a decrease in crowding in the cities compared with that which had existed earlier in the century. As would be expected, those who favored respiratory transmission took this as evidence for their theory, now supported by the documented existence of pharyngeal shedding. At the same time, the age distribution of cases in these cities had changed and the disease was no longer concentrated in the very young. Places where the change in incidence was clearly demonstrable were New York City, Cincinnati, Ohio, the State of Connecticut, and various cities in Sweden and Denmark (14). This phenomenon was not universal in all groups living in these locations; it was possible in some to distinguish disadvantaged segments of the population, and in these groups disease still predominated in infants and children aged 0 to 4 years, while in the remainder of the population the group most affected was children aged 5 to 9 years.

With the greater availability of laboratory techniques to identify antibody titer, serosurveys became possible in this period after World War II. Such surveys could then be used directly to confirm the extent of early, often inapparent infection, as well as to identify the groups remaining susceptible. One of the most important of these was carried out in sera collected from residents of various ages in Cairo, Egypt (34). It was demonstrated that antibody was acquired there very early in life, and that by age 2 years, 60–80 percent of the population was immune. This was contrasted with Miami, Florida, at approximately the same latitude, where a typical US pattern of seroprevalence was found; that is, the majority of children in the 5- to 9-year age group were still susceptible. These differences in seroprevalence further explained outbreaks that occurred in American school-aged children and the lack of similar outbreaks in Egypt. Further contemporaneous serosurvey data came from Charleston, West Virginia, which confirmed the importance in the US of the 5- to 9-year age group and also gave additional data on the distribution of antibodies by areas of residence. At ages 5–9 years, there was still 50 percent of the overall population without antibodies. However, in households rated as having poor cleanliness, over 80 percent of children in this age group already had antibodies. Similarly, children from families categorized as "middle class" were more susceptible than those documented as "low class" (35). Additional serologic studies documented that "virgin soil" outbreaks could be predicted and documented by antibody prevalence. Sera obtained from an isolated Alaskan community showed little antibody among younger individuals until a certain age group. Those younger then that age group had never experienced infection with a particular type of poliomyelitis, while in those older than that age group antibody was almost universally present (29). For one viral type it was found that there was no antibody present in individuals under 30 years of age. It could be expected that once introduced, an outbreak with high attack rate would result.

During the decades leading to the vaccine field trial, understanding the epidemiology was aided in a number of ways by the ability to detect the virus. For example, in terms of seasonality it was found that there were increased quantities of the agent in sewage associated with the summer transmission season (32). In terms of the individual, it was documented that persistent infection did not occur, and that the disease was truly acute with virus uniformly present in the blood. The two phases of disease were confirmed by laboratory studies, with the first phase related to gastrointestinal infection and the second associated with viremia and central nervous system invasion. These phases became a critical question in adopting a vaccine strategy, since inactivated vaccine would produce circulating antibodies but not coproantibodies, and thus not result in prevention of the first phase of viral replication, during which transmission to others could occur (36).

A final issue, later becoming a question of safety of vaccination, was initially viewed as epidemiologic since it was believed to be related to host or personal factors. The basic question was why some individuals

developed a paralytic disease as a result of their infection and others escaped with only an abortive illness or an inapparent infection. At this point it was already recognized that paralytic disease occurred in less than 1 percent of those infected, so any explanation for why certain persons were affected, and others not, was of major interest (37). A few identifiable events which appeared to be related to severity or localization of paralysis was referred to as "provocation." Among the events which were thought to provoke paralysis in a particular part of the body were accidents, surgical operations, and dental procedures (38, 39). There was universal acceptance of a relation between tonsillectomy and adenoidectomy and bulbar poliomyelitis (40, 41). However, most relevant to the vaccine trial was the increased probability of occurrence of paralysis in the limb in which a vaccination had been given recently.

DEVELOPMENT OF THE INACTIVATED VACCINE

The discovery that the various antigenic strains of polioviruses could be grouped into three distinct viral types and that protection from infection was type specific (reported above) meant that for a complete vaccine three different inactivated preparations would have to be made and combined (23). This complication was more than offset by a development which could truly be considered a breakthrough (a word the media tries to associate with any scientific advance). That breakthrough was the development in the late 1940s of modern cell culture technique, by Enders, Weller, and Robbins (42, 43); the importance of this advance was eventually recognized by their being awarded the Nobel Prize in Medicine. It is difficult 50 years later to appreciate how much this changed the state of affairs, especially since cell and tissue cultures had been in limited use for some years. However, the method was difficult and very limited in use, and the major problem was the requirement for strict aseptic techniques in the preantibiotic era. When antibiotics became available it was possible to prepare cultures of individual cells in quantity; previously, the manipulation necessary was extremely difficult if the cultures were to be kept free of contaminating bacteria. It was found that the polioviruses could easily be replicated in a number of cell cultures. The one chosen as ideal for vaccine purposes was monkey kidney, and the race was on to develop poliomyelitis vaccines, either inactivated or live attenuated or both. Even at that time there was a vigorous debate about the scientific and practical advantages and disadvantages of inactivated versus live vaccine, many elements of which have remained remarkably unchanged over time. The race was supported and organized in large part by the National Foundation for Infantile Paralysis, which as a voluntary organization could quickly move resources in specific directions, which would not have been possible otherwise.

It was decided that the inactivated vaccine approach was the one likely to be successful most quickly. There was a history going back to Pasteur of producing an inactivated vaccine, and the person given the responsibility for the eventual development of the poliomyelitis vaccine was Jonas Salk. There was also a precedent of chemical inactivation of the poliovirus for vaccine production, including the work in the 1930s described above and studies immediately preceding the work of Salk, particularly in the laboratories of the Department of Epidemiology of the Johns Hopkins University. These experiments used virus propagated in laboratory animals and took advantage of the recognition of the type specificity of protection in challenging monkeys with live virus after inoculation with the formalin-inactivated preparation. This allowed reduction in some of the inconsistencies found in previous studies, and identified that a reasonably high degree of protection could be achieved (44).

Salk and his Pittsburgh, Pennsylvania, colleagues pointed out the major advantages of cell culture-derived material for vaccine production (45). Virus could be produced in a concentrated state free of many of the extraneous proteins present in material derived from animal tissue. This had a number of positive results. First, the inactivation process was more predictable when working with a more purified preparation. The predictability was not only in terms of the safety in inactivating all virus, but also in insuring that the material retained its antigenicity. Second, it also made it possible to produce the vaccine in much greater volume using uniform production methods. Third, it decreased the reactivity of the vaccine since many adverse events are related to unnecessary foreign protein. However, it did not guarantee the absence of adventitious microbiologic agents, which could be derived from the material inoculated into the cell culture, the media in which the cells were propagated, or most likely, when using a source of cells, such as monkey kidney, from the animal from whom the organ was obtained. In terms of recognized contaminants, such as bacteria and known viruses, it was possible to use standard procedures to detect their presence. However, a concern was the possible presence of agents not yet recognized, since this was just at the dawn of the modern age of virology. Here, the inactivation process would be expected to destroy activity of these adventitious agents, but since they would be unrecognized by then available procedures, this could only be based on hope and not on certainty. In retrospect, this was a valid concern (46).

Salk had spent considerable time at the Department of Epidemiology of the University of Michigan under Francis, where he had worked with issues related to the inactivated influenza vaccine (47). It had been possible to develop this vaccine before cell cultures were available because the virus could be replicated in fertile hens' eggs. The concentrated influenza virus resulting was formalinized according to standard methods. There was never very great concern about completeness of inactivation, since non-inactivated influenza virions injected intramuscularly or subcutaneously would not be likely to cause any disease; however, with poliomyelitis, this would be much more critical. Thus, the kinetics of inactivation with formalin became a focus of research. The process was reported to proceed in a linear fashion, and to be affected by, among other factors, concentration of formalin, temperature, pH, and concentration of virus. Extraneous material such as cell debris, which might interfere with the process, was removed by filtration. Excess formaldehyde was destroyed by addition of sodium bisulfite. The method was developed to err on the side of complete inactivation of virus, even if this meant some loss of antigenicity. Safety testing was carefully designed to confirm the lack of active poliovirus or any other microbiologic contaminant, a point which later became critical (48).

Studies of immune response in humans followed the development of an apparently safe vaccine. These tests were in fact pilot studies for the field trial itself. Factors examined were the optimal dose required to produce an antibody response, the number of inoculations needed, and the value of booster doses. On the first point, reducing the viral load in the inoculum would allow more individuals to be vaccinated. There was examination of the use of adjuvants, but most attention was devoted to the aqueous preparation. One schedule that was examined was inoculation at 0, 2, 5, and 7 weeks. It was noted that even the first inoculation induced an antibody response. An inoculation at 7 months after the first injection produced a booster response in most recipients. A continuing concern, given the recent recognition that the various known polioviruses apparently fell into three different types, was whether all virus variants belonging to a single type would be affected by antibody raised by the strains included in the vaccine. While not studied extensively, it was shown for each of the three types that another variant of the same type was affected similarly to the homologous virus contained in the vaccine (48, 49).

THE FIELD TRIAL—PLANNING

The stage was then set for the evaluation of the efficacy and confirmation of the safety of the inactivated vaccine. As a large-scale national undertaking, there were currents and activities at various levels, public and personal, which affected the organization of and participation in the trial. The vaccine and schedule of inoculation by this time was not an issue. Before the trial began, a total of 7,000 children had been inoculated with vaccine prepared in the laboratories of Salk and coworkers at the University of Pittsburgh; Connaught Medical Research Laboratories (Swiftwater, Pennsylvania) used the same methodology (50). The design used in this pilot was to vaccinate certain children and observe others for comparison. The real purpose, while scaling up production of the trivalent vaccine, was to assure its safety. This had to be done in a very public manner because of the nature and scope of the forthcoming trial which was attracting speculation in the media about any possible side effect, including development of anti-kidney antibody in recipients in response to the injection of virus grown in monkey kidney.

The vaccine for the trial itself was prepared by a number of manufacturers, but even though significant variation in antibody response was later noted, each was always referred to only by number, thus preserving the anonymity of the producer. In addition to Connaught, other manufacturers were Eli Lilly and Company (Indianapolis, Indiana) and Parke-Davis (Detroit, Michigan). The name of the manufacturer also did not appear on the box containing the vaccine; the only identifier other than the lot number was that of the supplier, the National Foundation for Infantile Paralysis. Vaccine safety and antigenicity was determined by the manufacturer, confirmed in the Pittsburgh laboratories, and finally and officially by the Laboratory of Biologics Control, then part of the National Institutes of Health. The amount of vaccine required for the trial was large, but this system allowed systematic attention to be given to its production using methods that guaranteed safety.

The same could not be said for the much more formidable task of designing and organizing the trial itself. Books have been written about this subject and they have emphasized the personalities, the interpersonal relations, and the institutions involved (51). This review will concentrate on the key features of the trial, and will delve into the sometimes involved reasons, both of individuals and of policies, behind various choices made. The major position in the trial organization was its director. This appointment first went to Joseph Bell, a respected epidemiologist associated with the National Institutes of Health. During the time of his tenure, a design was endorsed which was similar to the pilot studies conducted by Salk. Based on the upward movement in age over the first half of the century to peak occurrence in children aged 5–9 years, it

was decided to conduct the trial in this age group. Involving children aged 5–9 years also had a logistic advantage, namely that they attend school, making them easily accessible for recruitment and for subsequent multiple contacts. The vaccine evaluation would involve children in grades 1, 2, and 3. The organizers were concerned that the various cooperating groups, such as local health departments and voluntary organizations, would not accept a design which included the injection of a placebo. This was based not only on the concern about unnecessary injections of non-vaccine-containing material, but the fact that it was thought that participation would depend on the hope that it would likely result in protection from poliomyelitis. Thus, it was decided to vaccinate any child in the second grade whose parents requested it, and compare the frequency of illness with that of the unvaccinated first and third grades. Since immunity increased with increasing age, it was thought that the second grade would be intermediate in susceptibility between the two observed grades.

When Bell resigned as director of the study, the position was offered to Thomas Francis, Jr., founding chairman of the Department of Epidemiology of the University of Michigan School of Public Health. Francis attached a number of conditions to his accepting the position. In this, as in many aspects of the trial, other groups and individuals also took part in the discussions (52). The most important one was a reexamination of the basic study design. This followed meetings with experts in biostatistics, such as Bradford Hill. Another condition was assured independence of the evaluation team so that, for example, neither Basil O'Connor, the President of the National Foundation for Infantile Paralysis, nor Jonas Salk, developer of the vaccine, would have access to the conduct of the trial and knowledge of the data accumulating. In this, as in other ways, the poliomyelitis trial developed the standard of independence and blinding which would be considered essential in all later vaccine evaluations.

In terms of reevaluating the study design, there was no disagreement with the need to involve young school-age children for the reasons noted above. However, the major question was lack of blinding and randomization and, thus, an additional design was proposed. This additional design would not replace the observed control design, given the commitment of certain jurisdictions to it. Instead of only the second-grade students being eligible for participation, all three grades would be eligible, but they would be randomized with half of the voluntary participants receiving vaccine and the other half receiving placebo. The placebo was to be an injected one, a most controversial issue, since it meant that an invasive action took place with no possible benefit to the recipient. It was, however, an essential element in the design, since without it true blinding would have been impossible. It was a double-blind design, with neither the participant nor the observer being aware of the content of the inoculation. The boxes containing the vials, and the vials themselves, were labeled identically. Care had to be taken in ensuring longitudinal continuity given the fact that each child received not one but a series of inoculations. These had to be either placebo or vaccine in each case. This was, in fact, originally considered a major barrier to the placebo design. The same continuity was required to be able, after the trial, to examine lot to lot variation in the antibody response to vaccine of different sources or periods of production so that children continued to be given vaccine from the same lot.

The most important advantage of this design, compared with the observed control one, was the ability to compare directly the vaccinated with the placebo groups. There were multiple reasons why this was the case. There was the obvious issue of lack of blinding in the observed design, with all those inoculated knowing they received vaccine in terms of recognition of the occurrence of the disease in question. This was less of a problem with poliomyelitis, which was reasonably well defined, than it would be with other diseases. Still there could be a question of bias in case finding. Then, there was a difference in age group in the observed design, represented by the three grades, which might lead to the two groups not being comparable. However, the critical problem was the lack of an appropriate comparison group. In the observed control approach, children in the second grade would either have informed consent from their parents to be vaccinated, or as it was called at that time, a "request to participate." This meant very clearly that those who were willing to participate were expecting to receive the inactivated vaccine and were potentially different in relation to their risk of poliomyelitis from those who were unwilling to participate. In contrast, no such vaccination was offered to children in the first and third grades, and the comparison data were collected from "the willing and the unwilling" as stated in the study report. The result in this design was that it was impossible to determine which children in these grades would have participated had that option been given, and which ones would not. Participation in experimental studies was known to have a number of determinants. For this trial, the one easiest to document was socioeconomic, with participants more likely coming from those with greater education and income. This meant, considering the known distribution of poliomyelitis antibodies, that those in second grade who were participating would be more likely to be sus-

ceptible to poliomyelitis, because of lack of past asymptomatic infection, than those not participating. The observed first- and third-grade children would be a combination of the two, in unknown proportions, because their participation had never been requested. Other factors less easy to document could also make the two groups noncomparable. In contrast, the placebo design, because of randomization, ensured that participants in the two groups would likely be comparable in numbers and characteristics.

Before Francis had been persuaded to accept the leadership of the evaluation center, there were a number of state and other jurisdictions that had accepted the observed design and were committed to it. As a result, with the addition of the placebo design there were two parallel methods for assessing the efficacy of the vaccine. Areas which participated are shown in figure 1, with the accepted design indicated. This produced an experiment within an experiment, with comparison of results of the two designs being possible. A complication was that it meant that both had to be analyzed separately, since they were in fact incompatible for pooling results. As it turned out, there were approximately equal numbers given the vaccine in both designs, although there were more comparison children in the observed design.

The selection of the geographic areas for participation was carried out in a relatively systematic fashion. Of course no area would be selected for participation without interest on the part of the residents and the local health officers and other officials. The aim was to identify areas large enough to contribute a reasonable number of participants, and which historically had a higher than average frequency of paralytic poliomyelitis. The work of Stickle had found that counties with a population of 50,000 to 200,000 experienced a higher than average annual attack rate than larger, more populous areas (50). Areas with less population experienced even higher rates, but were not suitable for logistic reasons. He also found that counties with the highest attack rates within this group continued for a period of years to demonstrate such high rates, and that variability among counties was more than three times greater than the year to year variance within countries. Thus it was recommended that areas should be selected in the appropriate population range which also had reported higher than normal attack rates in the period 1948–1952, the last period for which data were available. This plan would prove to be successful. The average annual attack rate in counties with a population of 50,000–200,000 in 1948–1952 was 24 per 100,000. In the trial year, the frequency in areas selected was actually 28 per 100,000 and in nontrial areas, 22 per 100,000. For operational reasons preference was given to jurisdictions with well organized health services as well as to regions where there was expressed interest in participation, especially from school officials, since schools would be the point of access to the children. A final consideration was that there not be active poliovirus transmission occurring at the time inoculations were to start, out of concern for the issues of provocation and safety of the vaccine, which could be difficult to evaluate in this situation. If this was the case, then the affected areas were dropped from participation. Nearly all of the study was conducted in the United States where the above data were available, but there were also participating areas in three Canadian provinces and a small area of Finland.

SIZE OF THE TRIAL/REQUIRED SAMPLE SIZE

The poliomyelitis field trial was unlike current clinical trials of vaccine and other interventions in that its size was driven as much by logistics and supply of vaccine as by sample size estimation. Another factor in the large size was the two designs, which in reality could not be combined in analysis. A total of 432,217 children were actually inoculated with vaccine at least once, 209,229 in the placebo areas and 231,902 in the observed areas. These numbers, as well as the numbers who received placebo in the first design and the observed comparison group or in the second design, are shown in table 1. If the study were being done today, its size would be determined by sample size calculations based on various estimates of disease rate, and vaccine effect. Generally these assumptions are difficult to develop since there is often imperfect information on many factors underlying disease rates, aside from the unknown efficacy of the vaccine. In the poliomyelitis field trail, there was better than usual ability to predict the incidence of disease. Incidence should have been higher than the average of 24 per 100,000 in the counties of the size preferentially chosen, since history of past higher incidence was also a selection criterion. On the assumption that the incidence would be 26 per 100,000, it is possible to estimate required numbers in the placebo control design. It is not possible to estimate numbers for the observed design without many more difficult assumptions, since this is not standard field trial methodology. Assuming 70 percent efficacy of vaccine in a two-sided test with an alpha of 0.05 and a beta of 0.10, approximately 107,100 per group would have been required to show a significant difference. If the assumption was that the vaccine was 80 percent effective, the number per group would drop to approximately 75,500. As can be seen from table 1, the actual numbers included in each arm of the placebo control design were almost twice that required for the more conservative assumption of efficacy. If the trial were done today, a reason for

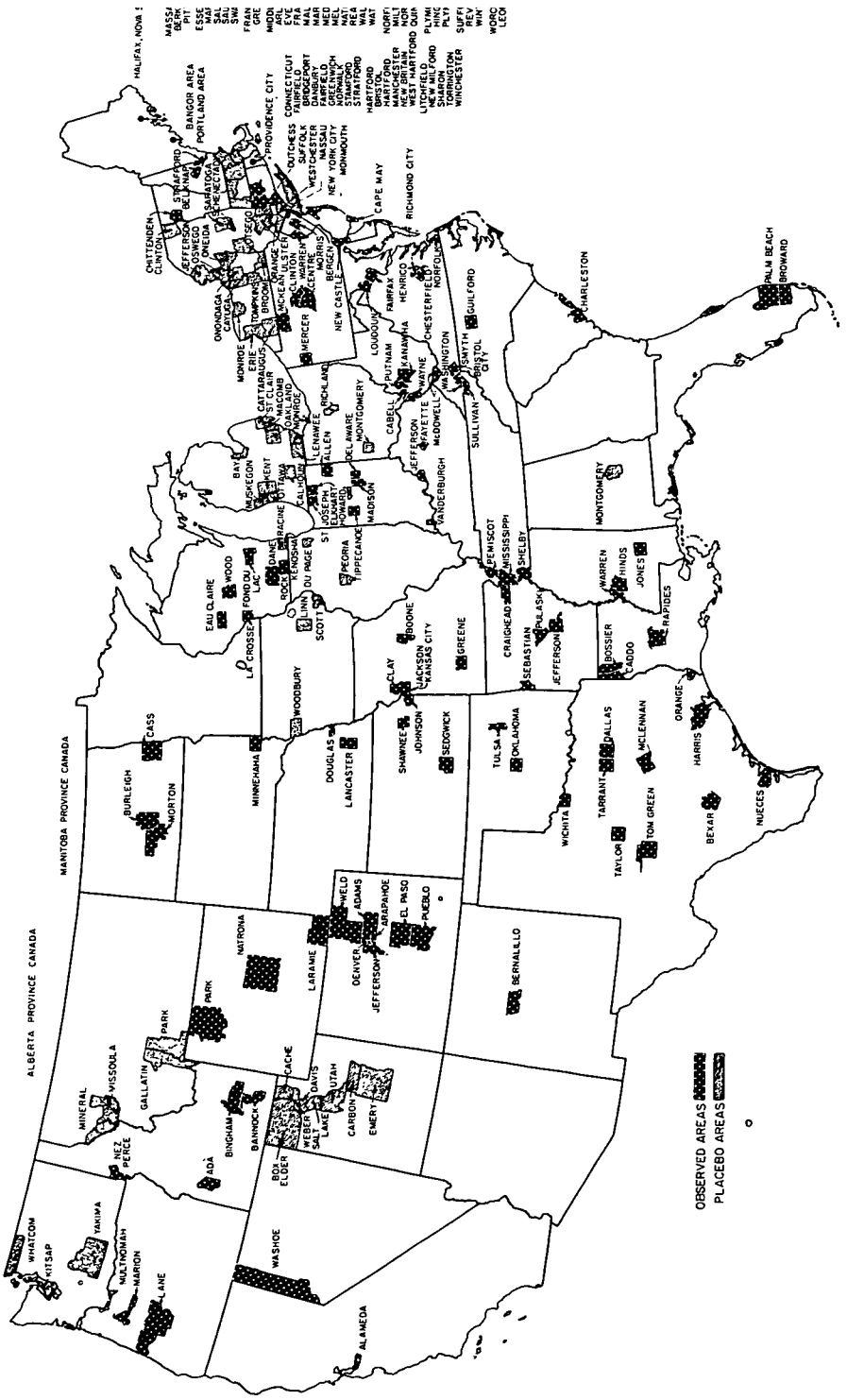

FIGURE 1. The 1954 poliomyelitis vaccine field trial areas.

TABLE 1. Numbers and distribution of the 1,829,916 children participating in the poliomyelitis field trial

	No.	%
Placebo design		
Vaccinated	200,745	26.8
Placebo	201,229	26.9
Incomplete vaccination	8,484	1.1
Incomplete placebo injections	8,577	1.1
Nonparticipants	330,201	44.1
Total	749,236	100.0
Observed design		
Vaccinated–second grade	221,998	20.5
First and third grades	725,173	67.1
Incomplete vaccination–second grade	9,904	0.9
Second grade, not inoculated	123,605	11.5
Total	1,080,680	100.0

increasing the sample size would be to make the confidence interval around the point estimate smaller. Confidence intervals were not generally reported at the time, although they were calculated for the scientific community.

The principal reason for having a larger sample size than estimated is to be able to achieve a clear result, even if the estimates are not current. There is nothing more difficult to explain than obtaining no clear answer, especially in something as public as this trial. For this reason one rule of thumb, if logistically possible, is to double the estimated numbers per group, but again, the trial went beyond this. It did allow the ability to analyze subset populations, which are equally important reasons for larger numbers. The observed design could not serve to augment numbers but only to give confirmation, since there was no way results from the two methods could be combined. The large size of the trial and the use of two designs had some practical consequences: both designs needed laboratory and administrative support, which was the reason Francis moved out of his departmental office in the University of Michigan School of Public Health and into special offices dedicated to the evaluation center, its staff, and records.

SELECTION OF ENDPOINTS

In designing the protocol of any clinical trial conducted today, there would be a requirement that the endpoints and case definitions be clearly laid out in advance. In fact, regulatory authorities hold the investigators to these predetermined endpoints to avoid what is sometimes termed "data dredging," or looking for those outcomes for which significant differences would be found. In the poliomyelitis trial, classification of cases was carefully derived from examining characteristics after they were reported. Classification was always made before breaking of the code so that the investigators were unaware of whether the child in question was a recipient of vaccine or placebo. This is, of course, a deficiency of the observed design since no blinding was possible, but the same case definition was used as in the placebo-controlled design (50).

A basic question in deriving the case definitions, given the ability at that time to determine whether a suspected case was poliomyelitis, was whether laboratory confirmation would be required or whether clinical characteristics would be sufficient to determine that a case had in fact occurred. The decision made was that laboratory confirmation was not going to be required since it might prove difficult to get the appropriate specimens in time; rather, virologic data was used as part of an overall process of making a decision on case status. The case definitions themselves basically categorized children reported to the study with illness on the presence and extent of paralysis. Paralysis became key for a number of reasons, including recognition of the role of other enteroviruses in producing illnesses which had considerable resemblance to cases of poliomyelitis but were without similar extent of clinical disease.

Data on potential cases occurring in any child in the first through third grades were collected and followed up whether participation had been requested or not. For completeness of reporting, the then named Communicable Disease Center (CDC) and its Epidemic Intelligence Service officers were involved in follow-up. Physical therapists were employed to determine the presence and extent of paralysis. Categories used were paralytic poliomyelitis, nonparalytic poliomyelitis, doubtful poliomyelitis, and not poliomyelitis. The decision about final classification was complicated, and, as pointed out repeatedly, was arrived at without knowledge of vaccination status. Today, such a complicated system would probably not be permitted in a definitive investigation under regulatory review, except perhaps in a phase II or pilot study. It is not at all clear that current insistence on an a priori classification scheme, and not one which evolves early in a study when blinding is still in place, has resulted in an improvement in precision of endpoint definition, especially when such a scheme is difficult to establish.

In practice, paralytic poliomyelitis, the most critical outcome, was first defined on clinical criteria. If there was also virologic evidence of infection, and the type was identified either by virus isolation or serology, then the case was assigned to that viral type. A problem arose when laboratory confirmation was negative or equivocal. In this situation "the tendency was clearly to lean to a diagnosis of paralytic poliomyelitis" (50, pp. 110–111). This was true even in the situation where

other viruses were isolated, as long as the clinical picture was compatible with a poliomyelitis diagnosis. The next diagnosis in the hierarchy, nonparalytic poliomyelitis, was, as stated, "a difficult group to define." (50, pp. 110–111). To be included, a case had to have comparable clinical characteristics, but no residual paralysis as determined by the physical therapist. This diagnosis was made with or without virologic evidence. The categories doubtful poliomyelitis and not poliomyelitis were even less specifically defined, and were included in the tabulations to ensure completeness. The key outcomes, then, were paralytic poliomyelitis, of which a large subset could be confirmed virologically (more than 70 percent of those with specimens collected), and the more questionable nonparalytic poliomyelitis.

CONDUCT OF THE TRIAL: RECRUITMENT AND INOCULATION

As can be imagined, the trial was an enormous undertaking, with the contribution of many groups and individuals such as Robert Korns, Fay Hemphill, John Napier, and Herbert Wenner. The schools and local health authorities were the main points of contact between participants and their families and the trial activities (50). In fact, the time when school was open determined much of the scheduling of contacts. Such collaboration between school administration and the health system would be difficult to envision now for many reasons, including privacy and other medicolegal issues. This level of cooperation reflects the intense public interest in the trial at the time and the feeling that it was a grand national undertaking. First, all children in the participating three grades were registered, and this register checked for completeness. This was to be used as the denominator in calculating certain frequencies of outcomes. The so-called "request for participation" was administered to families of all eligible children. A different request was used in the observed areas, where parents of children in the first and third grades were asked to agree even though no vaccine was to be given to these children. In fact, potential cases of poliomyelitis in participating schools were followed even when no individual consent had been given. The children who were to be inoculated would receive the poliomyelitis vaccine or, in the case of the randomized group, placebo on the schedule of 0, 1–2 weeks, and 5 weeks. This schedule emerged from the pilot tests of Salk et al. (48). The inoculations needed to be given before schools closed in 1954 and also before the start of the poliomyelitis epidemic season. It was well recognized that the epidemic season began earlier in warmer regions. The vaccination period ran from April to June 1954, with earlier inoculations given in the southern United States. The participating areas in Canada and Finland employed a delayed start.

There were dropouts in the course of the inoculation schedules, which produced another category, incomplete vaccinations. The possible differential antibody response to components in the vaccine was a major question, as was the proportion of children already naturally immune at the start of the course of immunization. Therefore, collection of blood specimens was a key part of the trial. This was done from a subset of participants in a systematic, rather than a random fashion. There was neither a necessity nor was it feasible to have these specimens collected from more than 2 percent (or a minimum of 100 children) in each participating study area. In the observed areas, control children were also included but limited to those whose parents had requested participation. These specimens were collected for comparison to detect the possibility that infection stimulated the antibody response between inoculations and the potential occurrence of illness over the subsequent summer. The first specimen was taken before the time of the first inoculation, or an equivalent time for the observed controls. The second was obtained 2 weeks after the time of the third injection. Collecting these specimens sometimes required obtaining the blood after schools had closed. This blood was timed to be at the point when antibody would have reached a peak. The third blood specimen was collected in November 1954, after the summer poliomyelitis season. The overall number of third bloods collected in the placebo area was 12,558, approximately equally distributed between vaccinated and placebo groups. In the observed areas, 20,944 third bloods were collected, with 44 percent of these from vaccinated children.

DATA MANAGEMENT

From a current perspective, the idea that a study which involved almost two million children could be analyzed with only the technology of the mid-1950s is hard to believe. One of the few groups of the time used to dealing with data from large numbers of individuals was the Bureau of the Census, and personnel from that organization were recruited for staffing the evaluation center. Data entry and management were contracted to International Business Machines (IBM), but given the state of automatic processing at that time, much of this work was done by clerical staff who entered the data in longhand as well as by punching IBM cards. Records for 1,873,483 children had to be created and maintained, as well as updated periodically (50). At the peak of activities, there were 118 persons employed as statistical clerks, supervisors, and typists. There was considerable attention to detail, with procedures in place for documenting receipt, for editing and coding data, and for detecting and correcting errors made in the field clinics. Standard proportions of data were verified, a method

still practiced in most large studies. Approximately two million basic study identifier cards were punched by the IBM Service Bureau in Detroit, Michigan, again with multiple quality control procedures. Tabulation was done mechanically using the largest machines available at that time, with further calculations carried out by the study's statisticians.

Vaccination and pre-outbreak bleedings concluded just before or shortly after the close of school in June 1954. The remainder of the summer was the period for collection of data on the outbreak and its results. Autumn and winter 1954–1955, were periods for conducting laboratory tests, refining and confirming diagnoses, and then performing analyses on the tabulated results (53). Data on side effects and other possible adverse effects were also gathered. The code was finally broken, but only at that time for those needing the information to conclude their analysis and to prepare documents containing summaries of the results (54, 55).

ANALYSIS OF DATA AND RESULTS

The evaluation and its analysis were done in a totally independent fashion, divorced from the developers of the vaccine and other intensely interested parties such as the National Foundation for Infantile Paralysis and the press. The announcement of the results was organized as a media event; this was in recognition of the fact that even if it were handled in the usual manner, that is, at a scientific meeting, it would still attract so much attention as to become the central focus and detract from everything else. The data were ready for release by spring 1955. There was a desire not to have a hiatus in vaccine distribution before the next summer poliomyelitis season, and the time of the first announcement was driven by this concern. In fact, the final study report did not appear for another 2 years. In what was referred to somewhat facetiously as a coincidence, the announcement was made at the University of Michigan at 10:00 a.m. on April 12, 1955, the anniversary of the death of the late President Franklin D. Roosevelt (51). The report that the vaccine "worked" set off national headlines and jubilation and was followed almost immediately by the licensure of the vaccine, which had already been produced and distributed. The essential results are shown in table 2, with little modification from the way they were originally presented except for certain combination of groups. An unusual feature in the table, to the modern reader, is the lack of any reference to statistical significance. This did not indicate, as will be discussed, that statistical issues, especially p values, were not recorded as a necessary consideration, but, rather, it reflected the era and the lack of our current slavish reverence for significance testing often over other relevant concerns. It also may have indicated the realization that differences in this trial could have been statistically significant even in the absence of effects that would have been important from a public health standpoint, given its large size. The key endpoint was paralytic poliomyelitis, a subset in the category of total poliomyelitis, which also included nonparalytic poliomyelitis. The placebo design is the one most relevant to the current observer, since it remains the standard for vaccine evaluation. Efficacy or percent reduction (1 minus incidence in the vaccinated/incidence in the comparison group) was not calculated in the summary, but was in the statistical section of the full report. The critical comparison was vaccinated individuals who had completed the full schedule of inoculations compared with placebo children who had also been completely inoculated. The efficacy of preventing paralytic poliomyelitis was 70.0 percent; the 95 percent confidence interval, calculated according to a one-sided

TABLE 2. Summary results: episodes of defined events in participants in the two designs and attack rates per 100,000*

	Paralytic poliomyelitis		Nonparalytic poliomyelitis		Doubtful poliomyelitis		Not poliomyelitis	
	No.	Attack rate*	No.	Attack rate*	No.	Attack rate*	No.	Attack rate*
Placebo design†								
Vaccinated	33	16.4	23	11.5	10	5.0	15	7.5
Placebo	110	54.7	28	13.9	7	3.5	17	8.4
Incomplete vaccination	2	24.5						
Incomplete placebo	4	46.6	2	23.3				
Nonparticipants	118	35.7	35	10.6	7	2.1	17	5.1
Observed design†								
Vaccinated, second grade	38	17.1	17	7.7	121	5.4	8	3.6
First and third grades (controls)	331	45.6	60	8.3	24	3.3	25	3.4
Incomplete vaccinations	4	40.4						
Second grade, not inoculated	42	34.0	11	8.9	6	4.9	6	4.9

* Attack rate per 100,000
† For numbers in groups, see table 1.

method used at the time, had a lower limit of 58 percent ($p < 0.001$). At present, most regulatory authorities would allow analysis limited to those completely vaccinated only as a secondary, and not as a primary, analysis. The point of randomization is considered the defining moment in a clinical trial, since it is at that point that the population in both groups should be totally comparable in terms of those characteristics affecting the endpoint. This is now called an "intention to treat," or ITT analysis. At the time of the poliomyelitis trial, this was not a concern of the investigators who never combined the partially inoculated groups with others. They were more concerned with the scientific question of the response to the recommended course of vaccination in the inoculated and in the comparable placebo group. When an ITT analysis is performed on the data presented in table 2, the efficacy determination only drops to 69.3 percent (1 – 16.7/54.3), only slightly lower than that in the completely inoculated. The issue of whether the results in the appropriately vaccinated or the ITT population should be the focus of attention in trials in which there is more divergence between results is an open one, but not, in general, to regulatory authorities. It would not have been a problem here, given the low frequency of noncompliance.

Results for other outcomes among the fully inoculated confirmed the lower specificity of these diagnoses. For example, the efficacy for nonparalytic poliomyelitis (17.9 percent) was much lower than the efficacy for paralytic poliomyelitis. Because of a commitment reached prior to breaking the code, the paralytic and nonparalytic cases were combined (not shown) into a category called total poliomyelitis. This was not used in discussions of the significance of results. Another interesting comparison, yielding information more on characteristics of participation in a trial of this sort, is the frequency of illness between the placebo group and the nonparticipants in the second grade. Frequency of paralytic polio per 100,000 was 54.6 in the placebo recipients and 36 in the "not inoculated" group. This indicates a greater susceptibility in those who agreed to be randomized, which is in keeping with the fact that volunteering for such a trial is more likely to occur in those from more educated and, in general, a higher socioeconomic background with more susceptibility to infection. This issue reappears in interpretation of the results of the observed design. Other issues which would have been raised if this study were done today are many. One would involve the question of multiple geographic sites. There is a tendency to stratify in analysis when there is evidence of differences in important variables such as attack rates. It is unlikely that any major change would have occurred in the level of statistical significance even if this had been done.

Results of the observed control design are also shown in table 2, with the outcome categories identical to those in the placebo design. Again, the outcome of paralytic poliomyelitis is the one least subject to misclassification and most comparable to the results of the other design. The internal comparison closest to that in the placebo design is between those in the second grade whose parents agreed to have them vaccinated and the entire first and third grades. This efficacy of vaccination is 62.5 percent, with a lower limit of the 95 percent confidence interval of 49.0 ($p < 0.001$). This lower point estimate of efficacy compared with that in the placebo design, while not statistically significant, can be explained by the same phenomenon already described in that analysis. The first and third grade controls contained both individuals who would have participated in a trial if given a chance, and those who would not. The latter would likely have had a lower attack rate because those in lower socioeconomic groups were no longer susceptible. With the lack of appropriate comparison groups in the results from this design, it is impossible to verify this explanation internally. However, it agrees with the internal comparisons from the placebo design. This lower efficacy estimate might have raised questions about the value of vaccination; these questions were not raised because of the results from the placebo design and other evidence from within the trial of differential antibody response by lot number and a new inoculation schedule resulting in higher antibody titers presented by Salk on the day of the announcement by Francis (56).

SEROLOGIC RESPONSE AND SAFETY

Examination of antibodies of children from whom blood had been collected gave information on the proportion of the population susceptible to infection with each of the three types of poliovirus, and the antibody response to the three types. These results were not used to modify the overall efficacy estimations of the vaccine; they were employed primarily to explain the results and to suggest ways to produce protection at a higher frequency than that achieved in this field trial. In keeping the focus on the primary outcome, the trial was similar to methods now used in clinical investigation. Indeed it would have been difficult, if not impossible, to use these findings to modify the outcomes because few events occurred in those from whom bloods had been collected. Results of examination of lot to lot response to the vaccine were reported in some detail, but it is difficult to relate these to a manufacturer or other obvious source of variation, except for one factor, use of merthiolate as a preservative (50, 57). This compound was added to some vaccine lots to preserve sterility and, as a result, inadvertently potency was lowered. Based on this examination of antibody response, it was obvious that the 70 percent efficacy estimate would have been higher if all of the vaccine had behaved as well as the better lots. In

fact, failures among vaccinees were individually evaluated and were related to lack of antibody response, and perhaps lack of duration of antibody. This was determined from blood specimens collected acutely when cases occurred, before there would be an antibody response to the infection itself (50).

Safety of the vaccine was always a prime concern and had been raised as a major issue by some in the media. It was quite clear with exhaustive testing that there were few side effects associated with the vaccine. In Pittsburgh, where Salk's laboratories were located, there was a follow up of school absenteeism following vaccination. The observed design seems to have been used in these schools, and there was actually somewhat more absenteeism in children who were not vaccinated than among those children who were. Absenteeism studies were also conducted elsewhere among students participating in the placebo design. Children in the placebo and vaccine groups had an equivalent frequency of absenteeism, but the nonparticipants had much lower frequency, because a chicken pox outbreak had involved mainly the participants. This was taken as again indicating the different backgrounds of participants and nonparticipants (50). Also, there was no evidence of infection by non-inactivated virus contained in the vaccine, another concern.

The issue of anti-kidney antibodies as a side effect of injecting a vaccine produced in monkey kidney had been raised prior to the trial. Neva and Salk (58) studied renal function in vaccinees and found no evidence of reduced activity by the then available techniques. The antibodies themselves were also sought and not found in small numbers of individuals. The question of provocation by the inoculations was taken very seriously and extensive tabulations did not indicate any evidence of difference in location of paralysis if it did occur. Provocation has recently been reconfirmed as a real phenomenon, but only when wild poliovirus is circulating (59).

After the morning announcement by Francis on April 12, 1955, Salk, who was a national hero in view of the rapid, successful development of the vaccine, addressed a news conference. In this setting, he presented a report, published shortly thereafter, concerning an improved schedule for vaccination, designed to induce antibodies more quickly among the next group of vaccinees (56). This was viewed by many as unfortunate timing, since it detracted from the main announcement of success of the trial and also addressed the issue of antibody response in relation to efficacy which was avoided so as not to confuse the message. First, he recommended separating the first two inoculations, which had been given close to each other in the trial, to 4 weeks apart; this schedule has become standard for many inactivated preparations. He also recommended that a booster inoculation be given no earlier than 7 months from the first dose. This shorter interval could be used to complete the three dose schedule before the summer poliomyelitis season, that is, when initial doses are given in the autumn. In addition, he also recommended that all children vaccinated in the 1954 trial be given another inoculation of vaccine since all that had been accomplished with the three doses given over 5 weeks would be primary immunization and a booster was still necessary. In fact, the validity of this recommendation was confirmed in a study in Michigan in which a booster dose was given 1 year after the immunization in the field trial (60). The bloods collected before this booster inoculation again demonstrated the dramatic lot to lot variation of the vaccine used in the field trial, reflected in antibody status, but all responded satisfactorily to the booster dose. Once this booster inoculation was given, antibody titers remained elevated for years (61, 62).

EVENTS FOLLOWING THE FIELD TRIAL: THE CUTTER INCIDENT AND LIVE VACCINE

The licensure of the inactivated poliomyelitis vaccine for nonexperimental national use followed immediately after the April 12, 1955, announcement. Vaccine was still in short supply, and the six manufacturers now involved were attempting to meet the pent-up demand. Starting April 25, 1955, cases began to be reported among the recipients of vaccine prepared by one of the manufacturers, Cutter Laboratories, Berkeley, California. By April 27, 1955, the vaccine produced by Cutter was recalled. In addition, the Public Health Service took other vigorous actions to address the problem represented by these cases, both in terms of laboratory manufacturing procedures and epidemiologic surveillance for potential cases. Because of questions regarding production, inoculations of vaccines from all manufacturers were suspended on May 7, until vaccine lots already produced could be recleared and inspection of the various plants and procedures could be accomplished. By June 1, 1995, the reclearance process was completed (63). However, in reality, because of the chaos resulting from these events and concerns about vaccinating in the midst of a summer with extensive transmission of wild poliovirus, the vaccine programs did not resume in earnest until autumn, 1955 (64).

The Cutter incident was temporally almost a continuation of the field trial, and in many ways the incredible speed and decisiveness of the official response grew out of it. Had the data from the trial not been so solid on the safety of the vaccine, the occurrence of vaccine-associated cases could not have been dealt with so decisively. The exact production problem that Cutter, and only Cutter, had was never accepted by all involved, since it involved legal liability. It was clearly related to

the much larger scale of production required for a licensed vaccine than for use in the experimental setting. The supposition was that virus may have clumped, and thus resisted inactivation by formaldehyde, or that it contained more foreign protein than optimal, thus also reducing the action of formaldehyde on the virus. Whether this was related to errors in following specifications or lack of anticipation of these factors in the specifications is not relevant; what is clear is that the problem was quickly and completely solved and the only reason that many individuals were affected in such a short time was related to the high demand for vaccine during this period. The rapid recognition of cases of vaccine-associated poliomyelitis was also related to the occurrence of the incident. Since this took place before the summer season, when wild virus would rarely be encountered, the cases could be more easily recognized (65).

For the next 6 years, inactivated vaccine was used extensively in children in the United States and many other countries. No further accidents occurred during this period despite continuation of intensive surveillance by the CDC, reassuring the public whose confidence had been rapidly eroded by the Cutter incident. The incidence of poliomyelitis had fallen dramatically to 0.8 cases per 100,000 (66). In 1961, the live attenuated vaccine or oral poliomyelitis vaccine (OPV) was licensed, leading to a further dramatic fall in cases over time (67). This vaccine had its most convincing effects in countries such as Israel and Czechoslovakia where the disease still predominated in young children, and groups which could be more easily immunized with a vaccine, such as OPV, not requiring several inoculations to achieve protection (68, 69). However, vaccine associated reactions began to be related to OPV as well (70, 71). It is instructive to compare the response and action taken to these adverse events with those in the Cutter incident. The vaccine-associated cases associated with OPV were harder to recognize definitively since the cause was a rare event, reversion of an attenuated vaccine virus to wild disease-producing status. Studies over several years were required, especially since wild nonvaccine-associated cases were still occurring. The epidemiologic studies were convincing; however it took much longer for appropriate decisions to be made because of resistance on the part of certain individuals to accept the fact that such events could be occurring. This shows the advantage of the strong consensus created by the 1954–1955 poliomyelitis field trial which allowed rapid response to the occurrence of vaccine-associated disease. The nature of the two problems, one a defect in production and testing of the product and the other an inherent characteristic of the vaccine viruses, made the response totally different. Still, had the acceptance of the situation come earlier, recommendations about use of OPV in, for example, unvaccinated adults who are at increased risk of vaccine-associated paralysis (compared with infants and children) could have been different, and supplies of inactivated vaccine, for a period unavailable in the United States, would have been maintained (71).

THE CURRENT SITUATION: RETURN OF THE INACTIVATED VACCINE

After its introduction, the oral poliomyelitis vaccine totally supplanted the inactivated vaccine in most of the world. In the developed and newly industrialized countries, the attraction was ease of administration and the fact that, with the generation of intestinal immunity, usually thought not to be produced by the inactivated vaccine, community control of transmission could be contemplated (72). Only in certain northern European countries had community control been achieved with the inactivated vaccine, indicating some enteric protection under appropriate circumstances (73, 74). Such community protection was actually demonstrated in the United States when high vaccination rates were achieved (75). In the developing world, there was little choice but to use OPV; here paralytic reactions were rarely reported and transmission of the vaccinating virus was actually used to overcome interfering infection with other enteric viruses. With global elimination of transmission impending and regional elimination already achieved, any paralytic reaction produced by the vaccine has become unacceptable, and the inactivated vaccine is now finding its appropriate place again in the United States (76, 77). Interestingly, the return of this vaccine has been accompanied by development of vaccines of increased potency, which allows reduction in the number of inoculations necessary (78–80). These vaccines also permit combination with other preparations, once again an approach which was being pursued at the time of introduction of the vaccines in the 1950s and 1960s (81).

LESSONS FOR TODAY FROM THE POLIOMYELITIS FIELD TRIAL

As new vaccines and combination vaccines are tested and introduced, many of the methods used date back to the poliomyelitis field trial. Sample size estimations were done but did not fully drive the size of the trial; rather, other considerations did. In reality, sample size estimations may guide decisions of numbers to be included in a trial, but other issues, especially feasibility, are of equal importance, although these factors may be concealed by modifying the assumptions under which the calculations are made. The case definitions may not have been developed in advance, but they were valuable enough to be used afterward in other studies, such as the

evaluation of the Cutter incident. They did set a precedent by being developed and enunciated before breaking of the code. The analysis was not the intent to treat type, but efficacy was calculated on the overall population, not stratified for antibody response. This was controversial at that time, especially given Salk's emphasis on improving immunogenicity, but also set the stage for the appropriate evaluation of the study as a whole. However, most important was the insistence on the double-blinded, placebo-controlled design. The need for it was internally validated by comparison with the observed group, strengthening the message that this method was the essential element for the future. Thus, this study, still in retrospect of monumental proportions, made it difficult to consider another design for a pivotal study of any vaccine or similar intervention.

REFERENCES

1. Paul JR. A history of poliomyelitis. Yale studies in the history of science and medicine. New Haven, CT: Yale University Press, 1971.
2. Paul JR. Endemic and epidemic trends of poliomyelitis in Central and South America. Bull World Health Organ 1958; 19:747–58.
3. Payne AM. Poliomyelitis as a world problem. In: Poliomyelitis: papers and discussions presented at the International Poliomyelitis Conference. Philadelphia, PA: Lippincott, 1955:393–400.
4. Melnick JL, Ågren K. Poliomyelitis and Coxsackie viruses isolated from normal infants in Egypt. Proc Soc Exp Biol Med 1952;81:621–4.
5. Nathanson N, Martin JR. The epidemiology of poliomyelitis: enigmas surrounding its appearance, epidemicity, and disappearance. Am J Epidemiol 1979;110:672–92.
6. John TJ. Oral polio vaccination of children in the tropics. II. Antibody response in relation to vaccine virus infection. Am J Epidemiol 1975;102:414–21.
7. Nicholas DD, Kratzer JH, Ofosu-Amaah S, et al. Outside Europe: is poliomyelitis a serious problem in developing countries?—the Danfa experience. Br Med J 1977;1: 1009–12.
8. Ofosu-Amaah S, Kratzer JH, Nicholas DD. Is poliomyelitis a serious problem in developing countries?—lameness in Ghanaian schools. Br Med J 1977;1:1012–14.
9. Paul JR. Epidemiology of poliomyelitis. In: Poliomyelitis. WHO monograph series no. 26. Geneva, Switzerland: World Health Organization, 1955:9–29.
10. Sabin AB. The epidemiology of poliomyelitis: problems at home and among the armed forces abroad. J Am Med Assoc 1947;134:749–56.
11. Paul JR. Poliomyelitis attack rates in American troops, 1940–1948. Am J Hyg 1949;50:57–62.
12. Monto AS, Koopman JS, Longini IM, et al. The Tecumseh study. XII. Enteric agents in the community, 1976–1981. J Infect Dis 1983;148:284–91.
13. Gust ID, Lehmann NI, Dimitrakakis M. A seroepidemiologic study of infections with HAV and HBV in five Pacific islands. Am J Epidemiol 1979;110:237–42.
14. Sabin AB. Epidemiologic patterns of poliomyelitis in different parts of the world. In: Poliomyelitis: papers and discussions presented at the International Poliomyelitis Conference. Philadelphia, PA: Lippincott, 1949:3–33.
15. Yorke J, Nathanson N, Pianigiani G, et al. Seasonality and the requirements for perpetuation and eradication of viruses in populations. Am J Epidemiol 1979;109:103–23.
16. Landsteiner K, Popper E. Übertragung der poliomyelitis acuta auf Affen. (In German). Z Immunitätsforsch exp Ther 1909;2:377–90.
17. Flexner S, Lewis PA. Experimental epidemic poliomyelitis in monkeys. Sixth note: characteristic alterations of the cerebrospinal fluid and its early infectivity; infection from human mesenteric lymph node. J Am Med Assoc 1910;54:1140.
18. Armstrong C. The experimental transmission of poliomyelitis to the eastern cotton rat, *Sigmodon hispidus hispidus*. Public Health Rep 1939;54:1719–21.
19. Kolmer JA, Klugh GF Jr, Rule AM. A successful method for vaccination against acute anterior poliomyelitis: further report. J Am Med Assoc 1935;104:456–60.
20. Brodie M, Park WH. Active immunization against poliomyelitis. Am J Public Health 1936;26:119–25.
21. Bodian D. Differentiation of types of poliomyelitis viruses. I. Reinfection experiments in monkeys (second attacks). Am J Hyg 1949;49:200–24.
22. Burnet FM, Macnamara J. Immunological differences between strains of poliomyelitic virus. Br J Exp Pathol 1931; 12:57–61.
23. Bodian D, Morgan IM, Howe HA. Differentiation of types of poliomyelitis viruses. III. The grouping of fourteen strains into three basic immunological types. Am J Hyg 1949; 49:234–45.
24. Bodian D. Poliovirus in chimpanzee tissues after virus feeding. Am J Hyg 1956;64:181–97.
25. Horstmann DM, McCollum RW, Mascola AD. Viremia in human poliomyelitis. J Exp Med 1954;99:355–69.
26. Trask JD, Vignec AJ, Paul JR. Poliomyelitis virus in human stools. J Am Med Assoc 1938;111:6–11.
27. Smith L. Isolation of poliovirus from spinal fluid. J Lab Clin Med 1962;59:490–5.
28. Schabel FM Jr, Smith HT, Fishbein WI, et al. Stool virus recovery in subclinical poliomyelitis during incubation, febrile, and convalescent periods. J Infect Dis 1950;86: 214–18.
29. Paul JR, Riordan JT, Melnick JL. Antibodies to three different antigenic types of poliomyelitis virus in sera from north Alaskan Eskimos. Am J Hyg 1951;54:275–85.
30. Wehrle PF, Carbonaro O, Day PA, et al. Transmission of polioviruses. III. Prevalence of polioviruses in pharyngeal secretions of infected household contacts of patients with clinical disease. Pediatrics 1961;27:762–4.
31. Ward R, Melnick JL, Horstmann DM. Poliomyelitis virus in fly-contaminated food collected at an epidemic. Science 1945;101:491–3.
32. Melnick JL. Poliomyelitis virus in urban sewage in epidemic and in nonepidemic times. Am J Hyg 1947;45:240–53.
33. Paul JR. The peripheral spread of poliomyelitis through rural and urban areas: observations from a recent epidemic. Yale J Biol Med 1947;19:521–36.
34. Paul JR, Melnick JL, Barnett VH, et al. A survey of neutralizing antibodies to poliomyelitis virus in Cairo, Egypt. Am J Hyg 1952;55:402–13.
35. Melnick JL, Paul JR, Walton M. Serologic epidemiology of poliomyelitis. Am J Public Health 1955;45:429–37.
36. Lipton MM, Steigman AJ. Human coproantibody against polioviruses. J Infect Dis 1963;112:57–66.
37. Horstmann DM. Poliomyelitis: severity and type of disease in different age groups. Ann N Y Acad Sci 1955;61:956–67.
38. Russell WR. Paralytic poliomyelitis: the early symptoms and the effect of physical activity on the course of the disease. Br Med J 1949;1:465–71.
39. Horstmann DM. Acute poliomyelitis: relation of physical activity at the time of onset to the course of the disease. J Am Med Assoc 1950;142:236–41.
40. Aycock WL. Tonsillectomy and poliomyelitis. I. Epidemiologic considerations. Medicine (Baltimore) 1942; 21:65–94.

41. Anderson GW, Rondeau JL. Absence of tonsils as a factor in the development of bulbar poliomyelitis. J Am Med Assoc 1954;155:1123–30.
42. Enders JF, Weller TH, Robbins FC. Cultivation of the Lansing strain of poliomyelitis virus in cultures of various human embryonic tissues. Science 1949;109:85–7.
43. Enders JF. General preface to studies on the cultivation of poliomyelitis viruses in tissue culture. J Immunol 1952;69: 639–43.
44. Morgan IM. Immunization of monkeys with formalin-inactivated poliomyelitis viruses. Am J Hyg1948;48:394–406.
45. Salk JE, Krech U, Youngner JS, et al. Formaldehyde treatment and safety testing of experimental poliomyelitis vaccines. Am J Public Health 1954;44:563–70.
46. Sweet B, Hilleman M. Detection of a "non-detectable" simian virus (vacuolating agent) present in rhesus and cynomolgous monkey-kidney cell culture material. Presented at the Second International Conference on Live Poliovirus Vaccines, Washington, DC, June 1960.
47. Salk JE. Principles of immunization as applied to poliomyelitis and influenza. Am J Public Health 1953;43: 1384–98.
48. Salk JE, Bazeley PL, Bennett BL, et al. Studies in human subjects on active immunization against poliomyelitis. II. A practical means for inducing and maintaining antibody formation. Am J Public Health 1954;44:994–1009.
49. Salk JE. Considerations in the preparation and use of poliomyelitis virus vaccine. J Am Med Assoc 1955;158: 1239–48.
50. Francis T Jr, Napier JA, Voight RB, et al. Evaluation of the 1954 field trial of poliomyelitis vaccine: final report. Ann Arbor, MI: Edwards Brothers, 1957.
51. Powers TE, Williams BA. Poliomyelitis and the Salk vaccine: a guide to resources in the Bentley Historical Library. Ann Arbor, MI: University of Michigan Printing Services, 1996.
52. Smith JS. Patenting the sun: polio and the Salk vaccine. New York, NY: W Morrow, 1991.
53. Brown GC. Laboratory aspects of field trial of poliomyelitis vaccine. Univ Mich Med Bull 1955;11:186–92.
54. Francis T Jr. Evaluation of the 1954 poliomyelitis vaccine field trial: further studies of results determining the effectiveness of poliomyelitis vaccine (Salk) in preventing paralytic poliomyelitis. J Am Med Assoc 1955;158:1266–70.
55. Francis T Jr, Korns RF. Evaluation of 1954 field trial of poliomyelitis vaccine: synopsis of summary report. Am J Med Sci 1955;229:603–12.
56. Salk JE. Vaccination against paralytic poliomyelitis performance and prospects. Am J Public Health 1955;45:575–96.
57. Salk JE, Lewis LJ, Bennett BL, et al. Antigenic activity of poliomyelitis vaccines undergoing field test. Am J Public Health 1955;45:151–62.
58. Neva FA, Salk JE. Serial urinary addis counts in patients inoculated repeatedly with poliomyelitis vaccine prepared from monkey kidney tissue cultures. J Lab Clin Med 1955;46:21– 7.
59. Sutter RW, Patriarca PA, Suleiman AJM, et al. Attributable risk of DTP (diphtheria and tetanus toxoids and pertussis vaccine) injection in provoking paralytic poliomyelitis during a large outbreak in Oman. J Infect Dis 1992;165:444–9.
60. Brown GC. Effect of booster inoculations on the serologic status of children vaccinated with poliomyelitis vaccine. Am J Public Health 1955;45:1401–8.
61. Brown GC, Napier JA. Serologic status of children four years after poliomyelitis field trial. J Immunol 1960;84: 463–8.
62. Salk D, van Wezel A, Salk J. Induction of long-term immunity to paralytic poliomyelitis by use of non-infectious vaccine. Lancet 1984;2:1317–21.
63. Nathanson N, Langmuir AD. The Cutter incident: poliomyelitis following formaldehyde-inactivated poliovirus vaccination in the United States during the Spring of 1955. I. Background. Am J Hyg 1963;78:16–28.
64. Auld PAM, Kevy SV, Eley RC. Poliomyelitis in children: experience with 956 cases in the 1955 Massachusetts epidemic. N Engl J Med 1960;263:1093–100.
65. Nathanson N, Langmuir AD. The Cutter incident: poliomyelitis following formaldehyde-inactivated poliovirus vaccination in the United States during the spring of 1955. II. Relationship of poliomyelitis to Cutter vaccine. Am J Hyg 1963;78:29–60.
66. Strebel P, Sutter RCS, Cochi SL, et al. Epidemiology of poliomyelitis in the United States one decade after the last reported case of indigenous wild virus-associated disease. Clin Infect Dis 1992;14:568–79.
67. Sabin AB. Oral poliovirus vaccine: history of its development and prospects for eradication of poliomyelitis. JAMA 1965;194:872-6.
68. Škovránek V, Žáček K. Oral poliovirus vaccine (Sabin) in Czechoslovakia. JAMA 1961;176:524–6.
69. Yofe J, Goldblum N, Eylan E, et al. An outbreak of poliomyelitis in Israel in 1961 and the use of attenuated type 1 vaccine in its control. Am J Hyg 1962;76:225–38.
70. Gelfand HM. Oral vaccine: associated paralytic poliomyelitis, 1962. JAMA 1963;184:948-56.
71. Henderson D, Witte J, Morris L, et al. Paralytic disease associated with oral polio vaccines. JAMA 1964;190:41–48.
72. Lepow ML, Robbins FC, Woods WA. Influence of vaccination with formalin inactivated vaccine upon gastrointestinal infection with polioviruses. Am J Public Health 1960;50:531–42.
73. Marine WM, Chin TDY, Gravelle CR. Limitation of fecal and pharyngeal poliovirus excretion in Salk-vaccinated children: a family study during a type 1 poliomyelitis epidemic. Am J Hyg 1962;76:173–95.
74. Salk J, Salk D. Control of influenza and poliomyelitis with killed virus vaccines. Science 1977;195:834–47.
75. Chin TDY, Marine WM, Hall EC, et al. Poliomyelitis in Des Moines, Iowa; 1959: the influence of Salk vaccination on the epidemic pattern and the spread of virus in the community. Am J Hyg 1961;74:67–94.
76. Hull HF, Ward NA, Hull BP, et al. Paralytic poliomyelitis: seasoned strategies, disappearing disease. Lancet 1994;343: 1331–7.
77. Poliomyelitis prevention in the United States: introduction of a sequential vaccination schedule of inactivated poliovirus vaccine followed by oral poliovirus vaccine. Recommendations of the Advisory Committee on Immunization Practices. MMWR Morb Mortal Wkly Rep 1997;46(RR3):1–25.
78. Adenyi-Jones SC, Faden H, Ferdon MB, et al. Systemic and local immune responses to enhanced-potency inactivated poliovirus vaccine in premature and term infants. J Pediatr 1992;120:686-9.
79. Moriniere BJ, van Loon FP, Rhodes PH, et al. Immunogenicity of a supplemental dose of oral versus inactivated poliovirus vaccine. Lancet 1993;341:1545–50.
80. Simoes EA, Padmini B, Steinhoff MC, et al. Antibody response of infants to two doses of inactivated poliovirus vaccine of enhanced potency. Am J Dis Child 1985;139: 977–80.
81. Halperin SA, Davies HD, Barreto L, et al. Safety and immunogenicity of two inactivated poliovirus vaccines in combination with an acellular pertussis vaccine and diphtheria and tetanus toxoids in seventeen- to nineteen-month old infants. J Pediatr 1997;130:525–31.