THE 1954 TRIAL OF THE POLIO VACCINE IN THE UNITED STATES

by

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I am honored by the invitation to speak to your society. Your journal, The Philippine Statistician, has already proved extremely useful to me for the basic information which it contains about important aspects of Philippine economy and demography. I note that the journal is establishing a tradition both for plain speaking about the present deficiencies in statistical information in your country and for making constructive proposals for improving the quantity and quality of data.

The 1954 field test of the effectiveness of the Salk polio vaccine is an interesting example of the application of statistical techniques to human affairs. Since Americans are supposed to be addicted to telling everyone how big things are in their country, I may mention that this seems to have been the largest experiment ever conducted with human subjects. Around 1-1/2 million children took part in the trial.

In laboratory research, Dr. Jonas Salk prepared a vaccine which produced rises in the protective antibody levels against each of the three principal strains of the polio virus. This looked encouraging. But to discover how much protection the vaccine would give against actual attacks of the disease, and to learn something about the duration of this protection, a field trial was necessary. The experimental subjects were children in the first 3 grades of school, i.e. aged from 6-9 years. I should like first to discuss some of the problems that arise in conducting a trial of this kind.

Some difficulties in the conduct of a trial

(1) Paralytic Polio is a relatively rare disease. From previous years the number of cases of paralytic polio in chil-

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dren aged 6-9 might be expected to be about 30 per 100,000 children. Suppose that a trial consisted of 200,000 children, half of whom receive vaccine and half receive no protection, and that the vacine is 50% effective. It follows that we would expect, on the average, 30 paralytic cases among the unvaccinated children and 15 among the vaccinated. But this calculation takes no account of sampling variation. With a little bad luck from sampling variation, we might actually get, sav, 25 cases among the unvaccinated and 20 among the vaccinated. It seems clear that if the vaccine were 50% effective in the long run, a trial involving 200,000 children might still give an inconclusive result.

This crude argument can be made more precise by modern techniques for estimating the sample size needed to detect the superiority of a vaccine of any given degree of true effectiveness. These calculations indicated that 600,000 children would be the minimum needed to give the trial a reasonable degree of sensitivity, and from some points of view even this figure looked unsafe.

(2) This meant that the trial could not be a small one, confined to some convenient area, where the field work and the collection and analysis of the data would be in the hands of expert medical research workers. Instead, it would have to be nationwide in scope, and to employ the ordinary medical practitioners and health services. From sad experience, statisticians have come to take a pessimistic view of the prospects of any large and extensive experiment involving human subjects. Instructions issued from a central office are liable to be misread, misinterpreted or simply ignored by persons who are a long distance away, and who feel that the central office does not understand their problems. Missing data are apt to flourish, and so on.

(3) The diagnosis of polio is difficult. In the non-paralytic form the symptoms are practically indistinguishable from those of numerous other common virus ailments. Even in the paralytic form, the milder cases cannot be diagnosed with certainty. One way out of this problem is to adopt stringent criteria, i.e., to recognize only the definitely severe forms as cases.

This suggestion, if carried too far, can defeat its own ends, however, because as the criteria become more stringent, the expected number of cases diminishes and the required sample size increases, sometimes by leaps and bounds.

(4) There is the question of public cooperation. Would parents give permission to have their children used in the large numbers required? Would local medical societies and health agencies cooperate? As things turned out, there was no occasion to worry on this score. From 60-70% of the parents who were approached allowed their children to take part as subjects. Support from local health services was generous.

(5) Finally, to mention a minor point, it was decided to give the vaccine in 3 shots, the second shot being one week after the first and the third, 4 weeks after the second. This meant that one had to get hold of the little darlings on three separate occasions in order to administer the vaccine.

The plans for the trial

To a statistician, the trial itself is of great interest methodologically, because two different plans, or experimental designs, were carried out side by side. The first plan was one which I believe most statisticians would regard as methodologically weak, while the second was much sounder. Before describing the plans, I should mention that in each State which participated, the trial was to be conducted in all schools in certain counties that had been chosen by the National Foundation for Infantile Paralysis (NFIP) as having higher than average attack rates of polio and also certain medical facilities that would be useful. The conduct of the trial was in the hands of Dr. Thomas Francis of the University of Michigan.

The first plan — the observed area

The plan announced by the NFIP was that second-grade children in the selected schools would receive the vaccine, while first and third grade children would be unvaccinated and would serve as controls. This plan had considerable administrative convenience, but it is subject to several potential sources of bias.

(1) This plan requires the assumption that in the absence of vaccination the attack rate for second-grade children is the same as the average attack rate for first- and third-grade children. This assumption is very unlikely to be exactly true, although it might be approximately true.

(2) Not all parents of second-grade children would give permission! As I have mentioned, about 70% of them did. Thus the plan actually compared first and third grades with a selected 70% of the second grades.

Could a bias arise from this selection? A layman might wonder at first sight why a parent's willingness or unwillingness to sign a form giving permission should have anything to do with his child's chances of catching polio. But it can be argued that a bias against the vaccine could arise from the source, and the results support the conclusion that such a bias did arise.

The argument runs as follows: On the average, parents who gave permission might be expected to be better situated economically, and to live in more hygienic and less crowded conditions than parents who refused. This hypothesis was supported by the results of a special sample survey, carried out to investigate differences in the characteristics of parents who gave permission and of parents who refused. Now it is known that many children receive natural protection against polio from a sub-clinical attack of the disease before they reach school age. *It seems likely*, then, that the children of 'refusers' would have more opportunities for receiving this natural protection than the children of 'accepters'. If this argument holds, the vaccinated children in the second grade would be a group with a higher than average risk of contracting polio.

(3) In the event of a local epidemic, everyone would know, under this plan, whether a child had been vaccinated or not. This knowledge might affect a physician's attitude while engaged in diagnosis, or it might influence parents in the steps which they took to protect their children.

Some persons maintained that the cumulative effect of these biases was bound to be small, and that they could not

seriously distort the results if the vaccine really was effective. The opposing view was that in a trial involving enormous amounts of labor, money and publicity, no loopholes that could be stopped should be allowed. In the trial itself, 33 states followed this plan, with about 220,000 second-grade children vaccinated and 725,000 first and third grade children as unvaccinated controls.

The Second Plan — The placebo area

In 11 states the responsible health officers stated that they preferred and were willing to conduct a plan that was more difficult administratively but was free from the defects mentioned above. Under this plan, premission to participate would be asked of parents of children in all 3 grades. The participating children would be divided at random into two groups. One group would receive the three shots of the vaccine. The other would receive in the same way three shots of an inert fluid, made up in vials to look exactly like vaccine and distinguished from it only by a secret code number. Adoption of this plan required courage, since it involved giving large numbers of children 3 shots of a fluid that would do them no good, although with care it would do them no harm.

With this plan, vaccinated and unvaccinated children are distributed in all 3 grades. Since only participating children are used, the possibility of a selective bias is absent. Further, nobody in the local areas knew whether a child had received vaccine or placebo. Just over 400,000 children participated in this plan.

FIELD OPERATIONS

Time permits me to mention only a few aspects of the complex task of conducting the field operations. To handle the large masses of data involved, Dr. Francis borrowed a capable team from the Bureau of the Census. This was an important and wise step. Not only was this group expert in the accurate and orderly coding, punching and processing of voluminous data, but from long experience they knew the many procedures and devices that must be used to ensure reasonable completeness of

data. Thanks to untiring efforts, the amount of missing data was inconsequential.

With regard to diagnosis, the initial symptoms in a suspected case were recorded by a local medical practitioner on a standard form. In an attempt to obtain some degree of uniformity for cases that might be paralytic, a team of physical therapists was recruited and given some common training. The physical therapist made detailed muscle function examinations 10-20 days and 50-70 days after the onset of any case. Her reports were checked in the field by a local physician experienced in polio. All these reports were sent to the Evaluation Center at Michigan, where a small team of experts had written down a series of criteria used to classify the cases as not polio, non-paralytic polio, or various degrees of paralytic polio. Perhaps the most important precautions were that all final diagnoses were made by the same team, that they used definite, written criteria, and that in no case did they know whether a child had received vaccine or not.

In fact, the code which distinguished the vaccine from the placebo was kept secret from all concerned with the gathering and processing of the data. This precaution guarded against any unconscious bias which might enter from persons recording or handling the data, and prevented premature leakage to the press of the supposed results of the trial. The precaution did, however, create some difficulties for those giving advice about the methods of statistical analysis, since this advice had to be constructed without seeing data that would have helped to make the advice better grounded.

SOME RESULTS

Among unvaccinated children, the paralytic case rate was close to 44 per 100,000 in both the placebo and observed areas. Since this figure is somewhat above the anticipated level of about 30, the trial was fortunate, from the scientific point of view, in taking place in a situation in which polio attack rates were on the high side.

In the placebo area the paralytic rate was 57 per 100,000 among children receiving the 3 shots of placebo, as against 16

per 100,000 for the vaccinated children. This indicates an effectiveness of 72% in reducing the risk of paralytic polio. In the observed areas the paralytic case rate amongst vaccinated children was 17, practically identical with that in the placebo areas. The rate amongst the first and third grade controls, however, was only 46, leading to a lower estimated effectiveness of 63%.

Although one cannot be certain, this difference in effectiveness may have been due to the selective bias against the vaccine in the observed areas which I have mentioned. Two other results support this hypothesis. In the observed areas, the second grade children whose parents refused participation had a paralytic rate of only 35, as against 46 for first and third grade children. Similarly, in the placebo areas, the children in all three grades whose parents refused had a rate of 36, as against 57 for placebo children.

During the trial, special precautions were taken to be on the lookout for any cases of polio that might be caused by live virus present in the vaccine, or for any harmful or unpleasant side effects from administration of the vaccine. Although over 420,000 children received the vaccine, no evidence was found of the presence of live virus or of other injurious effects. These results helped to inspire a degree of confidence in the safety of the vaccine which the later Cutter incident showed to be premature. Since the Cutter incident, millions of children have been safely vaccinated without further trouble.

In concentrating on the statistical and clinical aspects of the trial, I have omitted reference to a great volume of laboratory work that was conducted concurrently in order to measure the antibody rises given by different shots and different lots of vaccine, to perform safety tests, and to seek for virus in fecal specimens from suspected cases.