Report of the Eleventh Meeting of the STEERING COMMITTEE OF THE SCIENTIFIC WORKING GROUP ON VIRAL DIARRHEAS (Geneva, 26-29 August 1985)

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The eleventh meeting of the Steering Committee (SC) of the Scientific Working Group (SWG) on Viral Diarrheas was held in Geneva on 26 to 29 August 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 adopted the minutes and report of its tenth meeting.

2. REVIEW OF FOLLOW-UP ACTION TAKEN BY THE SECRETARIAT

The Committee reviewed and approved the follow-up action taken by the Secretariat in relation to individual proposals considered at its last meeting:

**82179 - Diarrhées d'origine virale (Senegal).** Based on Dr Diop Mar’s revised progress report, the Chairman of the SCs on VID and BEI had approved US$11 020 for the next 6 months.

3. BUDGET FOR 1985

The SC approved the proposed budget for the remainder of 1985 as given below:

<table>
<thead>
<tr>
<th>Item</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consultants</td>
<td>3 046</td>
</tr>
<tr>
<td>Travel</td>
<td>10 000</td>
</tr>
<tr>
<td>Contracts</td>
<td>285 290</td>
</tr>
<tr>
<td>Collaborating Centres</td>
<td>10 000</td>
</tr>
<tr>
<td>Meetings</td>
<td>18 457</td>
</tr>
<tr>
<td>Fellowship</td>
<td>5 000</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>1 803</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>343 596</td>
</tr>
</tbody>
</table>

4. DEVELOPMENT AND TESTING OF ROTAVIRUS VACCINE(S)

4.1 General

One day before its meeting the Committee met with representatives of three vaccine manufacturers (Smith Kline-RIT, Wellcome Laboratories, and Biomérieux) to review the development of three candidate vaccines: RIT-4237 (bovine), MMU-18006 (rhesus), and WC-3 (bovine). Rotavirus vaccine trials under way or planned by the Programme include studies of the RIT-4237 and MMU-18006 vaccines, evaluated either separately or in combined trials. RIT-4237 is currently being evaluated in Peru and The Gambia, and MMU-18006 in Sweden.

The immunization schedule recommended by EPI for the first 12 months of life was reviewed. Immunization with oral poliomyelitis vaccine (OPV) is recommended at birth (if poliomyelitis is a problem in the country) and at 6, 10, and 14 weeks of age. To simplify its delivery, an oral rotavirus vaccine would almost certainly need to be given with OPV at one or more of these times. Thus, there is a need to determine whether co-administration of OPV and oral rotavirus vaccine interferes with the immune response to either vaccine. It will also be important to determine how OPV and oral rotavirus vaccine can be prepared and/or administered as a combined vaccine.

Other considerations in vaccine development include:

- The vaccine should not cause fever, diarrhoea, or other side effects.

- The age for immunization must be defined. Because rotavirus diarrhoea attack rates between 3-6 months are significant in developing countries, immunization at birth or during the first few weeks of life may be required.
Information on secondary transmission of the vaccine strain is needed.

In view of the lack of data on the serotype specificity of vaccine efficacy, it may be necessary to include more than one virus strain to ensure protection against all serotypes.

To facilitate vaccine evaluation it would be desirable to initiate trials in developing countries as soon as possible after vaccine safety has been established in developed countries. As efficacy in developed countries may not predict efficacy in developing countries, it seems reasonable to conduct efficacy trials concurrently at both sites.

4.2 Smith Kline-RTI bovine vaccine (RIT-4237)

More than 2500 infants (including 35 neonates) have been immunized with this vaccine. It has no detectable side effects when given in a dose of \(10^8\)PFU. In developed countries, seroconversion after one dose was 35% in neonates and about 70% in bottle-fed infants 4-6 months of age. Vaccine efficacy has been determined in three trials—two in Finland and one in Belgium. In the Finnish trials infants 6-12 months of age received 1 or 2 doses of vaccine without a buffer to neutralize gastric acidity. These trials showed 82 to 88% protection against clinically significant diarrhoea lasting more than 24 hours; failures were related to poor serological response. The vaccine protected against type 1 rotavirus and may have been protective against types 2 and 3, but the number of cases was small. Vaccine efficacy lasted through two rotavirus seasons. The Belgian trial, in infants 4-12 months of age, showed 67% protection when doses were given at birth, 4 and 8 weeks of age without neutralization of gastric acid. However, diarrhoea in placebo recipients was mild. Seroconversion was closely related to the number of doses of vaccine; non-responding infants had threefold higher serum titres of maternal antibody than did responders. Measurement of gastric pH at the time of vaccination showed no difference between responders and non-responders. Protection occurred against both sub-group 1 and sub-group 2 rotaviruses.

Other findings have included:

- The optimal vaccine dose seems to be \(10^8\)PFU; a single dose of \(10^8\)PFU causes 74% seroconversion, whereas a single dose of \(10^7\)PFU causes 57% seroconversion in 6-month-old infants.

- Seroconversion was improved in infants breast-fed or bottle-fed prior to vaccination; in such infants a single dose of \(10^7\) or \(10^8\)PFU caused 75% seroconversion, whereas 53% seroconversion occurred in infants not fed before immunization.

The SC noted that the cost of producing this vaccine may pose a problem if the dose has to be as great as \(10^8\)PFU. If the vaccine can be grown on a less expensive substrate, the use of \(10^7\)PFU per dose may reduce the cost appreciably, but it may still be about US$ 0.30 per dose, and several doses may be required. If the vaccine is to be given with OPV it would have to be produced as a liquid. If given separately, it would probably need to be effective in a single dose and could be freeze-dried. It may also be necessary to give the vaccine with a buffer to neutralize gastric acid.

One important finding in vaccine trials with RIT-4237 is that one dose of OPV given with one dose of RIT-4237 significantly interferes with the serum antibody response to rotavirus. Whether one dose of RIT-4237 interferes with the response to one dose of OPV is uncertain.

The SC then considered the status of ongoing field trials in Peru and The Gambia.

84113 - Protective efficacy of live, attenuated rotavirus vaccine (RIT 4237) (C. Lanata, Instituto de Investigacion Nutricional, Lima, Peru, and R.E. Black, University of Maryland, Baltimore, USA)
This trial is an evaluation of 1, 2, or 3 doses of vaccine given to children aged 3-15 months. Preliminary data from the first 6 months of surveillance show that there have been 15 to 19 cases of confirmed rotavirus diarrhoea in each of the 3 study groups and the placebo group, suggesting that the vaccine is ineffective even when 3 doses are given.

The SC agreed that additional information from the trial was required before it could draw any conclusions. That would involve: (i) serotyping of the infecting rotavirus strains; (ii) serological studies to confirm vaccine "takes"; (iii) a comparison of case severity in the various immunization groups; (iv) confirmation that the administered vaccine had not lost potency; (v) determination of the incidence of mixed infections in the cases; and (vi) continuation of surveillance until at least one year after immunization. The SC approved $59,300 for the second year of the trial.

Consideration was given to the problem of defining the severity of diarrhoea in a standard manner in vaccine trials. The SC agreed that investigators could use definitions resembling those employed in the trials in Finland in which efficacy was determined for all episodes of rotavirus diarrhoea and for episodes lasting more than 24 hours. It recommended that guidelines be developed for use in future vaccine trials supported by the Programme.

Consideration was also given to the serological studies that should be used in vaccine trials. It was agreed that ELISA or complement fixation assays would be most practical, that neutralization assays would not be required, and that an IgM ELISA might be needed to distinguish vaccine-induced responses from maternal antibody in infants below 6 months.

84106 - A rotavirus trial in The Gambia (P. Hanlon and B. Greenwood, Medical Research Council Laboratories, Fajara, The Gambia)

In this trial, 3 monthly doses of RIT-4237 vaccine (with oral or parenteral poliovaccine) are being given to infants starting at age 2 months. Most are breast-fed and feeding is not interrupted when the vaccine is given. The vaccination of recruited children began in March 1985 and will be completed in March 1986. The SC approved $48,610 for the second year of the trial.

4.3 Rhesus rotavirus vaccine (MNU-18006)

Vaccine doses of 10⁴.5 or 10⁵.5PFU have caused 83% seroconversion in 4-12 month-old infants in the USA. However, the vaccine also caused side effects, especially fever and diarrhoea. About 70% of infants 4-12 months of age in Finland and Sweden developed fever after a single dose of 10⁵.5PFU, and in Sweden 40% also developed diarrhoea. Fever was also observed in the USA (primarily on days 3 and 4 after immunization), even when the vaccine dose was reduced to 10³.5PFU, but only in infants over 5 months of age. However, in Venezuela, infants aged 4-10 months given 10³.5 or 10⁴.5PFU showed no side effects. In that study the lower vaccine dose caused a seroconversion rate of 59%, whereas the higher dose caused 82% seroconversion. Seroconversion was also greater in infants with lower pre-immunization antibody titres. Shedding of the vaccine virus occurred in 53% of infants given 10⁴.5PFU and in 29% of those given the lower dose. Thus, the immunogenicity of the vaccine is dose-dependent and is diminished in the presence of pre-existing serum antibody. MNU-18006 is being cold-adapted to further attenuate the virus. Further passage of MNU-18006 might diminish its residual virulence, but it would probably be at least 3 years before such a vaccine would be ready for field testing.

The SC reviewed the results of a field trial of this vaccine being carried out with its support in Sweden:

84227 - Determination of the efficacy of rhesus rotavirus vaccination and protection against human rotavirus infection in children in a randomized double-blind study (L. Gotheors, Department of Pediatrics, University of Umeå, Sweden)
In this trial, infants aged 4–12 months were given one dose of vaccine (10^{2.5} PFU) after drinking buffered formula. The first year of surveillance has been completed but the results have not been analyzed. The SC was informed that the vaccine code had been broken and made known only to the principal investigators in order to analyze the side effects. The Committee recommended that the Programme participate in the analysis of vaccine efficacy after all stool specimens have been assayed for rotavirus.

The Committee next considered a report from the University of Maryland Center for Vaccine Development on a randomized, placebo-controlled trial to assess the reactogenicity, infectivity, and immunogenicity of the rhesus rotavirus vaccine given in doses of 10^{4.5} or 10^{4.2} PFU to infants aged 3–11 months; the vaccine was given in formula known to be negative for rhesus rotavirus vaccine antibody after the infants were fed one ounce of buffered formula. None of the infants developed diarrhoea; however, in those above 5 months of age fever occurred 3 or 4 days after immunization more frequently in vaccine recipients, even those who received the lowest dose, than in the placebo group. Surveillance during the past winter of another group of infants immunized in 1984 with 10^{3.5} PFU of MMU-18006 revealed 74% protection against diarrhoea in vaccinees, but the number of infants studied (24) was too few to permit firm conclusions regarding vaccine efficacy.

Based upon these results, and those from Venezuela, the SC considered a new proposal to study the efficacy of rhesus rotavirus vaccine:

84138 - Randomized double-blind placebo-controlled trial of oral attenuated rhesus rotavirus strain vaccine MMU 18006 in young children (M.E. Kennells and M. Levine, University of Maryland, Baltimore, USA)

The proposed study is a placebo-controlled, double-blind trial of rhesus rotavirus vaccine MMU-18006 given in one dose to infants aged 2–5 months in Maryland, USA. The sample size in the study would have a 90% power to detect a vaccine efficacy of 80%, assuming that the incidence of rotavirus diarrhoea over the two-year period is 0.6 and that no infants drop out of the study.

The SC recommended that the study be designed to detect a vaccine efficacy of 70% against rotavirus diarrhoea of any severity and 80% against rotavirus diarrhoea lasting longer than 24 hours, and that a more conservative estimate of the incidence of rotavirus diarrhoea be used. The Committee earmarked $38,900 for the first year of the study, pending receipt and approval of a revised proposal.

4.4 Study comparing RIT-4237 and MMU-18006 vaccines

85126 - Efficacy of the rhesus and RIT-4237 rotavirus vaccines in Lima, Peru (C. Lanata, Instituto de Investigacion Nutricional, Lima, Peru, R.L. Barua, Instituto de Medicina Tropical "Alexander von Humbolt", Lima, Peru, A.Z. Kapikian, National Institute of Allergy and Infectious Disease, Bethesda, USA, and R.E. Black, The Johns Hopkins University School of Hygiene and Public Health, Baltimore, USA)

The study aims to evaluate the efficacy of MMU-18006 (10^8 PFU) and RIT-4237 (10^8 PFU) vaccines in infants aged 2–4 months in Lima, Peru. The SC recommended revision of the study so that infants receive either 1 or 3 doses of vaccine as shown below:
Study design

<table>
<thead>
<tr>
<th>Group</th>
<th>No.</th>
<th>2 months</th>
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<tbody>
<tr>
<td>A</td>
<td>100</td>
<td>RRV**</td>
<td>RRV</td>
<td>RRV</td>
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<tr>
<td></td>
<td></td>
<td>OPV</td>
<td>OPV</td>
<td>OPV</td>
</tr>
<tr>
<td>B</td>
<td>100</td>
<td>RIT</td>
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<tr>
<td></td>
<td></td>
<td>OPV</td>
<td>OPV</td>
<td>OPV</td>
</tr>
<tr>
<td>C</td>
<td>100</td>
<td>RRV</td>
<td>Placebo</td>
<td>Placebo</td>
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<tr>
<td></td>
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<td>OPV</td>
<td>OPV</td>
</tr>
<tr>
<td>D</td>
<td>100</td>
<td>RRV**</td>
<td>Placebo</td>
<td>Placebo</td>
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<tr>
<td></td>
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<td>OPV</td>
</tr>
<tr>
<td>E</td>
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<tr>
<td></td>
<td></td>
<td>OPV</td>
<td>OPV</td>
<td>OPV</td>
</tr>
</tbody>
</table>

*All infants receive BCG at birth, DPT at 2 and 4 months, and OPV at 5 months.

**RRV and RIT to be given with formula and NaHCO3, except without NaHCO3 in Group D.

The SC agreed to provide $60,000 for a revised proposal which indicated (i) the design changes shown above; (ii) that batches of sera from the study would be analysed for evidence of interference with the OPV immune response as promptly as possible after infants have been immunized; and (iii) the method for blind allocation of the vaccines, in view of the fact that the placebo group is twice as large as any other, that a suitable placebo for OPV is required, and that one of the vaccines is lyophilized whereas the other is a liquid.

Protocol review - Rotavirus vaccine trial in Arizona, USA

The Committee reviewed a protocol for a field trial being supported by the United States Agency for International Development comparing the immunogenicity, safety and efficacy of MMU-18006 and RIT-4237 rotavirus vaccines in infants aged 2-6 months. The study will be divided into two parts. In the first, infants will receive a single dose of vaccine (RIT-4237, 10^6 PFU; or MMU-18006, 10^6 PFU) or placebo. In the second, there will be three immunization groups: (i) OPV plus MMU-18006 at 2, 4, and 6 months of age; (ii) injectable polio vaccine (IPV) plus MMU-18006 at 2 months of age (IPV plus placebo at 4 and 6 months); and (iii) OPV plus placebo at 2, 4 and 6 months of age. The second part of the study will examine possible interference between MMU-18006 vaccine and OPV.

4.5 Wistar Institute/Institut Mérieux vaccine

The SC reviewed information concerning the low passage bovine rotavirus candidate vaccine (strain WC3) developed at the Wistar Institute, Philadelphia, USA, and to be produced by Institut Mérieux, France. Vaccine strain WC3 is a bovine rotavirus whose
electrophoretic pattern differs from that of the NCD rotavirus; it has been passaged 12 times. Preliminary safety studies in infants in USA and Japan given $3 \times 10^7$PFU revealed no side effects. Thirty-one percent of vaccinees excreted the virus in faeces. About 70% of infants aged 5-12 months seroconverted to the WC3 strain. The vaccine is being produced at the Institut Mérieux using tertiary monkey kidney cells. Vaccine safety and efficacy will be studied in Philadelphia during the coming winter. In that study infants will receive one dose of vaccine or placebo, the vaccine dose being $3 \times 10^7$PFU given with an antacid. OPV will not be given with the vaccine. Infants will be aged 3-12 months and most of them will not be breast-fed.

The SC expressed the hope that it would have the opportunity to review the protocol for the vaccine trial and that it would be kept informed of the results.

4.6 Cold-adapted human rotavirus vaccine

81104 - Study on human rotavirus cultivation and vaccine development (R. Kono/S. Inouye, The Institute of Public Health, Tokyo, Japan)

The final report of the project was reviewed. The investigators have developed a human rotavirus serotype 1 strain which is now adapted to 25°C after multiple passages. Clones of this strain have been selected for further immunological studies.

85089 - Experimental infection of animals with cold-adapted mutants of human rotavirus (S. Inouye, The Institute of Public Health, Tokyo, Japan)

A new proposal for the further development of a cold-adapted human rotavirus vaccine was reviewed. The immunogenicity of clones of the strain will be studied in mice and suckling piglets with the aim of identifying those able to evoke protective immune responses against homologous and, possibly, heterologous serotypes. The SC agreed to award $10,000 for the first year of the study.

4.7 Cloned rotavirus vaccines

The SC reviewed two renewal applications and one new proposal:

84070 - Cloned rotavirus genes and vaccine development (A.R. Bellamy, Department of Cell Biology, University of Auckland, New Zealand)

The VP7 gene has been inserted into an expression vector, and an E. coli strain has been identified in which this vector is stable and the VP7 antigen is expressed. During the coming year it is proposed to purify the VP7 antigen from E. coli, study its antigenic properties, and begin collaborative studies on the immunization of mice. The SC approved $15,000 for the second year of the project.

84081 - Approaching the control of rotavirus gastroenteritis through the use of cloned rotavirus genes (Dr M.K. Estes, Baylor College of Medicine, Houston, USA)

Rotavirus genes encoding the VP6 antigen have been successfully cloned into cultured insect cells; it is expected that this can also be done for the VP7 and VP3 antigens. The SC approved $15,000 for the second year of the project.

85124 - Rotavirus vaccine based on cloned genes (I.H. Holmes, Department of Microbiology, University of Melbourne, Australia)

The study aims to develop a candidate rotavirus vaccine by cloning rotavirus antigens into a bacterial carrier, the Ty21a live oral typhoid vaccine. The SC agreed to award $15,000 for the first year of study.
5. REVIEW OF APPLICATIONS FOR RENEWAL OF SUPPORT

The Committee reviewed 4 final reports (1 under item 4) and 11 applications for renewal of support (4 under item 4). For all of the 11 renewal applications the SC agreed to provide support for an additional year. The SC also approved the extension of 2 projects without additional funds, and for a third project more information was required. The applications approved for continuation (in addition to those under item 4) were:

82156 - Horizontal and longitudinal study on the prevalence of rotavirus and other enteric pathogens in children of Hong Kong (J. Tam, Department of Microbiology, University of Hong Kong, Hong Kong)

82095 - Rotavirus infection in the first two years of life - a study of possible protective factors and of the local class specific antibody response (L. Mendis, Faculty of Medicine, Colombo, Sri Lanka)

82222 - Etude épidémiologique des infections à rotavirus chez l'enfant de la naissance à 2 ans (M.-C. Georges-Courbot, Institut Pasteur de Bangui, Bangui, Central African Republic)

81103 - Isolation and differentiation of human rotavirus strains prevalent in India (M. Shaila, Indian Institute of Science, Bangalore, India)

82089 - Immunologic and pathogenic aspects of gut-rotavirus interaction (M. Kleenhoff-Tally, Children's Hospital of Buffalo, Buffalo, USA)

84102 - Cellular immune responses to rotavirus infection (N.R. Blacklow, University of Massachusetts Medical School, Worcester, USA)

82092 - Studies on astrovirus, faecal adenoviruses, Norwalk virus and small round viruses (G. Grohmann, Institute of Clinical Pathology and Medical Research, Westmead, Australia)

6. REVIEW OF NEW AND REVISED PROPOSALS

The Committee reviewed 13 new proposals (including 9 under item 4). Of these:

- 4 were accepted for support (all under item 4).
- 7 were rejected.
- 2 were deferred for further information or revision.

7. REVIEW OF PROJECTS FUNDED TO DATE

The Committee examined the computer list of projects funded to date. Of the 55 projects funded by the SC prior to the present meeting, 24 (44%) were in developing countries.

8. SITE VISITS AND WORKSHOP

The Committee reviewed reports on site visits made to investigators in the Central African Republic, Hong Kong, and Mexico.

It noted that an Interregional Workshop on Electron Microscopy and Immune Electron Microscopy would be held at the Queen Mary Hospital, Hong Kong, in November 1985.

9. EVALUATION OF ROTAVIRUS DIAGNOSTIC TESTS

9.1 Evaluation of commercial rotavirus assays

The Committee reviewed its efforts to evaluate three commercial kits (Dakopatts, Orion, Biomérieux) for the diagnosis of rotavirus infection.
(a) Dakopatts ELISA

The kit has been modified to contain the control antigen and conjugated antibody in lyophilized form. It has been tested by three laboratories, which agreed that it performed extremely well, having a very low background and virtually 100% agreement with the WHO ELISA kit. The only shortcoming noted was that the positive control was either negative or only weakly positive. The kit instructions were very clear. It was found that clarification of the diluted stool sample by centrifugation was not absolutely necessary. An advantage of the kit was its built-in method for confirmation of positive reactions which gave immediate results, rather than requiring two days as is the case with the WHO kit. Results could be read easily and accurately by eye; an ELISA reader was not required. The estimated price per assay with this kit is US$ 0.50.

The SC concluded that the kit should be satisfactory for use in developing countries. It recommended that it be evaluated in several developing country laboratories after problems with the positive control antigen have been resolved.

(b) Orion Rotalex and Biomérieux Slidex

These are passive agglutination assays. The testing laboratories considered them less satisfactory because false negatives were unacceptably frequent, reading was sometimes difficult, and no blocking test was built into the assay. They also required a centrifuge and were more expensive per test than the Dakopatts ELISA.

9.2 The WHO ELISA kit

The supply of hyperimmune serum for the production of kits is adequate. The antiserum in the kit is now lyophilized for greater stability and to prevent loss by leakage. The kit could easily be modified to measure antibody to rotavirus, but the SC considered the assay would be of limited value as it would not permit the determination of antibody isotype and would require the development of a standard rotavirus antigen with which to confirm positive assays.

9.3 RPHA assay

Evaluation in two laboratories of the RPHA assay developed by the WHO Collaborating Centre revealed multiple non-specific results; it was also noted that the reconstituted red blood cells did not appear to be in good condition. The SC agreed that further work should be done to improve preservation of the red blood cells.

10. WHO COLLABORATING CENTRE FOR HUMAN ROTAVIRUSES

The Committee was informed that the Centre had distributed about 75 rotavirus ELISA kits to WHO-supported projects in 1984. By using the ELISA assay with monoclonal antibodies, large numbers of specimens could now be rapidly analysed. However, that applied only to serotypes 1, 2, and 3. The SC considered that RNA gels, which were more time-consuming, were not needed. The SC agreed to provide up to $30,000 for the production and distribution of ELISA kits in the coming year. It anticipated that, if further testing of the Dakopatts ELISA proved satisfactory, 1986 might be the final year for the production and distribution of ELISA kits by the Centre.

11. OTHER MATTERS

Non-group A rotaviruses

The Committee noted that two laboratories were reported to have ELISA assays for group B rotavirus; one might also be available soon at the WHO Collaborating Centre for Human Rotaviruses. EM screening for group B rotavirus might be insensitive because, in many cases, very few virus particles were present. Screening by IEM, using locally-obtained pooled human gamma globulin, should be more efficient. The Committee concluded that testing for group C rotavirus was of low priority because it was a rare cause of illness.
12. LIST OF PARTICIPANTS

Members:

Dr R.F. Bishop, Department of Gastroenterology, Royal Children's Hospital, Parkville, Australia (Chairman)

Dr T.H. Flewett, Regional Virus Laboratory, East Birmingham Hospital, Birmingham, UK

Dr A.Z. Kapikian, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA

Dr M.M. Mathan, Christian Medical College Hospital, Wellcome Research Unit and Department of Gastroenterology, Vellore, India

Dr G. Zissis, Department of Medical Virology, Infectious Diseases Unit, Hôpital St Pierre, Brussels, Belgium

Other participants (26 and 27 August only):

Dr R.E. Black, Department of International Health, School of Hygiene and Public Health, Johns Hopkins University, Baltimore, MD, USA

Dr J. Harris, International Centre for Diarrhoeal Disease Research, Bangladesh, Dhaka, Bangladesh

Representatives of vaccine manufacturers:

Dr F.E. André, Smith Kline-RIT S.A., Rixensart, Belgium

Dr A.J. Beale, Wellcome Research Laboratories, Beckenham, UK

Dr J. Armand, Institut Mérieux, Charbonnières/Bains, France

Dr B. Meignier, Institut Mérieux, Charbonnières/Bains, France

Dr S. Plotkin, Wistar Institute, Philadelphia, USA

Secretariat:

Dr M.H. Merson, Director, Diarrhoeal Diseases Control Programme, WHO, Geneva, Switzerland

Dr N.F. Pierce, Research Coordinator, Diarrhoeal Diseases Control Programme (Secretary)

Dr I. de Zoysa, Medical Officer, Diarrhoeal Diseases Control Programme