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ACTIVE IMMUNIZATION
AGAINST COMMON COMMUNICABLE
DISEASES OF CHILDHOOD

Report of a Group of Consultants
convened by the Director-General

Geneva, 25-28 May 1949

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WORLD HEALTH ORGANIZATION
PALAIS DES NATIONS
GENEVA
MARCH 1950

**ACTIVE IMMUNIZATION AGAINST
COMMON COMMUNICABLE DISEASES OF CHILDHOOD**

Consultants convened by the Director-General

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ACTIVE IMMUNIZATION AGAINST COMMON COMMUNICABLE DISEASES OF CHILDHOOD

Report of a Group of Consultants convened by the Director-General¹

1. Terms of Reference

The experts were requested to furnish technical advice to the Director-General of WHO regarding :

1.1 the desirability of convening a technical conference on procedures for active immunization against common communicable diseases of childhood, such as recommended by the Expert Committee on Maternal and Child Health in January 1949;²

1.2 the agenda of such a conference and the type of participants who should be invited to it;

1.3 lines of action that WHO might usefully adopt in the future as regards active immunization against common communicable diseases of childhood, i.e., for the diffusion and broader application of scientific knowledge recently acquired and for co-ordinated research on points on which such research is likely to yield early practical results.

2. Subjects Covered by the Experts

2.1 In order to give an answer on points 1.2 and 1.3 it was necessary for the experts to review existing knowledge on immunization procedures. It was accordingly found expedient to place on record such established facts as, in the opinion of the experts, could be of immediate practical value to health administrations.

2.2 The experts decided to exclude from their discussions those communicable diseases which were already receiving the attention of WHO

¹ The Second World Health Assembly adopted the following resolution:
The Second World Health Assembly

NOTES the reports of the following Study-Groups: ...
Expert consultation on active immunization against common communicable diseases of childhood. *Off. Rec. World Hlth Org.* **21**, 22

² *Off. Rec. World Hlth Org.* **19**, 46; **21**, 182

expert bodies, viz., smallpox, tuberculosis (BCG), cholera, and yellow fever.

2.3 They accordingly limited their discussions to immunization procedures directed against : diphtheria, whooping cough, scarlet fever, mumps, measles, tetanus, poliomyelitis, typhoid and paratyphoid fevers, each being considered in turn.

They also discussed a series of combined immunizations, together with time-tables in use for administering such combinations.

Their observations and suggestions are given in Annex 1.

2.4 The experts noted that research was still urgently needed on a series of points relating to immunization procedures. A list of subjects recommended for investigation is given in section 4.

3. Recommendations Relating to a Technical Conference on Immunization Procedures

3.1 The experts agreed that such a conference might facilitate the adoption of better techniques by laboratories now using older methods and issuing inferior products. They felt that this action would benefit not only institutions represented at the conference, but also many others.

They believed that the exchange of information on different methods of production might throw light on the reasons for discrepancies in the results obtained by the use of different immunizing agents.

They hoped that a conference might orientate and stimulate research on problems still unsolved and might later stimulate also the interest of public-health authorities, the medical profession, and even of the general public in immunization programmes.

3.2 The experts accordingly recommended that the conference on immunization procedures suggested by the Expert Committee on Maternal and Child Health be held.³

3.3 The experts believed that in order to get the best possible results the conference should be limited both as to its agenda and as to participants.

3.4 They agreed that its agenda be restricted mainly to techniques of production and evaluation of immunizing agents against :

- (a) diphtheria, and
- (b) whooping cough.

³ *Off. Rec. World Hlth Org.* 19, 46

3.5 They agreed also that the number of experts invited should be limited to about 12, in order to ensure informal discussions and free exchange of views. They further emphasized that in the selection of the experts consideration should be given to their knowledge not only of laboratory techniques, but also of epidemiological aspects of immunization.

4. Research Recommended in Immunization

The experts noted the following points as worthy of observation, investigation, or research ; the list is given by diseases, the order being no indication of priority :

4.1 General

4.1.1 Development of the antibody-response mechanisms (ability to build up immunity) during the first year of life.

4.1.2 Duration of immunity produced by the various immunizing agents with a view to timing the primary immunization and the injection of reinforcing doses.

4.2 Diphtheria

4.2.1 Development of an immunizing agent capable of protecting against diphtheria without causing general or local reactions, for instance by further trials of purified toxoid (such as PTAP).

4.2.2 Development of a vaccine against the diphtheria bacillus.

4.3 Whooping cough

4.3.1 Points of technique in the preparation of whooping-cough vaccines which might explain discrepancies in the results now obtained with different vaccines, such as : (a) choice of strains, (b) culture and harvesting, (c) sterilization, (d) preservation, (e) physical standardization, (f) biological standardization of the vaccines.

4.3.2 Reliable laboratory test for estimating protective potency of the vaccine for human beings (this need was considered most urgent).

4.4 Scarlet fever

4.4.1 Development of a suitable test for detecting individual susceptibility to scarlet fever.

4.4.2 Development of an immunizing agent, more reliable and giving fewer reactions than the existing toxin preparations.

4.4.3 Relationship of the various manifestations of streptococcus infections.

4.5 Measles

4.5.1 Development of an active immunizing agent capable of attenuating the disease without modifying its lifelong immunity.

4.5.2 Practical application of ultra-violet radiation for the killing of the virus of homologous serum jaundice in the sera or in the gamma globulins used for the passive immunization against measles.

4.6 Tetanus

4.6.1 Possibility of preventing tetanus neonatorum by the active immunization of pregnant mothers.

4.6.2 Development of a test making it possible rapidly and easily to determine whether an individual is protected against tetanus.

Annex 1

1. Introduction

1.1 In order to advise the Director-General on the desirability of convening a technical conference on immunization procedures, the experts consulted had to review the present state of knowledge concerning immunization against the various communicable diseases of childhood, with the exception of those already receiving attention from WHO expert bodies, viz., small-pox, tuberculosis (BCG), cholera, and yellow fever.

1.2 It was felt that a number of technical points and observations made by the experts during their discussions could be of immediate practical value to health authorities and they have been accordingly summarized in the present annex to the consultants' report.

1.3 The experts, however, felt that their personal experience was limited to a few countries and that their number was too small, and the time at their disposal too short, to enable them to cover the ground adequately and to pronounce authoritatively on the subject covered.

1.4 For the same reasons they stressed that the conclusions of their discussions could not be considered as formal recommendations.

2. General Observations Concerning Immunization Procedures

Apart from specific observations and recommendations concerning individual diseases, the experts wished to make some remarks bearing on the problem of active immunization in general.

2.1 The experts agreed that adequate and competent local health authorities are essential for the effective control of communicable diseases.

2.2 The experts, while convinced of the importance of immunization programmes in the protection of child life, stressed the need for health authorities to give proper emphasis to other methods for the control of communicable diseases and utilize immunization procedures in the manner in which they are most likely to be effective, as indicated in the local and general epidemiology of diseases.

2.3 The experts agreed on the principle that health authorities should recommend for general use only such immunizing agents as have been adequately tested in human beings and found to have a protective value far outweighing any danger inherent to their administration.

2.4 The experts emphasized that health authorities should continually re-evaluate the effectiveness of the immunizing products and procedures

being used. Laboratories responsible for the preparation of immunizing agents should keep themselves informed of new procedures and techniques, developed in the other areas for the preparation and standardization of such production.

Epidemiologists and other physicians, particularly health authorities, should continually observe in humans the effectiveness of the products and procedures used, and they should be particularly alert to any ill effects of their use. Such observations require carefully controlled studies in humans in areas where the disease remains prevalent in spite of control procedures.

2.5 The experts agreed that epidemiological conditions often varied greatly from country to country, from town to town, and from time to time, rendering it difficult to lay down any universal recommendations on immunization, or even to decide whether immunization in a particular locality is advisable at all. For example, in diseases spread exclusively by direct person-to-person contact, the morbidity and mortality of a disease will be determined by such factors as the number of infected persons, both cases and carriers, the number of susceptible persons, and the amount of opportunity for effective contact between them.

Such considerations should govern the choice of the immunizing agents, the methods to be used, and the age-groups and specially exposed groups of population in which those should be applied.

2.6 Personnel for carrying out immunization programmes

2.6.1 In the experience of the experts, immunizations should be included among the routine activities of infant and child health clinics, school health services, and public-health centres, rather than be left to the exclusive responsibility of private practitioners.

2.6.2 The keeping of accurate records of immunizations needed and performed at the various ages can be more easily and effectively carried out by the auxiliary staff of health services than by individual practitioners. But it must be emphasized that the help of the paediatricians and general practitioners is indispensable in carrying through an all-round immunizing programme.

3. Immunization against Specific Diseases

3.1 Diphtheria

3.1.1 *Indications*

The experts recommended that, in countries (with a temperate climate) where diphtheria is prevalent, all children be immunized against that

disease. This recommendation did not apply to tropical countries in which infection with the diphtheria bacillus existed but caused no clinical disease.

3.1.2 *Immunizing agent*

3.1.2.1 The experts recommended the use of either alum-precipitated toxoid (APT) or fluid toxoid, but preferred an alum-precipitated toxoid for the immunizing of infants and children.

3.1.2.2 APT permitted effective immunity to be established after 2 injections, while fluid toxoid required 3.

3.1.2.3 The experts recommended, in preference to APT, fluid toxoid or toxoid-antitoxin-floccules (TAF) for the immunization of adolescents and adults.

3.1.3 *Age for immunization*

3.1.3.1 The experts agreed that primary immunization should be carried out before the age of one year, preferably at the age of 6 to 12 months, by means of no less than 2 injections of APT (or 3 injections of fluid toxoid) made at one-month intervals.

3.1.3.2 One or 2 reinforcing (booster) doses should be given within 5 years of the primary immunization and further reinforcing doses may be given at intervals of 5 years, up to the age of 15.

3.1.3.3 Before immunization of adults a Schick test should invariably be carried out. This should include a control test with heated toxin (Schick control test) or with diluted toxoid (Moloney test). It is questionable whether individuals who react to the Schick control test should be artificially immunized. Schick-positive subjects who do not react to the control preparation may be immunized with fluid toxoid, TAF, or APT. It is wise to give a small first dose, since some persons who fail to give a pseudo-reaction in the Schick test or a positive Moloney reaction occasionally react severely to the injection of undiluted toxoid.

3.1.4 *Schick testing*

3.1.4.1 The experts agreed that the Schick test was the most practical method for estimating immunity status of the community against diphtheria. The antigenic potency of batches of toxoids can be assessed by Schick testing of groups of young children immediately before primary immunization and estimating the Schick conversion rate.

3.1.4.2 The experts agreed that it is unnecessary to use Schick testing as a routine control measure for the immunization of children up to 10

years of age. Whether a child is Schick-positive or Schick-negative, it is always wise to immunize it. A Schick-negative reaction indicates protection with a considerable margin of safety but affords no absolute guarantee against the development of diphtheria; and the injection of diphtheria prophylactic helps to prevent the child's immunity from waning.

3.1.5 *Immunizing potency*

Immunizing potency should be controlled by animal experiments and checked by observations on human beings. Many of the better immunizing agents (APT or fluid toxoid) contain as a rule 50 Lf/ml.

It should be noted that phenol should not be used in the preparation of diphtheria toxoid.

3.1.6 *Depth of injection*

The experts recommended that APT be injected deeply in the loose subcutaneous tissues or intramuscularly.

3.1.7 *Research recommended*

3.1.7.1 The experts recommended that further studies be carried out with a view to finding a vaccine capable of protecting against diphtheria without causing general or local reaction.

3.1.7.2 The experts noted that the new purified toxoid aluminium phosphate precipitated (PTAP) promised to give equally good, if not better, immunizing results than APT, and, if large-scale trials that are now being carried out supported the results of preliminary investigations, it might perhaps be recommended for general use in place of APT.

3.2 **Whooping cough**

3.2.1 *Indications*

3.2.1.1 The experts noted that whooping cough was one of the most important diseases of early childhood as regards both morbidity and mortality, even though its mortality is decreasing in a number of countries. Its prevalence is worldwide.

3.2.1.2 It would therefore be highly desirable to immunize infants and pre-school children, if a consistently potent vaccine was available for the purpose.

3.2.1.3 After considering a large number of both laboratory experiments and field trials, the experts agreed that some vaccines had indeed been prepared which proved capable of affording a considerable degree of

protection against the disease while other vaccines gave little or no protection.

3.2.1.4 They felt, however, that existing knowledge concerning the pertussis vaccines was still insufficient to make it possible to prepare vaccines of consistent protective potency.

3.2.1.5 The experts did not feel that the time was ripe for officially recommending a worldwide routine anti-pertussis vaccination of all children.

3.2.1.6 The experts further agreed that, in the event of any health authority's wishing to use pertussis vaccine, only products prepared in a manner like those which appear to have been effective in adequate field trials should be used in a routine general vaccination programme.

3.2.2 *Research recommended*

3.2.2.1 The experts agreed on the desirability of ascertaining the reason for the discrepancies observed in the results obtained with different vaccines and even different batches of the same vaccine.

3.2.2.2 They agreed that research on the following points should be undertaken with this end in view :

- (a) choice of strains ;
- (b) technique of culture and of harvesting ;
- (c) technique of sterilizing vaccine ;
- (d) mode of preservation of the vaccine before use ;
- (e) physical standardization of the bacterial content of the vaccine ;
- (f) biological standardization of the protective power of the vaccine.

3.2.2.3 The experts considered that the most urgent need was to find a reliable laboratory test for estimating the protective potency of the vaccine for human beings. The mouse protection test holds promise for this purpose.

3.3 **Scarlet fever**

3.3.1 The experts agreed that scarlet fever had in most countries become so mild as not to justify the wide application of vaccination, particularly since occasional severe and sometimes fatal reactions have been observed following such vaccination.

3.3.2 The experts nevertheless agreed that vaccination might be considered in areas where scarlet fever was still highly prevalent and severe and elsewhere in selected groups exposed to a high risk of infection, such as nurses in fever hospitals.

3.3.3 Further work is desirable on the development of :

- (a) a suitable test for detecting susceptibility of individuals ;
- (b) a more reliable and convenient immunizing agent than the present toxine preparations ;
- (c) further research on the relationship between the various manifestations of streptococcal infections.

3.4 Mumps

The experts considered that vaccines against mumps were still in the experimental stage.

They stressed the fact that, unless a vaccine was available that gave lifelong immunity, its use should be avoided in children, as postponing the disease after puberty increases the risk of complications.

3.5 Measles

3.5.1 The experts noted that in spite of the fall in its mortality in recent years in some countries, measles still caused a fairly high mortality under all climates and considerable loss of time and inconvenience through its extensive prevalence.

3.5.2 No effective prophylactic agent is known for active immunization against measles and, should it be developed, its use should be limited unless proved to confer a lifelong immunity with very little risks.

A method inducing an immunity of a few years only would result in postponing the disease from childhood, when it causes the least inconvenience and danger, to adult age when it is more serious than in childhood.

3.5.3 In the absence of a method of active immunization, a recourse must be made to passive immunization.

3.5.4 *Passive immunization*

3.5.4.1 *Agents.* At the present time, the following agents may be used for obtaining passive immunization : gamma globulin (of human beings having had measles) ; convalescents' serum and adult pooled human serum. Parents' whole blood may be substituted when these products are not available.

3.5.4.2 *Effects.* Immune globulin or convalescent serum may prevent the disease if given in adequate dosage within 3 to 4 days of exposure, and may attenuate the disease if given within 6 to 8 days after the exposure.

Under the same conditions pooled adult serum or parents' blood given within the same period may induce attenuation of the disease.

3.5.4.3 *Indications.* Passive immunization should be limited to :

- (a) infants and children under 3 years of age,
- (b) older children who are ill or in poor physical condition when they are exposed to measles,
- (c) children who are in hospitals, nurseries or in other institutions where it may be important to prevent an outbreak.

The experts stressed the undesirability of preventing measles in healthy children over 3 years of age through passive immunization, which only postpones the eventual attack.

3.5.4.4 *Risk of jaundice from serum and its prevention.* The danger of human serum hepatitis must be considered in the use of any of these products, although the gamma globulin is more likely to be free from this risk.

3.5.4.5 *Research.* Ultra-violet radiation seemed to provide a promising method for the killing of the icterogenic virus, and further research was desirable on its practical application for this purpose.

Research might profitably be directed towards the development of an active immunizing agent or any means of attenuating the disease without suppressing its resultant lifelong immunity.

3.6 Tetanus

3.6.1 Tetanus has a worldwide distribution, particularly in areas and conditions where wounds are likely to be contaminated with manured soil, and where improper handling of the umbilical cord might infect newborn babies.

3.6.2 Effective agents for active and passive immunization are available and should be extensively used to prevent this disease.

3.6.3 *Passive immunization*

3.6.3.1 Injection of antitetanic serum within 24 hours after receipt of a wound which may be infected with tetanus affords in most cases a considerable amount of protection, lasting for 2-3 weeks, especially when combined with proper surgical treatment.

3.6.3.2 Passive immunization with this (horse) serum has the following disadvantages :

3.6.3.2.1 It is often followed by serum sickness (5% of cases after the use of a refined product ; 30-40% in cases where a crude serum has been used).

3.6.3.2.2 It induces serum sensitiveness which may later cause fatal anaphylactic reaction when further doses of any horse serum are used.¹

3.6.3.2.3 Serum cannot be applied early enough to prevent tetanus neonatorum. The comparatively short duration of the immunity conferred may require repetition of doses and contribute to the development of sensitiveness.

3.6.4 *Active immunization*

3.6.4.1 *Indications.* The shortcomings of passive immunization justify the consideration of active immunization of the whole population or at least of those groups particularly exposed to infections, such as rural and certain industrial workers as well as army personnel. In view of differences in local epidemiology of tetanus, no general recommendation can be formulated.

3.6.4.2 Effective immunity can be produced by 2-3 well-spaced doses of tetanus toxoid, followed by reinforcing doses at intervals and after infliction of presumably infected wounds.

Observations now at hand indicate that immunity after a reinforcing dose lasts at least 5-6 years. Renewal of the reinforcing doses at such an interval appears desirable until further observations show that a longer interval may suffice. It must be noted that natural immunization to tetanus as the result of latent infections does not occur in the same ways as diphtheria and therefore reinforcing doses are of special importance.

3.6.4.3 In the case of a presumably infected wound in an individual who has received full basic immunization by means of a complete series of toxoid inoculation and reinforcing doses at regular intervals, full protection may be obtained by a further dose of tetanus toxoid immediately after receipt of the wound instead of tetanus serum.

Nevertheless, though such a procedure may be safely used in armies fully immunized against tetanus, it cannot be relied upon in the civilian population, except in those persons known to the physician to have been adequately immunized. In case of doubt, therefore, serum should be given as well as toxoid.

3.6.4.4 *Active immunization programme.* If a country decides to introduce a general programme of active immunization against tetanus, such immunization should be started in infancy, since tetanus affects all ages. There is no reason, however, why at the beginning of such a programme all persons in a given community should not be immunized, since the toxoid is borne well even by adults.

¹ The practitioner may be tempted to use the serum, even in case of minor wounds, for his own legal protection.

3.6.5 *Immunizing agent*

Since the precipitation of tetanus toxoid seemed to increase its antigenic potency (as is the case of diphtheria toxoid), it is advisable to use alum-precipitated tetanus toxoid in preference to ordinary fluid toxoid in infants and children.

3.6.6 *Research*

3.6.6.1 The experts recommended that observations be continued on the persistence of immunity after basic immunization in order to determine the interval at which reinforcing doses are really needed.

3.6.6.2 In areas with a high incidence of neonatal tetanus, the possibility of prevention of such tetanus by the active immunization of pregnant mothers should be investigated.

3.6.6.3 A test should be developed to determine rapidly and easily whether an individual has been actively immunized against tetanus.

3.7 **Poliomyelitis**

The experts agreed that no method of either active or passive immunization against poliomyelitis had left the experimental stage and could be recommended for general use at present.

3.8 **Typhoid and paratyphoid fevers**

As the prevalence of typhoid varies greatly from country to country and from place to place, no general recommendations can be made as regards the need of active immunization.

In countries where typhoid is highly endemic, such immunization may be included in the general health programme, but other methods of control are fundamental.

4. **Combined Immunizations and Vaccines**

4.1 The experts agreed that the combination of several antigens in mixed vaccines could not only decrease the number of injections required for the immunization against several diseases, but also produce antibodies against some of them equal to, or greater in amount than could be obtained by the separate inoculation of each antigen.

4.2 It has been shown, for instance, that pertussis vaccine when mixed with diphtheria toxoid not only produced an undiminished immunity to pertussis, but strengthened the antigenic potency of diphtheria toxoid.

4.3 Among the immunizing agents which have been used in combination, on a large scale, the most important are :

- (a) typhoid, paratyphoid, and cholera vaccines,
- (b) diphtheria and tetanus toxoids (fluid or alum-precipitated),
- (c) diphtheria toxoid and pertussis vaccine,
- (d) diphtheria and tetanus toxoids, and pertussis vaccine,
- (e) smallpox and yellow-fever vaccines.

4.4 The indications for combined immunization depend on the local epidemiology, local conditions regarding the existing health services, and the psychology of the populations concerned.

4.5 Time-table suggested for immunizations

For those countries wishing to immunize their population against the diseases listed below, the following suggestions are made as a guide for the timing of the immunizations :

4.5.1 *Smallpox*

Primary vaccination : between 1 and 6 months of age.

Revaccinations on entering school and on leaving school (or at 10 years of age).

At any time of special risk, and at frequent intervals in countries where the disease is endemic.

4.5.2 *Smallpox and diphtheria*

Smallpox : as under section 4.5.1.

Diphtheria : between 6 and 12 months, with reinforcing doses within 5 years and at intervals of 5 years until the age of 15.

4.5.3 *Smallpox, diphtheria, and pertussis*

Smallpox : as under section 4.5.1.

Diphtheria and pertussis : combined AP diphtheria toxoid and pertussis vaccine, 2 or 3 doses at one-month interval, starting at the age between 2 and 3 months if pertussis is prevalent in the community ; otherwise the starting date may be delayed to between 6 and 12 months.

The first reinforcing dose of the combined product should be given about 1 year after the primary immunization. The second at 5 years or on school entry. Further reinforcing doses at about 10 and 15 years need contain diphtheria toxoid alone.

4.5.4 *Smallpox, diphtheria, pertussis, and tetanus*

Smallpox : as under section 4.5.1.

Combined diphtheria, pertussis, and tetanus vaccine to be given as the combined diphtheria-pertussis vaccine under section 4.5.3, except that the reinforcing doses at ages 10 and 15 should include diphtheria and tetanus toxoid alone. Reinforcing doses of tetanus vaccine are to be later administered at 5 years' intervals.

4.5.5 *Smallpox, diphtheria, and tetanus*

As under section 4.5.2, but using a combined diphtheria-tetanus toxoid, instead of diphtheria toxoid.

4.5.6 In communities which are difficult of access to health personnel, smallpox vaccination and diphtheria immunization may be carried out simultaneously (one in each arm) without undue risk.

5. Recommendation of Research on Immunization in General

5.1 Apart from specific research listed under individual diseases, the experts recommended that the development of the antibody response mechanism (ability to build immunity) during the first year of life should be studied, with a view to protecting infants as early as immunization can be carried out with a lasting effect.

5.2 Further, the experts recommended that the duration of immunity produced by the various immunizing agents be investigated to determine the time for revaccinations and injections of reinforcing doses, with a view to restricting their number to those really needed for adequate protection.

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Volume 2, number 2 of the *Bulletin* contains, in addition to summaries of a Symposium on the Tubercle Bacillus held in Lausanne, April 1949, and a bibliographical section, the following articles:

- Disinsectization of aircraft — *J. Duguet*
- On pethidine and methadone derivatives — *P. O. Wolff*
- The biological unit of activity: its status and scope — *A. A. Miles*
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- Rapid treatment of syphilis with penicillin: I. A survey of the problem — *E. W. Thomas*
- Rapid treatment of syphilis with penicillin: II. Penicillin in prenatal and infantile syphilis — *E. W. Thomas*
- Rickettsioses in Equatorial Africa — *M. Gaud*
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