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ORGANISATION MONDIALE DE LA SANTE

WHO MEETING ON CASE DEFINITION  
OF PERTUSSIS

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Geneva, 10-11 January 1991

## REPORT OF THE MEETING

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INTRODUCTION

A meeting on Case Definition of Pertussis was held in Geneva from 10 to 11 January 1991. Dr P. H. Lambert, Chief, Microbiology and Immunology Support Services, opened the meeting on behalf of the Director-General. Dr D. T. Karzon was elected Chairman, Dr E. L. Miller, Vice-Chairman and Dr R. H. Bernier, Rapporteur.

The purpose of the meeting was (a) to reach a consensus on the use of case definitions for pertussis which could be employed in upcoming efficacy trials of acellular pertussis vaccines and (b) to develop case criteria applicable to efficacy trials in a variety of international settings and also useful for pertussis surveillance, reporting, and control.

1. VACCINE TRIALS

Eleven different acellular pertussis vaccines (see Annex 1) are being evaluated for safety and immunogenicity along with two whole cell pertussis vaccines in an ongoing phase II trial by the National Institutes of Health, (NIH) USA. The National Institutes of Health also plan to carry out an efficacy trial in collaboration with European or North American investigators beginning in September 1991. Based on the results of the phase II trial, plus characterization studies conducted by the U.S. Food and Drug Administration and consideration of all other available data, one or more acellular vaccines will be selected for the phase III efficacy trial. Plans also call for the inclusion of a whole cell vaccine in the NIH sponsored efficacy trial. Other groups are also carrying out or planning to conduct phase III efficacy trials, including the following:

| <u>Sponsor</u> | <u>Location</u>              | <u>Status</u>    |
|----------------|------------------------------|------------------|
| ORSTOM/Mérieux | Senegal                      | Ongoing          |
| Lederle        | Germany                      | Ongoing          |
| NIH/NIAID      | Canada, Italy, Sweden or UK* | Planned          |
| NIH/NICHHD     | Sweden (Gothenberg area)     | Planned          |
| Smith Kline    | Germany & Switzerland        | Under discussion |

\* Some of these countries may conduct a trial independently of NIH/NIAID if circumstances permit.

2. FACTORS INFLUENCING A CASE DEFINITION

The various complicating factors and difficult issues that need to be addressed to reach a consensus about a case definition for pertussis were discussed, including:

- the existence of a high rate of background illnesses which resemble pertussis, especially mild pertussis, and which are likely to vary by geographic location;

Dr James Cherry (UCLA, USA) presented a tentative case definition of pertussis based on clinical data only for a study planned by Lederle in Germany. It is:

>14 days of cough  
AND  
1 or more of the following:  
whoops  
OR  
paroxysmal cough  
OR  
post-pertussis vomiting

A second clinical definition in this trial is:

>21 days of cough without any other apparent cause

A third definition will include laboratory findings yet to be decided (e.g. a positive culture for B. pertussis or a significant antibody response).

Dr Patrick Olin (SBL, Sweden) presented data and the case definitions for the trial carried out in Sweden in the mid-1980's. In that trial, the primary case definition was:

any cough illness  
AND  
1 or more of the following:  
a positive culture for B. pertussis  
OR  
a significant rise in CHO cell and ELISA PT IgG and ELISA  
FHA IgG antibodies.

Dr Olin noted that clinical data from the Swedish trial indicated that greater than 80% of the placebo recipients with cases had more than 30 days of cough. Illness was milder in vaccinees who developed pertussis. Thus, vaccine efficacy estimates were lower when milder forms of illness were counted. In addition, the trial found evidence that cases of pertussis were not detected with equal sensitivity in vaccinees and placebo recipients using culture as the diagnostic method, and this bias tended to overestimate vaccine efficacy. This bias was less pronounced when the analysis was restricted to illnesses with cough duration of at least 30 days, which was typical of the illness in the placebo recipients.

In the post-trial follow-up of vaccinees from the Swedish trial, data have been collected from parents about clinical symptoms and from the laboratory. Using a case definition of any cough for 30 days or more and a positive culture for B. pertussis, the efficacy of JN1H-6 (Japanese National Institute of Health, FHA and PT in equal proportion) and JN1H-7 (Japanese National Institute of Health, only PT) has been estimated as 93% and 78% respectively. The differences in efficacy between these two vaccines is statistically significant. Estimates were lower when only the parental history of pertussis was used as the endpoint.

Dr Blackwelder (NIH, USA) provided further evidence for the lack of specificity of a clinical-only case definition. Using a definition consisting only of >21 or more days of paroxysmal cough, the estimated efficacy for JN1H-7 was only 27% compared to 78% when culture was included as a requirement.

Other points raised during Dr Olin's presentation relevant to the discussion of case definitions was the finding that older children had fewer coughing spasms. Any definition including a minimum number of coughing spasms might be biased if this were not taken into consideration.

In summary, Dr Olin stated that several lessons were learned from the Swedish trial experience that are relevant for this meeting. They are:

1. A key question to resolve in selecting a case definition is the exact condition that trial organizers wish the vaccine to protect against (e.g. control of typical disease or control of infection with minimal disease).
2. Vaccines composed differently (e.g. JN1H-6 and JN1H-7) protect differently against infection and disease.
3. Laboratory diagnostic tools (culture and serology) are biased in the ascertainment of cases in vaccinees and placebo recipients.
4. Using increasingly stringent criteria for defining a case of pertussis yields estimates of efficacy that are higher than with less stringent criteria.
5. The clinical illness of whooping cough is less severe in vaccinees than in unvaccinated children.
6. The age of the child may influence the clinical expression of illness.

In the afternoon of the first day, Dr Olin presented the case definition being proposed in Sweden by investigators at the SBL for a second efficacy trial being planned there in collaboration with NIH/NIAID. In the first part of this trial (designed to estimate the absolute efficacy of both acellular and whole cell vaccines against typical whooping cough), the case definition is:

>21 days or more of paroxysmal coughing  
AND

1 or more of the following:

a positive culture for B. pertussis  
OR

a significant rise in ELISA FHA IgG OR IgA OR in ELISA PT  
IgG in paired sera.

Dr Miller (PHLS, UK) presented a description of a clinical efficacy trial being planned in the United Kingdom. She pointed out, in principle, the need to frame the strategy of case ascertainment and case definition of pertussis to the circumstances of the site under consideration for the clinical trial. Dr Miller endorsed the case definition proposed by the Swedish investigators but emphasized that without a sensitive serologic method of detecting infection in whole cell vaccinees a case definition using culture will likely tend to falsely increase the relative risk in a comparative trial (Appendices II, III). In the British trial, preference is being given to the use of a

clinical only case definition. An analysis of the potential biases operating when differentially sensitive laboratory tests are used to detect cases has convinced the British investigators that a clinical only case definition used in a trial which compares only relative rather than absolute efficacy will provide acceptable data. The definition chosen for the UK trial is:

21 days or more of paroxysmal coughing

AND

at least one major diagnostic criteria

1. at least 10 paroxysms on one or more days
2. at least 1 paroxysm followed by whooping
3. lymphocyte count > 10,000
4. onset of cough within 28 days of onset of cough in a bacteriologically confirmed case in the home

OR

at least two minor diagnostic criteria

1. at least one paroxysm followed by apnea
2. at least one paroxysm followed by vomiting or cyanosis during or following at least one paroxysm.

Dr Just (BK, Switzerland) presented a brief description of plans being discussed by Smith Kline to conduct a clinical efficacy trial in Switzerland and Germany. A three-arm trial involving acellular and whole cell vaccinees and a placebo group is under discussion and might require approximately 20,000 children.

Drs Kimura and Sakai presented data from Japan. They noted that pertussis has decreased in Japan since 1981 when acellular pertussis vaccines were introduced, however, the disease still occurs in 3-4 year epidemic cycles. There was a small epidemic in 1990. They noted that 60-70% of all cases occurring in Japan now are in children less than 2 years of age. As a potential reflection of the efficacy of the acellular vaccines being used in Japan, Drs. Kimura and Sakai noted that the proportion of culture positive cases in 1988-90 with a history of 1-4 doses of vaccine (3.5%) was significantly lower than in 1973-74 (42%) when a comparable study was done and when the coverage rate for 3 doses of whole-cell DTP was the same in the population (85%).

Dr Galazka presented information on the routine surveillance for pertussis around the world. He noted that comparison of pertussis incidence in various areas is hampered by the differences in the reliability of the surveillance system, in the completeness of the reporting of pertussis and in the quality of the clinical and bacteriological diagnosis. He expressed the hope that this WHO group would also address the issue of a standard pertussis case definition for surveillance purposes.

He pointed out that the EPI case definition classifies cases into suspect, probable, or confirmed, the latter requiring bacteriological isolation or a positive immunofluorescence test.

Dr Wassilak presented the clinical case definition used for surveillance in the United States and the data that support its use. The definition in the setting of a highly vaccinated population is 14 or more days of cough with or without other symptoms, depending on the setting (epidemic or endemic).

Clinical case definitions might differ greatly under the different purposes of surveillance and clinical trials: under surveillance, moderate sensitivity with some sacrifice in specificity is acceptable; in clinical trials, high specificity is desired, accepting some loss in sensitivity.

Using a study of household contacts, data were also presented on the efficacy of whole cell pertussis vaccines using various definitions of disease. Data on the sensitivity of various clinical criteria in culture-confirmed cases, particularly modification of illness in vaccinated individuals, were presented. The discussion revealed that if laboratory confirmation is obtained, the clinical criteria are primarily an indicator of clinical significance. With vaccinated cases expected to experience modified disease, the number of cases in a comparative trial meeting the more restricted clinical case definitions would be limited.

Following the general reviews and discussion, the major components and individual elements of a case definition were analysed in detail (see Appendix IV) and discussion focused on achieving a consensus on the most appropriate case definition for the next major trial of pertussis vaccines. The consequences of modifying the consensus definition by confining it to clinical or clinical plus epidemiologic criteria or subtraction of laboratory elements were discussed. From these discussions the group proposed a case definition and made some recommendations for priority research:

#### RECOMMENDATIONS

##### A. Case Definition of Pertussis

>21 days of paroxysmal cough.

AND

1 or more of the following:

Positive culture for B. pertussis

OR

Serological evidence of Bordetella-specific infection by a significant rise in antibody. (As of January 1991, FHA IgG, IgA, PT IgG are acceptable. However, see Laboratory Research Priorities.)

OR

Household contact with a B. pertussis confirmed case.

- B. Some participants indicated in discussions that the consensus case definition is too restrictive to be used exclusively in a comparative clinical trial. In order to analyse the results over the full spectrum of clinical illness compatible with pertussis, data analyses of vaccine efficacy in future trials must explore the results using other case definitions besides the primary definition, including definitions of milder illnesses and clinical only definitions. Using a relatively broad definition for suspect cases that trigger further investigation (e.g. cough 7 days) would allow such data analyses.
- C. Further study of elements in the definition which may impart differential sensitivity in a comparative study of two or more vaccines should be carried out in advance of the trial.


#### Laboratory Research Priorities


Two laboratory research priorities were defined which may directly contribute to improved case definitions for efficacy trials or surveillance studies.

- A. Continued assessment of serological parameters, including but not limited to:
1. development and evaluation of antibody to B. pertussis components 69kd and agglutinogens 2 and 3.
  2. exploration of antibody systems to antigens which are absent in the acellular vaccines but which are regularly found to accompany infection with B. pertussis.
- B. The development of tests to detect B. pertussis organisms or the products of such organisms should be pursued.


APPENDIX I

**Merieux**  


**Smith-Kline**  


**Connaught/Biken**  


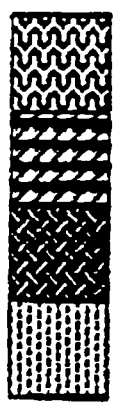
**NichPH**  


**MassPH**  


P T FHA

P T

**Lederle/Takeda**



**Lederle**

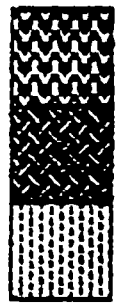


**Connaught Inc.**



P T FHA 69K Fim

**Porton (CAMR)**

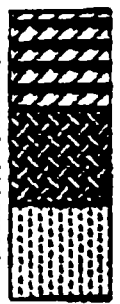


P T FHA Fim

**Sclavo**



**Smith-Kline**



P T FHA 69K



POSSIBLE BIAS IN ESTIMATING RELATIVE RISK (RR) IN ACCELLULAR : WHOLE CELL

GROUPS DUE TO CHOICE OF CASE DEFINITION

| CASE DEFINITION  | OBSERVED RELATIVE RISK |               |      |
|--|------------------------|---------------|------|
|  | True RR = 1.2          | True RR = 1.0 |      |
| <u>CLINICAL</u> : Predictive value in whole cell group                           | 70%                    | 1.14          | 1.00 |
|  | 50%                    | 1.10          | 1.00 |
|  | 30%                    | 1.06          | 1.00 |
| <u>BACTERIOLOGICAL</u> : Relative isolation rate in acellular : whole cell group | 1.5 : 1                | 1.80          | 1.50 |
|  | 1.2 : 1                | 1.44          | 1.20 |
|  | 1.1 : 1                | 1.32          | 1.10 |

POSSIBLE BIAS IN ESTIMATING VACCINE EFFICACY (VE) IN A PLACEBO CONTROLLED

TRIAL DUE TO CHOICE OF CASE DEFINITION

| CASE DEFINITION  | OBSERVED VACCINE EFFICACY |               |
|--|---------------------------|---------------|
|  | True VE = 80%             | True VE = 60% |
| <u>CLINICAL</u> : Predictive value in placebo group                            | 72%                       | 54%           |
|  | 56%                       | 42%           |
|  | 40%                       | 30%           |
| <u>BACTERIOLOGICAL</u> : Relative isolation rate in placebo : vaccinated group | 90%                       | 80%           |
|  | 87%                       | 73%           |
|  | 83%                       | 67%           |
|  | 2.0 : 1                   |               |
|  | 1.5 : 1                   |               |
|  | 1.2 : 1                   |               |

APPENDIX 4

Elements were clustered into 3 groups: clinical, laboratory and epidemiological.

Clinical

Laboratory

|                                 |   |
|---------------------------------|---|
| Cough,<br>paroxysmal            | (A) Bacteriologic isolation<br>or antigen detection |
| duration 7, 14, 21, 28, 35 days | <u>B. pertussis</u> isolation (+)                   |
| No. paroxysms (spasms)          | IFA   |
| vomiting                        | PCR   |
| apnea                           | DNA probe   |
| cyanosis                        |   |
| lymphocytosis $\geq 10,000$     | (B) Serology  |
| Complications                   | PT (IgG, IgA)                                       |
| pneumonia                       | FHA (IgG, IgA)                                      |
| seizures                        | 69kd (IgG, IgA)                                     |
| encephalopathy                  | agglutininogen 2, 3                                 |
| mucosal hemorrhage              | antibody to antigen                                 |
| hospitalization                 | absent in vaccine                                   |
| death                           |   |
| secondary bacterial infection   |   |

Epidemiologic History

History of household (or compound)  
contact with confirmed case of B. pertussis



WHO MEETING ON CASE DEFINITION  
OF PERTUSSIS

ANNEX 1

Geneva, 10-11 January 1991

MINUTES

Introduction:

A two-day meeting was convened by WHO to develop a consensus on the use of case definitions for pertussis, which could be employed in upcoming efficacy trials of acellular pertussis vaccines. Secondary objectives were to develop, if possible, case criteria applicable to efficacy trials in a variety of international settings which would also be useful for pertussis surveillance, reporting, and control.

On the first day, participants reviewed experiences with case definitions in past trials and heard the case definitions proposed in draft protocols for future studies. The second day was devoted to analysis of clinical, laboratory, and epidemiologic criteria which could be used in constructing a case definition. Such a definition was adopted and several recommendations were made concerning laboratory tests.

Background

The introductory presentation was made by Dr David Klein (NIH, USA) who described the ongoing phase II trial in the U.S. with 11 different acellular pertussis vaccines which are being evaluated for safety and immunogenicity along with two whole cell pertussis vaccines. The names of these vaccines and their antigenic composition are listed in Appendix I. Dr Klein described NIH plans to carry out an efficacy trial in collaboration with European or North American investigators beginning in September 1991. Based on the results of the phase II trial, plus characterization studies conducted by the U.S. Food and Drug Administration and consideration of all other available data, one or more acellular vaccines will be selected for the phase III efficacy trial.

Other groups were also noted to be carrying out or planning to conduct phase III efficacy trials.

The complete list includes:

| <u>Sponsor</u> | <u>Location</u>              | <u>Status</u>    |
|----------------|------------------------------|------------------|
| ORSTOM/Mérieux | Senegal                      | Ongoing          |
| Lederle        | Germany                      | Ongoing          |
| NIH/NIAID      | Canada, Italy, Sweden or UK* | Planned          |
| NIH/NICHD      | Sweden (Gothenberg area)     | Planned          |
| Smith Kline    | Germany & Switzerland        | Under discussion |

\* Some of these countries may conduct a trial independently of NIH/NIAID if circumstances permit.

The vaccine to be used in each of these trials has already been selected by each of the sponsors except NIH/NIAID which is awaiting the results of the ongoing phase II trial.

Participants identified the complicating factors and the difficult issues that would have to be addressed during the meeting in order to arrive at a consensus about pertussis case definitions. These were:

1. The existence of a high rate of background illnesses which resemble pertussis, especially mild pertussis, and which are likely to vary by geographic location.
2. The wide clinical spectrum of pertussis infection and disease.
3. The incidence and differing epidemiology of pertussis in vaccinated and unvaccinated populations in various countries.
4. The difficulties in finding a case definition that would be universally applicable in all countries conducting trials.
5. Making a choice between protection against infection or protection against disease as the primary consideration in selecting a case definition for a trial.
6. The prospect of having new diagnostic tools in the near future.
7. The complexity of basing disease definition on laboratory markers, e.g. bacterial isolation, serology.

Also by way of background, Dr Steve Wassilak (CDC, USA) gave a brief description of the ongoing ORSTOM/Mariéux trial in Senegal. A tentative case definition proposed for that study is:

>21 days of any cough

AND

1 or more of the following:

a positive culture for B. pertussis

OR

contact with a compound resident who is culture positive.

Currently, there are no plans to use serology to diagnose cases in the Senegal trial.

- the wide clinical spectrum of pertussis infection and disease;
- the incidence and differing epidemiology of pertussis in vaccinated and unvaccinated populations in various countries;
- the difficulties in finding a case definition that would be universally applicable in all countries conducting trials;
- making a choice between protection against infection or protection against disease as the primary consideration in selecting a case definition for a trial;
- the prospect of having new diagnostic tools in the near future;
- the complexity of basing disease definition on laboratory markers, e.g. bacterial isolation, serology.
- the significance of including more than one acellular product as well as a whole cell vaccine in a multi-armed study.

### 3. COMPARISON OF DIFFERENT CASE DEFINITIONS

A range of clinical and laboratory findings have been considered for case definitions in the above mentioned vaccine trials and are summarized in the table below.

| Sponsor                   | Country | Clinical signs<br>Cough (days) | Laboratory diagnosis |          | Other  |
|---------------------------|---------|--------------------------------|----------------------|----------|--|
|                           |         |                                | Culture              | Serology |  |
| ORSTOM/<br>Mérieux        | Senegal | ≥21 and                        | + or                 |          | Yes <sup>1</sup>   |
| Lederle - 1<br>- 2<br>- 3 | Germany | ≥14 and<br>21                  | + or                 | +        | Yes <sup>2</sup>   |
| NIH/NIAID                 | Sweden  | ≥21 paroxysmal<br>and          | + or                 |          | Rise in ELISA<br>FHA, IgG, or<br>IgA or in<br>ELISA FT IgG |
| NIH/NIAID                 | UK      |                                |                      |          | Yes <sup>3</sup>   |

<sup>1</sup> Epidemiological link to a bacteriologically confirmed case.

<sup>2</sup> One or more of the following: whoops or paroxysmal cough or post-pertussis vomiting.

<sup>3</sup> At least one major diagnostic criteria:

- 10 paroxysms on one or more days
- at least one paroxysm followed by whooping
- lymphocyte count >10,000
- onset of cough within 28 days of onset of cough in a bacteriologically confirmed case in the home

or at least two minor diagnostic criteria:

- at least one paroxysm followed by apnea
- at least one paroxysm followed by vomiting or cyanosis during or following at least one paroxysm

Clinical case definitions for surveillance and clinical trials might differ greatly: for surveillance purposes moderate sensitivity with some sacrifice in specificity is acceptable, whereas high specificity is desired for clinical trials, accepting some loss in sensitivity.

Several lessons learned from the Swedish trial experience are relevant for a universal case definition of pertussis:

- the exact condition that trial organizers wish the vaccine to protect against must be identified (e.g. control of typical disease or control of infection with minimal disease);
- vaccines composed differently (e.g. JNH-6 and JNH-7) protect differently against infection and disease;
- laboratory diagnostic tools (culture and serology) are biased in the ascertainment of cases in vaccinees and placebo recipients;
- increasingly stringent criteria for defining a case of pertussis yields estimates of efficacy that are higher than less stringent criteria;
- the clinical illness of whooping cough is less severe in vaccinees than in unvaccinated children;
- the age of the child may influence the clinical expression of illness.

#### 4. THE ROLE OF CASE DEFINITION IN WHO/EPI

Pertussis is one of the six diseases of the WHO Expanded Programme on Immunization and therefore subject to special surveillance. However, comparison of pertussis incidence in various areas of the world is hampered by the differences in the reliability of the surveillance system as well as the completeness of the reporting of pertussis and the quality of the clinical and bacteriological diagnosis. A standard pertussis case definition is, therefore, needed for surveillance purposes as well as for clinical trials. At present the EPI case definition classifies cases into suspect, probable, or confirmed cases. The latter requires bacteriological isolation or a positive immunofluorescence test. Efforts should be made to review the EPI definitions based upon the criteria developed for the future trials.

#### 5. RECOMMENDATIONS

The major components and individual elements of different case definitions were analysed for a consensus case definition to be applied in the next major efficacy trial of pertussis vaccines. The case definition takes into account the consequences of relying on clinical or clinical plus epidemiological criteria or subtraction of laboratory elements and is as follows:



A. Case definition of pertussis

≥21 days of paroxysmal cough

AND

1 or more of the following:

Positive culture for B. pertussis

OR

Serological evidence of Bordetella-specific infection by a significant rise in antibody. (As of 1991, FHA IgG, FHA IgA, IgG and IgA antibodies against agglutinogens 2 and 3, PT IgG, PT IgA are acceptable. However, see Laboratory Research Priorities.)

OR

Household contact with a B. pertussis bacteriologically confirmed case occurring within 28 days before or after the onset of illness in the trial child.

- B. Some participants indicated in discussions that the consensus case definition is too restrictive to be used exclusively in a comparative clinical trial. In order to analyse the results over the full spectrum of clinical illness compatible with pertussis, data analyses of vaccine efficacy in future trials must explore the results using other case definitions besides the primary definition, including definitions of milder illnesses and clinical only definitions. Using a relatively broad definition for suspect cases that trigger further investigation (e.g. cough ≥7 days) would allow such data analyses.
- C. Further study of elements in the definition which may impart differential sensitivity in a comparative study of two or more vaccines should be carried out in advance of the trial.

Laboratory research priorities

Two laboratory research priorities were defined which may directly contribute to improved case definitions for efficacy trials or surveillance studies.

- A. Continued assessment of serological parameters, including but not limited to:
- development and evaluation of antibody to B. pertussis components 69kd and agglutinogens 2 and 3;
  - exploration of antibody responses that are present in infected, but not immunized, individuals.
- B. The development of tests to detect B. pertussis organisms or the products of such organisms should be pursued (for example, pertussis antigens, IFA, PCR, and DNA probe).

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