Report of the Eleventh Meeting of the
STEERING COMMITTEE OF THE
SCIENTIFIC WORKING GROUP ON BACTERIAL ENTERIC INFECTIONS:
MICROBIOLOGY, EPIDEMIOLOGY, IMMUNOLOGY, AND VACCINE DEVELOPMENT
(Rangoon, 18-21 February 1985)

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The eleventh meeting of the Steering Committee (SC) of the Scientific Working Group (SWG) on Bacterial Enteric Infections was held in Rangoon, Burma, from 18 to 21 February 1985. The participants are listed at the end of the report.

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1. CONSIDERATION OF THE REPORT OF THE TENTH MEETING

The Committee reviewed and approved the minutes and report of the tenth meeting.

2. REVIEW OF FOLLOW-UP ACTION AND ONGOING ACTIVITIES

2.1 Follow-up action on proposals considered at the last meeting

The Committee considered the follow-up action taken on proposals considered at the last (tenth) meeting. It approved the awarding of support for a second year to the following project:

82193 - Development of an animal model for the assay of typhoid vaccines - B. Dieta, Laboratory Centre for Disease Control, Ottawa, Canada ($12 100)

It also approved the awarding of support to the following new project:

84012 - Giardia lamblia - is it a significant pathogen? A prospective study in a Peruvian village - R. H. Gilman, Francis Scott Key Medical Center, Baltimore, USA & C. Lanzata, Universidad Peruana Cayetano Heredia, Lima, Peru ($20 950)

This community-based study will determine the importance of G. lamblia and cryptosporidiosis as causes of diarrhea in Peruvian children.

2.2 Escherichia coli toxin testing (LT and ST)

2.2.1 Anti-LT sera

The Committee noted that the original lot of anti-LT, which had been stored by WHO and provided to various laboratories, was not effective in the Biken test and recommended that the remaining vials be destroyed. Investigators originally given the anti-LT should be sent vials from a new lot to be provided by Dr Takeda. The instructions for use of the sera should be the same as for the previous sera. The product should be stored at 4°C. It was agreed that a vial of the new sera should be returned to Dr Takeda to check that it had not deteriorated during shipment.

The SC was informed that the Swiss Serum and Vaccine Institute (SSVI) had now prepared anti-LT for commercial sale. It requested that additional information be sought from the institute concerning their methods of preparing and testing the serum. The Committee agreed that, following receipt and review of that information, the antiserum would need to be evaluated before it could be recommended for use in WHO-supported projects. Plans were made to evaluate it in the Biken test, the GM1 ganglioside ELISA test, the indirect ELISA, and the CHO assay.

2.2.2 ELISA ST assay

The Committee was informed that Dr F. Klipstein had modified his ST ELISA test to permit the use of horseradish peroxidase in place of alkaline phosphatase, since the former had better heat stability. The Ortho Company was apparently interested in commercializing an ST assay based on the test but preferred to use a monoclonal rather than a polyclonal antibody, and possibly a latex bead precipitin test rather than an ELISA. No decision was expected from the Company for at least 3 months. The SC agreed to evaluate Dr Klipstein's ST ELISA in Dr Rowe's laboratory, using materials provided by Dr Klipstein. It also requested that the Secretariat write to Ortho indicating the Committee's interest in the development of the assay, especially if it should prove to be inexpensive and technically simple.

The SC also reviewed the status of an ST ELISA developed by Dr R. Giannella (82068: Development of immunoassays for E. coli heat-stable enterotoxins (STa)). It considered that Dr Giannella had made good progress in developing his assay and awarded $12 000 for a final year, during which it believed the ELISA could be properly evaluated.
2.3 Campylobacter serotyping

The Committee considered a request from Dr H. Lior for additional funds for the ongoing evaluation of his Campylobacter serotyping scheme. It decided that it would prefer first to review any available results from the centres participating in the study. Following its analysis of such results, it would be in a position to decide how much, if any, additional support should be awarded. While the Committee realized that Dr Lior would not have sufficient resources to produce sera to recognize new serotypes, it hoped that, with the funds already made available, he could confirm a subsample (240 strains) of the isolates that the participating laboratories had been able to serotype, as originally planned.

2.4 Multicentre etiology study

(a) Burma (Department of Medical Research, Rangoon): The Committee reviewed additional studies completed since its last meeting. Concern was expressed about the low overall rate of identification of pathogens in ill children and the SC recommended that a consultant bacteriologist spend 2 months at the DMR during the peak diarrhoea season (August–September) to search for new diarrhoeal pathogens and review the laboratory methods in use. $13,000 were set aside for that purpose.

(b) Pakistan (National Institute of Health, Islamabad): The Committee considered Dr Rowe's report on his recent visit to the NIH and noted that, for the past 3 months, the Institute had been undertaking research in conformity with the global protocol. It agreed to provide support for a second year with the goal of bringing the skills at the Institute to the level required by the multicentre protocol during that period. The SC expected the total budget for the next year of the project to amount to $25,000. It agreed to provide up to 50% of that amount, in view of the fact that support might also be provided by the Steering Committee on Viral Diarrhoaeas and the WHO Regional Office for the Eastern Mediterranean. The SC also awarded a research training grant in the amount of $7500 to enable a microbiologist from NIH to receive 6 weeks' training at the WHO Collaborating Centre for Phage-Typing and Resistance of Enterobacteria and at a clinical microbiology laboratory in London, to be determined by Dr Rowe.

(c) Mexico (Hospital Infantil, Mexico City): The Committee noted the generally excellent results obtained in the study and the high rate of isolation of enteric pathogens in controls. It requested further information on the percentage of infections that were mixed and the method of selecting controls. It noted with satisfaction that epidemiological guidelines had been developed to detect and prevent any possible bias in the selection of controls. The SC considered it important that steps be taken to identify subsequent studies that the Institute could undertake with support from the Programme, and recommended that the Chairman visit Mexico City to assist in that process. A sum of $13,325 was awarded for the second year of the project.

(d) India (Christian Medical College, Vellore): An interim progress report providing full etiological data for the first year of the study was considered and found excellent. The SC requested further information on the frequency of mixed infections and the procedures followed for the selection of controls. As the number of controls was considerably less than the number of cases, it suggested that the investigators consider studying additional controls. It was hoped that a final report would be available for the next meeting of the SC.

2.5 Cholera vaccines

2.5.1 B-subunit/whole-cell vaccine field trial - Dhaka, Bangladesh

The Committee considered a report on the pretesting of the B-subunit/whole-cell vaccine trial at the ICDRR,B. It noted that no side reactions had been observed and that the serological responses were similar to those seen in an earlier trial done to evaluate the neutralizing buffer. The full vaccine trial had begun in mid-January 1985 and, although there had been some minor logistic problems, the first vaccination had been successful. The Committee agreed to provide an additional $50,000 for the project, if required.
2.5.2 Vaccine Trial Centre (Mahidol University, Bangkok)

The Committee was informed that there had been some delay in the construction of the Centre, though all the necessary funds had been obtained from USAID and WHO. The SC reaffirmed its willingness to support the training of a physician (6 months) and either a nurse or a laboratory coordinator (3 months) at the Center for Vaccine Development, University of Maryland. The Chairman of the SC would be visiting Bangkok immediately after the meeting to review progress at the Centre and make further arrangements regarding the recommended training. The SC agreed to finalize its recommendations concerning the first projects to be undertaken at the Centre when it met in Sweden in June. A consultant (Dr R. Black) would visit Thailand immediately after that meeting to assist in preparing the initial protocols.

2.5.3 Salmonella/V. cholerae hybrid vaccine

The Committee considered a report from Professor D. Rowley (University of Adelaide, Australia) regarding the development in his laboratory of S. typhi Ty21a strains that contain the genes for, and express, LPS Inaba, LPS Ogawa, or a 25K outer membrane protein which is believed to be an adhesin. Dr M. Levine (Center for Vaccine Development, Maryland) had agreed to test at least one of the strains in volunteers. The question had been raised whether WHO would be interested in providing partial support for the study. After considering the potential problems involved in the use of such a vaccine, the SC decided that it would be willing to provide partial support for a volunteer study to determine whether the vaccine offered protection against cholera and simultaneously stimulated an antityphoid immune response similar to that observed with unmodified Ty21a. Accordingly, it agreed that Professor Rowley and Dr Levine should submit an application for partial support for the volunteer studies on the understanding that the main support for such a trial would be provided by the University of Adelaide.

2.5.4 Pasteur Institute vaccine

The Committee was informed of discussions held by the Chairman and the Secretariat with representatives of the Pasteur Institute concerning the possible cholera vaccine that had initially been developed by Professor A. Dodin and had been discussed at the Scientific Working Group meeting in September 1984. Apparently, the current vaccine preparation differed considerably from that prepared by Professor Dodin, being essentially composed of disrupted V. cholerae organisms. The Pasteur Institute was now undertaking studies in animal models to ascertain the efficacy of the vaccine, and plans were being made to test it in volunteers at the Center for Vaccine Development, Maryland. The Secretariat was requested to determine the nature of these plans from Dr Levine.

2.6 Typhoid vaccines

2.6.1 Ty21a vaccine trials, Chile

The Committee considered progress reports for the 3 vaccine trials being carried out in Santiago (ID Nos. 80004, 83042, 84029), as well as requests for one year of additional funding for each project. To date, the trials had shown that Ty21a vaccine was safe, that the enteric-coated formulation was practical for large-scale use in persons above the age of 5 years, and that it was much more effective than vaccine given in gelatin capsules with bicarbonate. Two doses of the enteric-coated vaccine provided 50% protection in the first year following vaccination and 72% in the second year, whereas 3 doses of the vaccine provided 74% protection for one year following vaccination. Two doses of the vaccine also provided 50% protection against S. paratyphi B disease. In the 3-dose trial, vaccine doses spaced 2 days apart had the same efficacy as doses administered at 21-day intervals. The relative efficacy of 2, 3 and 4 doses of the vaccine was under study in a third trial. A declining rate of typhoid in the placebo groups was noted. The SC wondered whether that might reflect some degree of herd immunity, and felt that it deserved close observation. The SC agreed to provide financial support for an additional 6 months' surveillance for all 3 trials ($42,088) and to ask the Principal Investigators to submit a new 12-month budget with a progress report for each trial for consideration at its next meeting.
2.6.2 Candidate aromatic-dependent, live typhoid vaccine

The Committee considered whether it should support phase I/phase 2 studies in volunteers of a new live, attenuated S. typhi vaccine - an aromatic-deficient, histidine and purine-dependent mutant created by Dr B. Stocker, Stanford University, USA, using recombinant DNA techniques. The Committee agreed that the testing of an alternative to Ty2la was appropriate and recommended that Drs Levine and Stocker be asked to prepare a proposal for such studies at the Center for Vaccine Development.

2.6.3 83140: Preparation of a typhoid vaccine field trial site, Piaju, Sumatra

The Committee noted with satisfaction the progress made in the project and observed that, by mid-1985, the investigators would have obtained sufficient background census information to undertake a field trial. It further noted that laboratory workers had been trained and that the annual incidence of proved typhoid fever in the population, prospectively studied, might be as high as 6/1000. The SC reviewed a preliminary proposal for the field trial, but recognized that recommendations on trial design would need to await the latest results from the ongoing trials in Chile, which would be available in June 1985. In the meantime, the Secretariat was requested to determine from the WHO Secretariat Committee on Research Involving Human Subjects whether a placebo trial could be considered using Ty2la vaccine. The Committee approved US$27,700 for the trial and agreed to provide a consultant when needed.

2.7 Shigella vaccines

The Committee considered that priorities should be assigned by the Programme in the area of vaccine development against shigellosis, in view of the fact that several candidate vaccines might soon be developed using recombinant DNA technology. It agreed that the Programme could encourage applications aimed at the development of vaccines against disease caused by S. dysenteriae type 1 as well as polyvalent vaccines designed to protect against that and other major shigella serotypes (e.g., flexneri 2, 3, and 4).

3. BUDGET

The Committee reviewed and approved its proposed budget for 1985, as follows, noting that it represented an 11% increase over 1984 expenditure.

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<th>Proposed 1985</th>
<th>US$</th>
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<tr>
<td><strong>TOTAL</strong></td>
<td><strong>1 064 000</strong></td>
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4. REVIEW OF RENEWAL APPLICATIONS AND FINAL REPORTS

The Committee reviewed 3 final reports, 10 applications for a renewal of support, and 4 progress reports in which further support was not requested. It agreed to provide additional support for 5 of the 10 applications; for 3 others, more information was requested; and for the remaining 2 further funding was not approved. The 5 approved projects are:
5. REVIEW OF NEW AND REVISED PROPOSALS

The Committee reviewed 15 new or revised proposals, of which:

- 3 were approved for support either as originally submitted or pending minor technical or budgetary modifications;
- 1 was kept in abeyance, pending revision of the proposal;
- 11 were rejected (in one case a new proposal was invited).

The following is a summary of the 3 proposals approved for funding:

(a) 84215 - The Identification of enteroinvasive E. coli in Thailand - P. Echeverría, Armed Forces Research Institute of Medical Sciences, Bangkok, Thailand ($20,000)

The project represents a continuation of Dr Echeverría's epidemiological studies on acute diarrhoea in Thailand. The objective is to determine the incidence and clinical features of EIEC infections in children in Bangkok, using a DNA probe to identify EIEC.

(b) 84090 - Role of breast milk IgA antibodies to Campylobacter jejuni in a developed and a developing country - M. Blaser, University of Colorado Health Sciences Center, USA ($12,000)

The purpose of the project is to determine whether breast-milk antibodies protect children against disease due to C. jejuni. The study will be performed using milk samples collected during studies on the intrafamily spread of C. jejuni infections in Bangladesh.

(c) 84091 - A study of measles-associated diarrhoea - R.B. Sack, The Johns Hopkins University, Baltimore, USA and E. Salazar-Lindo, Universidad Peruana Cayetano Heredia, Lima, Peru ($16,500)

This study of measles-associated diarrhoea in Lima, Peru, has as its objectives: (i) to determine the etiology of diarrhoea that occurs during measles or within the following 4 weeks in children aged 7 months to 5 years, and (ii) to determine the incidence of diarrhoeal episodes in children with measles studied during the same period.

6. OVERVIEW OF PROPOSALS FUNDED TO DATE

The Committee reviewed a computer printout showing information on all projects funded by the Programme to date. The SC noted that, as in previous years, most of the projects it had funded were in the priority areas of epidemiology, laboratory diagnosis, pathogenesis and disease resistance, immune mechanisms and development of new or improved immunogens, and vaccine testing.
7. SITE VISITS AND TRAINING

7.1 Site visits

The Committee reviewed Dr. F. Blake's report on a site visit to Dr. F. Mhalu, Dar es Salaam, United Republic of Tanzania, and recommended that site visits be made to Mexico and Thailand.

7.2 Laboratory courses and other training activities

The SC expressed the view that training courses in microbiological methods were of limited value and that greater benefit was often derived from carefully planned site visits by microbiologists to centres in need of strengthening. Other possible research strengthening activities were discussed, including:

- Strengthening of epidemiological skills, especially in support of epidemiologically-based intervention-related studies to be promoted in developing countries.

- Strengthening of serological testing capability, especially for support of certain vaccine-related and epidemiological studies.

- Publication of revised research priorities, which should reflect the increasing emphasis of the Programme on support of research that is directly relevant to the development of improved tools for the prevention of morbidity or mortality due to diarrhoeal disease.

- Multicentre studies: the funding of additional centres, especially in Africa, was considered.

- SC meetings held outside Geneva: the SC agreed that it should continue to hold about one third of its meetings at important developing country research institutes, considering that such contact was of significant value both for the SC and for the host institution.

8. OTHER MATTERS

Nobel Conference

The Committee agreed to hold an extraordinary meeting on 7 June in Stockholm, following the 11th Nobel Conference, to review the ongoing typhoid vaccine trials in Chile and plans for a typhoid vaccine trial in Indonesia, and to recommend initial studies to be done at the Vaccine Trial Centre in Thailand.

9. TWELFTH STEERING COMMITTEE MEETING

The Committee agreed to hold its twelfth meeting in Geneva from 10 to 13 September 1983.

10. LIST OF PARTICIPANTS

Members:

Dr. J. Holmgren, Department of Medical Microbiology, University of Göteborg, Göteborg, Sweden

Prof. L. Le Minor, Institut Pasteur, Paris, France*

Dr. N.F. Pierce, Department of Medicine, Francis Scott Key Medical Center, Baltimore, MD, USA (Chairman)

Dr. B. Rowe, Director, WHO Collaborating Centre for Phage-Typing and Resistance of Enterobacteria, Central Public Health Laboratory, London, UK

* Unable to attend
Prof. Y. Takeda, Chairman, Department of Bacterial Infections, The Institute of Medical Science, University of Tokyo, Tokyo, Japan

Prof. L.R. Trabulsi, Department of Microbiology, Escola Paulista de Medicina, São Paulo, Brazil

Observer:

Dr Thane Toe, Department of Medical Research, Rangoon, Burma

Secretariat:

Dr M.H. Merson, Director, Diarrhoeal Diseases Control Programme (Secretary)