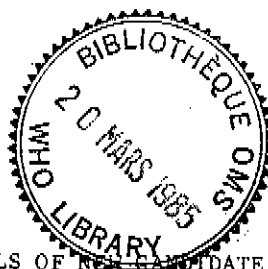




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MEETING ON CLINICAL TRIALS OF NEW AND MODIFIED
 PERTUSSIS VACCINES

(Geneva, 28-29 September 1984)

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*Pertussis vaccine - young
 clinical trials*

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A meeting on clinical trials of acellular pertussis vaccines was held in Geneva on 28-29 September 1984. Dr F. Assaad, Director, Division of Communicable Diseases of the World Health Organization, opened the meeting on behalf of the Director-General. The purpose of the meeting was to discuss issues relevant to the design of clinical trials with acellular pertussis vaccines and to propose guidelines for the conduct of such trials. Before discussing proposed guidelines, the group received reports on the WHO Collaborative Laboratory Study on acellular pertussis vaccines (see WHO/BVI/PERT.84.1) and on a proposed immunogenicity trial in Sweden.

1. WHO COLLABORATIVE STUDY ON ACELLULAR PERTUSSIS VACCINES

Results of the first collaborative study of one batch of Japanese acellular vaccine were presented (WHO/BVI/PERT.84.1). It was reported that from the results of the study, tests had been selected to estimate the antigen content, toxicity, purity and immunogenicity of acellular pertussis vaccines, as well as crude extracts and non-toxoid purified products.

In a forthcoming second collaborative study the selected tests will be used to examine a number of test samples in comparison with reference preparations. The freeze dried reference preparations are: purified pertussis vaccine, FHA antigen and purified PT antigen (LPF) produced by Dr Y. Sato (Japan), and a preparation of agglutinogens 2 and 3 prepared by Dr A. Robinson (United Kingdom). These reference preparations will be used only for the collaborative study and not for other investigations. Various test samples for use in the study will be prepared by certain of the participants. A draft protocol for this study is to be prepared by the coordinator and sent to the participants (see annex) for comment before the study starts. As soon as the results of the study are known, final decisions will be made about the use of the reference preparations, as proposed by International Standards.

2. SAFETY AND IMMUNOGENICITY TRIAL OF ACELLULAR PERTUSSIS VACCINE

The Group felt that a number of Phase 2 immunogenicity trials could be performed and that these could provide valuable information on dosage, route of administration and scheduling, as well as information on adverse reactions in vaccinees. It was thought desirable to compare an adsorbed acellular vaccine with an adsorbed whole-cell vaccine since it is important to compare reactions to vaccines, rather than to adjuvants or preservatives. The Group noted that the unadsorbed whole-cell vaccine has been reported to produce substantially more reactions than the adsorbed whole-cell vaccine. In addition, since different sites of injection may result in different rates of adverse reactions, the role of intramuscular (I.M.) vs. deep subcutaneous (S.C.) injection should be evaluated. The Group also discussed the appropriate tests which should be carried out during immunogenicity trials. The question was raised as to whether agglutinin response should be measured, since this would facilitate comparison with other trials. Potential indicators of mucosal immunity might also be useful.

The Swedish investigators presented the design of the proposed immunogenicity and safety trial, which is to begin in Sweden the first week in October 1984. This trial is designed to evaluate immunogenicity of an acellular adsorbed vaccine, a product of Biken Laboratories in Japan, in comparison with a whole-cell unadsorbed vaccine. It will also evaluate two vs. three doses of the acellular vaccine. All immunizations will be given in children at least six months of age. The Swedish group proposes to assay serum antibodies against LPF and against FHA and plans to obtain information on adverse reactions in a standard fashion from all vaccinees.

The Swedish investigators indicated that they were particularly concerned about the ratio of LPF to FHA in the vaccine and had therefore selected a specific vaccine product, which had approximately a 1:1 ratio. In explaining their reasons for choosing a specific product, they emphasized the need for appropriate data on the stability of the vaccine, especially with regard to the possibility of reversion of LPF toxicity.

The Group expressed appreciation to the Swedish investigators for their promptness in initiating clinical trials with the acellular vaccine, and for their willingness to present their protocol for discussion.

3. GUIDELINES FOR PLANNING A CLINICAL EFFICACY TRIAL FOR A NEW ACELLULAR PERTUSSIS VACCINE

3.1 Objectives of Efficacy Trials

3.1.1 To determine the percent reduction in disease due to pertussis among recipients of a new acellular pertussis vaccine compared to control children.

3.1.2 To determine which serological and/or other tests correlate(s) best with clinical protection.

3.1.3 To assess the incidence of adverse reactions with the new acellular vaccine.

3.2 Vaccine to be evaluated

3.2.1 The selection of a vaccine for inclusion in the trial should be made after consideration of the characteristics of the several possible candidates likely to become available.

Selection should be based on criteria agreed upon by a panel of international experts. The WHO collaborative study which has characterized the Japanese acellular pertussis vaccine should provide data on vaccine characteristics and standard techniques for measuring them.

3.2.2. All the children in the vaccine group in the trial should receive vaccine from a single lot.

3.2.3 Vaccine from the same lot should be stored for future reference.

3.2.4 If a sufficient sample size is available, more than one promising candidate vaccine may be selected for inclusion in a single trial, as simultaneous evaluation of different candidate vaccines would have advantages.

3.3 Comparison Groups

Besides the acellular vaccine group or groups, one or more of the following control groups must be included:

3.3.1 Controls not receiving pertussis vaccine but receiving DT (diphtheria and tetanus toxoids) or placebo: Such a group might be feasible in areas where whole-cell vaccine is not given. This type of trial would be a randomized allocation controlled trial among all eligible children. The study design would permit a statement to be made about the percent reduction in pertussis among vaccinated children relative to those who are not vaccinated, and the benefits of vaccination would be measured definitively.

3.3.2 Study in a group refusing whole-cell vaccine: In areas where the current whole-cell vaccine is in use, the randomization of children accepting pertussis vaccination to groups receiving the whole-cell vaccine, the new pertussis vaccine or no pertussis vaccine is not appropriate on ethical grounds. However, in these areas, parents of children who refuse whole-cell pertussis vaccine might volunteer to enter their children in a trial of the acellular vaccine. These children could be randomized to receive either DT as given routinely or DT containing an acellular pertussis vaccine. Such a design would also give information on the absolute efficacy of the new vaccine as in 3.3.1 above. To ensure that parents and children are not influenced to refuse whole-cell vaccination in order to make them eligible for the study, the body assessing refusal should be independent of the group conducting the trial. The latter group would then present those refusing vaccine with the option of random allocation to DT or DT containing the acellular pertussis vaccine. A national body should oversee this process.

3.3.3 Whole-cell vaccine control: In areas where the whole-cell vaccine is recommended for routine use, a new acellular vaccine might be compared with the existing vaccine, allowing assessment of the relative efficacy, on the basis of the percent difference in attack rates between the two vaccinated groups. Such a trial would determine whether the acellular vaccine is more, less, or equally as effective as the whole-cell vaccine. This study will require large sample sizes to complete expeditiously, particularly if disease incidence is low, or the study is designed to detect small differences between the vaccines (see below). No statement about the effectiveness of the acellular vaccine compared to no vaccine would be possible.

3.4 Recruitment/Assignment

3.4.1 Recruitment

3.4.1.1 Eligibility criteria for inclusion in the trial should address the following:

Age - where possible, children in an age group where maternal antibody has waned should be selected so as not to confound the results. The age group 6 months to 5 years would seem to be appropriate, but account should be taken of any specific requirements applicable in the country where the pertussis vaccine is being evaluated. If disease incidence is high, it may be preferable to vaccinate only the youngest age group (e.g. 6 months-1 year) as many older children may no longer be susceptible.

Since pertussis is particularly serious in infants under 6 months, additional studies may be required to evaluate use of the vaccine in very young infants. In the clinical trial, if an indirect assay can be shown to correlate with clinical protection, it would be possible to use this assay to ascertain the best approach for protecting young infants.

3.4.1.2 The recognized contraindications to pertussis vaccine applicable in the country where the clinical trials are to be conducted should be incorporated into the eligibility criteria.

3.4.1.3 The children recruited into the study should be representative of the population of normal, healthy infants in the country where the trial is being conducted.

3.4.1.4 Other criteria may be applied as appropriate, e.g. exclusion of children whose parents are illiterate, or do not speak the native language.

3.4.2 Assignment

3.4.2.1 All study participants should be assigned randomly from the population of children accepted for study. Special randomization schemes may be desirable in areas where disease incidence varies greatly by place of residence or other variables.

3.4.2.2 All study subjects and investigators should be blind as to the group to which the participant is assigned. A safety monitoring committee will be appointed and will have access to codes defining which vaccine was received by study subjects (see 3.10.2). This double-blind design will ensure an unbiased determination of all endpoints in the study (e.g. pertussis disease, side-effects, immune response). However, maintenance of double-blinding may be difficult if one vaccine in the trial gives a markedly higher rate of local reactions than another. In such a situation, special efforts may be needed to assess the extent of lack of "blinding" and to ensure non-biased assessment of the outcome.

3.5 Study site

The number of controlled trials in which the protective efficacy of a given type of acellular pertussis vaccine can be assessed in normal children is limited, possibly to one or two trials, due to ethical considerations. Additional trials of efficacy will be justified only if they involve a vaccine with a substantially different formulation or a population with a very different immune responsiveness. For these reasons, all countries have a major interest in the design and conduct of pertussis clinical efficacy trials. International coordination is desirable by whatever mechanisms are appropriate (e.g. WHO organized peer review of proposals, WHO advisory committee, WHO endorsement).

The following minimum criteria would apply in selecting a site for a clinical trial:

- a) Adequate surveillance to accurately ascertain baseline incidence for trial design.
- b) Incidence of pertussis sufficiently high to permit the study to be completed in a reasonable period of time (see 3.9 below).
- c) Laboratory and clinical capability to diagnose cases accurately.
- d) Mechanisms for adequate surveillance for cases, either through the current systems in place or by special efforts in the study site.
- e) A population suitable for the design proposed, e.g. large families for intra-familial studies; substantial number of children in day care centre.

3.6 Vaccine Administration

Decisions on issues such as the route of injection (I.M. vs. S.C.), the use of syringe or podojet, the number of doses, the interval between doses, and relationship to use with other antigens in the childhood vaccination schedule, should be based on data collected in initial immunogenicity and safety testing (phase 1 and phase 2 trials).

3.7 Follow-up

3.7.1 Ascertainment of Cases

The investigators should be blind to the subject's study group. Clear criteria should be developed to identify and classify carriers, cases, and deaths on the basis of clinical, laboratory and serologic data. Efforts should be made to confirm cases of pertussis by culture.

3.7.2 Ascertainment of laboratory values

Laboratory workers should be blind as to the study group from which the specimens come.

3.7.3 Ascertainment of Common Adverse Reactions

Investigators assessing adverse reactions should be blind to the study group of the participant.

Standard methods and/or questionnaires should be developed and used to reduce inter-observer variations in the reporting and recording of adverse reactions. Standard forms will also permit comparisons between different studies.

Both early and late adverse reactions (e.g. 30 days) should be actively ascertained.

3.7.4 Ascertainment of Rare Adverse Reactions

It will not be possible to estimate the frequency of rare adverse reactions during a clinical efficacy trial since sample size will be too small. However, since serious rare reactions may occur in the study population, investigators should be prepared to investigate thoroughly suspect events, some of which may not be attributable to vaccination. A standard protocol for collection of clinical data and specimens should be developed to characterize cases of suspect reactions precisely and to evaluate other possible causes for the condition.

Since a major reason for introducing an acellular pertussis vaccine is to decrease the risk of rare, serious adverse reactions attributable to the whole-cell vaccine, special efforts should be made to collect data on serious adverse reactions routinely as experience accumulates with use of acellular vaccines in Japan or elsewhere. The standard protocols mentioned above should be used for case investigation and reporting. Laboratory studies should be developed which may provide information on vaccine safety in the absence of controlled clinical studies.

3.8 Specimen Collection

The appropriate specimens to be collected, and the suitable times for collection will be determined from the results of immunogenicity trials, and availability of well validated tests at the time of the trial. Aliquots of specimens collected such as serum should be stored frozen at -70C for possible use in other assays as they are developed.

The desirability of collecting specimens in addition to serum (e.g. nasal swabs, aspirates, saliva, urine) should be decided after evaluating the validity of the tests proposed and the invasiveness of specimen collection procedures.

Collection of specimens on as many children in the trial as possible will increase the probability that pre-morbid specimens will be available on children who develop pertussis. These specimens may be the most important for determining serological or other correlates of clinical efficacy.

3.9 Sample Size

In order to calculate the number of children who should be enrolled in a clinical efficacy study, various parameters need to be determined. The working group could not make a numerical estimate, since data were not available for a specific potential site on the baseline incidence of disease, using the case definition and age group proposed for a trial. However, the group did discuss the minimal level of vaccine efficacy it would be important to be able to detect, either in comparison with a control group not receiving pertussis vaccine, or with a group receiving whole-cell vaccine. They also discussed the appropriate level of Type I error (i.e. the probability that a study would find a vaccine to be efficacious when it was not in fact efficacious) and Type II error (i.e. the probability that the study might not have sufficient sample size to find that a vaccine was in fact efficacious at the chosen level or above, when it in fact was efficacious). The suggested levels are:

3.9.1 Control group not receiving pertussis vaccine

Vaccine efficacy: at least 50%

Type I error should be 5%

Type II error should be 10%

i.e. the test of the null hypothesis that vaccinees and non-vaccinees have an equal attack rate should have a 90% power to detect a 50% or greater vaccine efficacy. The power to detect a 70% or greater vaccine efficacy would require a smaller sample size and might be justifiable since a vaccine judged to be approximately 80% effective already exists.

The duration of the trial will be determined by the necessary sample size calculated from the above parameters and the baseline incidence.

3.9.2 Whole-cell vaccine control

Type I error should be 5%

Type II error should be 10%

The test of the null hypothesis that vaccinees in both groups have equal attack rates should have a 90% power to detect 10% increase (or decrease) in efficacy, assuming efficacy for the whole-cell preparation is 80%.

The sample size required in a comparison with whole-cell vaccine will be substantially larger than that for a comparison with a group receiving DT or a placebo both because the difference to be detected will be smaller, and because the baseline incidence of disease will be likely to be lower in a region with a high proportion of vaccinated individuals. Furthermore, the trial will only provide information on efficacy relative to the whole-cell product.

A comparative study of a particular acellular product with whole-cell vaccine should be done if clinical efficacy of the acellular product (when compared to placebo) is significantly less than 70%, $\alpha = .05$.

Two tailed tests should be used.

3.10 Ethics

3.10.1 Informed consent should be obtained from all parents of children in the study using procedures established by human subjects' protection committees.

3.10.2 A Data and Safety Monitoring Group should be appointed with no vested interest in the trial.

The meeting recommended that WHO assume a coordinating function, acting as a repository for data and fostering the exchange of information between nations, both before and during clinical trials of new pertussis vaccines.

It was reported that the Swedish group is in the preliminary stage of designing a clinical efficacy trial of acellular vaccine to begin at the end of 1985. The Swedish investigators indicated their willingness to share their protocol for the proposed efficacy trial for timely review by a small group of international experts designated by WHO.

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