DIARRHEAL DISEASES CONTROL PROGRAMME

Report of the Eleventh Meeting of the

STEERING COMMITTEE OF THE
SCIENTIFIC WORKING GROUP ON DRUG DEVELOPMENT
AND MANAGEMENT OF ACUTE DIARRHOEAS

(Geneva, 7-10 October 1983)

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The eleventh meeting of the Steering Committee (SC) of the Scientific
Working Group (SWG) on Drug Development and Management of Acute Diarrhoea (DDM)
was held in Geneva on 7-10 October 1983.

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leurs auteurs.
1. CURRENT STATUS OF THE PROGRAMME

The Committee was briefed on the revised guidelines for management of the research activities of the Programme. It was explained that the present SWGs and SCs would be replaced by new ones, as follows: (a) SWG on Immunology, Microbiology and Vaccine Development (SWG/IMV), (b) SWG on Case Management (SWG/CMT), and (c) SWG on Epidemiology and Disease Prevention (SWG/EDP). The existing SC on DDM would function until the new SWG on Case Management met in April 1986.

2. CONSIDERATION OF THE REPORT OF THE TENTH MEETING

The Committee approved, without revision, the report of its tenth meeting.

3. 1985 BUDGET

The Committee approved the following budget for the funds available to it for the remainder of 1985:

<table>
<thead>
<tr>
<th>Item</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consultants</td>
<td>12,964</td>
</tr>
<tr>
<td>Duty travel</td>
<td>2,662</td>
</tr>
<tr>
<td>Contracts</td>
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<tr>
<td>Meetings</td>
<td>30,148</td>
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<tr>
<td>Fellowships</td>
<td>5,000</td>
</tr>
<tr>
<td>Supplies</td>
<td>14,741</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>282,399</strong></td>
</tr>
</tbody>
</table>

4. IMPROVED ORS FORMULATIONS

4.1 Ongoing studies and research recommendations

The Committee reviewed the status of all research projects on improved ORS formulations that had been proposed and approved for Programme support, noting that 15 projects were under way or would start shortly and that 4 more were under consideration. It also reviewed a summary of planned or ongoing studies of cereal-based ORS formulations at the ICDRR, B. The SC noted that results should be available from a number of these studies early in 1987. In the meantime, it recommended that additional studies be developed using ORS formulations not adequately represented in present studies, such as l-alanine ORS and ORS containing cereals and other staples such as maize, sorghum, wheat, bananas, and potatoes.

The SC reviewed the report of a study conducted in the USA which demonstrated that infants with acute diarrhoea given a lactose-free soy milk formula and ORS had markedly reduced stool output and duration of diarrhoea when compared with controls given only ORS (and no formula). That suggested that the soy milk formula enhanced ORS absorption and raised the possibility that other diets given with ORS might act similarly, thus obscuring, at least in part, the beneficial effects of improved ORS. Accordingly, the SC requested the Secretariat to see if it would be possible to incorporate an initial 24-hour period of fasting in the protocols of several studies which had been approved for funding but not initiated. It was agreed that that would be possible only if (a) children in the study were non-breastfed, well-nourished, and aged 3 months or more, (b) food was not withheld for more than 24 hours and the local practice for treatment of diarrhoea frequently included fasting, and (c) ethical approval of the revision was provided by the participating institution.

The SC recommended that the Programme organize a meeting to review the findings and consider further research on improved ORS after most of the current studies have been completed. The meeting might be held in May 1987.
The SC reviewed information provided by several cereal manufacturers on the cost, stability, and packaging requirements of pre-cooked cereals that might be used in pre-packaged, cereal-based ORS formulations. It noted that little information was available on their stability under tropical conditions, but that most manufacturers believed their product to be stable for up to one year. The SC requested the Secretariat to undertake further evaluation of the stability and packing requirements of such formulations.

4.2 Review of progress reports and new proposals

The Committee reviewed the progress reports of 2 ongoing projects, and approved additional funding for both. It also reviewed 6 new or revised proposals. Of these:

- 2 were accepted for funding (with or without minor modifications);
- 2 were approved pending receipt of required national or institutional approval;
- 1 was returned to the Principal Investigator for revision and resubmission;
- 1 was rejected.

The projects for which additional funding was approved are:

84073 - Improved oral rehydration solution(s) with anti-diarrhoeal properties: A controlled clinical trial - Phase 1 - Khin Maung U, Department of Medical Research, Rangoon, Burma (US$ 2 500)

84057 - Oral rehydration therapy with glycine-ORS in infantile diarrhoea: A controlled clinical trial - E. Salazar-Lindo, Universidad Cayetano Heredia, Lima, Peru (US$4 200)

The 2 new proposals approved for funding were:

(a) 86035 - A controlled clinical trial comparing new ORS formulation containing glycine-glucose and citrate-based ORS - M. Moechtar, Infectious Diseases Hospital, Jakarta, Indonesia ($24 758)

The study will evaluate an improved ORS formulation containing glycine (8 grams) and glucose (20 grams) as its organic constituents in patients aged 12-60 years with acute cholera or cholera-like diarrhoea.

(b) 85085 - Comparative study to assess the efficacy of super ORS and rice-based ORS with standard WHO/UNICEF ORS - A.F.M. Salim, Bangladesh Institute of Child Health, Dhaka, Bangladesh ($17 550)

The study will compare a rice-based ORS containing 50 grams cooked rice-powder per litre and an improved ORS formulation containing 50 grams maltodextrin as their organic constituent in infants and children aged 3 months to 2 years with acute diarrhoea.

5. OTHER STUDIES ON ORAL REHYDRATION THERAPY

5.1 Flavoured/coloured ORS

The Committee reviewed (a) a document summarizing information on 200 ORS products marketed globally, which revealed that most ORS preparations produced by major multinational drug firms were flavoured and some were coloured, (b) the results of a small study on the acceptance of flavoured and plain ORS conducted by a pharmaceutical firm, (c) comments from a pharmaceutical company on the clinical and market evaluation of flavoured ORS and related marketing issues, and (d) a draft set of guidelines for preparing protocols to evaluate the possible risks and benefits of flavoured ORS.
The SC recognized that no data existed on the benefits and risks of flavoured ORS and accepted the Technical Advisory Group's recommendation that research on that topic be supported.

The SC then considered a new proposal for a study on flavoured ORS, which was not approved.

5.2 Guidelines for studies on early home therapy for acute diarrhoea

The SC gave high priority to studies on early home therapy. It considered the most important questions to be: (a) what proportion of all acute childhood diarrhoea cases become dehydrated with traditional home practices? (b) what is the efficacy of early home therapy in preventing dehydration? (c) what is the impact of early home therapy on nutrition? and (d) what is the most effective and most easily promoted method of early home therapy — e.g., (i) liberal use of fluids usually available in the home, such as soups and certain drinks, or (ii) use of home-made sugar-salt or cereal-salt solutions? Since some home fluids were hypertonic due to their high sodium and/or sugar content, the SC recommended that available solutions used at home be analysed to identify those that were most appropriate for use in preventing dehydration.

The SC reviewed the efforts made to develop guidelines for studies on the impact of early home therapy on the incidence of dehydration in children with acute diarrhoea. It recognized the logistical and ethical difficulties in undertaking prospective surveillance of cases in "control" communities and suggested that alternative approaches be explored. While it would be ethically difficult to conduct a study comparing early home therapy with no treatment, a study comparing early treatment using a sugar-salt or "household food" solution with ORS solution would be possible. The SC also recognized that it would be very difficult to determine the incidence of dehydration in the absence of any outside intervention. It suggested that the Secretariat enquire whether data relevant to that point had been obtained in field studies already completed in Bangladesh, Panama, Peru, and Senegal.

The SC then considered a proposal for a study on early home therapy, which was rejected.

6. REVIEW OF RENEWAL APPLICATIONS, PROGRESS REPORTS, AND FINAL REPORTS ON OTHER TOPICS

The Committee reviewed 2 renewal applications, 2 progress reports (which did not request additional funds), and 3 final reports. It approved funding for the renewal applications:

84029 - Détermination et essais cliniques contrôlés des plantes médicinales antidiarrihéiques malgaches - M. Razanamparany, Hôpital Général de Befelatanana, Antananarivo, Madagascar (US$6,500)

83137 - Oral rehydration therapy for severely malnourished marasmic children - E. Salazar Lindo, Universidad Cayetano Heredia, Lima, Peru ($5,525)

7. REVIEW OF NEW PROPOSALS

The Committee reviewed 8 proposals for research on topics other than improved ORS and oral rehydration therapy. Of these:

- 5 were accepted for funding (with or without minor revisions);
2 were not approved;

a decision was deferred on 1 for technical reasons.

The 5 proposals approved for funding are:

84226 - A longitudinal study on the effect of systematic educational intervention in the postpartum period on promotion of breastfeeding and on frequency of diarrhoeal episodes in the first 6 months of life - O. Neyzi, Institute of Child Health, Istanbul, Turkey ($20 300)

The study will evaluate the effectiveness of an educational intervention for mothers during the immediate postpartum period and intended to encourage exclusive breastfeeding in the first 4 months of life. The impact of exclusive breastfeeding on the frequency of diarrhoea episodes in the first 6 months of life will also be determined.

84172 - Dietary management of acute childhood diarrhoea using common lactose-containing or lactose-limited foods - K. Brown, Instituto de Investigacion Nutricional, Lima, Peru ($35 905)

It is planned to evaluate the clinical course of diarrhoea in infants and young children fed diets containing varying amounts of lactose. Nutrient absorption will be determined and outcome will be related to the specific etiology of the diarrhoeal episode.


In a double-blind controlled trial, single-dose doxycycline will be compared with multiple-dose tetracycline for the treatment of cholera. The goal is to determine whether single-dose therapy is effective in the treatment of this disease.

83018 - Pathogenesis and nutritional consequences of prolonged diarrhoea - K. Brown, Instituto de Investigacion Nutricional, Lima, Peru ($35 529)

The study aims to define bacteriological and functional abnormalities of the bowel in children with persistent diarrhoea.

83004 - Food contamination and weaning diarrhoea - A. Pertet, Medical Research Centre, Nairobi, Kenya ($31 174)

A longitudinal study will be performed to determine the relationship between growth, incidence of diarrhoea, and feeding patterns in infants. Efforts will be made to define the role of bacterially contaminated weaning foods in the causation of diarrhoea.

8. CLINICAL RESEARCH CENTRES

The Committee reviewed the present status of the three clinical research centres. It recognized a need for additional centres, which should be selected among institutes successfully performing clinical trials for the Programme.

The SC then considered and approved the progress report and renewal request (second year) from one centre:

83101 - Clinical Trials - Research strengthening - A.S. Kassem, University of Alexandria, Egypt ($23 000)

9. PROPOSED WORKSHOP ON CLINICAL TRIALS IN ACUTE DIARRHOEA

The Committee agreed in principle that a francophone workshop on clinical trials should be held in 1986 and approved the estimated budget of $45 000. It also agreed to the proposed venue at El Chatby Children's Hospital, Alexandria, Egypt.
10. REPORTS ON AND PLANS FOR SITE VISITS

Reports on site visits made and plans for future visits were discussed. It was agreed that visits should be made to investigators in Bangladesh, Chile, Costa Rica, Egypt, India, Indonesia, Kenya, Madagascar, Philippines, Rwanda, and Turkey.

11. COLLABORATION WITH THE PHARMACEUTICAL INDUSTRY

The Committee reviewed ongoing collaborative activities with specific pharmaceutical companies:

Beaufour

Additional documents concerning the antidiarhoeal properties of “Smectite” (a clay classed as an absorbent) were reviewed. The SC recommended that a clinical trial of Smectite be undertaken to determine its efficacy.

Rorer Group Inc.

The SC reviewed information on lidamidine, including a study on its use in acute diarrhoea in adults in Mexico. The Committee was not convinced of the claim that lidamidine had an antisecretory effect and asked that the manufacturer be requested to refrain from making such a claim in promotional materials. The SC did not recommend a clinical trial with lidamidine at the present time.

Virdalm

The SC noted the paucity of information of any kind on the product Pecatin and suggested that the manufacturers be informed of the need for documentation of its clinical efficacy and safety before WHO could consider a clinical trial.

12. PLANS FOR THE STUDY OF PERSISTENT DIARRHOEA

The Committee requested that the document “Persistent diarrhea in children - research priorities” be sent to investigators interested in that topic to encourage appropriate research. The SC also noted that a review on persistent diarrhoea was being prepared for publication in the near future.

13. REVISED RESEARCH PRIORITIES FOR NEW SCIENTIFIC WORKING GROUP ON CASE MANAGEMENT

The Committee reviewed the draft revised priorities for the new SWG and suggested some additions and alterations.

14. LIST OF PARTICIPANTS

Members:

Dr J-F. Desjeux, INSERM U290, Hôpital Saint Lazar, Paris, France
Professor D. Haile, Addis Ababa University, Addis Ababa, Ethiopia
Dr J.R. Hamilton, Hospital for Sick Children, Toronto, Ontario, Canada
Professor D.R. Laurence, Department of Clinical Pharmacology, University College, London, UK (Chairman)
Dr M. Molla, International Centre for Diarrhoeal Disease Research, Dhaka, Bangladesh

Professor R.B. Sack, The Johns Hopkins University, School of Hygiene and Public Health, Baltimore, MD, USA

Secretariat:

Dr D. Mahalanabis, Diarrhoeal Diseases Control Programme (Secretary)

Dr N.F. Pierce, Diarrhoeal Diseases Control Programme