THE EPIDEMIOLOGICAL PRINCIPLES AND PROCEDURES INVOLVED IN A STUDY OF THE PROPHYLACTIC VALUE OF AN ALUM-PRECIPITATED MIXTURE OF DIPHTHERIA TOXOID AND PERTUSSIS VACCINE.

THESIS
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THE EPIDEMIOLOGICAL PRINCIPLES AND PROCEDURES
INVOLVED IN A STUDY OF THE PROPHYLACTIC VALUE
OF AN ALUM-PRECIPITATED MIXTURE OF PERTUSSIS
VACCINE AND DIPHTHERIA TOXOID

INTRODUCTION

1. There has been a downward trend in United States mortality from pertussis and diphtheria but current reports show that several thousand young children continue to die every year from these diseases. It is believed that many of these deaths will be prevented when effective prophylactic agents are extensively used. Such agents will be used more extensively when it becomes generally accepted, through extensive studies or otherwise, that effective prophylactic agents are at hand which can be administered in a simple and convenient manner without causing undue reactions.

2. The history of the development of a simple and effective prophylactic agent against diphtheria is well known. Volk and Bunney (1) found that two doses of alum-precipitated diphtheria toxoid is the simplest and most effective procedure for immunising young children against diphtheria. The history of the development of pertussis vaccine has been reviewed by Lapin (2), Felton and Willard (3), Lewis (4), and others. Harrison et al introduced alum-precipitated pertussis vaccine in 1938 (5). Bell (6) found that two doses of A-P pertussis vaccine is the simplest of the effective procedures for immunising young children against pertussis. Inasmuch as neither of these two prophylactic agents have produced undue reactions, it appeared that two doses of a mixture of these antigens offered the simplest and most promising means for immunising children against both diseases.

3. Others (7) (8) (9) (10) (11) (12) have studied mixtures of diphtheria and pertussis antigens and have reported favourably on their human use, however the
various studies differ from each other in many respects. They differ in the method of preparation of the antigen, the size and number of doses, the intervals between doses, and the ages at which the product is administered. Furthermore, the study procedures used in the various studies differ as to environmental groups studied, differ as to adequacy of observation, differ as to the adequacy of controls, and differ in criteria for evaluating protection against pertussis and diphtheria. The differences are so multiple that it is practically impossible to make a comparative evaluation of the various results of the different studies, and no one study demonstrates effective control of these diseases with a mixed antigen and in a manner sufficiently complete and generally acceptable to permit sound recommendations for its general widespread use.

4. Thus, in 1941 an intensive epidemiological study was undertaken to determine the prophylactic value of two doses of an A-P mixture of diphtheria toxoid and pertussis vaccine. The study was deliberately designed to furnish the information needed to make recommendations for or against the general use of the study product. The results of this study are to be published in a series of papers, two of which are now in press (13) (14). In the planning, operational, and analytical phases of the study considerable attention was given to the epidemiological principles involved and considerable effort was expended to devise and carry out procedures for the practical application of those principles. Inasmuch as the problems encountered were similar to those encountered in other epidemiological research studies of a prophylactic agent, it was thought worth while to discuss the experience of this study in considerable detail. It might have some value to others contemplating similar studies.

5. For convenience the presentation is divided into three parts embracing the planning phase, the operational phase, and the analytical phase of the study. The first part formulates the basic premise for study, evolves the objectives, enumerates the epidemiological principles, and elaborates the procedures designed to achieve the objectives. This part is weighted with discussion of the reasons why each procedure was considered necessary. The second part describes the actual operation of the study. It describes the method of preparation and administration of the study
products and the method of observation and collection of data. It discusses the reasons for each procedure only when they are not obvious and when they have not been adequately discussed in Part I. The third part describes and discusses the methods used to assemble and analyse the data and presents the results of the analyses made to date. This part also includes pertinent discussions. In all, the aim is to describe and discuss the epidemiological principles and procedures involved in the planning, operational, and analytical phases of the study. Minutia of detail is relegated to an appendix so that the body of the paper will include the minimum of detail considered necessary for a coherent story of the experience.
6. At the start of any study to evaluate a prophylactic agent it is necessary to formulate the premise upon which the study is based. The premise should embrace a justification for the study, should indicate what is included in the term “prophylactic value”, and should suggest the scope, nature, and objectives of the study. This involves a review of the literature to permit an estimate of the situation, that is, an evaluation of the effects of the disease pertussis on the people of the United States and an evaluation of the known effects of pertussis vaccines. It was necessary to review the known facts and to decide whether the effects of the disease appears amenable to control through use of a prophylactic agent and to decide whether a prophylactic agent can be prepared for general use in a manner which promises effective control. The general considerations involved in the estimate are mentioned in the introduction, and certain detailed considerations are to be discussed later. From the estimate of the situation the following basic premise for this study was evolved: The number of human deaths and the amount of human suffering, disability, apprehension and inconvenience resulting from the disease pertussis are of sufficient moment to warrant the routine, general use of a prophylactic pertussis vaccine in young children, providing that the vaccine can be administered at a reasonable cost and with little inconvenience to the public, and providing that its general administration will give substantial protection against the disease without causing undue reactions.

7. In addition to formulating a basic premise it is necessary to determine whether the conditions of the premise can be expected to persist over a period of years. If it appears imminent that more effective control procedures, other than those being studied, will be developed before the study can be completed, then there would be considerable doubt as to whether the study should be undertaken. For diphtheria and pertussis there were no reported prospects of any new therapeutic agents being developed which would be so extensively used as to alter the premise in any short period of years. It was felt that the downward trend in the reported mortality from these diseases would likewise not appreciably alter the situation in the immediate
future. Thus the premise appeared sufficiently stable to warrant several years study of a prophylactic agent, and it was decided to prepare a pertussis vaccine which appeared to best fit the premise and to subject it to thorough epidemiological trial to determine whether its routine, general use could be recommended.

8. The next step was to formulate the specific questions to be answered by the study. These questions or objectives must be selected so that their answers will permit recommendations with respect to the general use of the product selected for study. The objectives should be itemised in a precise and concise manner. They should be limited to those of major importance to the basic premise and limited to those amenable to epidemiological study and to those which appear practical to include in a single study. The objectives serve not only to define what is involved in the term “prophylactic value”, but further, they dictate the nature, extent, frequency, and intensity of the epidemiological observations to be made. There are so many known and unknown variations in the biological phenomena of disease that the nature of the epidemiological observations to be recorded in a particular study must be predetermined in full view of a limited number of carefully chosen objectives if one is to arrive at definitive rather than tentative conclusions.

9. The following objectives, or questions to be answered by the study, were derived through careful consideration of the basic premise and the nature of the particular vaccine product selected for study. They were designed to elicit answers to the major questions that would arise in formulating recommendations for the general public health use of an A-P mixture of pertussis vaccine and diphtheria toxoid. This required that the answers be obtained in a manner which could be projected to portray that which would occur in the general population.

1. Will two doses of an A-P mixture of diphtheria toxoid and pertussis vaccine, when given routinely to young children in the general population with a 4-week interval between doses, confer substantial protection against clinical pertussis? (See paragraph 10 below)
2. Will such a mixed product cause undue local or general reactions?

3. Will such a mixed product confer protection against diphtheria (as measured by a Schick test) as well as ordinary A-P diphtheria toxoid? (See paragraph 11 below)

4. Will such a mixed product confer substantial protection against clinical pertussis when given at 2-5 months of age? (See paragraph 12 below)

5. Will such a mixed product confer substantial protection against diphtheria (as measured by a Schick test) when given at 2-5 months of age?

10. Although the general reasons for selecting the particular objectives listed above are rather obvious, certain details deserve elaboration here and others are to be discussed later. It will be noted that question 1 requires demonstration of protection against clinical pertussis. This was prescribed because a modification or alleviation of the clinical manifestations of pertussis would directly alleviate the deaths, suffering, disability etc., attributed to the disease. It was also prescribed because clinical trial and experience constitutes the ultimate test of the value of any prophylactic agent against disease. It was fully recognised that a tremendous amount of work would be necessary to carry out such a demonstration in a manner adequate to yield a definitive result. However, no alternative procedure was available. It is recognised that a positive cough plate, the presence of agglutinins, opsonins, precipitins, and complement-fixing antibodies in the blood sera, or a lymphocyte response or even a skin test may individually or collectively lend confirmation to the diagnosis of a case of pertussis. On the other hand, their absence does not necessarily establish the absence of pertussis. In general, laboratory tests and skin tests have not been adequately demonstrated to be a satisfactory index of clinical protection; certainly present knowledge would not permit their exclusive use within the scope of the premise upon which this study was founded. Thus the more difficult task of determining protection against clinical manifestation of the disease was prescribed in the objectives.
11. With respect to questions 3 and 5, the Schick test was chosen as an index of protection against diphtheria for several reasons. Obviously a study group of small enough size to permit the intensive observations necessary to evaluate clinical protection against pertussis is too small to evaluate clinical protection against diphtheria. The incidence of clinical diphtheria in the United States is too low for such an evaluation and no epidemics were anticipated. Thus two generally accepted indices of clinical protection were available – the Schick test and blood antitoxin titrations. Both include the inherent errors of skin testing to a greater or less degree. The objectives prescribed the Schick test for use in this study not only because of its simplicity and time honoured use but because the study is concerned with the proportion of children protected rather than the degree of protection in the individual. In addition, it is possible that the Schick test may be a better index of clinical protection than the amount of circulating antitoxin in the blood. (15)

12. Questions 4 and 5 are concerned with the age of injections of the study product. It was recognised that neither pertussis vaccine nor diphtheria toxoid are ordinarily given to children before they are 6 months of age. With either product there exists some question as to whether children less than 6 months of age will respond to antigenic stimuli as effectively as children 6 months of age or older. Whether this is due to age per se or to a temporary passive immunisation at birth, or to these or other causes is not clear. In any event the United States mortality reports show that a very high proportion of the deaths from pertussis occurs at less than 6 months of age. It has been shown that two doses of A-P pertussis vaccine, when given with a 4-week interval between doses to infants as young as 2 months of age, conferred substantial protection against pertussis (6). Unpublished data further indicated that the product was as effective at the young age as when given at an older age. Sake et al. (10) have confirmed that A-P pertussis vaccine confers protection in very young children. Hence questions 4 and 5 were included in the objectives as they constitute an essential attribute of the basic premise.

13. In planning the study so as to obtain unqualified answers to the above questions it was considered essential that certain fundamental criteria or epidemiological principles be enumerated and meticulously adhered to throughout
the study. The principles are enumerated below for convenient reference. Each one is
discussed in a following paragraph which also elaborates the procedures which were
designed in the planning stage of the study to achieve the objectives in accordance
with these principles.

A. The study group must be representative of the group for which the study
product is intended to be recommended.

B. The study group must be large enough to achieve the objectives in a
reasonable time and small enough to be adequately observed by the fewest possible
investigators and small enough so that the use of the study products will not greatly
influence the community occurrence of the phenomena to be observed.

C. The study children must be observed with sufficient frequency, intensity,
and competency to permit reasonably accurate and uniform recognition of all
pertinent immunological phenomena and of all attributes relating thereto which have
occurred during the lifetime of each child. This includes observations on the
occurrence of communicable diseases and immunisations other than those which are
the subject of this study.

D. A predetermined strictly random sampling procedure, based on a simple
attribute entirely unrelated to immunological phenomena, must be used to separate
the study children into comparable test and control groups.

E. All study children must receive a study product, and the products given to
the test and control groups must be identical except for the specific antigen being
tested.

F. A test product must be prepared in a manner suitable for commercial
reproduction and distribution.

G. A single lot (having uniform consistency) of the products used for
immunisation and for testing immunity must be used throughout the study and tested
as necessary to ensure maintenance of potency.

H. Each child of the test and control group must receive the test and control
products respectively in such a manner that the recipients and their families cannot
know whether they belong to the test or control group nor whether they received the
test or control product.
I. The study products must be administered by various medical personnel in a routine manner, and the persons administering the study products must not know which product is given to any child.

J. The observers must not know which children received which product, nor which child belongs to which group, nor whether any child received the same product as any other child.

K. The observers must know the idiomatic language of the community and be well schooled in the technique of epidemiological investigation. They must work in such liaison with each other as will insure uniformity of observation and record of events.

L. Definite criteria must be predetermined for diagnosis of a case of pertussis and for classifying reactions. The observations must be recorded in sufficient extent to permit analysis by different criteria.

M. The records must be kept currently complete to the extent that all events may be classified in four categories – definitely yes, definitely no, doubtful, unknown.

N. The analysis of the data must include tabulations which will demonstrate whether the operational phase of the study effectively carried out the epidemiological principles and procedures set forth in the planning phase.

O. The analysis of the data must include tabulations which show whether the children of the two groups as predetermined by the criteria for their identification (odd and even month of birth) show any significant difference with respect to the immunological phenomena being studied (the Schick reaction and the occurrence of pertussis) throughout their whole life experience from birth to the end of the observation period regardless of whether they received immunisations outside the study or had pertussis prior to administration of the study products.

F. The tabulation and analysis of the events must be such as to not only elucidate differences that may occur in the test and control group but also to give substantial evidence as to whether such differences are the result of the particular product given and not the result of incidental attributes or methodology.
14. Principle A. – The study group must be representative of the group for which the study product is intended to be recommended. The basic premise suggests the desirability of determining whether the mixed product is suitable for routine use in the general population of young children of the United States. Obviously a single study cannot accomplish this because a random sample which would be representative of such children would be impossible to study with the degree of intensity and uniformity necessary to achieve other important objectives of the study. Thus, in accord with the stated objectives, it is necessary that the study be carried out in some community of moderate size which, in a broad sense, is not unlike other communities in the United States. It is noteworthy, for example, that institutions are not suitable for such a study because the mode of life and the occurrence of the disease in institutions are not representative of the general population, and the results of study using a prophylactic vaccine in institutionalised children could not be projected to portray with any degree of confidence what would occur when the vaccine was used in the general population. It is neither practical nor suitable for the study group to be a strictly random sample of all children in a community, as such children do not constitute a group which is routinely available for voluntary immunisations. Thus the procedure devised to achieve the objectives in accord with the principles was to conduct the study in Norfolk, Va., and environs and to select a study group of children representative of all children in the study area who are available for routine, voluntary immunisations. With this procedure the findings with respect to the prophylactic value of the study product can be safely projected, within the limits of sampling variation, to portray the value of its routine use in this community. The prophylactic value of the study product for routine, general use throughout the country can then be deduced exclusively through taking account of the possible differences between other communities and the study community of Norfolk, Va., and environs. Such a deduction is by far more simple and more accurate than any similar deduction which depends upon comparing the possible differences between communities in general with some study group which is not a representative sample of anything. To carry out the principle in accord with the above considerations it was decided that the study group would comprise all children
2-23 months of age who attended the public clinics in the study area and who received at least one dose of the study products. Attendance at the clinics would be stimulated only in a routine way, that is, by sending form letters urging immunisation to mothers of children born in the area. No advertising and no immunisation campaigns would be undertaken, as this might alter the composition of the group so as not to portray the effect of the routine use of the product.

15. Principle B. – The study group must be large enough to achieve the objectives in a reasonable time and small enough to be adequately observed by the fewest possible investigators, and small enough so that the use of the study products will not greatly influence the community occurrence of the phenomena to be observed. Many considerations are involved in determining the number of children to be included in a study group. Obviously the size of the group depends upon the number of cases of pertussis which will occur in the test and in the control group in a given period of time. By estimating the expected number of cases in each group one can calculate the size of the groups necessary to give a statistically conclusive result within any assumed limits of chance probability. In such a calculation the size of the study group is function of time; the same statistical result will occur when a large study group is observed for a short period of time as when a small group is observed for a long period of time. Thus time becomes an important factor determining the size of the study group after expected numbers of cases in the test and control group have been estimated. Offhand one would like to carry out the study in the shortest possible time but there are limits to the size of group that can be observed in a manner adequate to accomplish all the objectives. If a short period of time were used, for example, one year, six full-time nurse observers might be required, whereas two nurse observers might be adequate if a smaller group and 3 years’ time were allowed for the study. It is believed that a few nurses can obtain more accurate and uniform observations than a larger number of nurses. In determining the time factor, another consideration is the stability of the estimate of the expected number of cases. In a single community the estimate is more stable if it covers several years’ time rather than a single year. Another consideration pertinent to determining the size of the study group is the stability of the population in the community, i.e., the number
of children who will be lost from observation during the period of study – some will move away from the study area and others will just be lost. Still other children would also be lost in the sense that they cannot be used for some analyses on account of having pertussis prior to receiving the study product or on account of receiving pertussis vaccine outside the study. Still another consideration is the relation of the size of the study group to the total number of young people in the community. Obviously if the vaccine was highly effective and it was given to a large proportion of all children in a community, the herd immunity might be raised to a point where so few cases would occur that the study would be fruitless. This was taken into consideration in the selection of the study area. Pertussis vaccine was not being used extensively in the study area and the study group was to include only part of the children of limited age range (2-23 months) selected from the entire study area, thus leaving the remainder of children of this age range and all at other ages to maintain the normal incidence of disease in the community. After reviewing the various considerations, the basic factor which determined the size of the study group was that two full-time, competent and experienced public health nurses could carry out the observations required on not more than ten to twelve hundred children. It was considered that the accuracy and uniformity of the observations was the most important consideration and that this might suffer if more than two nurses were employed. It was estimated that a good vaccine should completely prevent some two-thirds of the cases and that some one third of the children would be lost from observation during 3-4 years, and that the pertussis attack rate in young non-immunised children would approximate 10 percent of the susceptibles per year. Using these estimates and allowing a margin of safety, it was decided that a 3-5 year study would be planned embracing 1,200-1,500 children at the time the study products were administered, i.e. at the time the study was started.

16. Principle C – The study children must be observed with sufficient frequency, intensity, and competency to permit reasonably accurate and uniform recognition of all pertinent immunological phenomena and of all attributes relating thereto which have occurred during the lifetime of each child. This includes observations on the occurrence of communicable disease and immunisations other
than those which are the subject of this study. The chief immunological phenomena to be observed are the occurrence of clinical pertussis and the results of Schick testing. It was necessary to arrange the study so that the observations would permit reasonably accurate recognition of these phenomena together with the attributes which influence their occurrence. The reasons for carrying out this principle are obvious but a brief review of the procedural considerations are mentioned so that the scope of its significance will be apparent. With respect to diphtheria immunity it was recognised that a few children do not respond to the usual dose of diphtheria toxoid and that among those who do respond a few do not long retain a good level of immunity. Thus to get the best view of the effect of the study products, it was decided that the Schick tests would be accomplished one full year after the first dose of the study product was given. It was further decided that a heated Schick toxin control would be used and that all reactions would be observed on the fourth day and as many observed on the second and seventh day as available time and personnel would permit. The Schick reactions were to be observed by the nurses, and in all children having any reaction whatsoever they were to be measured and described by the author. In the recognition of clinical pertussis it was believed essential to have a record of the clinical manifestations of the disease. This was necessary to insure that cases be defined and classified by definite predetermined clinical criteria and further to permit analysis according to various criteria for definition of a case. To obtain a clinical history required that the nurses be present and make frequent visits during the course of an attack of pertussis and that the mothers cooperate to the extent of keeping a daily record of symptoms. For this, routine monthly visits were prescribed, and the mothers were to be persuaded to phone the nurses whenever exposures or suspicious symptoms occurred so that weekly and more frequent visits could be made.

17. Of the many known and suspected attributes which might influence the occurrence of pertussis or diphtheria immunity, only a few of the less obvious are mentioned here; the others will be mentioned later. The mothers were to be Schick tested at the same time as their children. The study area was to be subdivided into areas representing epidemiological groups. All children less than 10 years of age
who lived in the family household of the study child were to be observed in the same manner as the study child and their tenure in the household recorded. All common communicable diseases of childhood and exposures thereto were to be recorded for all children in the household of a study child. The observation and recording of the occurrence of diseases other than pertussis and diphtheria is important not only to help conceal the observer’s main interest in pertussis and diphtheria but also as a check on the comparability of the study groups, the uniformity of observation of the groups, and the specificity of the antigen being studied. The details of all immunisations against disease were to be recorded. All this and other information was to be as complete and accurate as possible and cover the whole life period of each child. The above procedures were considered necessary to achieve the objectives in accordance with this principle.

18. Principle D. – A predetermined strictly random sampling procedure, based on a simple attribute entirely unrelated to immunological phenomena, must be used to separate the study children into comparable test and control groups. From time immemorial people have puzzled over the word “if”. What would have happened if some particular event had not previously occurred? Answers commonly follow post hoc ergo propter hoc reasoning. Fortunately in many instances the answer happens to be correct but unfortunately in many instances the answer is wrong. To avoid such a pitfall it was necessary to follow the above principle to obtain definite and correct answers to the questions asked. Through use of the above principle one can divide a heterogeneous group into two random samples, treat each sample alike in all respects except for a single variable, and predict from the total experience, within range of chance sampling variation, what would have occurred in either sample if the single variable had not been introduced.

19. To go beyond the scope of the objectives it would be desirable to have at least four strictly random groups of children under uniform and simultaneous observation. One group should receive the mixed diphtheria and pertussis antigen, one should receive diphtheria antigen alone, one should receive the pertussis antigen alone, and one group should receive no antigen whatsoever. To go further beyond the objectives, it would be desirable to add other groups receiving different amounts
of the antigen. Theoretically it would be desirable to have many groups. Practically, however, the objectives had to be limited to those which could be achieved with reasonable certainty in a single study. The efficacy of the diphtheria antigen is so well established that it not only appeared unnecessary to include a group with no diphtheria antigen but also unwise. There is no good evidence suggesting that the administration of A-P diphtheria toxoid would appreciably influence immunity to pertussis. In addition, a previous study carried out in the same manner in the same area and by the same personnel, demonstrated that two doses of A-P pertussis vaccine conferred substantial protections against pertussis when compared with a random group who for the most part did not receive A-P pertussis vaccine (6). Accordingly the objectives were designed to require that only the first two groups be studied.

20. A predetermined random sampling procedure is essential because one does not know all the attributes which influence immunity to diphtheria and pertussis. Thus a predetermined sampling procedure must be used in order to assure that all unknown attributes, in addition to the known attributes which influence immunity, are distributed between the two groups in a manner that will exert an equal influence (within the limits of chance sampling variation) on immunity to these diseases. There is no other known method which will assure such a result. It is true that one could obtain two groups by other methods and then determine whether they are comparable with respect to certain known attributes, but this would not assure that the unknown attributes are similarly distributed. Of course if all attributes influencing immunity were known, then no such sampling procedure would be needed, in fact no study would be necessary. In addition to the above, it is necessary to divide the study group into two strictly random samples because it assures comparability between the groups with respect to the known attributes which are considered to influence immunity. Such an assured distribution facilitates and simplifies analysis; it does not require complicated statistical adjustments to compare observed differences between the two random groups, and the simpler and the more direct the analysis, the more likely it is to be free from errors of methodology. Of course it is desirable to supplement such a simple analysis with more complicated
statistical adjustments for the influence of known attributes as will be described in part III, but one cannot rely exclusively on the latter for a sound conclusion; the former which gives an assured, nearly equal distribution of unknown attributes is essential for a sound conclusion. It is not necessary that the groups be of equal size but each must be large enough for statistical stability. From published reports it may be anticipated that the test group receiving pertussis vaccine will have incidence of pertussis lower than the control group. Thus it is preferable to have the test group slightly larger than the control group, as this would lend the maximum of statistical stability to differences occurring between the groups as compared to the total experience.

21. Obviously the attribute to be used for determining which children would belong to the test and control groups must be entirely unrelated to immunological phenomena. To carry out the principle it was decided that children born in an odd month of the year – January, March, etc. – should receive the test or mixed product, and children born in an even month – February, April, etc. – should receive the control product. It is believed that even the astrologists would agree that this attribute, birth in alternate months, is entirely unrelated to immunological phenomena. Since there are more days in the odd months than in the even months, this should give a slightly larger test than control group. This attribute has advantages over many other possible attributes that might be used for selection of test and control groups. It is definite, permanent, and can easily be determined and can be checked at any subsequent date. This is essential because a definitive conclusion primarily depends upon the occurrence of events in the two strictly random groups as predetermined by this attribute, and only in a secondary manner does it depend upon the occurrence of events in the children who received this or that product.

22. **Principle E.** All study children must receive a study product, and the study products given to the test and control groups must be identical except for a single variable. This principle is necessary to enhance the uniform treatment of all study children. Since it was decided that the study children would be separated into only two groups, it is essential that the two groups be identical except for a single
variable. If more than one variable is introduced, then more than two groups will be needed. It is essential to assure that the procedures used for introducing this single variable do not at the same time introduce other variables. If one desires to study the effect of pertussis vaccine as a single variable and attempts to inject one and not the other of two random groups, he automatically introduces other variables. Some persons of the group to be injected will refuse the injection, and this attribute may be related to attributes which influence immunity to pertussis. Inasmuch as the results must be based on a comparison of the two predetermined random groups, the procedure whereby only one group is offered an injection introduces errors which quantitatively depend upon the proportion of children who refuse injection. If the proportion is large no significant result may be obtained. It is noteworthy that a previous study used this procedure (6). Fortunately the proportion who refused injection was so small that the error was insignificant. The published results of that study did not compare vaccinated children with un-vaccinated children; they compared only the occurrence of pertussis in the preselected random groups even though some of the test group did not receive the vaccine and some of the control group did receive pertussis vaccine. To eliminate the above possible errors in this study the procedures were designed in consonance with the stated principle. Two study products were to be used, one for each group. One was ordinary A-P diphtheria toxoid and the other an A-P mixture of diphtheria toxoid and pertussis vaccine. Both products were to contain the same quantity of diphtheria toxoid from the same crude lot; the single variable was to be the addition of pertussis vaccine to one product. Only those children who received one or more doses of either product were to be entered into the study and all such children were to be entered if they could be located for observation. In the absence of administrative errors in which the wrong product may be given to a child, this procedure assures that all children of the strictly random test group will receive the mixed product and all children of the strictly random control group will receive the unmixed product. The procedure enhances the accuracy and surety that the objectives will be achieved.

23. **Principle F.** A test product must be prepared according to predetermined specifications and in a manner suitable for commercial reproduction and distribution.
It has been previously stated that the ultimate test of the value of a prophylactic agent rests with its use in humans. Humans should not be used for indiscriminate testing of products. Epidemiologists are physicians and the interest of the patient is a fundamental responsibility. There are so many unknowns involved in such testing that human trials should not be undertaken without full consideration of the possible value of the results. Obviously if the method of preparation of a test product will need modification for commercial reproduction and distribution of such a product, then a serious question exists as to whether the product should be used in epidemiological trial. It is likely that the trial will have to be repeated after such modifications are made. To exemplify, one may seriously question whether extensive human trials of BCG for immunisation against tuberculosis should be carried out when the present preparation of the product is not amenable to safety tests which are considered adequate for its mass production and distribution. If modifications are necessary for its general use, then another trial may be necessary to insure that the modifications do not nullify its value. Thus in this study the specifications for the manufacture of the study product were prepared in consultation with two former chiefs of the Biologics Control Division of the National Institute of Health and with a competent representative of a commercial producer. The product used was prepared commercially in a manner suitable for mass reproduction with reasonable accuracy to the extent of existing knowledge and it was prepared in a manner acceptable for widespread general use. It is pertinent to point out that to date we have no good laboratory method for bio-assay of pertussis vaccine and bacterial counts are far from accurate and no standard unit for comparison is at hand. Even though a relatively new mouse protection test appears promising for bio-assay, it must be kept in mind that the present test involves artificial mechanism of producing pathology in a mouse and there is no evidence that mouse protection is in any way comparable to human protection. Thus the reproduction of the study product with reasonable accuracy is limited to preparation in precisely the same manner and this in turn is limited to existing knowledge, which is not as extensive as desired.

24. **Principle G.** A single lot (having uniform consistency) of the products used for immunisation and for testing immunity must be used throughout the study
and tested as necessary to assure maintenance of potency. The limitations of existing knowledge with respect to accuracy with which a pertussis vaccine can be reproduced so as to give an identical product has been discussed above. The objectives of this study do not encompass a determination of the accuracy with which such products can be reproduced. If such reproductions have any variation, then no matter whether they are small or large the use of as few as two different lots in the study would introduce a variable which might nullify the results. Thus a single lot of the study products was to be used throughout the study. The known stability of A-P diphtheria toxoid is sufficient to require no tests for continued potency other than that which will be found in the data. Since there exists no satisfactory test for the pertussis vaccine, the date of the study will have to suffice in determining its continued potency. It is important that adequate samples of the study products be kept in reserve for a reasonable time after their use. This is necessary because some new laboratory standard of potency may be developed and the standard could be checked with the human experience. It is also necessary because some unusual phenomenon may be elicited through its use and a sample would be desired for subsequent testing. The well recognised instability of diluted Schick toxin posed a problem because at the start of the study the length of its period of use was unknown. Dr. Edsall (16) was getting promising results in stabilising the potency of diluted Schick toxin through the addition of human serum. It was decided to start the Schick testing with a single lot or Dr. Edsall’s product sufficient for the entire study and to test the diluted toxin from time to time and to discontinue its use in the event its potency began to decrease.

25. **Principle H.** – Each child of the test and control group must receive the test and control products respectively in such a manner that the recipients and their families cannot know whether they belong to the test or control group nor whether they received the test or control product. A previous paragraph set forth that the test and control groups must be strictly random samples of the combined group in order that all known and unknown attributes aside from the study products which might influence diphtheria and pertussis immunity would be comparably distributed between the groups. Such a sampling procedure will immediately accomplish this
end but once it is accomplished the groups will not necessarily remain comparable. People have the prerogative to obtain pertussis vaccine from sources outside the study and this obviously would occur to a disproportionate extent in the control group. Thus there is no known way to maintain the comparability of the groups when the test group knows that it has received pertussis vaccine as part of the test. One might say, “Why not delete such children from the analysis of results?” This cannot properly be done in the basic analysis because the two strictly random groups comprise all the children who entered the study who were born in an odd month and all the children who entered the study who were born in an even month. No selective fraction of the two respective groups can be considered as random samples unless the attribute upon which the fraction is selected is not only entirely unrelated to immunological phenomena but also unrelated to the attribute upon which the groups were originally designated, i.e., birth in an odd or even month. Thus it was decided that none of the study children or their families should know that pertussis vaccine was included in the study products. The families were to be told that a communicable disease study was being undertaken and that two doses of an A-F diphtheria toxoid was being given free to children 2-23 months of age, that a Schick test would be given one year later to assure that they were protected against diphtheria, and that the children would be observed for the occurrence of communicable disease. Another reason for adhering to this principle is to assure uniformity of observation. If the children and their parents do not know to which group the child belongs nor that pertussis vaccine is involved in the study, there is no possible way for them to bias the results in accord with their opinion or the effects of a vaccine.

26. **Principle I** – The study products must be administered by various medical personnel in a routine manner, and the persons administering the study products must not know which product is given to any child. To make a recommendation on the general use of a prophylactic agent one needs to have data on the results of its general use. The experience of persons who have studied a particular product and have special knowledge and practice with the administration of the product will not necessarily portray that which will result from the administration of the product by
general practitioners, nurses, and medical technicians. Thus it was decided that the doctors and nurses who routinely carry out immunisations at the clinics in the study area would administer the study products. It is important that the persons administering the study products should not know which product is given to any child. This is essential to remove any possible conscious or unconscious introduction of bias in the treatment of the two groups. If the persons administering the study products do not know that one product contains pertussis vaccine then there is no way in which they can administer the products to favor children who have had the disease or who have had pertussis vaccine outside the study. To carry out this principle it was decided to have a lay person attend each clinic and be responsible for the study products. The lay person would be told that two different preparations of diphtheria toxoid were being evaluated and they would see that each child received the product specified by the code number on the vial and in consonance with his month of birth. It was foreseen that some children would be brought to the clinic by persons who would not know the month of birth. It was estimated that this would be uncommon and that at least half would guess correctly whether birth was in an odd or even month. Hence it was decided that these children would be placed under observation the same as all other children.

27. Principle J – The observers must not know which children received which product, nor which child belonged to which group, nor whether any child received the same product as any other child. It is obvious that the nurse and physician observers must follow this principle. Otherwise when making fine discriminations in the classification of clinical manifestations of disease they may consciously or unconsciously lean one way or another, which might bias the results. It was foreseen that if the observers could determine which children were in which group even though the observers did not know which group received which product, then if the mixed product was very effective in preventing pertussis, the observers would soon be able to determine which product a child had received. Thus it was decided that the observers should not know the attribute upon which the children were selected for the test and control group, i.e., the odd and even month of birth. As a further safeguard it was decided that the study products be packaged in 20-dose vials, each
with a different code number and each otherwise identical in appearance. Each would be labelled “A-P Diphtheria Toxoid”. Thus the vial numbers on the visiting record cards would be so dissimilar that practically no children would be found who received the same products as any other child. It was recognised that no matter how much care might be taken to carry out this principle it still would remain possible for someone to figure out which children belonged to one or the other group and, in the event the vaccine was a very effective prophylactic against pertussis, to figure out which product was given to which group. This, however, could not be done without deliberate effort and this was forbidden. Actually it was not necessary to forbid such an effort as all observers were trained to know the superior value of objective observations.

28. Principle K. – The observers must know the idiomatic language of the community and must be well schooled in the technique of epidemiological investigation. They must work in such liaison with each other as will insure uniformity of observation and record of events. In order to obtain accurate information on the occurrence of clinical manifestations of disease in the study children and their families, carefully chosen non-leading questions must be asked. The investigator must know the background of the people in order to evaluate the answers. From the previous study some experiences may be cited. (a) The symptoms of pertussis may terminate rather abruptly if the mother is anxious to get the child back in school, but the true facts can be obtained if the investigator knows well the family background. (b) In some families one will get a negative response to a question about vomiting whereas if one asked if the child “puked” a different answer is obtained. (c) Obviously we cannot ask about “paroxysmal cough”. The only way to get at the facts is to ask, “Does the child cough like this . . . or this . . . or this . . .” and demonstrate three types of cough. (d) People have different terms for time. One may find a child has not coughed today or yesterday but unless one inquires whether he coughed during the night and erroneous deduction may be made. A careful routine was used in determining the date of past events. For example, to find the birth date one asks, “When is John’s birthday?” “How old was he on his last birth day?” “Let’s see now, when was he born?” Give time for the informant to figure out
the date of birth while the investigator computes the birth date. “Then he was born on March 27, 1941. Is that correct?” “Mable was only 20 months old when John was born. Is that correct?” The above exemplifies the need for the observers to know the idiomatic language of the community and to know epidemiological technique. It was decided to use full-time public health nurses experienced in communicable disease investigations in the area of study.

29. As set forth in a previous paragraph, the fewer the observers the more successful will be an attempt at uniformity in collection of data. Obviously when a careful evaluation of histories of communicable diseases is necessary the results of different investigators may vary to an extent that may introduce considerable error unless close and continuous liaison is maintained to promote uniformity. It is also recognized that no one person can maintain a uniform method of approach over a long period of years. Hence it was decided to have only two nurse observers who would work in close liaison with each other and only one physician who would constantly check both nurses in order to give the best possible uniformity over the period of years necessary to collect the data.

30. **Principle L.** – Definite criteria must be predetermined for diagnosis of a case of pertussis and for classifying Schick reactions. The observations must be recorded in sufficient extent to permit analysis by different criteria. It is obviously essential for the observations to be as objective as possible. This requires identification and recording of all components of the ultimate end points to be evaluated. It was decided to use the criteria for definition of a case of pertussis which was used in the previous study (6) as it defines the components involved. (See Appendix D) It was recognised that the definition must be somewhat arbitrary and might be too liberal or too conservative. Hence it was decided to record the existence, duration, frequency, and intensity of cough, paroxysmal cough, whooping and vomiting so that the data could be analysed according to various criteria for diagnosis of a case. In a similar manner it was decided that the Schick reactions would be measured and described so that different end points could be used and so that the classification would be as objective as possible.
31. **Principle M.** – The records must be kept currently complete to the extent that all events may be classified in four categories – definitely yes, definitely no, doubtful, unknown. Obviously it was decided that records should be kept in a manner that would embrace all possible categories. Since all gradations of biological phenomena occur, it was decided that the above classification would be used and further subdivided where indicated.

32. **Principle N.** – The analysis of the data must include tabulations which will demonstrate whether the operational phase of the study effectively carried out the epidemiological principles and procedures set forth in the planning phase. In the planning of the study an attempt was made to foresee and solve all pertinent problems which would arise in the conduct of the study. It was recognised that foresight is not as good as hindsight and it remained possible that during the course of the study some well-intentioned procedure might inadvertently effect the comparability of the groups in a manner which would be recognizable only by hindsight. Therefore it was decided that the tabulations would be made to check whether the study children were representative of all children in the area who are available for voluntary immunisations, to check whether the sampling procedures effectively separated the study children into a comparable test and control group, to check whether the observations were uniform and were carried out without knowledge as to which children received the test and control products, and to check whether the study products and the Schick toxin remained of uniform potency throughout their period of use. These and other tabulations were considered essential to assure that the principles were effectively carried out.

33. **Principle O.** – The analysis of the data must include tabulations which show whether the children of two groups as predetermined by the criteria for their identification (odd and even month of birth) show any significant differences with respect to the immunological phenomena being studied (the Schick reaction and the occurrence of pertussis) throughout their whole life experience from birth to the end of observation period regardless of whether they received the products intended or the amounts intended and regardless of whether they received immunisations outside the study or had pertussis prior to administration of the study products. This is a
rather severe but essential analysis. The objectives of the study were to be achieved in a manner which would determine whether the routine use of the study products at 2-23 months of age would effectively control diphtheria and pertussis. Inasmuch as in the natural course of these diseases many children may be infected before they become available for immunisation, it is necessary to determine whether the routine general use of the study products given at the ages specified will have significantly influenced their total life experience with such infections by the time they have reached 4 to 7 years of age.

34. **Principle P.** – The tabulation and analysis of the events must be such as not only to elucidate differences that may occur in the test and control group but also to give substantial evidence as to whether such differences are the result of the particular product given and not the result of incidental attributes or methodology. There are so many known and unknown attributes which influence immunological phenomena that unless one takes all these influences into account one can never be certain that a particular phenomenon was the result of a particular treatment given. Thus even though two presumably random groups show a significant difference in immunological response when they have been treated alike except for a single variable, it does not necessarily follow that that particular variable was responsible for the difference in immunological response. Thus the observations must include data on all known and suspected attributes which might influence the phenomenon. Then if the variable was responsible for the phenomenon it should be manifest independently of the influence of the various attributes. It is recognised that the objectives do not specifically include a determination of which and to what extent each of the known and suspected attributes influence the occurrence of diphtheria and pertussis immunity. However, it is essential that they be analysed in order to accumulate evidence as to whether the observed results are directly caused by the particular study product administered. Furthermore, such an analysis may not only add to our knowledge of epidemiology but it may serve as an alternative method of analysis of the data which can be held in reserve and used to derive tentative conclusions in the event some unforeseen circumstance arises which disturbs the comparability of the two study groups. In addition, such an analysis may enhance a
quantitative estimate of the value of the study products. For example, suppose the
attack rate for pertussis in one group was 6 percent and the numerical stability of the
group was such that the true rate could lie anywhere between 5 and 7 percent and
suppose the attack rate in the other group was 10 percent and its stability ranged
from 9 to 11 percent. In the absence of knowledge as to the influence of attributers
other than the study product, an estimate of the value of the products would
necessarily lie between 7/9 and 5/11, which is a considerable difference, and does
not permit much of an estimate of the amount of protection induced. Now it is
reasonable to assume that the known attributes which influence the occurrence of
pertussis exert a greater influence than the unknown attributes because, without too
great an error, one can predict, for example, that a susceptible child will develop the
disease following an intense, prolonged exposure. Thus if the intensive exposures of
one group are disproportionately high, even though the numbers of such exposures
lie within the expected range of chance sampling variation, one may be able to arrive
at more reliable estimate of the amount of protection induced by the study products
by adjusting for the influence of this and other known attributes which influence the
occurrence of the disease. Accordingly it was decided to elicit information in a
uniform manner on all known and suspected attributes which might influence
immunity to diphtheria and pertussis so that those which influence the occurrence of
immunity could be identified and taken into account in evaluation of the effects of
the study products.
35. In 1941 several methods for preparation of the study products were given consideration. One suggested method was the absorption of a pertussis suspension on a preformed alum precipitate. Another was the simple mixing of A-P diphtheria toxoid and A-P pertussis vaccine. These and other suggested methods were rejected in favor of preparation of the products in a manner as nearly as possible like that used in the previous study (6). In the absence of definite knowledge as to the role played by specific antigenic fractions of H. pertussis in the protection of humans, it was thought best to use a method of preparation of the study products whereby a suspension of killed phase I H. pertussis organisms was precipitated with alum together with whatever antigenic substances may be contained.

36. The study products were prepared by Parke, Davis and Company according to specifications drawn up by the author in consultation with two former chiefs of the Biologics Control Division of the National Institute of Health, Dr. J. P. Leake and Dr. W. T. Harrison, and with the late Dr. L. T. Clark of Parke, Davis and Company. The products were purchased in 1941 in a quantity sufficient for the entire study and stored until used at 4º to 7º C. A single lot of fluid diphtheria toxoid was used in the preparation of both the mixed and the unmixed product. For the mixed product, 2 parts of the toxoid were mixed with 1 part of a suspension containing 30 billion Phase I H. pertussis organisms per cubic centimetre which were grown on blood agar and killed with 1: 10,000 merthiolate. For the unmixed product, 2 parts of the toxoid were mixed with 1 part physiological salt solution instead of the pertussis suspension. Separately the mixed and unmixed products were then precipitated by adding 4 percent alum solution and the precipitates washed twice. The products were passed through a colloid machine in order to obtain a fine division of the alum precipitate and finally were subjected to the usual sterility and safety tests. Titrations of both the mixed and unmixed products indicated that there was slightly less than 0.1 percent alum equivalent in each. The crude toxoid had an LF value of 9, and each dose of the mixed and unmixed products by calculation had an LF value of 6 and an L+ value of 0.30 units per dose. Each dose of the mixed and unmixed products
contained the same quantity of diphtheria toxoid and differed only in that each dose of the mixed product contained 10 billion killed H. pertussis organisms, and each dose of the unmixed product contained no pertussis vaccine. The two products were packaged in 20-dose vials and each vial was labelled “A-P Diphtheria Toxoid”. The vials were identical in appearance except that each had a different code number consisting of three digits. In 1941 Dr. J. F. Leake selected the code numbers from “Tippetts Random Sampling Numbers” (17) and placed them on the vials so that when the vial contained the mixed product the sum of the first two digits was odd and when the vial contained the unmixed product the sum was even. The contents of the vials could be determined only by the code numbers, and during the observation period this code was unknown to the author and the visiting nurses.

37. Two liters of the A-P mixed and two liters of the A-P unmixed product were prepared in 1941 but only one liter of each product was filled in dispensing vials. During the first few months of use of the study products, it was found that a one cc. dose was a rather large amount for injection into the small arms of two-month old infants. Hence in 1942 it was decided that the supernatant fluid of the remaining two liters would be decanted and the precipitate resuspended to one-half the original volume. Thus each dose of each product would be one-half cc. instead of one cc., however the one-half cc. dose would contain the same amount of antigen as the one cc. dose. The one cc. doses were continued in use until the products were used up and the one-half cc. doses thereafter administered. Thus the first half of the children – those injected from January to June 1942 – received two one-cc doses, whereas the last half – those injected from July 1942 to June 1943 – received the same amount of antigen in two one-half cc. doses.

38. Many persons assisted in the conduct of the study and for convenience in presentation this general contribution of the chief contributors are described in this paragraph. Dr. I. C. Riggin, the state Health Officer, Dr. William Grossmann, Director of the State Bureau of Communicable Diseases, and Dr. William P. McDowell and Dr. Charles P. Brown, both of Norfolk, approved the general plan of the study. The late Dr. Josiah Leake, the Norfolk County Health Officer, and Dr. J. C. Sleet, the former Norfolk City Health Officer, also approved the plan and agreed
that their personnel, particularly Public Health Nurses Eliza M. Gallup and Lavinia Tate, would routinely administer the study products. The City Health Department sent out the letters to mothers of 2-12 months old infants urging attendance at clinics for immunisation. (See Appendix B) The study was carried out in cooperation with the King’s Daughters Visiting Nurse Association under its able director Miss Elizabeth McKenzie. This organization furnished office space, telephone service, and medical clinic and hospitalization service for study children in families needing such service and unable to bear the cost thereof. The King’s Daughters Association also furnished the following personnel to supervise the administration of the study products and to prepare the preliminary identification data on children receiving the study products and to prepare the letters to mothers urging attendance at the King’s Daughters clinics for immunisations: Mrs. A. D. Parker, Mrs. Richard Cook, Mrs. M. C. Chapman, Mrs. Cornell Berry, Mrs. Fenner Meads. These people volunteered their services and their extensive assistance was a great help. Head Public Health Nurse Anne C. Hodges is one of the fulltime nurses employed to make the routine household visits and to record the basic observations of the study. Mrs. Hodges was similarly employed throughout the previous study (6) and is thoroughly acquainted with the idiomatic language and habits of the community and is well experienced in obtaining accurate, research-epidemiological information on the common communicable disease of children. Head Public Health Nurse Ruth Sargeant was similarly employed, experienced, and qualified but had to leave the work in 1942. Public Health Nurse Edna McCaleb was trained and became experienced and qualified to continue in place of Mrs. Sargeant. Mrs McCaleb had to leave the work in 1946 but Public Health Nurse Mary Miller has been trained and has become experienced and qualified to continue in place of Mrs. McCaleb. Mrs. Marie Burklin kept check on all records and tabulated the results of the study. Medical Director James P. Leake (Retired 1945) was responsible for many of the ideas which stimulated the incorporation of a number of the epidemiological principles used in this study. In addition, Dr. Leake solely conducted the study from July 1943 to July 1945 in lieu of the author who was then on overseas duty.
39. The study area is in Virginia and comprises the cities of Norfolk and South Norfolk and the Tanners Creak District of Norfolk County. The population of the entire area is estimated at 250,000, of which 69 percent are white and 31 percent colored. The population is relatively stable except for the families of Navy personnel. The study area was divided into 14 geographic subdivision’s in an effort to group people according to their usual associations at schools, churches, theaters, and shopping centers. Each health section was made up of either colored or white persons; no section contained both. The study area was divided into geographic sections because of the possible influence of such sections on the occurrence of communicable disease. Appendix A shows a map of the study area with the health sections delineated. The city expanded considerably during the war and the boundaries of certain sections, particularly Sections 10 and 11, have been expanded to include the study children who moved to new housing projects in these areas. Each geographic section contained one King’s Daughters Well Baby Health Station where immunisations were administered. Sections 7 and 8 represent a highly congested colored area which was divided arbitrarily for convenience. At the start of the study Section 7a had no community center of its own and therefore it was not differentiated from Section 7. Certain sparsely populated, very small areas along the LaFayette River were not included as the few children who lived in these areas did not attend the King’s Daughters Clinics for immunisation.

40. The study products were administered to all children 2-23 months of age who attended the King’s Daughters Well Baby health Stations during the period January 1942 to June 1943. There were very few refusals. The Health Department personnel who administered the study products were advised that a communicable disease study was being made and that two different preparations of diphtheria toxoid were being used and that effort should be made to immunise all children aged 2-23 months who attended the clinics. Two doses of one cc. each were to be given with a 4-week interval between doses. Immunisation was to be postponed for children who were obviously ill or who had extensive skin rashes. The toxoid was to be thoroughly shaken before being withdrawn from the vial. The injections were to be made in the deltoid region after washing the arm with alcohol. A clean sterile
needle was to be used for each injection, and the toxoid was to be injected deeply in the loose subcutaneous tissue.

41. A lay person attended the clinics with a supply of the study products and with sterile needles and syringes and visiting record forms. The lay person obtained identification data on each child to be immunised, e.g., name, address, sex, birth date, and endeavoured to assure that each child received the product intended. Children born in an odd month (January, March, May, etc.) were to receive a product from a vial on which the sum of the first two digits of the vial number was odd, and children born in an even month (February, April, June, etc.) were to receive in a similar manner the even numbered product. The lay person also recorded on the record card the vial number of the product given and requested the mother to return with the child for a second dose in 4 weeks. When the child received the second dose, the record card was immediately given to the visiting nurses. When a child failed to return for a second dose by the fifth week, a post card reminder was sent to the parents, and if he failed to return by the eighth week the record was given to the visiting nurses.

42. With the above procedure the King’s Daughters personnel, the lay person, and the Health Department personnel attending the clinics did not know that pertussis vaccine was involved in the study, and the mothers did not know that two different preparations of diphtheria toxoid were being given. When inquires were made, parents were told that a communicable disease study was being conducted and that a nurse would visit once a month for information on communicable diseases. They were also told that Schick tests would be done 1 year after immunisation to assure that all children were protected against diphtheria. Thus neither the personnel administering the study products nor the persons receiving the products know that pertussis vaccine was in any way involved. Attendance at the health stations was stimulated in a routine manner by sending letters to the parents of 2-12 months old children urging immunisation against diphtheria and smallpox. (See Appendix B) The names and addresses for such letters were obtained in a routine manner by a review of all birth certificates of the city during the period February 1941 to April 1943.
43. As the visiting nurses received the records from the health stations where the children were immunised they immediately proceeded to make a household visit. Every child who received one or more doses of the study products was visited unless he could not be located or lived outside the study area. In order to keep account of all records, a ledger was prepared listing the name of each child who received one or more doses of the study products together with his birth date, the dates of injection of the study products, and the vial numbers of the product injected. Many of the children were from families under observation in the former study, and the nurses in the course of their previous work with the King’s Daughters Visiting Nurse Association, knew many families in the city. Hence the new records of the present study were distributed to the nurse who best knew the family and the remainder were distributed alternately to the nurses to the limit of keeping the case load somewhat equalised. To assist entry to the household and enhance cooperation, the nurses offered their public health nursing service to the families and full medical care to children when they needed it and were unable to afford it. The nurses made every effort to know the families intimately and to get them to keep daily records of all symptoms of communicable disease when they occurred. A family roster was prepared (see Appendix C) which recorded the name, sex, birth date, and communicable disease history and immunisation history of every child in the household less than 10 years of age. The histories were checked and rechecked many times on subsequent visits, particularly when a communicable disease was prevalent in the neighbourhood and the informant’s cognizance of the disease was stimulated thereby.

44. After the initial visit, routine monthly visits have been made to each family to date unless the study child moved out of the study area or otherwise could not be located. Weekly and more frequent visits have been made whenever any person in the household was exposed to or had symptoms of a communicable disease. Much to the disturbance of the nurses’ evening peace the families frequently telephoned such instances. The monthly visits were standardised to a limited extent; the questioning had to include information about the coughs, colds, fevers, skin rashes, and visits to doctors or clinics for each child in the household and had to
specifically mention exposures to measles, chickenpox, mumps, and whooping cough. The record of the visit always certified, e.g., “No I.C.E, except so and so etc….” I.C.E. stands for illnesses, coughs, and exposures of any member of the household to communicable diseases. The nurse’s task is to be present during the course of every communicable disease that occurred in the household and to record the day-by-day symptoms and signs of such diseases. Every 1 to 4 weeks the author of Dr. J. F. Leake visited all families in which any person had symptoms suggestive of pertussis, and also visited families having other diseases in which there was any doubt as to diagnosis. The criteria used for diagnosis of a case of pertussis was the same as that used in the previous study. (See Appendix D.) To prevent Dr. Leake from knowing which product a child had received when he was visiting the families for diagnosis, he was given the age rather than the birth date of the children visited, and the vial number indicating the product received was concealed with gummed paper. This later proved unnecessary as Dr. Leake had forgotten the criteria used for administration of the products. It was incidentally found that he could not recall whether he had used the odd and even day or birth or the odd and even month of birth and had to look up his files to find out which was correct.

45. The nurses frequently checked a child’s clinic or hospital record and checked with physicians to determine diagnoses and dates of occurrence of disease or immunisation. The occurrences of measles, chickenpox, mumps, and pertussis was not reported to the health department by the nurses, and the nurses had nothing official to do about quarantine or isolation. This was agreed upon by the health department and was understood by the study families. The purpose was to assure that that the informants would not conceal evidence of such diseases. Of course the nurses knew the health department rules and regulations and with hardly any exception were able to get voluntary cooperation of the families to abide by these regulations. The nurses and the author prescribed no treatment for the patients but gave medical advice and urged the attendance of the families’ private physician for care when indicated or, when the circumstances warranted, urged the attendance at the King’s Daughters Clinic.
46. A sample of an actual visiting record form with fictitious names and addresses is contained in Appendix C together with instructions for the use of the form which includes pertinent definitions. Five by eight inch record cards were used and bound together in book form with gummed tape. Three forms were used, one of which was the face card which contained identification data, a household roster, and dates of occurrence of all common communicable diseases and immunisations. This form was arranged so as to permit continuous record of a changing situation. It was designed so that all data recorded thereon could be readily evaluated. The latter was accomplished by using a system of reference notes together with endorsements on the back of the face card in order that all pertinent consideration of the data could be evaluated. It was recognised that the long period of study would produce a large volume of notes from the numerous household visits and that tabulations of the observations would become a herculean task if these notes had to be reviewed for each item of the data. The face card and the case record card were designed to facilitate tabulations and to present a convenient and current summary of events, and further to provide an index to the visiting record notes were detailed descriptions of events could be readily found. The date of the event could be readily traced in the chronological, dated visiting notes. The visiting record form and the pertussis summary form are described in Appendix C.

47. A single lot of diluted Schick toxin was used throughout the study. It was prepared and furnished by Dr. Geoffrey Edsall at the Antitoxin and Vaccine Laboratory of the Massachusetts Department of Health. The product differed from ordinary Schick toxin in that it was stabilised with human serum as described by Dr. Edsall (16). In October 1942 he sent to the National Institute of Health a quantity of the diluted toxin and control material sufficient for the entire study. It was promptly placed in the refrigerator where the temperature was kept between 4º and 7º Centigrade. A quantity sufficient only for each clinic was transported to Norfolk in ice and kept on ice until the day of its use. From time to time a sample of the toxin was tested for potency by injecting it into guinea pigs.

48. From February 1943 to July 1944 six regular Schick testing clinics were held and an effort made to Schick test all children who received their study products.
12 or more months previously. A post card request was sent urging attendance at a clinic for Schick test. (See Appendix F.) When a child did not come to the clinic as intended, an effort was made to locate him at home for Schick testing and otherwise he was sent a card requesting attendance at the following clinic. In February and again in May 1945, an effort was made to Schick test the few remaining children who were under observation but who had not been tested previously at the regular clinics. All mothers who accompanied children at the time of Schick test were invited to have a Schick test. This was done because of the possibility that the immunity status of the mothers tested in this manner might have some influence on the child’s reaction. It was also done because the mothers could be expected to show more positives than the children and the data would assist in determining the continued potency of the toxin. A heated toxin control was used for all tests with the single exception that it was omitted for very young children at the second regular Schick test clinic. The temporary omission was permitted on account of the rush at this clinic and because the control reactions observed at the first clinic in these very young children were so insignificant as to be of little value in classification of the reaction. Incidentally, subsequent analyses lent confirmation of the belief that this small omission did not alter the results.

49. Many of the Schick reactions were observed on the second, fourth, and seventh day. The nurses examined the site of the Schick and control tests in all children, and the author or Dr. Leake examined all who had any reaction whatsoever. All observations were made in daylight out of doors in the open shade. The arms were washed rather vigorously and a record made of the transverse and longitudinal diameters of redness and edema when it occurred. In addition, a description of the reaction was recorded, noting particularly the presence or absence of wrinkling, edema, desquamation, and pigmentation. Reactions were classified according to the area of clear definite redness on the fourth to seventh day following injection. The area was computed by assuming it equivalent to a circle with a diameter equal to the mean of the vertical and transverse measurements. If the area of redness at the test site exceeded the area of redness (if any) at the control site by the area of a circle 10 mm. diameter, the reaction was classified positive, otherwise the reaction was
classified negative. The reaction was classified negative in the few instances where
definite evidence existed that the maximum local reaction at the test site occurred
within 48 hours after injection and the nature of the reaction was similar to that at the
control site. The reaction was classified as positive in a few instances (particularly in
the colored where discolorations are less evident than in the white skin) where, due
to the intensity and the duration of the reaction, the original observer (JAB or JPL)
judged it to be positive even though the measured area of redness was slightly less
than set forth above. All reactions were observed and classified without knowledge
as to what immunisations the child may have received.

50. At the start of the study observations on the occurrence of reactions to
injection of the study products were recorded on the form shown in Appendix E.
Observations were made on each of the three days following administration of the
products, at weekly intervals for the first 4 weeks, and more often when indicated.
After 98 of these forms had been completed, it was obvious that the negligible
reactions did not justify continuance of these observations on such an intense scale.
Hence, thereafter parents were told to call the nurses in the event of any reaction, and
the nurses made inquiry as to the occurrence of reaction on their first visit and on
subsequent visits when indicated. The nurses also inspected the site of injection to
see whether a lump persisted and whether there was any evidence that the injected
material had discharged through the skin. When parents asked what reactions might
be expected, they were told that usually none except the formation of a hard lump
which would persist for several months. They were also told that occasionally a child
would be fretful and irritable for 12 but not to exceed 24 hours. The form (Appendix
E) indicates the type of information obtained in the study of reactions.
51. The study arrangement described in Part II held promise of yielding epidemiological information other than that specified in the objectives. Hence, the observations are being continued and no child has been dropped from observation unless he moved away from the study area or otherwise could not be located for continued observation. In February 1947, a preliminary tabulation showed that some 300 of the 1,238 children selected for study had developed a definite case of pertussis. This was considered sufficient to give definite answers to the specific questions of the study. Thus all analyses to date cover the experience of the children selected for study from their date of birth to March 1, 1947, or to exit if lost from observation prior to that date.

52. Before any analyses could be made it was necessary to review all records to assure that the classification of immunological phenomena on the basic records was correct. This required a review of the visiting records to see that all children classified as having definite cases of pertussis had symptoms which fulfilled the predetermined criteria for such classifications. (See Appendix D.) It also required a review of the Schick test reading to assure that the classification of positives and negatives was correct. (See paragraph 49.) The Schick test readings were recorded directly on the post cards sent to the parents requesting that the children be brought to the clinic for testing. A sample of this card is shown in appendix F. All these cards showing that the child had any reaction whatsoever were sorted out, and the size and nature of reactions were tabulated according to the day of observation. From this tabulation a final check was made on the classifications of positives and negatives. The classification of pertussis cases and the Schick reactions was made without knowing which product the child had received and without knowing to which group the child belonged.

53. The basic data of the study was kept on the visiting record forms which are in continual use at Norfolk, Va., and the analyses were to be made at the National Institute of Health in Bethesda, Md. Hence it was necessary that the essential data for analysis be transcribed to another form. A 7½ or 8½ inch double-hole Key Sort
punch card was used. A sample is shown in appendix G, together with instructions for transcribing the data and the code for punching the cards. Each nurse transcribed the essential data from her visiting records to the Key Sort card and the other nurse then checked the transcription. The cards were then taken to the National Institute of Health where the age and time intervals of occurrence of certain events were computed and recorded and the cards marked for punching. Ages and time intervals were computed by numbering each month and 1/10 of a month consecutively from January 1928 forward. Age and time intervals to the nearest 1/10 month were then computed by simple subtraction. These computations were checked with a special 15-inch 10-year cycle slide rule. The cards were then punched as marked and the marks checked at the time of punching. A sample of the punched card is also shown in Appendix G.

54. Before tabulations could be prepared to answer the specific questions asked by the study, it was necessary to determine whether the dates confirmed that the operational phase of the study effectively carried out the principles outlined in the planning phase. Do the data support the view that the study children were representative of all children in the community who were available for voluntary immunisation? Was the sampling procedure adequate? Did the single lots of the study products and the Schick toxin maintain their potency throughout their long period of use? The next six paragraphs analyse the data with respect to these three questions. The answers to other similar questions on the effectiveness with which the procedures were carried out will be obvious in subsequent analyses of results.

55. Table 1 was prepared to check the effectiveness with which the method pursued in obtaining the study children provided a study group which was an adequate and representative sample of all young children in the area who are routinely available for voluntary immunisation. The method of selection must be relied upon to establish representativeness but a few crude checks are available. If the study group is representative it would be expected to have a disproportionately large number of children from large families, to have a disproportionately large number of colored children, and to have no disproportion by sex. These are the characteristics expected in groups of children who respond to routine public pleas for
immunisation. Table 1 compares the study group with estimates prepared from vital statistics reports on colour, sex, and family size. It shows that the expectations were fulfilled. This crude but confirmatory check permits the belief that the study group is adequate in size (see estimate in paragraph 15) and representative to the extent that the results from the use of the study products may be projected to portray that which would result from their routine use in the study area.

56. Table 2 was prepared to check the effectiveness with which the sampling procedure was carried out to divide the study children into a comparable test and control group. The predetermined and meticulously executed random sampling procedures based on an odd or even month of birth (an attribute entirely unrelated to diphtheria or pertussis immunity) should divide the study children into a test and control group so that each group will have a nearly equal distribution of all known and unknown attributes which might influence the occurrence of diphtheria or pertussis immunity aside from the influence of the study products given. This can be checked by observing whether all known and suspected attributes are equally distributed within reasonable limits of chance sampling variation. It must be pointed out, however, that only a check can be made and that the meticulous execution of an adequate and predetermined sampling procedure is the all important factor. In the absence of such a procedure there can be no assurance that a disproportionate distribution of an unknown attribute may not have occurred and significantly influenced the results in an unknown manner and to an unknown extent.
Table 1. A comparison of the Number of Births and Families in the Study Area with the number of Study Children and Families by Sex, Color, and Family Size.

<table>
<thead>
<tr>
<th></th>
<th>White</th>
<th></th>
<th>Colored</th>
<th></th>
<th>Total</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>Percent</td>
<td></td>
<td>Number</td>
<td>Percent</td>
<td></td>
</tr>
<tr>
<td>Number of reported births in study area</td>
<td>M</td>
<td>4,228</td>
<td>1,645</td>
<td>5,873</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>3,614</td>
<td>1,487</td>
<td>5,101</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Total</td>
<td>7,842</td>
<td>3,132</td>
<td>10,974</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number and percent entering study</td>
<td>M</td>
<td>299</td>
<td>7.1</td>
<td>348</td>
<td>21.2</td>
<td>647</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>292</td>
<td>8.1</td>
<td>299</td>
<td>20.1</td>
<td>591</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>591</td>
<td>7.5</td>
<td>647</td>
<td>20.7</td>
<td>1,238</td>
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<table>
<thead>
<tr>
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<th></th>
<th>Total</th>
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<tr>
<td></td>
<td>Number</td>
<td>Percent</td>
<td></td>
<td>Number</td>
<td>Percent</td>
<td></td>
</tr>
<tr>
<td>Estimated no. families in area with children &lt;10 years old</td>
<td>1 child</td>
<td>4,956</td>
<td>1,804</td>
<td>6,762</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;1 child</td>
<td>2,643</td>
<td>2,017</td>
<td>4,660</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>7,599</td>
<td>3,821</td>
<td>11,420</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number and percent entering study</td>
<td>1 child</td>
<td>287</td>
<td>5.8</td>
<td>240</td>
<td>13.3</td>
<td>527</td>
</tr>
<tr>
<td></td>
<td>&gt;1 child</td>
<td>279</td>
<td>10.6</td>
<td>358</td>
<td>17.7</td>
<td>637</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>566</td>
<td>7.4</td>
<td>598</td>
<td>15.7</td>
<td>1,164</td>
</tr>
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</table>

Table 2. A Comparison of Children Born in the Odd with Those Born in the Even Months According to Specified Attributes

<table>
<thead>
<tr>
<th>Attributes</th>
<th>Month of Birth of Child</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odd</td>
<td>Even</td>
</tr>
<tr>
<td>Total no. of children entering study</td>
<td>646</td>
<td>592</td>
</tr>
<tr>
<td>Male</td>
<td>337</td>
<td>310</td>
</tr>
<tr>
<td>Female</td>
<td>309</td>
<td>282</td>
</tr>
<tr>
<td>Health section at entry 4-6, 9-11</td>
<td>146</td>
<td>128</td>
</tr>
<tr>
<td>Health section at entry 1,12,14</td>
<td>166</td>
<td>151</td>
</tr>
<tr>
<td>Total White</td>
<td>312</td>
<td>279</td>
</tr>
<tr>
<td>Health section at entry 2,3,13</td>
<td>105</td>
<td>112</td>
</tr>
<tr>
<td>Health section at entry 7,8</td>
<td>229</td>
<td>201</td>
</tr>
<tr>
<td>Total Colored</td>
<td>334</td>
<td>313</td>
</tr>
<tr>
<td>1st dose injected Jan-June 1942</td>
<td>337</td>
<td>324</td>
</tr>
<tr>
<td>1st dose injected July '42-June '43</td>
<td>309</td>
<td>268</td>
</tr>
<tr>
<td>1st dose age 2-4 months</td>
<td>281</td>
<td>256</td>
</tr>
<tr>
<td>1st dose age 5-23 months</td>
<td>365</td>
<td>336</td>
</tr>
<tr>
<td>Others age &lt;10 in h'hold at entry</td>
<td>366</td>
<td>345</td>
</tr>
<tr>
<td>No others age &lt;10 in h'hold at entry</td>
<td>280</td>
<td>247</td>
</tr>
<tr>
<td>Mothers of children Schick tested</td>
<td>367</td>
<td>340</td>
</tr>
<tr>
<td>Lost from obs. Prior to Schick test</td>
<td>103</td>
<td>100</td>
</tr>
<tr>
<td>Observed and Schick tested</td>
<td>540</td>
<td>485</td>
</tr>
<tr>
<td>Rec’d 2 doses mixed product</td>
<td>461</td>
<td>11</td>
</tr>
<tr>
<td>Rec’d 2 doses unmixed product</td>
<td>13</td>
<td>410</td>
</tr>
<tr>
<td>Other (1 dose aa, 1 dose, etc.)</td>
<td>66</td>
<td>64</td>
</tr>
</tbody>
</table>
57. Table 2 shows that 52.2 percent of the total 1,238 children who entered the study were born in an odd month. It lists some of the known and suspected attributes which might influence diphtheria or pertussis immunity in this study. Additional attributes are listed in other tables. It will be noted that very close to 52 percent of the children were born in an odd month in all attributes except those relating to the study products given. Further analyses showed that the percent of children born in an odd month of the total under observation during each year from 1942 to 1947 was 52.0, 52.2, 52.1, 52.1, 52.6, and 53.0, respectively. Thus the sampling procedure was effective in giving comparable periods of observation. Of the 270 study children who received prophylactic pertussis vaccine by private physician outside the study, 53.3 percent were born in an odd month. Thus the families of the children did not know that pertussis vaccine was included in one study product. Of the 792 children who did not have onset of paroxysmal cough of pertussis prior to first dose and who did not receive pertussis vaccine outside the study and who received two doses of the study product as intended, 51.4 percent were born in an odd month. Similarly, in all attributes observed, except the different study products given and the attributes related thereto, e.g., the Schick reaction and the occurrence of clinical pertussis, very close to 52.2 percent of the children were born in an odd month. Thus all observations confirm that the procedure used to divide the children into two nearly equal and strictly comparable groups and to observe and treat them so that they would remain strictly comparable throughout the observation period was effective and adequate. Within the range of chance sampling variation, the children born in an odd month are strictly comparable with children born in an even month in all respects except for the different study products given.

58. In the administration of the study products some difficulties were anticipated. (See paragraph 26.) At the time the products were given, the health department policy was to give only one dose for immunisation against diphtheria. Incidentally two doses are now urged. Thus, of the total 1,238 children selected for study, 114 or 9.2 percent received only one dose of the study product and 48.3 percent of these were born in an odd month. A few of the people who brought children to the health stations for immunisation did not know the correct month of
birth of the child. Thus 28 children, 15 born in an odd month and 13 born in an even 
month, received two doses of the wrong product. Thirty-seven other children 
received two doses, one each of the mixed and unmixed product. Twenty-six of 
these, a disproportionately large number, were born in an odd month. The 
disproportion was due to the fact that in the early part of the study the persons 
administering the study products had the erroneous impression that the number zero 
on a vial was an odd number. This impression was corrected before the second dose 
was given to these children. In all, 94.7 percent of the total 1,238 children received 
one or two doses of the study products as designated by their month of birth and 85.5 
percent received two doses as intended. Of the latter, 51.9 percent were born in an 
odd month. Thus the administration of the study products was accomplished with a 
satisfactory degree of success and the sampling procedure used to divide the children 
into strictly random groups was effective.

59. Table 3 was prepared to check whether the single lot of Schick toxin used 
throughout the Schick resting period remained of uniform potency. In each of the 
seven groups of mothers and children Schick tested at various time intervals there 
was no significant variation in the percent Schick positive. In the laboratory tests, all 
animals used died and had pathology demonstrating death from diphtheria toxin. 
There was no significant variation in the average survival time at the different dates 
on which the toxin was tested. Thus it is concluded that the Schick toxin used 
remained remarkably uniform in potency throughout its long period of use.

60. Checks on the maintenance of potency of the study products have been 
discussed in paragraph 24. Table 3 and attribute 8 of table 4 support the view that the 
diphtheria toxoid maintained its potency throughout its period of use. With respect to 
the pertussis vaccine, the children who received their first dose from January-June 
1942, July-December 1942, and January-June 1943, respectively had average annual 
pertussis attack rates of 2.7, 3.9, and 4.4 percent. These differences are considered 
not significant, and it is concluded that there was no appreciable change in potency 
of the study products throughout their period of use.
Table 3. A Time Comparison of Schick Test Results and Laboratory Tests for Potency of the Schick Toxin Used – Lot AS3

<table>
<thead>
<tr>
<th>Year</th>
<th>Month</th>
<th>Test</th>
<th>No. of G.Pigs</th>
<th>Does Dil.</th>
<th>Avg.No.Days Survived</th>
</tr>
</thead>
<tbody>
<tr>
<td>1942</td>
<td>July</td>
<td>I</td>
<td>5</td>
<td>5cc</td>
<td>3.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>II</td>
<td>5</td>
<td>5cc</td>
<td>4.4</td>
</tr>
<tr>
<td>1942</td>
<td>Sept.</td>
<td>III</td>
<td>5</td>
<td>5cc</td>
<td>3.4</td>
</tr>
<tr>
<td>1943</td>
<td>Jan.</td>
<td>I</td>
<td>5</td>
<td>5cc</td>
<td>3.4</td>
</tr>
<tr>
<td></td>
<td>Feb-Mar.</td>
<td>II</td>
<td>5</td>
<td>5cc</td>
<td>4.2</td>
</tr>
<tr>
<td></td>
<td>May</td>
<td>III</td>
<td>5</td>
<td>5cc</td>
<td>3.7</td>
</tr>
<tr>
<td></td>
<td>June</td>
<td>IV</td>
<td>5</td>
<td>5cc</td>
<td>3.8</td>
</tr>
<tr>
<td>1943</td>
<td>July</td>
<td>V</td>
<td>2</td>
<td>5cc</td>
<td>3.7</td>
</tr>
<tr>
<td></td>
<td>Aug-Sep.</td>
<td>IV</td>
<td>2</td>
<td>7cc</td>
<td>3.8</td>
</tr>
<tr>
<td></td>
<td>Nov.</td>
<td>V</td>
<td>2</td>
<td>5cc</td>
<td>3.7</td>
</tr>
<tr>
<td>1944</td>
<td>Feb</td>
<td>V</td>
<td>4</td>
<td>5cc</td>
<td>4.1</td>
</tr>
<tr>
<td></td>
<td>May-July</td>
<td>VI</td>
<td>1</td>
<td>5cc</td>
<td>9.5</td>
</tr>
<tr>
<td>1945</td>
<td>Feb-May</td>
<td>VII</td>
<td>2</td>
<td>7cc</td>
<td>3.8</td>
</tr>
<tr>
<td>1946</td>
<td>Jan.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1947</td>
<td>Jan.</td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>I-VII</td>
<td>1732</td>
<td>243</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td></td>
<td>I-VI</td>
<td>32</td>
<td>5cc</td>
<td>4.2</td>
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<td>2</td>
<td>7cc</td>
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</tbody>
</table>
61. In the study of reactions (see paragraph 50 and Appendix E) the rather intensive observations were discontinued after 98 children had been studied because no reaction of significance occurred. In the subsequent, less intensive observation on the mass of the study of children, the reactions were so minor in nature that they have not yet been tabulated for the entire study group. Tabulations of the reactions observed in the first 98 children showed that (1) The rectal temperatures of the children immediately prior to injection tended to be higher than the rectal temperatures taken on the two successive days. This was true regardless of whether the children received the mixed or unmixed product, and there was no significant difference between groups. (2) About 9 percent of the children had fretfulness or irritability during the 48 hours following injection. The occurrence of this symptom was equally distributed between the two groups. When this symptom did occur, it was commonly associated with teething and thus it is questionable as to what part of the 9 percent was due to the administration of the study products. (3) Vomiting, diarrhea, constipation, anorexia, and insomnia seldom occurred and had no time relation with administration of the study products. (4) Local reactions consisting of an indurated subcutaneous nodule, redness, or tenderness were more common in children receiving the mixed product but none were of any consequence. These reactions were seldom discovered by the parents and were usually noted by them only when called to their attention by the investigators. Comparing the occurrence in children receiving the mixed and unmixed products, a definite nodule occurred in 85 percent and 45 percent respectively, redness or discoloration occurred in 63 percent and 45 percent respectively, and tenderness to firm pressure was manifest in 26 percent and 4 percent respectively. The painless indurated nodules persisted for many months, the discoloration or redness lasted from a day or so to a week or more, and tenderness seldom persisted for more than a few days. In the less intensive observations for the occurrence of reactions which have not yet been tabulated, the reactions appeared to follow those above described. It is concluded that neither the mixed nor the unmixed study product caused undue reactions and from this experience would appear to be suitable for general use.
62. In analysing the results of Schick testing, the two groups of children who are strictly comparable are those that include all children born in an odd month and all children born in an even month. (See paragraph 25.) Of the 1,238 children who received one or more doses of the study product and were located for observation, 203 were lost from observation prior to the Schick testing and 10 were either not Schick tested or not read at a proper time for classification of reactions. Of the remaining children, 540 were born in an odd month and of these, 33 or 6.1 percent were Schick positive, whereas of the 485 born in an even month, 85 or 17.5 percent were positive. One can assume that the disproportionately smaller number of Schick positives that occurred in children born in an odd month was due to the superiority of the mixed product as an immunizing agent against diphtheria but further analyses are necessary to determine whether or not the disproportion was due to other attributes or methodology.

63. Table 4 was prepared to identify attributes which may have influenced the Schick reaction. It lists the data available on all known and suspected attributes which might influence diphtheria immunity and shows for each the results of the Schick tests performed one year after immunisation. It shows the number of children tested according to the product received and the number and percent who were Schick positive, i.e., who failed to immunise. The “Pm” is the calculated probability in 1,000 trials of a difference in the number of Schick reactors as great as or greater than observed occurring through change sampling variation of independent attributes. Yates modification of Chi-square was used in computing the “Pm” on all four-fold tables having less than 10 individuals in any cell. In attribute No.1, 32 percent of the children who received only one dose of a known product were Schick positive as compared with 10 percent who received two doses. This difference is consistent and significant both in the children receiving the mixed and the unmixed product. On account of this finding, the remainder of table 4 and other analyses of the Schick test except table 9 includes only children who received two doses of the same known product. It will be noted that children receiving the unmixed product had about three times as many Schick positives as those receiving the mixed product, and this difference is consistent and fairly uniform throughout all attributes tested. It
will be noted that attributes Nos. 2 to 11 inclusive were not significantly associated with the Schick reaction in this experience. *

* Some of these attributes are known to be correlated with the Schick reaction in the general population, e.g., No. 11 – age at time of Schick test. This study was designed to minimise the influence of attributes not pertinent to the questions propounded. For the vast majority of children, the age spread at time of Schick test was less than 14 months and thus no significant age correlation was to be expected.

In attribute No.12, age at time of injection, it is significant that children who received both their doses before they were 6 months of age had a higher proportion of Schick positives that those who received at least one of their doses when they were 6 months of age or over. It will be noted that there is an association of questionable significance between the Schick reaction and the remaining attributes Nos. 13, 14, and 15. In summary of table 4, it appears that the Schick reaction is definitely correlated with the type of study product received, the number of doses received, and the age at time of injection. There appears to be a correlation of questionable significance between the Schick reaction and the attributes concerning breast feeding at time of first dose, race, and the presence or absence of other children in the household less than 10 years of age. There appears to be no correlation between the Schick reaction and any of the other attributes observed.
### Table 4. Schick Test Results in Children One Year after Receiving the Mixed and Unmixed Product According to Specified Attributes

<table>
<thead>
<tr>
<th>Attributes</th>
<th>Product Received</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mixed (Odd)</td>
<td>No.</td>
<td>No.+</td>
<td>%+</td>
<td>“p”* m</td>
<td></td>
<td>Unmixed (Even)</td>
<td>No.</td>
</tr>
<tr>
<td>Received one dose</td>
<td>42 8 19</td>
<td>472 24 5</td>
<td>1</td>
<td></td>
<td></td>
<td>55 23 42</td>
<td>423 63 15</td>
<td>1</td>
</tr>
<tr>
<td>Received two doses</td>
<td>106 3 3 938</td>
<td>97 2 2</td>
<td></td>
<td></td>
<td></td>
<td>86 11 13</td>
<td>83 16 19</td>
<td>250</td>
</tr>
<tr>
<td>Section 4-6, 9-10</td>
<td>179 12 7 943</td>
<td>90 7 8</td>
<td></td>
<td></td>
<td></td>
<td>87 15 17</td>
<td>167 21 13</td>
<td>312</td>
</tr>
<tr>
<td>Section 1,2,14,15</td>
<td>229 11 5 787</td>
<td>243 13 5</td>
<td></td>
<td></td>
<td></td>
<td>229 36 16</td>
<td>194 27 14</td>
<td>604</td>
</tr>
<tr>
<td>Measles, Chicken pox, mumps</td>
<td>355 20 6 482</td>
<td>117 4 3</td>
<td></td>
<td></td>
<td></td>
<td>91 13 14</td>
<td>332 50 15</td>
<td>854</td>
</tr>
<tr>
<td>W.C. vaccine outside study</td>
<td>386 22 6 309</td>
<td>86 2 2</td>
<td></td>
<td></td>
<td></td>
<td>74 14 19</td>
<td>349 49 14</td>
<td>284</td>
</tr>
<tr>
<td>Mother Schick positive</td>
<td>282 16 6 366</td>
<td>57 1 2</td>
<td></td>
<td></td>
<td></td>
<td>50 6 12</td>
<td>244 42 17</td>
<td>485</td>
</tr>
<tr>
<td>Mother Schick negative</td>
<td>233 12 5 952</td>
<td>239 12 5</td>
<td></td>
<td></td>
<td></td>
<td>224 32 14</td>
<td>199 31 16</td>
<td>710</td>
</tr>
<tr>
<td>Injected before July 1942</td>
<td>138 10 7 169</td>
<td>334 14 4</td>
<td></td>
<td></td>
<td></td>
<td>308 48 16</td>
<td>115 15 13</td>
<td>514</td>
</tr>
<tr>
<td>Injected after July 1942</td>
<td>281 12 4 329</td>
<td>191 12 6</td>
<td></td>
<td></td>
<td></td>
<td>178 23 13</td>
<td>245 40 16</td>
<td>331</td>
</tr>
<tr>
<td>Schick at &lt;18 mth. old</td>
<td>240 10 4 356</td>
<td>232 14 6</td>
<td></td>
<td></td>
<td></td>
<td>220 37 17</td>
<td>203 26 13</td>
<td>247</td>
</tr>
<tr>
<td>Schick at &gt;17 mth. old</td>
<td>271 9 3 70</td>
<td>201 15 8</td>
<td></td>
<td></td>
<td></td>
<td>187 40 21</td>
<td>236 23 10</td>
<td>&lt;1</td>
</tr>
<tr>
<td>2nd dose age 2-5 months</td>
<td>231 8 4 111</td>
<td>220 16 7</td>
<td></td>
<td></td>
<td></td>
<td>205 36 18</td>
<td>193 25 13</td>
<td>202</td>
</tr>
<tr>
<td>2nd dose age &gt;5 months</td>
<td>269 19 7 41</td>
<td>203 5 3</td>
<td></td>
<td></td>
<td></td>
<td>169 27 16</td>
<td>254 36 14</td>
<td>610</td>
</tr>
<tr>
<td>Breast fed at 1st dose</td>
<td>181 2 1 4</td>
<td>291 22 8</td>
<td></td>
<td></td>
<td></td>
<td>250 41 16</td>
<td>173 22 13</td>
<td>296</td>
</tr>
</tbody>
</table>

*See text. “p” = probability in a thousand, using Yates modification.
64. Table 4 shows that incidental attributes and methodology cannot account for the disproportionately fewer Schick positives that occurred in children receiving the mixed product, since the disproportion was manifest in all attributes observed. It also shows (attribute 12) that the children who received the mixed product at 2-5 months of age had fewer Schick positives than children receiving the unmixed product at any age from 2 to 23 months. Thus the question propounded on diphtheria immunity (see paragraph 9) can be answered; however further analyses are indicated. For example, it is obvious that the group of children injected at the earlier age must include a large proportion of children who were still feeding at the breast, and it should be determined whether age at time of injection or breast feeding or both were responsible for the correlation. Other similar but perhaps not so obvious interrelationships may exist between the various attributes listed in table 4. Thus it is desirable to analyse further the correlations observed so as to identify the independent attributes which influenced diphtheria immunity. Such analyses are not only of epidemiological interest but may serve to enhance a quantitative estimate of the value of the missed product (see paragraph 34) and should enhance the acceptability of the conclusions.

65. Table 5 was prepared to determine whether the questionable correlation between the Schick reaction and breast feeding at time of first dose was due to breast feeding or to the result of interrelationship with other attributes. It shows the Schick test results according to breast feeding at first dose among the 849 children who received two doses of the study product and on whom a history of breast feeding was obtained. The total group of 849 children are subdivided according to the age at time of injection, the presence or absence of other children less than 10 years of age in their household, and according to the study product received. In each subdivision the number of children tested and the observed number of Schick positives is recorded, and the “T”, the theoretically expected number of Schick positives, is computed. The computation is based on the assumption that breast feeding exerted no influence on the Schick reaction, and the “T” is derived by applying the percent positive in the total of each subdivision to the number of children tested. Table 5 was prepared
exclusively to derive the theoretically expected total number of Schick positives that would have occurred in each of the two groups of children who were and who were not feeding at the breast at the time of their first dose if such breast feeding had no influence on the Schick reaction. It was not prepared to observe the significance of other attributes, as these are to be observed in subsequent tables. It was prepared to give due weight to the distribution of other attributes suspected of influencing the Schick reaction. A comparison of the observed total number of Schick positives in each group with the total of the expected number, as derived in table 5, more accurately reflects the influence of breast feeding per se than a comparison of the observed number with an expected number computed from the crude totals which are not adjusted for the influence of other attributes. By using the crude totals the expected number of Schick positives among the group of 425 children who were feeding at the breast is 42 (425 X 85/849), whereas after adjusting for the influence of other attributes, table 5 shows that the expected number of Schick positives among this group is 50, which is very close to 52, the observed number of Schick positives in this group. Thus it is concluded that breast feeding did not significantly influence the Schick reaction in this experience. In a similar manner table 6 was prepared to determine whether race influenced the Schick reaction after adjusting for the influence of other attributes. The computed “Pm” was 688, and it is concluded that race did not significantly influence the Schick reaction in this experience.
Table 5. Schick Test Results by Duration of Breast Feeding after Adjusting for Influence of Other Attributes

<table>
<thead>
<tr>
<th>Product</th>
<th>No other children in h'hold</th>
<th>Age at last dose</th>
<th>Breast Feeding at first dose</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Breast fed</td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td>None</td>
<td>2-5 mth.</td>
<td>43</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;5 mth.</td>
<td>33</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>1 or more</td>
<td>2-5 mth.</td>
<td>89</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;5 mth.</td>
<td>55</td>
<td>5</td>
</tr>
<tr>
<td>Unmixed</td>
<td>None</td>
<td>2-5 mth.</td>
<td>56</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;5 mth.</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>1 or more</td>
<td>2-5 mth.</td>
<td>76</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;5 mth.</td>
<td>53</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>2-5 mth.</td>
<td>43</td>
<td>0</td>
<td>1.2</td>
</tr>
<tr>
<td></td>
<td>&gt;5 mth.</td>
<td>33</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>1 or more</td>
<td>2-5 mth.</td>
<td>89</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;5 mth.</td>
<td>55</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>2-5 mth.</td>
<td>56</td>
<td>6</td>
<td>8.4</td>
</tr>
<tr>
<td></td>
<td>&gt;5 mth.</td>
<td>20</td>
<td>0</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td>1 or more</td>
<td>2-5 mth.</td>
<td>76</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;5 mth.</td>
<td>53</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>425</td>
<td>52</td>
<td>50.1</td>
</tr>
</tbody>
</table>

Computation of Chi Square, Adjusted Experience

<table>
<thead>
<tr>
<th></th>
<th>Breast fed</th>
<th>Not B. fed</th>
<th>Total</th>
<th>Adjusted Chi Square</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schick positive</td>
<td>52</td>
<td>50.1</td>
<td>33</td>
<td>34.9</td>
</tr>
<tr>
<td>Schick negative</td>
<td>373</td>
<td>374.9</td>
<td>391</td>
<td>389.1</td>
</tr>
<tr>
<td>Total</td>
<td>425</td>
<td>424</td>
<td>849</td>
<td>87</td>
</tr>
</tbody>
</table>

Table 6. Schick Test Results by Race after Adjusting for Influence of Other Attributes

<table>
<thead>
<tr>
<th>Product</th>
<th>No other children in h'hold</th>
<th>Age at last dose</th>
<th>Race</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>White</td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td>None</td>
<td>2-5 mth.</td>
<td>23</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;5 mth.</td>
<td>69</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>1 or more</td>
<td>2-5 mth.</td>
<td>38</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;5 mth.</td>
<td>73</td>
<td>4</td>
</tr>
<tr>
<td>Unmixed</td>
<td>None</td>
<td>2-5 mth.</td>
<td>23</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;5 mth.</td>
<td>50</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>1 or more</td>
<td>2-5 mth.</td>
<td>24</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;5 mth.</td>
<td>72</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>2-5 mth.</td>
<td>23</td>
<td>4</td>
<td>3.7</td>
</tr>
<tr>
<td></td>
<td>&gt;5 mth.</td>
<td>50</td>
<td>8</td>
<td>4.7</td>
</tr>
<tr>
<td></td>
<td>1 or more</td>
<td>2-5 mth.</td>
<td>24</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;5 mth.</td>
<td>72</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>372</td>
<td>32</td>
<td>30.3</td>
</tr>
</tbody>
</table>

Adjusted Experience Chi square = 0.1611

“P”m = 688
66. Similar tables were prepared to determine whether age at last dose (table 7), the product received (table 8), and the presence of other children less than 10 years old in the household (table 9) influenced the Schick reaction after adjusting for each of the other two attributes. The adjustment did not alter the fact that these three attributes independently influence the Schick reaction to a significant extent. Now there remained the remote possibility that some of the other attributes listed in table 4 might have exerted some influence on the Schick reaction without it being manifest in table 4 on account of interrelationship with these three attributes. Hence, each of these three attributes – age at last dose, product received, and the presence of other children in the household – was checked with the other attributes listed in table 4, and none of these other attributes was found significant. On the other hand, the influence of each of these three attributes was manifest in every instance insofar as the small numbers would permit comparison. Thus it is evident that only four of the attributes observed are significantly correlated with the Schick reaction in this study and that each of these four are independently significant after taking account of all other attributes (a) Children receiving two doses of either product had disproportionately fewer Schick positives than children receiving only one dose of the same product. (b) Children receiving their second dose of either product at 6-23 months of age had disproportionately fewer Schick positives than children receiving their second dose of the same product at 2-5 months of age. (c) Children receiving the mixed product had disproportionately fewer Schick positives than children receiving the unmixed product. (d) Children living in single-child households had disproportionately fewer Schick positives than children living in households with other children less that 10 years of age.
### Table 7. Schick Test Results by Age at Injection after Adjusting for Influence of Other Attributes

<table>
<thead>
<tr>
<th>Product Rec’d</th>
<th>No.other children in h’hold</th>
<th>Age at Last Dose</th>
<th>Total</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>2-5 months</td>
<td>&gt; 5 months</td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td>None</td>
<td>72</td>
<td>2</td>
<td>0.8</td>
</tr>
<tr>
<td></td>
<td>1 or more</td>
<td>129</td>
<td>13</td>
<td>9.8</td>
</tr>
<tr>
<td>Unmixed</td>
<td>None</td>
<td>87</td>
<td>14</td>
<td>11.1</td>
</tr>
<tr>
<td></td>
<td>1 or more</td>
<td>100</td>
<td>26</td>
<td>16.4</td>
</tr>
<tr>
<td>Total</td>
<td>388</td>
<td>55</td>
<td>38.1</td>
<td>507</td>
</tr>
</tbody>
</table>

Adjusted Experience Chi Square = 14.7768
“P”m = <1

### Table 8. Schick Test Results by Product Received after Adjusting for Influence of Other Attributes

<table>
<thead>
<tr>
<th>Age at last dose</th>
<th>No.other children in h’hold</th>
<th>Product Recieved</th>
<th>Total</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mixed</td>
<td>Unmixed</td>
<td></td>
</tr>
<tr>
<td>2-5 mth.</td>
<td>None</td>
<td>72</td>
<td>2</td>
<td>7.2</td>
</tr>
<tr>
<td></td>
<td>1 or more</td>
<td>129</td>
<td>13</td>
<td>22.0</td>
</tr>
<tr>
<td>&gt;5 mth.</td>
<td>None</td>
<td>109</td>
<td>0</td>
<td>4.5</td>
</tr>
<tr>
<td></td>
<td>1 or more</td>
<td>162</td>
<td>9</td>
<td>12.5</td>
</tr>
<tr>
<td>Total</td>
<td>472</td>
<td>24</td>
<td>46.2</td>
<td>423</td>
</tr>
</tbody>
</table>

Adjusted Experience Chi Square = 25.1938
“P”m = <1
67. The observation that the presence or absence of other children in the household influenced the Schick reaction was not surprising, as existing theories on the natural acquisition of diphtheria immunity would be compatible with the finding of fewer Schick positives in children who lived in a household with other children. However, it is astounding to find that the opposite was manifest in this study. If the attribute had been observed to have no influence on the Schick reaction, that might be acceptable on account of the short period of time involved – the median age at Schick test was 18 months. However the fact that fewer Schick positives were observed in the group who had no other children in their households required further investigation of the phenomenon.

68. A careful recheck showed that no transcribing or tabulating errors were responsible for the phenomenon mentioned above. When each of the other attributes listed in table 4 were analysed by this attribute, the phenomenon was consistently manifest in each. As shown in table 9, the influence exerted by this attribute was not great but was of unquestioned significance. A review of the manner in which the children were brought under observation leaves little room for the introduction of any selective factors which would produce the phenomenon. The fact that the household status was classified as of the date the children were brought under observation can hardly account for the phenomenon because this date would appear to be an optimum time to record static information as an index of a dynamic situation. Practically all entries were within 2-4 months following date of first dose, and more than half the children received their first dose before they were 6 months of age and more than half were Schick tested before they were 18 months of age. The date of entry is very close to the midpoint between birth date and date of Schick test and too early for younger siblings to be included. Thus the phenomenon appears to be no artifact and needs still further investigation.

69. One wonders whether these study children at this very young age might be expected to reflect an increased risk of exposure to infection by reason of the presence of other children less than 10 years of age in their household. Table 10 was prepared to check this with respect to the occurrence of measles, chickenpox and mumps prior to Schick test. It is seen that the study children who lived in a
household with other children less than 10 years of age had a consistently higher proportion attacked with each of these diseases than study children who lived in single-child households. Table 11 shows that the occurrence of these diseases did not per se influence the Schick reaction. One also wonders whether immunisation against other diseases might influence the Schick reaction and be disproportionately distributed according to the presence or absence of other children in the household. Table 10 shows that a higher proportion of the study children living in single-child households received smallpox vaccination and pertussis vaccination outside the study (both prior to Schick test) than children living in multiple-child households. However, table 12 shows that such immunisations did not influence the Schick reaction. Thus it is concluded that some unexplained factor associated with the presence or absence of other children in the household consistently influenced the Schick reaction in this study.

70. Now, since the various attributes which influence the Schick reaction have been identified and quantitatively assessed, an estimate can be made of quantitative difference in the Schick test results among children receiving the mixed and unmixed product. From table 8 it can be seen that the distribution of the attributes, age at last dose, and number of other children in the household, was such that one would expect 46.25 (9.79 percent) Schick positives in the 472 children receiving two doses of the mixed product and 40.8 (9.65 percent) positives in the 423 receiving the unmixed product. The differences between these proportions are so small that a quantitative estimate of the difference between the effects of the two study products adjusted for the distribution of those attributes known to have influenced the Schick reaction would not be different from that in the unadjusted experience. It is pointed out that this near identity would not necessarily be manifest in repeated similar trials. Thus, with a fair degree of reliability, one can make a quantitative estimate that the unmixed product produced three times as many failures to immunise (14.9 percent positives) as the mixed product (5.1 percent positive). (See table 4.)
Table 9. Schick Test Results by Size of Household after Adjusting for Influence of Other Attributes

<table>
<thead>
<tr>
<th>Product Rec’d.</th>
<th>Age at last dose</th>
<th>No. Other Children &lt;10 in h’hold</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>None</td>
<td>One or More</td>
</tr>
<tr>
<td>2 Doses</td>
<td>2-5 mth.</td>
<td>72</td>
<td>129</td>
</tr>
<tr>
<td>Mixed</td>
<td></td>
<td>2</td>
<td>5.4</td>
</tr>
<tr>
<td></td>
<td>&gt;5 mth.</td>
<td>109</td>
<td>162</td>
</tr>
<tr>
<td>Unmixed</td>
<td>2-5 mth.</td>
<td>87</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>14</td>
<td>18.6</td>
</tr>
<tr>
<td></td>
<td>&gt;5 mth.</td>
<td>86</td>
<td>150</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8</td>
<td>8.4</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>354</td>
<td>541</td>
</tr>
</tbody>
</table>

Adjusted Experience Chi square = 7.5702  “P”m = 6

Other (1 dose aa, 1 dose, etc.) adjusted for age at last done

<table>
<thead>
<tr>
<th></th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mixed</td>
<td>54</td>
<td>12.9</td>
</tr>
<tr>
<td></td>
<td>96</td>
<td>18.1</td>
</tr>
<tr>
<td>Grand Total</td>
<td>408</td>
<td>48.9</td>
</tr>
</tbody>
</table>

Adjusted Experience Chi square = 11.2906  “P”m = <1

Table 10. A Comparison of Diseases and Vaccinations (other Study Products) with Schick Test Results According to Size of Household and Study Product Received.

<table>
<thead>
<tr>
<th>Product Rec’d.</th>
<th>Other children in h’hold</th>
<th>Positive Schick</th>
<th>Measles</th>
<th>Chickenpox</th>
<th>Mumps</th>
<th>Smallpox Vaccine</th>
<th>W.C. Vaccine Outside Study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Children No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>Mixed</td>
<td>No 181</td>
<td>2</td>
<td>10</td>
<td>6</td>
<td>10</td>
<td>6</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td>Yes 291</td>
<td>22</td>
<td>13</td>
<td>6</td>
<td>46</td>
<td>27</td>
<td>48</td>
</tr>
<tr>
<td>Unmixed</td>
<td>No 173</td>
<td>22</td>
<td>11</td>
<td>6</td>
<td>46</td>
<td>27</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>Yes 250</td>
<td>41</td>
<td>16</td>
<td>6</td>
<td>46</td>
<td>15</td>
<td>94</td>
</tr>
<tr>
<td>Total</td>
<td>No 354</td>
<td>24</td>
<td>21</td>
<td>6</td>
<td>16</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Yes 541</td>
<td>63</td>
<td>16</td>
<td>6</td>
<td>14</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Total</td>
<td>895</td>
<td>87</td>
<td>107</td>
<td>11</td>
<td>89</td>
<td>51</td>
<td>6</td>
</tr>
</tbody>
</table>
Table 11. A comparison of Schick Reaction in Children Having Measles, Chickenpox and/or Mumps Prior to Schick Test with Children Not Having Such Diseases

<table>
<thead>
<tr>
<th>Product Rec'd</th>
<th>No. other children in h'hold</th>
<th>Age at last dose</th>
<th>Measles, Chickenpox and/or Mumps</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mixed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>5</td>
<td>0</td>
<td>0.1</td>
<td>67</td>
</tr>
<tr>
<td>&gt; 5 months</td>
<td>17</td>
<td>0</td>
<td>-</td>
<td>92</td>
</tr>
<tr>
<td>1 or more</td>
<td>28</td>
<td>1</td>
<td>2.8</td>
<td>101</td>
</tr>
<tr>
<td>&gt; 5 months</td>
<td>67</td>
<td>3</td>
<td>3.7</td>
<td>95</td>
</tr>
<tr>
<td>Unmixed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>8</td>
<td>2</td>
<td>1.3</td>
<td>79</td>
</tr>
<tr>
<td>&gt; 5 months</td>
<td>11</td>
<td>3</td>
<td>3.0</td>
<td>75</td>
</tr>
<tr>
<td>1 or more</td>
<td>22</td>
<td>5</td>
<td>5.7</td>
<td>78</td>
</tr>
<tr>
<td>&gt; 5 months</td>
<td>50</td>
<td>3</td>
<td>5.0</td>
<td>100</td>
</tr>
<tr>
<td>Total</td>
<td>208</td>
<td>17</td>
<td>19.6</td>
<td>687</td>
</tr>
</tbody>
</table>

Adjusted Experience Chi square = 0.4920
“P”m = 483

Table 12. A comparison of Schick Reaction in Children Having Smallpox and/or Pertussis Vaccine (Outside Study) Prior to Schick Test with Children Not Having Such Vaccine.

<table>
<thead>
<tr>
<th>Product Rec’d</th>
<th>No. other children in h’hold</th>
<th>Age at last dose</th>
<th>Smallpox and/or Pertussis Vaccine (Outside Study)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mixed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>26</td>
<td>0</td>
<td>0.7</td>
<td>46</td>
</tr>
<tr>
<td>&gt; 5 months</td>
<td>45</td>
<td>0</td>
<td>-</td>
<td>64</td>
</tr>
<tr>
<td>1 or more</td>
<td>36</td>
<td>1</td>
<td>3.6</td>
<td>93</td>
</tr>
<tr>
<td>&gt; 5 months</td>
<td>41</td>
<td>2</td>
<td>2.3</td>
<td>121</td>
</tr>
<tr>
<td>Unmixed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>29</td>
<td>3</td>
<td>4.7</td>
<td>58</td>
</tr>
<tr>
<td>&gt; 5 months</td>
<td>37</td>
<td>7</td>
<td>3.4</td>
<td>49</td>
</tr>
<tr>
<td>1 or more</td>
<td>25</td>
<td>6</td>
<td>6.5</td>
<td>75</td>
</tr>
<tr>
<td>&gt; 5 months</td>
<td>45</td>
<td>6</td>
<td>4.5</td>
<td>105</td>
</tr>
<tr>
<td>Total</td>
<td>284</td>
<td>25</td>
<td>25.7</td>
<td>611</td>
</tr>
</tbody>
</table>

Adjusted Experience Chi square = 0.0299
“P”m = 863
71. To the above findings an over-all consideration of diphtheria immunity should be added. In the absence of artificial immunisation, very few children 6-30 months of age are immune to diphtheria, whereas adults for the most part are immune. In this study, a total of 1,025 children of median age 18 months were Schick tested one year after they were given only one or two doses of the mixed or unmixed study products and 90.6 percent were found immune, whereas in adults, 82.3 percent of the 707 mothers Schick tested were found immune, as measured by Schick test. Thus the over-all effort to immunise at a young age was highly successful. With respect to the age of immunisation and the products given, it should be noted that although children 2-5 months of age did not immunise as well as children 6-23 months of age, as indicated by Schick test, the mixed product was so superior to the unmixed product that it appeared to be as good if not a better immunising agent at the young age than the unmixed product at any age. Actually 8 percent (15/201) of the children who received both doses of the mixed product at 2-5 months of age were Schick positive, as compared with 11 percent (19/175) of the children who received both doses of the unmixed product at 6-23 months of age.

72. Thus by using the Schick test performed one year after immunisation as an index of diphtheria immunity, it is concluded that:

(a) Children who received two doses of the unmixed A-P diphtheria toxoid had three times as many failures to immunise against diphtheria as children who received two doses of the A-P mixture of diphtheria toxoid and pertussis vaccine. Children who only received one dose of these products exhibited a similar difference.

(b) Children who received only one known dose had three times as many failures to immunise against diphtheria as children who received two doses. This was true no matter which product was given.

(c) Children who received both doses at 2-5 months of age had twice as many failures to immunise against diphtheria as children who received at least one of their doses at 6-23 months of age. This was true no matter which product was given.
Children who received two doses of the mixed product before they were 6 months of age had fewer failures to immunise against diphtheria than children receiving the ordinary unmixed product at any age from 2-23 months.

73. The analysis of pertussis immunity is more complex than that for the Schick test. In the latter the end point was rather finite, the intervals between the time of injection and Schick test were comparatively short and had a small range of variation, and the age at Schick test was quite young and had a rather small range of variation. Therefore it was comparatively simple to elucidate the various attributes that influenced the Schick reaction and to take account of these attributes in estimating the quantitative differences in diphtheria immunity (as measured by the Schick test) between the children receiving the mixed and unmixed product. On the other hand, in the analysis of immunity to pertussis, the end points are not as finite, the intervals between the time of injections and the occurrence of the disease vary from zero to 5 years or longer, and once a child has developed the disease he is for practical purposes no longer at risk for an attack of the disease. Thus a similar analysis of the pertussis experience, including the identification of the various attributes which influence pertussis immunity and the use of such attributes in estimating the quantitative differences in pertussis immunity between the two groups, is a lengthy and tedious process. It required a listing of the various attributes which might influence pertussis immunity (analogous to those listed for diphtheria in table 4) and then the computation of the number of person years’ experience as vaccinated and nonvaccinated children in each group. As with the analysis of the Schick test results, it is further desirable to analyse the pertussis experience to identify the independent attributes which influence protection against pertussis. This is of epidemiological interest and may serve to enhance a quantitative estimate of the amount of pertussis protection conferred by the mixed product. Such analyses of the pertussis experience are being carried out, but they constitute refinements which are not yet tabulated and hence they are not included in this presentation.

74. Table 13 was prepared to compare the total occurrence of measles, chickenpox, mumps and pertussis in children born in an odd and even month. It covers the entire life experience of each study child from birth to March 1, 1947, or
until exit if lost from observation prior to that date. It covers their total experience
with these diseases regardless of whether they actually received pertussis vaccine in
or outside the study, and regardless of whether they received vaccine at the
beginning or the end of the observation period, and in fact without regard for any
attribute which might influence the occurrence of these diseases. Incidentally, 94.7
percent of the children born in an odd month received one or more doses of pertussis
vaccine at some time during the observation period, whereas 24.8 percent of the
children born in an even month received at least one prophylactic dose of some
bacterial pertussis vaccine. Table 13 merely shows the total number of children born
in an odd and even month, the average number of years they had lived to date of
March 1, 1947, and the total number of cases of these diseases that occurred during
their life from birth to the end of their observation period. It shows that the total
percent attacked and the average annual attack rate for measles, chickenpox, and
mumps is nearly equal in the two groups. In striking contrast, the total percent
attacked and the average annual attack rate for pertussis is decidedly lower among
children born in an odd month as compared with those born in an even month.
Another tabulation was prepared showing the attack rate for these diseases by
separate 6-month periods from 1940 – 1947. This tabulation showed that the attack
rate for pertussis was uniformly lower in children born in an odd month in every
single 6-month period from 1942 to 1947, whereas no consistent difference between
the groups was evident for the other diseases. It is thus obvious that some selective
influence other than chance variation produced the difference in the occurrence of
pertussis in the two groups. It would appear that this influence lowered the incidence
of pertussis in the odd group rather than increasing the incidence in the even group,
as the attack rate in the even group is not higher than that usually reported in
children in similar age group. Since the two groups are comparable in every respect
with the single exception of the study product given, one can assume that the
lowered incidence of pertussis in the odd group was due to the mixed product and
can proceed to examine the experience to determine whether the assumption is
consistent with all observations.
Table 13  A Comparison of the Total Occurrence of Measles, Chickenpox, Mumps, and Pertussis in Children Born in an Odd Month and in an Even Month. *

<table>
<thead>
<tr>
<th>Experience</th>
<th>Month of Birth</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odd</td>
<td>Even</td>
<td>Total</td>
</tr>
<tr>
<td>Number of Children</td>
<td>646</td>
<td>592</td>
<td>1,238</td>
</tr>
<tr>
<td>Average No. Years Observed</td>
<td>4.062</td>
<td>4.054</td>
<td>4.058</td>
</tr>
<tr>
<td>No. Person Years Observed</td>
<td>2,624</td>
<td>2,400</td>
<td>5,024</td>
</tr>
<tr>
<td>Measles Cases</td>
<td>276</td>
<td>244</td>
<td>520</td>
</tr>
<tr>
<td>Average Annual Attack Rate %</td>
<td>10.5</td>
<td>10.2</td>
<td>10.4</td>
</tr>
<tr>
<td>Total % Attacked</td>
<td>42.7</td>
<td>41.2</td>
<td>42.0</td>
</tr>
<tr>
<td>Chickenpox Cases</td>
<td>175</td>
<td>179</td>
<td>354</td>
</tr>
<tr>
<td>Average Annual Attack Rate %</td>
<td>6.7</td>
<td>7.5</td>
<td>7.0</td>
</tr>
<tr>
<td>Total % Attacked</td>
<td>27.1</td>
<td>30.2</td>
<td>28.6</td>
</tr>
<tr>
<td>Mumps Cases</td>
<td>83</td>
<td>55</td>
<td>138</td>
</tr>
<tr>
<td>Average Annual Attack Rate %</td>
<td>3.2</td>
<td>2.3</td>
<td>2.7</td>
</tr>
<tr>
<td>Total % Attacked</td>
<td>12.8</td>
<td>9.3</td>
<td>11.1</td>
</tr>
<tr>
<td>Pertussis Cases</td>
<td>90</td>
<td>211</td>
<td>301</td>
</tr>
<tr>
<td>Average Annual Attack Rate %</td>
<td>3.4</td>
<td>8.8</td>
<td>6.0</td>
</tr>
<tr>
<td>Total % Attacked</td>
<td>13.9</td>
<td>35.6</td>
<td>24.3</td>
</tr>
</tbody>
</table>

* This table covers the entire life experience of each study child from birth to March 1, 1947, or until exit if lost from observation prior to March 1, 1947. It covers the total experience of these children without regard for immunizations or other attributes which might influence the occurrence of these diseases.
75. If the above assumption is true, then after excluding children who received pertussis vaccine outside the study, the observed difference in the number of cases of pertussis vaccine which occurred in the odd and even groups should be manifest only after and not before the children received the study products. Also, when children who had pertussis before the study products were given are excluded, the difference in the occurrence of pertussis among children of the odd and even groups who received two doses of the study products as intended should be greater than in the crude experience of table 13. Furthermore, in such children the difference between the groups should be manifest in the white children as well as in the colored, in males and in females, and in every other possible attribute by which the children may be subdivided into groups of adequate size.

76. Table 14 presents some of the tabulations prepared to check these assumptions. It shows that prior to receipt of the study products there was no appreciable difference in the occurrence of the pertussis in the odd and even groups. It also shows that among the 792 children who received two doses of the study products as intended, 48 cases occurred among the 407 born in an odd month, whereas 158 cases occurred among the 385 children born in an even month. This represents a proportionate difference greater than that of the crude experience shown in table 13. These 792 children were subdivided into groups according to various attributes, namely, ages at time of first dose, date of first dose, interval between doses, sex, race, geographic section of residence, nurse observer, the occurrence of other diseases and immunisations, and the occurrence of pertussis in other children living in the household. In each of these attributes there were disproportionately fewer cases of pertussis among children born in an odd month compared with children born in an even month. To exemplify, table 14 includes the attribute of age at time of first dose. It shows that the disproportionately small number of cases that occurred in the odd group was manifest no matter whether the children received their first dose at 2-4 months of age or at 5-23 months of age. As a further example, one attribute which is somewhat akin to secondary household exposure, subdivided the children into groups according to whether they had lived in the family household with a definite case of pertussis in another child less than 10 years of age. In the 407
children of the odd group, 109 had such association with another case and 33 (30.6 percent) were attacked. In the 385 children of the even group, 115 had such association with another case and 100 (87.0 percent) were attacked. To supplement these observations, further analysis, which will be discussed in future reports, showed that the average annual attack rate in children who received no pertussis vaccine whatsoever was 11.2 percent, the rate in children receiving only one dose of the mixed product was 8.2 percent, the rate in children receiving two doses of the mixed product was 3.3 percent, and the rate in children who received three doses of pertussis vaccine outside the study was 4.1 percent. It is obvious that all observations are consistent with the assumption that the mixed product was responsible for the disproportionately few cases of pertussis observed in children born in an odd month.
Table 14. The Occurrence of Pertussis Prior to and After Receipt of First Dose of Study Product

<table>
<thead>
<tr>
<th>Experience</th>
<th>Mth.of Birth</th>
<th>Age at First Dose</th>
<th>No.of Children</th>
<th>No. of person-Yrs. Observed</th>
<th>No.of Cases</th>
<th>Total % Attacked</th>
<th>Avg. Ann. Attk. Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>*Prior to 1st Dose</td>
<td>Odd</td>
<td></td>
<td>624</td>
<td>332</td>
<td>19</td>
<td>3.0</td>
<td>5.7</td>
</tr>
<tr>
<td></td>
<td>Even</td>
<td></td>
<td>567</td>
<td>294</td>
<td>13</td>
<td>2.3</td>
<td>4.4</td>
</tr>
<tr>
<td></td>
<td>Odd</td>
<td>2-4 Mths.</td>
<td>204</td>
<td>755</td>
<td>28</td>
<td>13.7</td>
<td>3.7</td>
</tr>
<tr>
<td></td>
<td>Even</td>
<td>Mths.</td>
<td>193</td>
<td>721</td>
<td>83</td>
<td>43.0</td>
<td>11.5</td>
</tr>
<tr>
<td>**After 1st Dose</td>
<td>Odd</td>
<td>5-23 Mths.</td>
<td>203</td>
<td>686</td>
<td>20</td>
<td>9.9</td>
<td>2.9</td>
</tr>
<tr>
<td></td>
<td>Even</td>
<td>Mths.</td>
<td>192</td>
<td>671</td>
<td>75</td>
<td>39.1</td>
<td>11.2</td>
</tr>
<tr>
<td></td>
<td>Odd</td>
<td>2-23 Mths.</td>
<td>407</td>
<td>1,441</td>
<td>48</td>
<td>11.8</td>
<td>3.3</td>
</tr>
<tr>
<td></td>
<td>Even</td>
<td>mths.</td>
<td>385</td>
<td>1,392</td>
<td>158</td>
<td>41.0</td>
<td>11.4</td>
</tr>
</tbody>
</table>

* This includes all study children who had no prophylactic pertussis vaccine prior to receipt of first dose of the study product. It covers the experience from date of birth to date of first dose.

** This includes all study children who received two doses of the study product as intended, and who did not have pertussis prior to first dose, and who did not receive prophylactic pertussis vaccine outside the study. It covers the experience from the date of first dose to March 1, 1947, or to exit if prior to that date.
77. This conclusion is based on the clinical criteria for definition of a case of pertussis as previously set forth. The clinical basis was used because the ultimate value of any vaccine depends upon its ability to ameliorate or prevent the clinical disease. Even though the criteria used in this study are intended to include only frank cases, it is recognised that the criteria are more or less arbitrary. Accordingly, detailed records were kept for each child, recording the occurrence, duration, frequency, nature and intensity of paroxymal cough, whooping, vomiting, and other symptoms and signs of pertussis. The main purpose for collecting this data was to study the clinical disease as it occurs in the community; however, it serves to permit analysis of the data using various arbitrary diagnostic criteria for definition of a case of pertussis. Table 15 arranges the 206 cases of pertussis, that occurred in children after receiving two doses of the study products as intended and no other prophylactic pertussis vaccine, by mutually exclusive groups according to the number of days’ duration of paroxysmal coughing and whooping. It shows that the occurrence of cases having paroxysmal cough of 9-27 days’ duration was nearly equal in the two groups but that a marked difference occurred in cases having paroxysmal cough for longer than 27 days. This result is amenable to diverse interpretations. It would appear possible that the clinical definition of pertussis used in this study was too broad and possibly included diseases not due to H. pertussis infection. This cannot be denied, but another interpretation seems more likely. The distribution of cases in the even group by percent of the total cases in that group should be nearly equal to that in the strictly comparable odd group. By applying the proportionate distribution of the 158 cases observed in the odd group, according to clinical classification A, B, and C respectively, 5, 22, and 21 cases would be expected in the odd group, whereas 22, 17, and 9 cases were observed. This would indicate that part of the effect of the mixed product was to modify the clinical manifestations. With either interpretation the conclusion is inescapable that if this study had used more conservative criteria for the definition of a clinical case of pertussis, the difference in the observed occurrence of pertussis between the children receiving the mixed and unmixed product would have been even more striking than with the criteria used.
Table 15. Clinical Classification. Distribution of Cases of Pertussis Occurring in Children of the Odd and Even Groups, According to Duration of Paroxysmal Coughing and Whooping. *

<table>
<thead>
<tr>
<th>Classification</th>
<th>No. of Days Duration</th>
<th>Odd Birth Date (Mixed Product)</th>
<th>Even Birth Date (Unmixed Product)</th>
<th>Total 792 Children</th>
<th>Ratio Even % To odd %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paroxysmal Cough</td>
<td>Whooping Cases</td>
<td>% of Children</td>
<td>Cases</td>
<td>% of Children</td>
<td>Cases</td>
</tr>
<tr>
<td>A</td>
<td>9-27</td>
<td>0-27</td>
<td>22</td>
<td>5.41</td>
<td>18</td>
</tr>
<tr>
<td>B</td>
<td>&gt;27</td>
<td>0-27</td>
<td>17</td>
<td>4.18</td>
<td>71</td>
</tr>
<tr>
<td>C</td>
<td>&gt;27</td>
<td>&gt;27</td>
<td>9</td>
<td>2.21</td>
<td>69</td>
</tr>
<tr>
<td>Total Cases</td>
<td>48</td>
<td>11.79</td>
<td>158</td>
<td>41.04</td>
<td>206</td>
</tr>
</tbody>
</table>

* This table includes all study children who received two doses of the study product as intended, and who did not have pertussis prior to the first dose, and who did not receive prophylactic pertussis vaccine outside the study. It covers the experience from the date of first dose to March 1, 1947, or to exit if prior to that date.
78. Incidentally it may be added that table 15 exemplifies one of the many difficulties involved in efforts to compare the effectiveness of vaccine products used in different studies. In addition to many differences in the conduct of reported studies, table 15 shows that the criteria for diagnosis of a case can produce large differences in results. With the criteria used in this study the percent attacked in the unvaccinated group was 3.48 times that for the vaccinated group. By using more conservative criteria, the percent attacked in the unvaccinated group was 8.11 times that of the vaccinated group. Thus when criteria for diagnosis and other attributes in different studies are not comparable, it is difficult to determine whether the product used in one study is more or less efficacious than a product used in another study. (See paragraph 3.)

79. Thus from this study of pertussis immunity it is concluded that two doses of the A-P mixture of pertussis vaccine and diphtheria toxoid, which contained only 10 billion killed *H. pertussis* organisms per dose and which were given routinely to children representing the general population with a 4-week interval between doses, conferred substantial protection against clinical pertussis when the first dose was given to children at either 2-4 or 5-23 months of age.
Summary and Recapitulation of Major Conclusions.

80. An effort has been made to present a detailed description of the epidemiological principles and procedures involved in a study of the prophylactic value of two doses of an alum-precipitated mixture of pertussis vaccine and diphtheria toxoid. The purpose of the study was to prepare a simple and effective prophylactic product which would be suitable for general public health use in preventing or ameliorating the hardships resulting from diphtheria and pertussis. The study was designed to give answers to the major questions that would arise in formulating recommendations for the general use of the product. The answers were elicited in a manner which can be projected to show the effects of the general use of the product in the community. The answers are:

1. Two doses of the A-P mixture of diphtheria toxoid and pertussis vaccine, when given routinely to young children in the general population with a 4-week interval between doses, conferred substantial protection against clinical pertussis.

2. The A-P mixed product caused no undue local or general reactions. The reactions were negligible.

3. The A-P mixed product gave much better protection against diphtheria (as measured by a Schick test performed one year after immunisation) than an equivalent amount of ordinary A-P diphtheria toxoid given in a similar manner.

4. The A-P mixed product gave substantial protection against clinical pertussis when given at 2-5 months of age. The protection was as good when the product was given at the young age as when given at 6-23 months of age.

5. The A-P mixed product gave substantial protection against diphtheria (as measured by a Schick test performed one year after immunisation) when given at 2-5 months of age. The protection against diphtheria was not as good when the mixed product was given at this young age as when the mixed product was given at 6-23 months of age; however, the A-P mixed product when given at the young age gave protection against diphtheria as good as that resulting from the unmixed A-P diphtheria toxoid when given at 6-23 months of age.
Acknowledgment.

81. The author is grateful for the assistance given by the many participants of this study, mentioned in paragraph 38. The author especially desires that the great assistance of Dr. J. P. Leake be recognised and that the contributions of the nurses, particularly Mrs. Anne Hodges, and the mothers of the study children be appreciated.
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AUTOBIOGRAPHY

March 1904  Born in Trinidad, Colorado.


June 1929  Graduated University of Colorado School of Medicine, M. D. degree.

June 1930  Completed 1 year rotating internship, U. S. Marine Hospital, San Francisco, California.

July 1930  Commissioned Assistant Surgeon, U. S. Public Health Service.

August 1932  Completed 2 years duty Maritime Quarantine and Medical Examination of Aliens, U. S. Quarantine Station, Angel Island, California.

July 1933  Completed 1 year duty in hospital practice of internal medicine, U. S. Marine Hospital, San Francisco, California.

July 1933  Commissioned Passed Assistant Surgeon, U. S. Public Health Service.

November 1934  Served 1-1/3 years as Medical Officer in Charge of U. S. Quarantine Station and Second Class Medical Relief Station and in Charge of the Medical Inspection of Aliens for Port of San Diego and Mexican Border.

September 1936  Served 1½ years as Assistant Chief of Foreign Quarantine and Immigration Division, U. S. Public Health Service, Washington, D. C.

June 1937  Completed 1 year post graduate study at Johns Hopkins School of Hygiene and Public Health. Graduated. Master of Public Health degree.

July 1942  Commissioned Surgeon, U. S. Public Health Service.

January 1943  Completed 5½ years duty Epidemiology Unit, Division of Infectious Diseases, National Institute of Health, Bethesda, Maryland.

May 1943  Completed 4 months course U. S. Army School of Military Government, University of Virginia. Graduated. No degrees conferred.

September 1973  Commissioned Senior Surgeon, U. S. Public Health Service.

September 1945  Completed 2-3/4 years duty with U. S. Army as Public Health Officer, Military Government, in Mediterranean and European Theaters.
September 1947  Candidate for degree of Doctor of Public Health from Johns Hopkins School of Hygiene and Public Health.

April 1948  Served 2½ years as Chief Epidemiology Unit, Division of Infectious Diseases, National Institute of Health, Bethesda, Maryland.

**PUBLICATIONS**


APPENDICES
Dear Mrs. John Doe:

Our records show that Baby Doe is now two months old. I am sure you would not want your child to suffer from diphtheria or smallpox when these diseases can be prevented so easily.

The danger of epidemic disease in Norfolk is now increased because of crowding brought about by our war activities. I urge you to take your child to a physician for protection against smallpox and diphtheria at the earliest practicable date. If you feel unable to engage a physician for such protection, bring your child to one of the health stations on the attached list, where protection will be given gladly and without charge.

Children should have their first vaccination against smallpox in early infancy when it is safest and bothers the child the least. They should again be vaccinated against smallpox at 5 or 6 years of age. Second vaccinations performed at this time give increased protection, are practically unnoticed by the child, and hardly ever produce a scar.

Diphtheria protection has been given usually at age 6-12 months, but records show that many children die from diphtheria before they reach 12 months of age. The U. S. Public Health Service has made available to all health stations on the attached list a limited supply of diphtheria toxoid specially prepared to protect children as young as 2 months old.

This helpless child of yours depends entirely upon you for the very best of care. Your physician and health department will do all they can to help. Won’t you take your child to them now for protection against these dread and killing diseases?

Sincerely,

J. C. Sleet, M.D.
Health Commissioner
The visiting nurses’ records are kept on 5x8-inch record cards which are bound together with gummed tape in book form. The cards are of three types: (1) Form C, the face card, which provides for a family roster with identification data. It has space for recording the name, address, sex, birth date, period of household residence, and history of communicable diseases and immunisations. The back of the card is ruled for the reference notes which further elucidate or modify the data recorded on the face card. (2) Form R-583 is the household visiting record card. (3) Form 583-A is the case record card. The face of this card provides space for the recording the clinical manifestations of a case of pertussis, and the back of this card is for exposure history and case summary.

Form C Face Card. The top line, reading from left to right, is, first, the number of the selected child. The selected child is one who received one or more doses of the study product; he is the child who brings the household under observation. When more than one selected child is in the household, this number should be the lowest of the group and this automatically becomes the household number. When more that one selected child resided in the same household, the numbers of the other selected children are written above the household number. Next is the name and address of the parent or guardian; the surname is placed first, and the address is that where the selected child was first located for observation. The next is the total number of persons in the household at the time the selected child first came under observation. The next space is for health section of residence at start of the study, and the following three spaces are for successive changes in health section of residence during the study.

Lines 2 and 3 include blocked spaces for six changes in residence during period of observation. In each block the first item is the date of change of residence. This is recorded with the number of the month above the diagonal and the year below the diagonal, and at the right end of the diagonal there is indicated whether or not the change in residence constituted a change in health section by recording “O” if no change and “Y” if such a change occurred. In the latter event, the number of the health section
of the new residence is indicated successively in the last three spaces in the top line. The rest of the block includes the new address of residence and at the right end is recorded the total number of people in the household after residence is established at the new address.

The remainder of the face card is a roster of the children under 10 years of age living in the household, including the selected child. Spaces for ten children are provided, and when more than ten children reside in one household a second face card is attached. In the main, the headings of the roster are self-explanatory with certain exceptions to be noted. The horizontal spaces are numbered and the vertical columns lettered. Whenever there is insufficient room for pertinent data or when any cell contains information which cannot be accepted at face value, the identifying letter is placed in the appropriate column (k, t, Re, y or s) and the number and letter endorsed on the back of the card with explanatory notes.

Columns h, i, and j originally concerned residence in the household but due to some confusion resulting from children moving from one household to another, both of which are observation, column h, has been changed so as to pertain to dates under observation and not dates of residence in the household. The upper half of column h includes the date when that particular child came under observation in the study and the lower half included the date when he is permanently exited from observation. Columns i and j indicate by dates the tenure of residence, regardless of whether temporary or permanent, of each child in the household of the selected child of whose family roster the face card represents. If the date of beginning observation is the same as that of beginning residence in the household, that date is not recorded twice; it is omitted from column i. In the event there are more changes than those for which space is provided, appropriate notation is made in column k and those additional changes are endorsed on the back of the face card.

Residence in family household (FHH) is defined to include only children who live together as a family unit under the same roof in a room or group of rooms common to each child and who for most part play together, eat together, and sleep in the same abode. Roomers, boarders, employees, and the like are not included as residents unless they are considered and treated as one of the family. This definition is strictly adhered to
and the following rules are in effect to insure uniform treatment of dynamic changes in household composition: 1. The selected child is the “keystone” of the household, and associates are observed only so long as they reside in the household of a selected child and remain less than 10 years of age. Temporary absences, of course, are expected. Residence and absence from residence are classified as permanent or temporary according to duration of greater or less than 90 days respectively. 2. Temporary residence or absence changes the composition of the household only when longer than 48 hours and when it occurs during the infectious stage of any common communicable disease in the visitor or absentee or any permanent or temporary residence of the household of whatever age. For this purpose the infectious period of measles is considered to include the 4 days prior and 5 days subsequent to onset of rash; chickenpox, 1 day prior and 8 days subsequent to onset of rash; mumps, 2 days prior and 7 days subsequent to onset of swelling in the salivary glad; pertussis, 14 days prior and 28 days after onset of paroxysmal cough. All permanent residents are treated exactly like the selected child for the duration of such residence. Temporary residents are similarly treated except detailed histories and confirmations of past experience the communicable diseases are solicited for the disease necessitating their classification as a temporary resident.

For each disease, measles, chickenpox, mumps, and pertussis, a column is provided to indicate whether each child had onset of those diseases prior to date of first observation in the study (indicated in column h). The letter “O” indicates no prior case, “Y” indicates definite prior attack, and “X” indicated unknown if prior attack occurred, “XY” and “XO” indicate doubtful attack, The “XY”, doubtful yes, and “XO”, doubtful no, indicates the impression of the investigator as to whether or not a prior case has occurred. In order to be recorded as a definite prior attack (“Y”), a history must be obtained of clinical manifestations which leave no reasonable doubt but that the child had the disease. In the absence of history of such a degree of completeness, the case may be classified as “XY” in the event the epidemiological circumstances together with the clinical manifestations make it likely that the child had a prior attack of the disease.

Columns m, o, q, and v record the date of onset of the disease in question as close as it can be reasonably approximated, both for prior and observed experience. The date
of onset for measles and chickenpox is the date that the rash becomes manifest, the date of onset for mumps is the date the swelling of the salivary gland becomes manifest, and the date of the onset of pertussis is the date of onset of cough.

Columns r and s are for common communicable diseases of children which occur in the household, other than measles, chickenpox, mumps and pertussis, and these columns are filled out in the same manner as for those diseases.

Column t is for record endorsement on back of the card of such diseases other than those noted in columns m, o, q, r, s, and v as may occur during the observation period.

Under pertussis, columns u and v are to be used in a manner similar to that for other diseases, for example, lm, no, pq, etc. The column labelled “Class” is not to be filled out by the nurses; it is reserved for unforeseen use and if this does not arise may eventually be used for a code of case classification.

Column w is for dates of receipt of study products and the vial numbers of the product received are recorded in column x in opposite each date.

The column entitled “Reaction” is to be used for recording the receipt of pertussis vaccine other than study products and the dates and type of product received are to be endorsed on back of card.

Under column x, the end of the slanting line is marked with a “O” or a “Y” to indicate whether the child had diphtheria toxoid prior to beginning of observation (indicated in column h). Whenever diphtheria toxoid is administered, the date is recorded, the enumerator being the month and the denominator the year. Calendar months are recorded by numerals, vis., 1 = January; 2 = February; 3-9 = March – September; O = October; X = November; Y = December.

In column y; the title “Age weaned” is to be disregarded and the upper half is marked with an “O”, “X” or “Y” to indicate whether a child has ever had successful smallpox vaccination, and the lower half of the column is used similarly for typhoid vaccination. When “Y” is recorded, the date is endorsed on the back of the card as accurately as can be reasonably approximated with particular attention to its chronological occurrence with reference to disease attacks. Smallpox vaccine is recorded as “Y” only when successful, i.e., when a vesicle, scab and scar result. Typhoid
is recorded as “Y” even if only one dose is administered. “X” means unknown or not certain that injection was typhoid and information available is to be endorsed on back of card.

The last column (References) includes for each child the letter heading of the column in which the information recorded requires qualification, and on the back of the card the child number and column reference identifies the pertinent qualifying data.

The household visiting card is for notes describing the clinical manifestations of communicable disease and all attributes relating thereto. The date of each visit and the initials of the investigator are also noted thereon together with the name of the informant if other than the mother or usual guardian. The date of visit is encircled with red ink when the notes record an exposure to pertussis. (See paragraph 44.)

The case record card provides space for recording the symptoms of pertussis of four children. It graphically portrays the dates of onset and duration of cough, paroxysmal cough, whooping, and vomiting, and shows the duration of the most severe period of the disease. The latter represents the period of greatest departure from normal health; it is the period during which one cannot say the patient was better or worse. At the right end of graph is recorded the average number of paroxysms per day and night during the most severe period. The number of such paroxysms which are accompanied by whooping or vomiting is also noted. A narrative summary of each case is recorded at the bottom of each of the four graphs.

On the back of the case record a summary of exposure is recorded together with other pertinent information.
<table>
<thead>
<tr>
<th>GIVEN NAME</th>
<th>LAST NAME</th>
<th>RELATION</th>
<th>BIRTH DATE</th>
<th>PERM. DATE</th>
<th>OUT DATE</th>
<th>OOS DATE</th>
<th>DISEASE</th>
<th>IMMUNIZED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Robert</td>
<td>Terry</td>
<td></td>
<td>8-5-42</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Damien</td>
<td>Michael</td>
<td></td>
<td>8-5-42</td>
<td>7-6-42</td>
<td>7-17-42</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Roland</td>
<td>Emmett</td>
<td>House</td>
<td>8-5-42</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linda</td>
<td>Jean</td>
<td>Smith</td>
<td>8-5-42</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cherry</td>
<td>May</td>
<td>Cooper</td>
<td>8-5-42</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Appendix C  Sample 1

Fever onset New in Morning 9:15 AM
and having 3 or 4 watery stools & vomits
per day. Offensive stools. M. called Dr.
Black 9-15. She saw his sample
but didn't return symptoms. Started
having 10-12 stools per day. Dr. Black
sent him to hospital 9-16-12.icitin
Medicine. Dr. told him "I had developed
inflammation of intestines."
Next day I transfused him. It has been
quite ill, but is improving now. He felt
return home to 1 week.

2:00 p.m. pains around nose
occasionally felt 3 months.
On 9-10 he had pains and Dr. Black
sent him to hospital 9-16-12 for
observation. Dr. thinks he has asthma
Appendicitis. No vomiting.
On 9-12 he had worms. On 9-13 he
passed a long white worm. M. states
lives in box. Chewing gum and
m. due to pick him up the slice
pains. She states he calmly
and solution was out of his mouth
no pain there. No fever.

He passed another worm 9-17.
He has a fever since yesterday.

Had severe bowel movements with
2 much stool and food taken up to
Dr. Black visit yesterday and plans
on giving him vitamin medicine. He
sent as fever subsided and stools
are Normal.

11:42 AM "I returned from 10:25. No much weight
Stools Normal."
"Stools were normal in 24hr. But
itch and about 1/2 liter of urine.
Medicine. No abdominal pain since then.
Mother was except *2 seen at 10-12.18"
Appendix C Sample 1

<table>
<thead>
<tr>
<th>Date</th>
<th>Time</th>
<th>Event</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>01/01/20XX</td>
<td>08:00</td>
<td>Arrived</td>
<td>01:00</td>
</tr>
<tr>
<td>01/01/20XX</td>
<td>09:00</td>
<td>Breakfast</td>
<td>01:00</td>
</tr>
<tr>
<td>01/01/20XX</td>
<td>10:00</td>
<td>Work</td>
<td>06:00</td>
</tr>
<tr>
<td>01/01/20XX</td>
<td>16:00</td>
<td>Lunch</td>
<td>01:00</td>
</tr>
<tr>
<td>01/02/20XX</td>
<td>08:00</td>
<td>Arrived</td>
<td>01:00</td>
</tr>
<tr>
<td>01/02/20XX</td>
<td>09:00</td>
<td>Breakfast</td>
<td>01:00</td>
</tr>
<tr>
<td>01/02/20XX</td>
<td>10:00</td>
<td>Work</td>
<td>06:00</td>
</tr>
<tr>
<td>01/02/20XX</td>
<td>16:00</td>
<td>Lunch</td>
<td>01:00</td>
</tr>
</tbody>
</table>
## Appendix C  Sample 2

<table>
<thead>
<tr>
<th>NAME</th>
<th>BIRTH DATE</th>
<th>MEASLES SHOT</th>
<th>DIPHTHERIA</th>
<th>PERTUSSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>John</td>
<td>10/12/42</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sally</td>
<td>12/9/42</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sarah</td>
<td>1/13/43</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Notes:**

- Complete details filled in by professional and adequate.
- Diphtheria shot given.
- PERTUSSIS: 5/24/42, 6/20/42.
Appendix C  Sample 2

<table>
<thead>
<tr>
<th>DATE</th>
<th>INV.</th>
<th>HOUSEHOLD VISITS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-7-43 AM</td>
<td>No ice except <em>2 was born in 1943.</em></td>
<td></td>
</tr>
<tr>
<td>2-8-43 AM</td>
<td>Home.</td>
<td></td>
</tr>
<tr>
<td>2-11-43 AM</td>
<td>No ice.</td>
<td></td>
</tr>
<tr>
<td>3-8-43 AM</td>
<td>No ice except <em>2 has a bad hacking cough, worse now. No cold.</em></td>
<td></td>
</tr>
</tbody>
</table>
| 3-20-43 AM | May beAustin or Austin. He had a hacking cough. On 2nd visit I found *2* had a hacking cough continued and gradually grew worse until it became typical of whooping cough. He coughed and vomited that night. In addition I observed that all of his symptoms had onset that day. M.J. states that *2* coughed intensely, 2/12 (date on prescription), that he had Dr. Blake. He had flu-like symptoms. I questioned whether they were whooping cough. He denied any whooping cough. He had an old cough. He had 3 coughs.

**Symptoms:**
- Cough relieved by getting worse. He described cough as: *2* started coughing, *2* coughed, *2* coughed. He noted that *2* coughed and continued until the coughs culminated in clear, thick mucus. He stated that he had a history of coughing and almost lost his breath. On static, coughing, he would cough and vomit. He had a cough, coughing him from a sound sleep and also pukes him up and puts him in the back. *2* had a sit up, in fact, he is sitting up. *2* had a cough, coughing, choking, choking, choking, choking, choking, choking, choking, choking. *2* coughed and then there was a whooping cough, which produced what described phlegm.

**Notes:**
- During visit *2* had a typical cough. He added whooping cough produced a small amount of clear, thick phlegm. *2* coughed 3-4 rapid coughs, then coughed 2 coughs, whooping cough, coughed 3 coughs and then coughed and then lost his breath.

**Description:**
- No further progress on results was made rapid in succession - *2* feels he is...
<table>
<thead>
<tr>
<th>Date</th>
<th>Specimen</th>
<th>Condition</th>
<th>Temperature</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/36</td>
<td>88</td>
<td>Fever</td>
<td></td>
</tr>
</tbody>
</table>

**Notes:**
- Fever present.
- Patient complained of body aches and headache.
- Received aspirin and bed rest.

**Health Section:**
- Adequate rest provided.
- Patient observed to be improving gradually.

**Sample 2:**
- No significant findings.
- Patient to continue rest and observe for further symptoms.

**History of Symptoms During This Week Prior:**
- No history of symptoms.
- Patient reported feeling well.

**Diagnosis:**
- Mild fever.
- Body aches.
- Headache.

**Treatment:**
-继续观察，如有进一步的症状通知医生。
- 保持充足休息。

**Diagnosis (continued):**
- 轻微发烧，身体疼痛，头痛。
- 继续观察，如有进一步的症状通知医生。
- 保持充足休息。

**Treatment (continued):**
- 保持充足休息。
- 如有进一步的症状通知医生。
- 保持充足休息。
APPENDIX D

Minimal Criteria for Diagnosis of a Case of Pertussis

(a) The child must have a cough lasting longer than 18 days, and for at least 8 days of this time the cough must be unremittently paroxyamal in type and recur at least three times each calendar day of the 8. The paroxysm is defined as a spasm, or fit of coughing with a sudden onset at a not definitely predictable time. The child must be practically, if not absolutely, free from cough during the period between paroxysms; due allowance in judgement, however, was permitted for children having coughs due to other causes upon which pertussis infection may be superimposed.

(b) The paroxysm must consist of a rapidly repeated series of coughs, most of which result in almost complete exhalation of supplemental air as evidenced by history or observation of suffusion of the face and watering of the eyes, and either whooping following most of the series of coughs or the repeated occurrence of four or more successive coughs without intervening inhalation. The intensity of the paroxysm must be sufficient to arouse the child from a deep sleep on many occasions and to cause him, if physically able, to sit up in bed, or at least to get up on his knees to cough and get his breath.

(c) Clinical pertussis must be the most likely clinical diagnosis in the judgement of the examining physician, regardless of information concerning a prior attack of pertussis, a recent exposure to the disease, or prior vaccination against the disease.

(d) The information concerning the clinical syndrome must be sufficiently reliable and complete to establish beyond reasonable question the true existence of the above minimal criteria.
NO. 2015  
NORFOLK COMMUNICABLE DISEASE STUDY  
Name: Doe, John  
Address: 120 Jones St.

<table>
<thead>
<tr>
<th>Date</th>
<th>Time</th>
<th>Event</th>
<th>Duration</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>7/18</td>
<td>A.M.</td>
<td>4:45 P.M.</td>
<td>4 days</td>
<td></td>
</tr>
<tr>
<td>7/19</td>
<td>A.M.</td>
<td>2:15 P.M.</td>
<td>2 days</td>
<td></td>
</tr>
<tr>
<td>7/21</td>
<td>A.M.</td>
<td>1:15 P.M.</td>
<td>4 days</td>
<td></td>
</tr>
<tr>
<td>7/22</td>
<td>A.M.</td>
<td>10:35 a.m.</td>
<td>12 hours</td>
<td></td>
</tr>
<tr>
<td>7/23</td>
<td>A.M.</td>
<td>1:35 a.m.</td>
<td>12 hours</td>
<td></td>
</tr>
<tr>
<td>7/24</td>
<td>A.M.</td>
<td>9:00 a.m.</td>
<td>12 hours</td>
<td></td>
</tr>
<tr>
<td>7/25</td>
<td>A.M.</td>
<td>4:25 P.M.</td>
<td>12 hours</td>
<td></td>
</tr>
</tbody>
</table>

Remarks

Mild = || Moderate = || Severe = || None = --
APPENDIX F

Post Card Request for Schick Test and Record of Reaction

A Sample is shown of the post card request for Schick test as it was sent to the parents. The second sample shows the information recorded on the card at the time of Schick test and at the various dates of observation. At the top of the card is the date and time of Schick test and the history as to duration of breast feeding. At the bottom of the card are the dates of observation and the measurements of the reaction and the final classification of the reaction encircled. The left-hand side was used for the child’s Schick reaction and the right-hand side for the mother’s reaction.

One-tenth cc. of Schick toxin was given intracutaneously on the upper half of the ventral surface of the left forearm (Lt) and the heated control was similarly given on the right forearm (Rt).
Our records show that John was immunized against diphtheria about one year ago. It is now time for a Schick test so that you will know whether your child is still protected.

Be sure to get this simple skin test for your child at King's Daughters Health Station, 38 St. and Broadway Ferry Rd.  
Time 2 o'clock; Day June 27 Friday afternoon  
Please bring this card with you.  

The U. S. Public Health Service.
APPENDIX G

Key Sort Card Used for Record and Analysis of Data

The code is more complicated than needed for present analysis. The complexity results from the fact that the same code and card are used for recording future results of continued observations, and furthermore the same code is to be used to record the observations of the prior study. An attached sample shows the nature of the data to be recorded on the Key Sort card and another sample shows the recorded data and card punched ready for sorting.

For convenient reference these notes are itemised:

A = Basic data – top of Key Sort card
B = Diseases – left side of card
C = Household status – bottom of card
D = Schick tests, vaccinations, exit – right side of card
(The subheadings read from right to left)

A. Basic Data

A 1. Product. Interval. Age. (First double hole not to be used)

(a) Age at first dose of study product in years and months.
   4 months = no punch in year and 3+1 in month
   1 year, 3 months = punch 1 and 3 in Yr. and Mth. respectively
   3 years, 6 months = punch 2 and 18 in Yr. and Mth. respectively

(b) No. of weeks interval between 1ˢᵗ and 2ⁿᵈ dose of study product.
   <6 weeks = no punch
   6-8 weeks = shallow punch
   >8 weeks = deep punch

(c) (1) Type of study product given and (2) Number of doses.
   (1) A-P Pertussis vaccine = P
       A-P Diphtheria toxoid unmixed = D
       AP Mixture diphtheria toxoid and pertussis vaccine = DP
   (2) Two or more doses of (1) = shallow punch
       Only one dose of (1) = deep punch

A 2. Date of birth of selected child, years and months.
(a) Year, tens  
1920-29 = shallow punch  
1930-39 = deep punch  
1940-49 = no punch  

(b) Year, units  
1 - 9  

(c) Months, ½ months = Multiply month of birth by 2 and add 0 if day 1-15, add 1 if day 16-31, and punch result  

A 3. Sex. Color  
(a) Punch females only  
(b) Punch whites only  

A 4. Child Number  
(a), (b), (c), (d) = thousands, hundreds, tens, and units, respectively.  

B. Diseases in Selected Child and Family Household Exposures.  

B.1 Measles.  
(a) Age in ½ years:  
0-5 mths. = 1  
6-11 mths. = 2  
12-17 mths. = 3  
16-23 mths. = 4  
Multiply year of age by 2 and add 1 if months 0-5, add 2 if months 6-11, and punch result  

(b) Family Household (FHH) Exposure*  
No FHH exposure = no punch  
FHH exposure = shallow punch  
Unknown FHH = center punch  
more than 1 FHH = deep punch  

(c) Classification:  
No case = no punch  
XY case = shallow punch  
Definite case = deep punch  

* Criteria for Classification of Family Household Exposure. Family household exposures are rather difficult to classify with uniformity but some criteria are essential to secure uniformity even though arbitrary and points must be used. One must define some minimum duration of a defined type of residence in the household with a definite case during some specified period of course of the disease in another child who has a definite case according to some minimal standards. In addition, the person exposed must be kept under adequate observation for some specified period long enough to determine whether or not he develops a definite case of the disease. Furthermore, the complete past history
of the exposer must be known insofar as he may have had a prior attack or prior immunisation or prior intense exposure and escape from the disease.

For the purpose of this code, the latter is tabulated elsewhere on the card and the definition of criteria for diagnosis of a case and a definition of a household and residence therein has been described. Thus the following arbitrary and points were used as a minimum for definite family household exposure:

1. Measles. Exposee must reside with exposer for at least 3 days (72 hours) during the period 2 days prior to 4 days after onset of rash in exposer. Exposee to be observed throughout period of 7-21 days after onset of rash in exposer.

2. Chickenpox. Exposee must reside with exposer for at least 3 days (72 hours) during the period from 0 to 6 days following onset of rash in exposer. Exposee to be observed throughout period of 7-33 days after onset of rash in exposer.

3. Mumps. Exposee must reside with exposer for at least 5 days during the period 2 days prior to 7 days after onset of swelling of salivary gland in exposer. Exposee to be observed throughout period of 8-42 days after onset of swelling in exposer.

4. Pertussis. Exposee must reside with exposer for at least 7 days during the period 5 days prior to 16 days after onset of paroxysmal cough in exposer. Exposee to be observed throughout period of 5-42 days after onset of paroxysmal cough in exposer.

B 2. Chickenpox
   (a), (b), (c) same as for Measles

B 3. Mumps
   (a), (b), (c) same as for Measles

B 4. Pertussis
   (a) Age in years: 0 = no punch, 1 year = punch 1, etc.
   (b) Age in months: 0 = no punch, 1 month = punch 1, etc.
   (c) FHH exposure: No FHH = no punch
       FHH = shallow punch
       Unknown FHH = center punch
       More than 1 FHH = deep punch
   (d) Classification: Same as for Measles
(e) Paroxysmal Cough and (f) Whoop (Pc and W holes):

1 = Pc 8-27 days
2 = W O a b
3 = W c
4 = W c
5 = Pc > 27 days
6 = W O a b
7 = W c
8 = W c

O following W (Whoop) above = definitely no
a = less than 4 paroxysms with whooping
b = 4-9 paroxysms with whooping
c = more than 9 paroxysms with whooping

Same for Vomiting (V)

(Where existence or duration of whoop or vomit is unknown, it is considered as no (O) Whoop or Vomit above, i.e., W O a b or V O a)

(g) Immunity status 3 weeks prior to onset:

No punch = Susceptible, i.e., no vaccine, no definite or XY case, and no FHH exposures and escapes.
Shallow punch = At least one dose pertussis vaccine, no prior definite case.
Deep punch = Prior definite case.
Center punch = Prior XY case of FHH escape, no prior definite case, no prior vaccine

C. Household Status, Other cases of Pertussis in FHH, Nurse, etc.

C1. Other cases of pertussis in FHH during HH experience with pertussis infection, etc.

(a) No punch = No other cases in child <10 yrs. old in FHH
Shallow punch = one other case in child <10 yrs. old in FHH
Deep punch = >1 other case in child <10 years. old in FHH
Center punch = Unknown if other definite cases in FHH

C1. (b) Nurse Observer: As indicated by initial of last name.
(Oth. = MM and NP)

(c) Interval in weeks from onset of Pc to weekly visits:
0 = no punch; 1,2,3,4,5,6 = 1-6 weeks respectively;
7 = 7-8 weeks; 8 = over 8 weeks

C 2. Duplicate experiences with Measles, Chickenpox, Mumps or Pertussis.
(Blank holes adjacent to “Interval to Nurse’s visit”)

Shallow punch = duplicate experience
Deep punch = Detailed information not at hand on any one or more of these diseases.

C 3. Household status.

Number of other children <10 years old in FHH who are S V I X
(Susceptibles, Vaccinated, Immunes and Unknowns) on birth date of selected child and on each anniversary thereof, i.e., age 0,1,2,3—10 and at “H”. The selected child is not included in this recording; only FHH residents <10 years of age are recorded. “H” refers to status 2 weeks prior to onset of paroxysmal cough in first definite case of pertussis in the household, or at date of entry of initial case if not in household 14 days prior to onset of paroxysmal cough and FHH exposure obtains. “H” is designed to reflect the household status prior to pertussis infection, therefore at “H” infected persons are tabulated as Susceptibles; whereas at “0-10” infected persons are tabulated as Immunes since they are no longer infectible. This difference between “H” and “0-10” is necessary to answer different questions. At “H” is recorded the types of household that gets infected, and at “0-10” is recorded the type of household that exists in the study at each anniversary of selected child’s birth date. At “H” an infected child in the household is considered susceptible until the 16th day of paroxysmal cough and immune on the 17th day or later day. At “0-10” an infected child in the household at an anniversary date is considered immune 5 days prior to onset of paroxysmal cough.

Each section comprising four marginal and four deep holes is for use of two successive anniversaries. The punches indicate only presence in the household of 0 and >0 other children who are S, V, I, and X, e.g., the S at age 0 and 1 is punched:

<table>
<thead>
<tr>
<th>Presence or Absence of other children</th>
<th>Age 0</th>
<th>Age 1</th>
<th>Punch</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10 years of age in FHH who are</td>
<td>No S</td>
<td>No S</td>
<td>No punch</td>
</tr>
<tr>
<td>susceptible to pertussis</td>
<td>No S</td>
<td>1 or &gt;1 S</td>
<td>Shallow punch</td>
</tr>
<tr>
<td></td>
<td>1 or &gt;1 S</td>
<td>No S</td>
<td>Center punch</td>
</tr>
<tr>
<td></td>
<td>1 or &gt;1 S</td>
<td>1 or &gt;1 S</td>
<td>Deep punch</td>
</tr>
</tbody>
</table>
D. Tests, Immunisations, Exit

D 1. Two double holes blank.

D 2. Age as of March 1, 1947, exclusively in those under observation as of that date, in half years.

Two double holes adjacent to “Schick”

<table>
<thead>
<tr>
<th>Age Range</th>
<th>Punch</th>
</tr>
</thead>
<tbody>
<tr>
<td>3½ completed years of age at 3/1/47</td>
<td></td>
</tr>
<tr>
<td>1 = 4 completed years of age at 3/1/47</td>
<td>3 1</td>
</tr>
<tr>
<td>2 = 4½ completed years of age at 3/1/47</td>
<td>6 2</td>
</tr>
<tr>
<td>3 = 5 completed years of age at 3/1/47</td>
<td></td>
</tr>
</tbody>
</table>

No punch = 3½ completed years of age at 3/1/47
1 = 4 completed years of age at 3/1/47
2 = 4½ completed years of age at 3/1/47
3 = 5 completed years of age at 3/1/47

D 3. Schick tests satisfactorily completed:
Punch shallow or deep respectively for negative or positive reaction.

D 4. Typhoid vaccine:
Punch shallow if interval between consecutive doses is <10 months
Punch deep if interval between consecutive doses is >9 months

D 5. Diphtheria toxoid other than study product:
(a) Punch ½ years of age (same as age B 1 (a) Measles) for one or more doses other than study product within <10 month period.

(b) Other diphtheria toxoid:
Shallow punch = Two or more doses with >9 month period between any two successive doses and <10 month period between all other successive doses.
Deep punch = Any unknown or questionable information as to what or whether diphtheria toxoid received.

D 6. Whooping Cough vaccine:
Punch in same manner as for Diphtheria (D 5) a and b.

D 7. Smallpox vaccine, successful primary:
(a) Punch ½ years of age same as D 5 a, Diphtheria.

(b) Revaccination:
Shallow punch = Immune type reaction
Deep punch = Accelerated or vaccinia or unknown reaction.

D 8. Age Exit (those who were not under observation as of March 1, 1947):
Punch year and month as in A 1 a.
Age at entry is recorded but not punched.
D 9. Death

Shallow punch = Death – date, cause and other particulars are recorded.
APPENDIX G Sample 2