World Health Organization
Technical Report Series
No. 2

EXPERT COMMITTEE ON BIOLOGICAL STANDARDIZATION

Report on the Third Session

London, 2-7 May 1949

WORLD HEALTH ORGANIZATION
PALAIS DES NATIONS
GENEVA
FEBRUARY 1950

EXPERT COMMITTEE ON BIOLOGICAL STANDARDIZATION

Third Session

Members :

Professeur E. Grasset, Directeur de l'Institut d'Hygiène, Geneva, Switzerland

Dr A. A. Miles, Director, Department of Biological Standards, National Institute for Medical Research (Medical Research Council), London, United Kingdom

Dr J. Ørskov, Director, State Serum Institute, Copenhagen, Denmark

Major-General Sir Sahib Singh Sokhey, Director, Haffkine Institute, Bombay, India

Dr W. Aeg. Timmerman, Director, Rijks Instituut voor de Volksgezondheid, Utrecht, Netherlands (*Chairman*)

Professeur J. Tréfouël, Directeur de l'Institut Pasteur, Paris, France

Dr M. V. Veldee, Chief, Biologics Control Laboratory, National Institutes of Health (US Public Health Service), Bethesda, Md., USA

Co-opted Members :

Dr J. Bretey, Chef de la Division de la Tuberculose, Institut Pasteur, Paris, France

Dr J. Chevé, Directeur de l'Annexe de l'Institut Pasteur, Laroche-Beaulieu (Dordogne), France

Dr N. K. Jerne, Acting Chief, Department of Biological Standardization, State Serum Institute, Copenhagen, Denmark

Secretary :

Dr R. Gautier, Assistant Director-General, WHO

The report on the third session of this committee was originally issued in mimeographed form as document WHO/BS/70, 13 May 1949.

EXPERT COMMITTEE ON BIOLOGICAL STANDARDIZATION

Report on the Third Session[1]

The Expert Committee on Biological Standardization held its third session in London on the premises of the Medical Research Council, 26 Old Queen Street, from 2 to 7 May 1949.

In addition to the members and co-opted members, one expert on blood groups (Dr R. R. Race, Director, Blood-Group Research Unit, Lister Institute of Preventive Medicine, London), two experts on endocrinology (A. S. Parkes, National Institute for Medical Research, London, and C. Hewett, Organon Laboratories, Glasgow), two experts on immunology (Dr A. Felix, Director, Central Enteric Reference Laboratory and Bureau, Public Health Laboratory Service, London, and Dr D. A. Long, National Institute for Medical Research, London), one expert on pharmacology (Dr W. L. M. Perry, National Institute for Medical Research, London), and one expert on vitamin B_{12} (E. Lester Smith, Glaxo Laboratories, Greenford, Middlesex) attended part of the session.

The Assistant Director-General outlined the steps taken to implement the decision of the First World Health Assembly[2] regarding the establishment of an expert committee on biological standardization.

Dr Timmerman was elected chairman and Dr Miles rapporteur.

The chairman felt sure that the committee would first wish to express its sorrow for the recent death of Mr P. Bruce White, who had attended the second session of the Interim Commission's expert committee as a specialist on cholera. The committee would remember Mr Bruce White not only as an outstanding bacteriologist and serologist, but also as a good friend.

---

[1] The Executive Board at its fourth session adopted the following resolution:

"The Executive Board (1) NOTES the report of the Expert Committee on Biological Standardization on its third session and the report of its Subcommittee on Fat-Soluble Vitamins, and (2) AUTHORIZES their publication." *Off. Rec. World Hlth Org.* **22**, 3

[2] *Off. Rec. World Hlth Org.* **13**, 307

1. Ogawa and Inaba Cholera Vaccines and Diagnostic Antisera [3]

The committee noted that the recommendations made by the Expert Committee on Biological Standardization of the Interim Commission of the World Health Organization at its second session, regarding the provision of reference prophylactic vaccines, of freeze-dried living cultures, and of freeze-dried antigens for the production of diagnostic antisera in rabbits, had been implemented.[4] In the light of recent advances in the antigenic analysis of the cholera and other vibrios, however, the committee decided to defer the establishment of the freeze-dried antigens for rabbit immunization as reference preparations, pending a reinvestigation of the strains employed.

The committee recommends that the suitability of the Ogawa and Inaba prophylactic vaccines as reference preparations should be tested by comparative assay against three "unknown" vaccines of different potencies. Sir Sahib Singh Sokhey agreed to prepare the unknown vaccines. Laboratories in five countries will take part in the assay.

2. Anti-Pertussis Vaccine [5]

The committee decided to defer the establishment of an international standard preparation for an *Haemophilus pertussis* vaccine until sufficient information was available on the following points:

(1) The relation between immunizing potency in laboratory animals and in man. It was noted that information on this point would probably be forthcoming within a year.

(2) The consistency of results obtained by independent workers when several vaccines are compared with a standard preparation.

Among the difficulties in reaching agreement about the potency of pertussis vaccines as measured by current methods are the variable interpretations of turbidity of vaccines in terms of bacterial content, and the variable results obtained in the intracerebral tests in mice.

Dr Veldee agreed to place at the disposal of the interested laboratories samples of the US National Institutes of Health (NIH) turbidity standard, which is a suspension of particles of Pyrex glass in water, together with samples of the NIH reference vaccine measured against this standard,

---

[3] White, P. Bruce, WHO/BS/52; Sokhey, S.S., WHO/BS/66; Gallut, J., WHO/BS/69; unpublished working documents

[4] *Off. Rec. World Hlth Org.* **11**, 8

[5] Veldee, M. V., WHO/BS/54; Evans, D. G., WHO/BS/62; unpublished working documents

with a view to obtaining opinions in various countries regarding the suitability of a Pyrex glass suspension as a turbidity standard; and to make available the strains of *H. pertussis* and of mice used in the NIH laboratories for the intracerebral test.

3. Smallpox Vaccine

The committee considered the investigations necessary for the definition of minimum requirements for smallpox vaccines. To this end it recommended that the seed vaccinia virus used in different countries for the preparation of smallpox vaccines be tested in rabbits for its immunizing potency against freshly isolated human variola virus.

The committee considered that India was a suitable country for such investigations and, at the suggestion of Sir Sahib Singh Sokhey, it recommended that WHO should ask the Government of India to arrange for the testing of seed virus in this manner through the mediation of WHO.

4. Diphtheria and Tetanus Toxoids [6]

The committee decided that the purified diphtheria and tetanus toxoids intended to serve as international standard preparations should be compared with the plain toxoids currently prepared in different countries for the immunization of man, with a view to ascertaining the amount of the proposed standard preparations to which convenient unit immunizing potency might be assigned.

5. Streptococcus Antitoxin [7]

A suitable preparation of streptococcus antitoxin has been procured by the Department of Biological Standards, National Institute for Medical Research (NIMR), London. Preliminary tests indicate that the preparation is suitable for an international standard. Estimation of the potency of this preparation in terms of the US National Institutes of Health standard streptococcus antitoxin is to be made by laboratories in four countries.

6. Tetanus Antitoxin

The committee noted that informal opinion in various countries was in favour of unifying the dual notation of potency—the international and US units—in current use. Having regard to the circumstances of the original definition of the first international unit for tetanus antitoxin, it

---

[6] Department of Biological Standardization, State Serum Institute, Copenhagen, WHO/BS/48; Jerne, N. K., WHO/BS/68; unpublished working documents

[7] Department of Biological Standards, National Institute for Medical Research, London, unpublished working document WHO/BS/60

recommended that the weight of the international standard preparation, to which international unit potency is at present assigned, should be doubled, so that in future the international unit for tetanus antitoxin will be equal to the US (NIH) unit. The committee recommended that this change be announced as soon as possible and that this notation should be universally adopted for new issues not later than 1 July 1950.

7. Detection of Tubercle Bacilli [8]

The committee considered that the problem of devising standard techniques for the detection of tubercle bacilli in pathological material should be studied in close collaboration with the Expert Committee on Tuberculosis, preferably by a joint subcommittee.

8. Serodiagnosis of Typhoid and Paratyphoid Infections [9]

The committee accepted the proposal of Dr A. Felix to prepare eight horse antisera for the specification of agglutinating suspensions for use in the serodiagnosis of typhoid and paratyphoid infections. Antisera specific for the following antigens will be made: *Salmonella typhi* (H); *Salmonella typhi* (O); *Salmonella typhi* (Vi); *Salmonella paratyphi A* (H); *Salmonella paratyphi A* (O); *Salmonella paratyphi B* (H); *Salmonella paratyphi B* (O); *Salmonella paratyphi*, non-specific (H).

The committee recommended that the antisera should be examined in laboratories in six countries for their suitability as standard preparations, and that, if suitable, they should be adopted as international standard preparations. It decided to defer the definition of agglutinating potency until its next meeting.

9. Serodiagnosis of Rickettsial Infections [10]

The committee accepted the proposal of Dr A. Felix to prepare horse antisera for the specification of the X strains of *Proteus* for specifying agglutinating suspensions to be used in the serodiagnosis of rickettsial infections. Antisera for the following antigens will be made: *P.* OX19; *P.* OXK; *P.* OX2. The committee recommended that the antisera should be examined in laboratories in six countries for their suitability as international standard preparations.

---

[8] Timmerman, W. Aeg., unpublished working document WHO/BS/57

[9] Felix, A., document WHO/BS/53; to be published in *Bull. World Hlth Org.* 1950, **2**, No. 3

[10] Felix, A., document WHO/BS/63; to be published in *Bull. World Hlth Org.* 1950, **2**, No. 3

The committee recommended that interested workers be asked for their opinion about the desirability of standard antisera for specifying rickettsial suspensions.

10. Serodiagnosis of Syphilis

The committee noted that the question of the serodiagnosis of syphilis was being considered by a special subcommittee of the Expert Committee on Venereal Infections [11] and expressed a wish that a member of the Expert Committee on Biological Standardization should be invited to attend the meetings of the subcommittee and the planned International Serological Laboratory Conference.

11. PPD [12]

Further tests of various preparations of PPD have shown that their sensitizing properties do not debar them from use as standard preparations. The reaction they produce in hypersensitive animals and man, however, are qualitatively different in a significant degree. Moreover, PPD and similar materials prepared in different ways contain variable proportions of active fractions of different molecular weight. The committee therefore decided to defer the establishment of a reference preparation until its next session, and meanwhile recommended and arranged for a comparative biological and physiochemical examination in five laboratories of representative types of purified tuberculo-proteins.

12. BCG [13]

The committee approved the reports submitted at the request of the United Nations International Children's Emergency Fund (UNICEF) by Drs Timmerman & Gautier, Dr Timmerman, and Sir Sahib Singh Sokhey on the preparation of BCG at the State Serum Institute, Copenhagen, the Institut Pasteur, Paris, the Institut Pasteur d'Algérie and the King Institute, Madras.[14]

The committee discussed the conditions necessary for the production of safe and effective BCG vaccine and defined them (see Annex 1, page 14).

---

[11] Expert Committee on Venereal Infections. Report of the Subcommittee on Serology and Laboratory Aspects (unpublished working document WHO/VD/38). After approval by the Executive Board, this report will be published as *World Health Organization : Technical Report Series*, no. 15.

[12] Grasset, E., WHO/BS/59 ; Long, D. A., WHO/BS/64 ; unpublished working documents

[13] Holm, J., unpublished working document WHO/BS/45

[14] Timmerman, W. Aeg. & Gautier, R., JC2/UNICEF/WHO/1, JC3/UNICEF/WHO/2 ; Timmerman, W. Aeg., JC3/UNICEF/WHO/32 ; Sokhey, S. S., JC3/UNICEF/WHO/1 ; unpublished working documents. See also *Off. Rec. World Hlth Org.* **22**, 42, 44

It recommended that laboratories manufacturing BCG on behalf of UNICEF should conform to the specifications contained in this document.

The committee noted that the Institut Pasteur, Paris, was now ready to serve as the world centre for the preparation and distribution of freeze-dried cultures of living BCG for use as seed culture for the preparation of BCG vaccine. The distribution will be made monthly, direct to the laboratories producing BCG for the UNICEF vaccination campaign and to other interested laboratories on the recommendation of the national control centres.

13. Digitalis [15]

Fifteen of the 17 participants in the comparison of the proposed third international standard for digitalis with the second international standard have submitted their results. The proposed standard preparation is of suitable quality and its potency is almost identical with that of the second international standard. The exact designation of potency must await the completion of the assays. The committee recommended that the Department of Biological Standards, National Institute for Medical Research, London, be authorized, after due consultation with participating laboratories, to assign to this standard the potency indicated by the combined results of the 17 assays.

14. Sulfarsphenamine

A suitable batch of sulfarsphenamine has been procured by the Department of Biological Standards, National Institute for Medical Research, London. Preliminary comparisons with the second international standard sulfarsphenamine indicate that the new preparation is suitable for the third international standard. A final comparison of the two preparations is to be made by laboratories in five countries.

15. Anti-Pernicious-Anaemia Factor [16, 17]

A standard preparation for the measurement of the anti-pernicious-anaemia potency of extracts of liver and other animal tissues is urgently required. The recent isolation of vitamin B_{12} provides a substance which may prove to be suitable for such a preparation. The scarcity and high

[15] Department of Biological Standards, National Institute for Medical Research, London, unpublished working document WHO/BS/51

[16] Smith, E. Lester, document WHO/BS/61; to be published in *Bull. World Hlth Org.* 1950, **2**, No. 3