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LARGE-SCALE FIELD TRIALS OF ACTIVE IMMUNIZING AGENTS

With Special Reference to Vaccination against Pertussis

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SYNOPSIS

In this discussion of the methods to be used in large-scale field trials of active immunizing agents and of the results to be expected from such trials, special emphasis is laid on pertussis vaccine trials in Great Britain. After a review of the criteria for strictly controlled field studies and of the investigation of typhoid vaccines conducted in 1904-08 by the Antityphoid Committee of the British Army, the author describes the pertussis vaccine studies which have been and are now being carried by the Whooping-Cough Immunization Committee of the Medical Research Council of Great Britain.

The original strictly controlled trials have been completed and the results published. Studies are now being made of vaccines prepared by different methods and evaluated both in the field and in the laboratory. Each vaccine is given to some 2000-3000 children of 4-6 months to 4 years of age. By the end of the studies 30 000-40 000 children will have been followed up for a period of two years. Since in the current studies all the children are vaccinated and none are left as unvaccinated controls, the relative and not the absolute protective value of the vaccines will be measured.

In discussing the clinical evaluation of chemotherapy in tuberculosis Daniels[3] stated :

" We should have no illusion concerning the character of this type of clinical research. The major research, the original work, has been done before this clinical stage, in the laboratories of the biochemists and bacteriologists, working as individuals or as teams. The methods I have outlined are designed to explore the application of their results to clinical medicine, to replace the old method of trial and error which was so costly in time and in human lives."

With only minor alterations this appraisal of the place of clinical trials in medicine can be applied to trials of active immunizing agents. If " all science is measurement ", then, as Sir Henry Dale has observed, " all true measurement is essentially comparative ".

In field studies of new immunizing agents the first aim is to measure the value of an antigen in the prevention or modification of disease by comparing the experience of a group of immunized persons—the test group—with that of a group of persons to whom the antigen has not been administered—the control group. This type of study, designed to determine whether an antigen is of sufficient value to warrant its use may be described as a strictly controlled trial. If the results of the strictly controlled trial are favourable it will probably be necessary to carry out more studies for the comparison of the potencies of antigens prepared by different methods or by the same methods in different laboratories. These further studies may be described as comparative. They differ from the strictly controlled studies in that all persons are given one of the two or three antigens the potencies of which are being compared. In both types of study, particularly in the second, attempts should be made to relate the field observations to the results of laboratory tests so that information may be obtained on the best methods of preparation of high potency antigens and on suitable tests for the assay of potency before batches are issued for routine use.

Controlled Studies

Field studies are not of recent development. The Antityphoid Committee of the British Army Council [5] made as large an investigation of the value of typhoid vaccines as any which has been undertaken with new antigens in recent years. Between 1904 and 1908 specially appointed medical officers were attached to each of 24 army units about to leave Britain for India or Egypt. Each medical officer was instructed to accompany the unit for three years, to inoculate all those who volunteered to be inoculated, to keep records of the numbers of inoculated and uninoculated men, and to keep records of the numbers of cases in each of the two groups. This extensive study was not executed with knowledge of the problems of interpretation which arise when persons are moved from the uninoculated group to the inoculated group during the period of the study. Further, the incidence of the disease in inoculated volunteers was compared with that in uninoculated non-volunteers and many soldiers were inoculated during or after outbreaks occurring in the units. These factors greatly reduced the value of the investigation as evidence of the protective effect of typhoid vaccines, though the results were accepted as entirely convincing at the time and led to the extensive use of typhoid and, later, TAB vaccines. I mention this not to suggest that typhoid vaccines are of no value, but to illustrate the importance of making sound controlled studies before an antigen is generally accepted as effective. Once an antigen is shown to be safe and is believed to have some value it is difficult to imagine circumstances in which it would be considered justifiable to withhold it from practitioners who wish to use it or patients who wish to have it.

Criteria for Strictly Controlled Field Studies

In recent years strict criteria for controlled trials have been defined and have been applied particularly to studies of pertussis vaccine and, more recently, to the investigation into the value of BCG. The observations have to be made on groups of persons and the indispensable element is that the test and the control group should be alike in every relevant respect. This does not mean that each child in each group should be exactly similar but that the sum of the characters of the individuals in one group should be similar to the sum of the characters of the individuals in the other group. Bradford Hill [7] has pointed out that the onus lies on the investigator to show when he publishes his findings that the groups were similar during the period of the observations.

Many studies have been shipwrecked on this rock of similarity. It was previously common practice for comparisons to be made, as in the Anti-typhoid Committee studies,[5] between the experience of inoculated volunteers and uninoculated non-volunteers. The fact that a person consents to inoculation (or that his parents consent for him to be inoculated) immediately indicates that he differs in some way from his fellows. The difference may influence the results. For example, in a survey of diphtheria immunization in England and Wales,[11] it was observed that, at the age of 2 years, 80% of first-born children in families were immunized compared with 71% of second or third children and 50% of fourth or higher-order children. Similar differences, though not always of the same degree, were found in all social classes. If parents of small families are more likely to seek protection for their children than parents of larger families, the incidence of disease in inoculated children from small families should not be compared with the incidence in uninoculated children in the general community even if they are of the same age and come from the same social class. A child in a small family runs less risk of being exposed to infection from a sibling than a child in a large family; Lidwell & Sommerville,[9] for example, found that the presence of schoolchildren in a household approximately doubled the number of common colds experienced by children under school age. Not only may the risk of infection within the family be less, but mothers of small families may well devote more care than mothers of larger families to protecting their children from infection outside the home.

Satisfactory groups for strictly controlled studies can only be obtained if volunteers, who have not had the disease and who have not been given the prophylactic previously, are divided at random into two groups—one to be given the antigen under test and the other to be retained as the control group. Compulsory inoculation, especially of untried antigens, is indefensible.

Even when relying on volunteers it is necessary to ensure that persons in the control group (or their parents) will retain as much interest in the study

as those in the inoculated group. Otherwise it may be difficult to obtain information of the same quality from the members of each group. The control group might well be disappointed that they were not given the apparent advantage of the inoculations, and might lose interest and refuse to co-operate further. For this reason the test and control groups should receive the same number of injections with the same size of dose and at the same intervals, but the inoculation given to the control group, though similar in appearance, and giving approximately the same degree of reaction, should not contain the antigen under test. The procedure is feasible with pertussis vaccine, TAB, and diphtheria and tetanus toxoids though it would not be possible with smallpox vaccines or BCG as the local lesions could not be simulated.

If a person (or his parent) does not know whether he is in the test or control group, his interest is more likely to be maintained. Giving injections to the control group has another advantage. If the investigator who gives the inoculations and makes the subsequent follow-up observations is unable to distinguish the antigen from the control inoculum until the end of the trial, and thus does not know whether a particular child is in the test or control group, he will be released from the anxiety of making a wrong decision when he investigates a doubtful case. I have found from experience in pertussis vaccine studies that, where the observer knows to which group the child he is examining belongs, he tends, in order to convince himself that he is unbiassed, to record the doubtful case in the controls as " not attacked " and the doubtful case in the test group as " attacked ". This kind of difficulty occurs less often if a diagnosis can be established by objective means such as the isolation of the infecting organism from persons with clinical evidence of the disease. Not only in mild or doubtful cases but also in the typical case objective evidence is of the utmost value in establishing the accuracy of the clinical diagnosis.

Though the methods outlined will ensure that the test and control groups are similar, it has already been shown that volunteers are not representative of the population as a whole. It is conceivable that the results from strictly controlled studies in volunteers, or in the children of parents who have agreed to allow them to be injected, might not, in certain circumstances, be applicable to the section of the community who failed to volunteer to take part in an investigation. Bell [1] had this in mind when he made his excellent study of a mixed adsorbed diphtheria-pertussis vaccine. He injected half the children with diphtheria prophylactic alone and half with the mixed vaccine but he did not inform the parents or the nurse-investigators who made the follow-up observations that any of the children were being given pertussis vaccine. The parents and investigators were under the impression that all the children were being protected against diphtheria only. By this means he obtained a sample of children representative of those whose parents have their children immunized with a vaccine of proved potency used routinely.

To this extent his sample was more representative of the community in which the study was made than a sample of children whose parents agreed to have them injected with a vaccine of unproved potency would have been. There are ethical objections to this method, however. In studies of new antigens the volunteers or their parents must be told that an investigation is being made and they must know the nature of the antigens which are to be used. It is impossible to envisage any circumstances which would allow departure from this principle.

British Medical Research Council Pertussis Vaccine Studies

In the planning and execution of the pertussis vaccine studies of the Medical Research Council, the factors discussed were taken into account and the studies were made on children whose parents volunteered to have them injected. In the first series [6] groups of children vaccinated with one of five batches of vaccine were compared with similar unvaccinated groups given an inoculation of inert turbid fluid. Each child was given three inoculations at monthly intervals and was followed up by nurse-investigators who visited the homes at monthly intervals for 2-2½ years. Detailed information of exposures to pertussis and of the severity and duration of symptoms when the disease developed was obtained, and efforts were made to confirm all cases bacteriologically. The method of the study was described and the results were given in the report [6] and need not be repeated here, but certain points are of general interest.

The trials were made in collaboration with the medical officers of health and their staffs in six towns or cities, and, though the trials were financed and carefully supervised by the Whooping-Cough Immunization Committee of the Medical Research Council, the main burden fell on the pertussis teams set up in each health department. The teams comprised a part-time medical officer, a clerk, and one nurse-investigator for every 400-600 children. The parents of every child in the inquiry were informed before they consented to have their children inoculated (1) that only half the children would receive the vaccine and that others would receive an injection which, though it looked like pertussis vaccine, would not protect the child against whooping cough; (2) that neither the day-to-day observers nor the parents would know until the end of the inquiry whether a particular child was in the pertussis vaccine or the control vaccine group; (3) that the object of the trial was to determine whether whooping cough vaccine was of any value.

Altogether the parents of some 8 900 children agreed to take part in these strictly controlled trials, and 7 558 children completed the course of inoculations and were taken into the follow-up group.

The similarity of the vaccinated and control groups is shown in Table I, from which it is clear that the numbers in each group were approximately the same, and the average age, the average duration of observations, and the

TABLE I. SIMILARITY OF VACCINATED AND CONTROL GROUPS

	Vaccinated group	Control group
Number of children entered for inoculation	4 515	4 412
Number of children given three inoculations	3 801	3 757
Average age (months)	12.2	12.2
Average duration of observation per child (months)	27.1	27.2
Number of cases of certain infectious diseases recorded during the trials:		
measles	920	891
varicella	289	280
broncho-pneumonia	95	94
diphtheria	1	1
all infections noted	1 305	1 266

incidence of infections other than whooping cough were very similar. The numbers of children exposed to pertussis in each group were also similar. For example, vaccinated children were exposed to cases in their own families on 203 occasions and unvaccinated children on 173 occasions; and there were 566 exposures outside the home in the vaccinated and 561 in the unvaccinated. The number of cases of pertussis was notably different in the two groups—there were 149 cases in the vaccinated and 687 in the controls.

From these results it was reasonable to assume that the fourfold reduction in the incidence of pertussis in the vaccinated group was due to the protective effect of the antigen.

Current studies

These results did not bring the studies to an end. Though all five batches of vaccine tried reduced the incidence of pertussis, there were differences in the potency of the five antigens (Table II). The Michigan vaccines were 2-4 times as potent as the other antigens and in the current studies attempts are being made to elucidate the reasons for these differences and to investigate the possibility of devising a laboratory test by which antigens of poor potency can be distinguished from antigens of high potency before issue.

The importance of ensuring the uniform effectiveness of batches of antigen for routine issue has already been mentioned. It can be illustrated by experience in England early in the diphtheria campaign during the 1939-45 war, when a poor antigen was distributed in certain areas. The failure of this antigen to protect the children inoculated might have brought the immunization campaign into disrepute. As a result of field and labora-

TABLE II. NUMBER OF CASES OF PERTUSSIS AND ATTACK-RATES PER 1 000 CHILD-MONTHS OF OBSERVATION IN THE VACCINATED AND CORRESPONDING CONTROL GROUPS FOR EACH OF THE 5 VACCINES EMPLOYED

Vaccine	Vaccinated group		Control group		Ratio of attack-rates (vaccinated: control)
	number of cases	attack-rate per 1 000 child-months	number of cases	attack-rate per 1 000 child-months	
Sauer	32	2.64	89	6.72	1: 2.5
Michigan D 231	17	0.97	129	7.04	1: 7.3
Michigan A 236	19	0.60	195	6.48	1: 10.8
Glaxo 61	27	2.02	85	6.61	1: 3.3
Glaxo 174	54	1.91	189	6.83	1: 3.6

tory studies, however, a "minimum requirements" test was devised before too much damage had been done to the campaign. All diphtheria antigens now issued in Britain conform to the test and the risk of using an unsatisfactory batch of toxoid is very small.

In the present investigations, pertussis antigens prepared by different methods are being evaluated in the field and at the same time are being tested by a number of laboratory tests, including the intracerebral mouse challenge test which has already been accepted in the United States of America.[14] The procedure followed is similar to that in the early strictly controlled trials with the important difference that all children are now being vaccinated with a pertussis vaccine. This means that we are now restricted to measuring the relative protective value of the antigens and are no longer estimating their absolute protective value. Once it had been clearly shown that pertussis vaccination could be effective under certain conditions we did not feel justified in asking parents to allow some children to be unvaccinated controls. On ethical grounds I do not see how we can depart from this, but if it were possible, there would be advantages in continuing to employ strict control groups to measure absolute protective values, particularly where it may be necessary to try to compare the efficacy of antigens given at different times. One can never be certain that observations are not influenced by changing factors outside the control of the investigators. For example, the treatment of whooping cough with chloramphenicol and Aureomycin might have reduced the intensity and duration of exposure of vaccinated children to infection from treated cases and by reducing the secondary attack rates might have erroneously led us to believe that the present vaccines were more effective than those used in the past. As it happens, the usefulness of chloramphenicol in pertussis is strictly limited and the difficulties I have outlined

have not arisen. Nevertheless, it was necessary to ensure that information was obtained about the use of these drugs in cases in children to whom our vaccinated children were exposed.

Comparing two or three antigens which may differ only slightly in potency is a formidable task in the field, and requires that very large numbers of children should be inoculated with each vaccine. The statisticians, however, wish to have information on as many batches of vaccine as possible for the correlation of field and laboratory results. In practice, therefore, we have had to balance the number of batches of vaccine we should like to test from the point of view of correlation between protection in children and results of laboratory tests against the numbers of children required on each vaccine to obtain significant answers in the field. When the studies have been completed about 28-30 different batches of vaccine will have been tested. They include vaccines grown on solid or in liquid media, vaccines prepared by different methods in the same laboratories or by the same method in different laboratories, vaccines mixed with diphtheria toxoid, and the soluble fraction of Pillemer.[10]

We do not know whether we shall be able to obtain as much information as we should like. The trials are an experiment in epidemiological methods as well as an investigation into pertussis vaccination. There can be no doubt, however, that the experience gained will be of value in the planning of future large-scale studies, and the results may also help in solving some of the many remaining general problems of bacterial immunity.

Numbers of children in current studies

In the present comparative studies we have vaccinated with the two, or sometimes three vaccines as many children from 4 or 6 months to 4 years of age as the size of the batches of vaccine allowed. The size of the batches varied but, apart from pilot studies, we have tried to have from 2 000 to 3 000 children inoculated with each vaccine in the follow-up groups at one time. As in the strictly controlled studies, some of the children are visited after each injection to estimate reaction rates and each child is visited each month and its history of respiratory tract infections and pertussis, or exposure to pertussis, is recorded for about 2 years after the last injection has been given. Even with pertussis, from which probably more than 70% of children suffer a clinically-recognizable attack before they are 15 years old, most children in the studies are not known to have been exposed to risk during the two-year follow-up period. From the experience of the strictly controlled studies, we may estimate, by assuming that the incidence of pertussis has remained about the same as it was when the first trials were made, that for every 100 children vaccinated, 15 will be exposed to infection outside their own families and 5 will be exposed to another case in the same household within two years. In the strictly controlled studies exposures outside the

family were of considerable value as 38% of the unvaccinated children developed pertussis. With the present high potency vaccines, however, these casual exposures are of less value; vaccinated children seldom develop symptoms from a casual exposure. Also, it is more difficult to be sure of the accuracy of the diagnosis in children of neighbours, who may not always be co-operative, than in children of the same family as the vaccinated child. It is, for example, sometimes difficult to obtain permission to take swabs from the neighbour's child. We have come to depend more than we used to do on the known exposure of the vaccinated children to cases in other (usually older) children in the same family. In these circumstances there are greater opportunities for swabbing the infective cases, and thus obtaining concrete evidence of exposure of the vaccinated children. In some trial areas over 70% of the clinically-diagnosed cases in siblings of vaccinated children have been bacteriologically confirmed. In our earlier studies [6] we observed that the attack-rate in the control children exposed to infective cases in their own homes was very high and did not vary very widely from area to area (Table III). The findings confirm those of workers in the United States of America and Canada (Table IV) and indicate that home-exposure (i.e., secondary familial) attack-rates in whooping cough could be used for comparisons of vaccines given at different times or in different areas provided the limitations of the method are clearly understood. Concentration upon home-exposures increases the accuracy of our observations though it decreases the

TABLE III. ATTACK-RATES IN PRESUMED SUSCEPTIBLE (CONTROL) CHILDREN UNDER 5 YEARS OF AGE EXPOSED TO CASES IN SIBLINGS *

Area	Trial number	Number of exposures	Number of cases	Attack-rate (%)
Manchester	I	20	17	85
	II	12	9	75
	III	21	19	91
Leeds	I	21	19	91
	II	24	21	88
Tottenham and Edmonton	I	15	14	93
	II	16	15	94
Wembley	I	12	8	67
	II	13	11	85
West Ham	I	19	18	95
All areas and trials		173	151	87

* Based on Table VI of the report of the Whooping-Cough Immunization Committee of the Medical Research Council* by kind permission of the editors of the *British Medical Journal*.

TABLE IV. ATTACK-RATES IN PRESUMED SUSCEPTIBLE CHILDREN EXPOSED TO INFECTION BY SIBLINGS, OR OTHERWISE VERY INTIMATELY EXPOSED

Observer	Age-group (years)	Number of exposures	Number of cases	Attack-rate (%)
Wheeler [15]	0 — 5	69	64	93
Doull et al. [4]	less than 5	62	61	98
Kendrick & Elderling[8]	up to 5	160	143	89
Silverthorne [13,*]	not stated	52	43	83
Singer-Brooks [13]	½ — 5	51	46	90
Coppolino [2]	0 — 5	49	43	88
All observers	—	443	400	90

* " Direct house-contacts "

number of useful observations made. As the children are visited each month, 2 400 visits are made to every 100 children during the course of the follow-up, and in these 2 400 visits evidence may be obtained of 5 home exposures to infection. One nurse cannot visit more than 400-600 children each month, and the trials are therefore expensive. Excluding the expenditure on vaccines and record cards the cost is about £2 10*s.* 0*d.* to £3 (US $7.00-8.50) for each child followed up during the two-year period of each trial. Before the end of the investigations some 30 000-40 000 children will have been followed up. The cost is not too much to pay for the production of safe and effective antigens against pertussis, but it does emphasize that large-scale field studies planned to obtain definitive answers are the final stage in the evaluation of an antigen. They do not take the place of careful observations in the laboratory or on small numbers of persons, in the early stages of the development; indeed, unless there was evidence that an antigen was free from risk and was likely to provide a substantial degree of immunity over a sufficiently long period, large-scale field studies could not be justified.

Discussion

The present pertussis studies will not answer all the questions outstanding. We shall not have information on the value of vaccines in children below 4 months of age, though this question is of the greatest practical importance. Our efforts have been concentrated on obtaining information on how to standardize antigens and we were unwilling to complicate matters by bringing in very young children. Serological observations have been made in all the trials, but we may not be able to add much to what is already known of the significance of serological responses, though the soluble

antigen study may help here. We have made no study of the minimum dosage required for a satisfactory immunity response nor have we made studies on the effect of different spacing of doses. Finally, we are unlikely to be able to obtain conclusive information on the duration of immunity other than to say that in the strictly controlled studies there was no evidence of waning of protection 2½-3 years after vaccination. I doubt whether even this evidence is necessarily of real value, as our observations have been made in populations where pertussis is common and where presumably the immunity of the vaccinated is reinforced by occasional contact with the infecting organism; whether the immunity will last as long when all children are protected by vaccination and when they have little opportunity of coming into contact with *Haemophilus pertussis* is a different question.

When the present series of studies has been completed, we shall be unable to carry out any further field investigations based on observations of the infection in the inoculated. Though the Ministry of Health have not officially sponsored vaccination—they are unlikely to do so until the results of the current studies have been fully analysed—more and more medical officers of health and general practitioners are employing pertussis vaccines prepared by the methods which gave good results in the controlled studies. In the circumstances further field studies in England are unlikely to yield information commensurate with the cost of carrying them out. Until such time as pertussis immunity following vaccination can be reliably estimated in the laboratory, further information on pertussis vaccination must be sought for in field studies in areas where vaccines are not at present widely used. Workers in such countries should give some thought to carrying out studies on the questions still to be answered when they are planning vaccination campaigns.

In this description of the studies of pertussis vaccines it must be clear that for their successful planning and execution close collaboration of those interested in the many aspects of the problem was required. In field and laboratory studies of this kind, no one person or group of persons can make a sufficient number of observations to answer all the questions. Collaboration requires that all make some sacrifice of their individuality, and it is a tribute to the medical officers of health, the statisticians and laboratory workers, the nurse-investigators, and the parents of the children that close and effective co-operation has already continued over seven years. Trials have now been made in fourteen towns and cities and at any one time 10 part-time medical officers and 50 nurse-investigators may be making observations. We have found from experience that producing a good plan for a trial, though important, is not nearly enough. Frequent and detailed discussion with the members of the teams in each area is essential if uniformity in the methods of making and recording observations is to be maintained, for the success of the trials ultimately depends on meticulous and often tedious attention to minute detail day after day during the entire period of the investigation.

RÉSUMÉ

Les études portant sur l'immunisation active de groupes de population étendus doivent, pour donner des résultats valables, satisfaire à certaines conditions. Celles-ci ont été définies de façon précise au cours des récentes années et appliquées en particulier à l'immunisation contre la coqueluche et contre la tuberculose au moyen du BCG.

L'auteur décrit la façon dont ces conditions ont été observées dans les études sur la vaccination anticoquelucheuse effectuées en Angleterre sous les auspices du British Medical Research Council, depuis un certain nombre d'années.

Les groupes vaccinés et les groupes témoins doivent, au départ, être « semblables » sur les points essentiels pouvant influencer les résultats. Beaucoup d'études ont échoué, faute de remplir cette condition. Il faut éviter en particulier d'affecter les volontaires au groupe « traité », les sujets du groupe témoin, « non traités », étant choisis d'office. Les volontaires — tous indemnes de la maladie sur laquelle porte l'étude, n'en ayant pas été atteints antérieurement et n'ayant pas été traités par la substance soumise à l'essai — seront répartis au hasard en deux groupes. L'inoculation expérimentale obligatoire, particulièrement celle d'antigènes essayés pour la première fois, est une mesure injustifiable. Afin d'entretenir l'intérêt pour l'étude à laquelle ils participent, tous les sujets recevront une injection, mais ignoreront s'ils font partie du groupe « traité » ou du groupe « témoin ». Les uns recevront la substance soumise à l'essai, les autres une substance thérapeutiquement inactive, qui donnera, dans la mesure du possible, une réaction locale analogue. Cela est aisément réalisable lorsqu'il s'agit de vaccin anticoquelucheux, de TAB, des anatoxines diphtérique et tétanique; mais ce n'est pas possible lorsqu'il s'agit de variole ou de BCG, dont les réactions locales ne peuvent être imitées.

L'étude sur la vaccination anticoquelucheuse fut entreprise en collaboration avec les médecins de la santé publique de six villes et leur personnel auxiliaire. Chacune des équipes chargées de l'inoculation et du contrôle ultérieur comprenait, pour chaque groupe de 400-600 enfants, un médecin occupé à temps partiel, un secrétaire et une infirmière.

Dans la première partie de l'étude, 7558 enfants de 6 mois à 4 ans furent soumis au cycle complet des inoculations, avec l'assentiment des parents. Chaque enfant a reçu trois inoculations à un mois d'intervalle et a été suivi par une infirmière visitant les familles tous les mois pendant deux ans et plus. Ces infirmières recueillaient des renseignements détaillés sur les risques d'infection coquelucheuse auxquels les enfants étaient soumis dans le milieu familial ou scolaire, sur la durée et la gravité des symptômes, lorsque la maladie se déclarait.

Les similitudes étroites entre les groupes témoins et traités, quant à l'âge moyen (12,2 mois), les maladies intercurrentes, les risques de contamination par le bacille coquelucheux, assurent la validité des résultats de cette étude comparative. La différence entre le nombre des cas de coqueluche survenus dans l'un et l'autre groupe est frappante: 149 cas (sur quelque 3800 enfants) chez les vaccinés et 687 chez les témoins.

La valeur absolue de protection du vaccin étant ainsi démontrée, d'autres questions restaient à résoudre. Il s'agissait de comparer la valeur relative des principaux antigènes coquelucheux. Bien que tous les vaccins aient contribué à diminuer l'incidence de la maladie dans les groupes vaccinés, les vaccins Michigan se sont montrés deux à quatre fois plus actifs que les autres. On cherche actuellement à mettre au point une épreuve de laboratoire qui permette de distinguer, avant qu'ils ne soient mis dans le commerce, les antigènes très actifs de ceux qui le sont moins. Actuellement, les antigènes préparés par diverses méthodes sont mis à l'épreuve dans les études pratiques de vaccination et soumis également à des tests de laboratoire, en particulier au test intracérébral sur la souris.

Il reste en outre à établir la valeur de la vaccination chez les enfants de moins de quatre mois. L'enquête n'a pas porté non plus sur la dose minimum nécessaire pour

susciter une réponse immunologique, ni sur l'intervalle optimum entre les doses successives. Enfin, les données manquent sur la durée de l'immunité. On sait seulement, à la suite des expériences en question, que deux ans et demi ou trois ans après l'immunisation, le niveau de protection n'avait pas baissé. La solution de cette dernière question n'est du reste pas essentielle dans une collectivité où la coqueluche est fréquente et où le contact avec l'agent infectieux assure la persistence de l'immunité. Il peut en être autrement dans les communautés où les occasions de contact avec le bacille coquelucheux sont rares.

Ces études pratiques sur des groupes importants d'enfants ne pourront être répétées en Angleterre, car depuis qu'elles ont été instituées, la vaccination anticoquelucheuse par les médecins privés s'est généralisée à tel point qu'il serait très difficile et très coûteux de réaliser à nouveau les conditions qui ont permis les premières études. Il appartient maintenant aux chercheurs d'autres pays d'inclure dans leurs programmes d'études les questions qui attendent encore une solution.

REFERENCES

1. Bell, J. A. (1948) *J. Amer. med. Ass.*, **137**, 1276
2. Coppolino, J. F. (1942) *J. Pediat.*, **21**, 348
3. Daniels, M. (1951) *Brit. med. Bull.*, **7**, 325
4. Doull, J. A. et al. (1939) *Amer. J. Dis. Child.*, **58**, 691
5. Great Britain, Army Council, Antityphoid Committee (1913) *Report . . .* , London
6. Great Britain, Medical Research Council (1951) *Brit. Med. J.*, **1**, 1463
7. Hill, A. B. (1951) *Brit. med. Bull.*, **7**, 278
8. Kendrick, P. L. & Eldering, G. (1939) *Amer. J. Hyg. (Sect. B)*, **29**, 133
9. Lidwell, O. M. & Sommerville, T. (1951) *J. Hyg. (Lond.)*, **49**, 365
10. Pillemer, L. (1950) *Proc. Soc. exp. Biol. (N.Y.)*, **75**, 704
11. Rowntree, G. (1950) *Monthly Bull. Ministr. Hlth (Lond.)*, **9**, 134
12. Silverthorne, N. (1939) *Canad. med. Ass. J.*, **41**, 263
13. Singer-Brooks, C. H. (1939) *J. Pediat.*, **14**, 25
14. United States of America, Federal Security Agency, National Institutes of Health (1948) *Minimum requirements: pertussis vaccine*, Bethesda, Md.
15. Wheeler, R. E. (1936) *Milbank mem. Fd Quart.*, **14**, 180