



DIARRHOEAL DISEASES CONTROL PROGRAMME

*Diarrhea - P + C
Research*



BIOMEDICAL AND EPIDEMIOLOGICAL RESEARCH PRIORITIES
OF GLOBAL SCIENTIFIC WORKING GROUPS

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1. INTRODUCTION

The research component of the WHO Diarrhoeal Diseases Control (CDD) Programme has two main objectives:

- (a) to develop new or improved methods for prevention and treatment of diarrhoeal diseases caused by infection by supporting Biomedical and Epidemiological Research; and
- (b) to enhance the capabilities of developing country institutions to conduct research on diarrhoeal diseases through Institutional Development Activities.

The Programme has established three global Scientific Working Groups (SWGs) which consider biomedical and epidemiological research proposals: the SWG on Immunology, Microbiology and Vaccine Development (IMV), the SWG on Case Management (CMT) and the SWG on Epidemiology and Disease Prevention (EDP). Institution strengthening is usually done within the framework of a research project supported by one of the SWGs.

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1.1 Application for research support

Scientists seeking support for research on diarrhoeal diseases should first consult the list of research priorities of the Programme and then describe their proposed studies in a two or three page letter of intent. Letters of intent should be sent to the:

**Research Coordinator
Diarrhoeal Diseases Control Programme
World Health Organization
1211 Geneva 27
Switzerland**

The letter should briefly describe the objectives of the research, the methods to be used, events to be measured or observations to be made, and the method of data analysis. Letters will be reviewed and the writers informed whether or not the preparation of a formal research proposal is advised; specific recommendations regarding the preparation of the proposal may also be provided. Formal proposals should be prepared only on application forms provided by the Programme. Encouragement to submit a formal proposal is no guarantee that the project will be approved or given financial support. Collaborative research projects involving scientists from developing and developed countries are encouraged.

Background documents that may facilitate the preparation of suitable research proposals are available on request from the Programme. These include guidelines for conducting clinical trials in diarrhoeal diseases and reviews or guidelines that would be useful for designing projects on specific topics; in most instances, the availability of these documents has been noted in the relevant section of the list of research priorities.

Research proposals are reviewed, and recommendations made regarding support, by SWGs that meet twice a year. The dates of their meetings and deadlines for the submission of proposals are available from WHO Headquarters or Regional Offices.

1.2 Research priorities

As the research supported must be closely related to the CDD Programme's overall objective - that is, the control of diarrhoeal diseases, especially among young children, in developing countries - the SWGs have specified research topics that are of highest priority and will be given preference for funding. In most instances, these are topics directly related to the development, evaluation or implementation of new or improved methods for the prevention of diarrhoeal disease morbidity or mortality, such as vaccines or improved methods of treatment, research on how diarrhoeal diseases are spread and how their spread may be interrupted, or studies of other measures that may be taken to increase resistance to diarrhoeal illness.

The Programme also provides support to a limited number of projects addressing relevant questions at the basic science level. In such proposals, applicants should explain clearly the potential importance of their project in relation to the research objectives of the Programme.

The following is a list of the biomedical and epidemiological research topics that have been identified as priorities by the three SWGs. An asterisk indicates topics considered to be of **highest** priority for research support. This list reflects the viewpoints of the SWGs and is not meant to be exclusive or to preclude support for research on topics not listed. Support may also be awarded to research in other areas, especially when the applicant provides a clear rationale for its contribution to diarrhoeal disease control efforts.

2. IMMUNOLOGY, MICROBIOLOGY AND VACCINE DEVELOPMENT

2.1 Viral diarrhoea

2.1.1 Rotavirus diarrhoea

The major goal is the development of a rotavirus vaccine for worldwide use. The vaccine must be safe in infants, effective (even when infants are breast-feeding), inexpensive, prevent serious rotavirus diarrhoea caused by all human rotavirus serotypes, and be suitable for inclusion in the WHO Expanded Programme on Immunization (i.e., ideally it could be given with other EPI vaccines, especially oral poliomyelitis vaccine). The required research, in addition to the development and testing of candidate vaccines, includes studies of the immunology and epidemiology of rotavirus infections due to different serotypes, especially in newborns and infants, and the development of improved diagnostic tests of increased sensitivity.

2.1.1.1 Rotavirus vaccine

(a) Vaccine development

- * Various strategies should continue to be used in developing candidate attenuated live oral vaccines, including: attenuation of human and heterologous rotavirus strains and production of reassortant strains containing both human and animal rotavirus genes. To evoke protection against all important serotypes, it may be necessary to include more than one attenuated strain in the vaccine.

Research may also be supported on other approaches to vaccine development, including the use of recombinant DNA techniques to construct microbial strains that produce protective rotaviral antigens. Such strains may be evaluated as live oral vaccines. Similar methods may be used to produce purified antigens for parenteral immunization. Vaccines based on synthesized polypeptides of rotavirus antigens may also be considered.

(b) Vaccine testing

- * Candidate vaccines should be tested for safety and immunogenicity in volunteers, including infants and small children, and for safety, efficacy and duration of protection in field trials. Efficacy studies should be done in both developed and developing countries among populations in whom the epidemiology of rotavirus diarrhoea has been defined. Vaccine efficacy should be evaluated in infants under 6 months of age, including newborns, and protection against the different serotypes determined. The role of maternal antibody in protection against vaccine-induced side effects and its possible interference with vaccine efficacy should be studied in newborns and infants. The need for gastric acid buffering and the effect of recent feeding, including breast-feeding, on oral vaccine efficacy should be determined, as should possible interference between live rotavirus vaccine and live oral polio vaccine given concurrently. The extent of transmission of vaccine virus to close contacts should be determined for vaccines of proven safety and efficacy.

2.1.1.2 Determinants of susceptibility to and severity of rotavirus infection

Factors determining susceptibility to symptomatic rotavirus infection, and its severity, require further study. In particular, the immunizing effect of rotavirus infection should be studied, comparing the severity and duration of virus excretion for primary infections and reinfections with the same or with different serotypes in neonates and older children. Such studies should be carefully designed to control for the possible protective effect of maternal antibodies. Some of this information may be obtained during rotavirus vaccine trials. Detailed studies should also be done to characterize and compare rotavirus isolates from asymptomatic neonatal infections and symptomatic infections in older infants and children.

2.2 Bacterial diarrhoeas and typhoid fever

2.2.1 Vaccines

New or improved vaccines are required for four bacterial enteropathogens: Vibrio cholerae O1, enterotoxigenic Escherichia coli, Salmonella typhi and Shigella (especially Shigella dysenteriae type 1 and Shigella flexneri). Others will be considered if new evidence of their importance as a cause of diarrhoea is obtained.

2.2.1.1 Cholera

- * The major objective is to develop an effective oral cholera vaccine, using either avirulent live bacteria or non-living antigens, that is safe, produces lasting protection against both illness and, if possible, asymptomatic infection after 1 or 2 oral doses, and is inexpensive. Support will be directed mostly toward the sequential evaluation of candidate vaccines in animal models, volunteers and field trials. Some support may also be provided for the development of new candidate vaccines, especially for research to render live V. cholerae O1 totally avirulent by gene deletion methods, to improve the immunogenicity of non-living antigens of V. cholerae O1, possibly by oral adjuvants, and to identify important protective antigens of V. cholerae O1, other than lipopolysaccharide and cholera toxin; studies to develop genetic hybrid vaccines may also be supported, e.g., Salmonella that produce protective antigens of V. cholerae O1. Studies are required to identify the factor or mechanism responsible for diarrhoea caused by tox⁻ (A⁻B⁺ or A⁻B⁻) V. cholerae O1. If this is due to a "toxin" other than cholera toxin, strains from which the genes encoding the "toxin" have been deleted should be developed as candidate vaccines.

2.2.1.2 Enterotoxigenic E. coli (ETEC)

- * A vaccine for ETEC should protect against disease caused by strains of differing serotype, that produce different colonization factors, and elaborate either type of enterotoxin (ST, LT or both). As with cholera, immunization is likely to be oral and may involve avirulent live bacteria or non-living antigens. Support will be provided for the development of candidate vaccines and their evaluation in animal models and volunteers; vaccines that are proved to be safe and effective in these preliminary studies will need to be evaluated in controlled field trials.

The protective antigens of ETEC should be better defined and the requirement for shared antigens (e.g., LT, ST, adherence factor) in a vaccine should be evaluated. Live vaccines may need to contain several avirulent strains that produce important virulence antigens. Non-living antigens may require efficient oral adjuvants.

2.2.1.3 Typhoid fever

(a) Vaccine development

- * A vaccine for typhoid fever should be safe, nonreactogenic and inexpensive, and evoke lasting protection. Vaccine development may be guided by research on vaccines for similar Salmonella infections in animals. Candidate live oral vaccines should be studied first for safety, genetic stability and immunogenicity in volunteers. Strains that prove to be satisfactory may be evaluated for efficacy in field trials. These studies should also define the most effective mode of formulation and administration. Support may also be provided for the evaluation of parenteral vaccines for typhoid fever (other than the killed whole-cell vaccine), especially if they contain antigens (or antigen combinations) that cause few or no side effects.

(b) Assessment of immunity to typhoid fever

An important priority is the development of a convenient immunological test (or tests) that indicates whether vaccination has produced protective immunity. To develop such a test, support may be given to some preliminary studies of a more basic nature on the mechanisms of immunity to typhoid fever.

2.2.1.4 Shigellosis

(a) Vaccine development

- * The major objective is a vaccine that will protect against illness caused by Shigella dysenteriae type 1 and prevalent serotypes of Shigella flexneri. A safe and effective vaccine for these infections will probably be composed of live, avirulent bacteria given orally. These may be either Shigella strains with the genes for critical virulence factors deleted, or hybrid organisms expressing important protective antigens of Shigella, e.g., the lipopolysaccharide or outer membrane protein antigens required for mucosal penetration. Studies to develop candidate vaccines and test them for safety and immunogenicity in volunteers will be funded. Support will be given to field trials of vaccines that prove to be protective in animal models and are safe, immunogenic and protective in volunteers.

(b) Immunity to shigellosis

To aid vaccine development, some studies on basic mechanisms of immunity to shigellosis, and on the role of specific antigens in the stimulation of protective immunity may also receive support, as well as studies to develop a practical animal model (not requiring monkeys) in which to evaluate vaccines and characterize immune mechanisms.

2.2.2 Other research related to vaccine development

2.2.2.1^a Development of effective bacterial carriers for enteric hybrid vaccines

Effective bacterial carriers for hybrid enteric vaccines are required. These should be avirulent but probably need to colonize the human small bowel mucosa efficiently and be readily transported across Peyer's patch epithelium. Strains having these features are most likely to be effective in delivering critical antigens to responsive intestinal lymphoid tissue. Whether direct mucosal invasion is required for efficacy in the case of some vaccines, e.g., Shigella vaccines, is uncertain. Strains should be well suited for genetic manipulation and probably should not be ones to which humans are frequently exposed prior to the age when they are likely to receive them in oral vaccines. Animal studies may be useful but will require early confirmation in man.

2.2.2.2^a Development of adjuvants and delivery techniques for oral vaccines

Simple, safe, effective and inexpensive methods of enhancing the immunogenicity of specific oral vaccines are required. Research in this area should include delivery techniques that assure optimal survival (or recovery) of bacteria or viruses, e.g., when given in lyophilized form, and practical methods to protect vaccines during passage through the stomach. Delivery techniques should be developed that are suitable for all ages, including infants.

Research is also needed on methods to induce immunogenicity by non-immunogenic polypeptides and to enhance the immunogenicity of poorly immunogenic proteins and polysaccharides when given orally. Adjuvants should be sought that can enhance both mucosal humoral (sIgA) and cell-mediated immune responses to specific enteric vaccines. Studies will require an ability to accurately measure specific mucosal immune responses in humans and experimental animals. These studies should use antigens of relevance to priority vaccines (described above) and, ideally, demonstrate that the induced immune responses are protective.

^aWork described under items 2.2.2.1 and 2.2.2.2 may also receive support from the WHO Programme on Applied Vaccinology, especially when it does not involve vaccines (or antigens) designated as priorities for the CDD Programme.

2.2.2.3 Development of field trial sites

In some instances, support will be provided for the preparation of an area for use as a field trial site for the testing of specific candidate vaccines. Such studies will require adequate epidemiological, statistical and microbiological resources. They will usually be community-based and involve active surveillance methods, although in some instances hospital- or clinic-based surveillance would be appropriate. The objective would be to define the incidence of illness due to specific enteropathogens in the target age group, and the pattern of acquisition of immunity to disease, so that the vaccine trial can be planned, and to gain the required experience in surveillance techniques.

2.3 Studies to define the importance of specific enteropathogens

Support will be provided to epidemiological studies that seek to define the importance of certain enteric pathogens. These include (i) newly recognized pathogens whose importance as a cause of diarrhoea or dysentery in infants and young children is not well understood, and (ii) established pathogens, the importance of which may be better understood by the application of new descriptive or diagnostic methods. In both instances, studies should describe age distribution, seasonality, severity of illness and the occurrence of asymptomatic infections; other information, including the occurrence of coinfection with other pathogens, may also be required.

2.3.1 Recently recognized enteric pathogens

These are agents that have recently been recognized as enteric pathogens, for which satisfactory diagnostic methods exist, and whose relative contribution to acute diarrhoeal disease in young children may be appreciable but remains inadequately defined. Studies should be controlled and may be either community-based or focused on children attending a treatment facility. It is expected that, initially, only one or two studies on each new pathogen will receive support.

2.3.2 Established enteric pathogens

2.3.2.1 Enteropathogenic (EPEC) and enteroadherent (EAEC) E. coli

Support will be provided to studies that use new diagnostic methods to precisely define the importance of EPEC and EAEC as causes of acute diarrhoea in children under 2 years of age. These will require that E. coli from cases and controls be characterized with regard to O and H antigen type, production of verotoxins I and II, localized and diffuse adherence to HeLa cells, and production of enterocyte adherence factor (EAF). Additional tests may also be required and identification of coinfection with other enteropathogens will be necessary. Studies may be either community- or treatment centre-based. The clinical patterns of illness caused by these agents should be described and the proportion of cases that are prolonged (diarrhoea lasting more than 14 days) should be defined.

2.3.2.2 Enterohaemorrhagic E. coli (EHEC)

Studies similar to those described above should be carried out to define the importance of EHEC as a cause of acute diarrhoea and to describe the clinical syndromes and the frequency of complications (e.g., haemolytic uraemic syndrome) associated with this infection. EHEC should be characterized with regard to serotype and the production of verotoxins I and II.

2.3.2.3 Entamoeba histolytica

* The relation between zymodeme type and virulence of E. histolytica requires confirmation and further study. The goal should be to establish the risk of invasive disease associated with specific zymodeme types and the prevalence of virulent zymodemes in both healthy subjects and persons with invasive disease. These studies should also develop accurate population-based data on the incidence of invasive intestinal disease caused by E. histolytica, especially in areas of high disease prevalence.

2.4 Development of new or improved diagnostic tests

Diagnostic tests that are simple, sensitive, specific, rapid, relatively inexpensive and suitable for performance in developing country laboratories are required for use in epidemiological or community-based studies, and in some instances to guide the treatment of enteric infections. Such tests should not require expensive or delicate instruments, costly or labile reagents or radioisotopes. The ability to detect certain pathogens directly in faeces or environmental samples would be advantageous. Assays considered to be of highest priority for research support are:

2.4.1 Rapid diagnosis of typhoid fever

- * An assay is required that can reliably and rapidly diagnose most cases of typhoid fever without a requirement for blood or bone marrow culture. The technique would probably involve detection of an S. typhi antigen in blood, urine or faeces.

2.4.2 Rapid diagnosis of shigellosis

- * A simple, inexpensive and rapid test that can detect Shigella (especially Shigella dysenteriae type 1 and Shigella flexneri) in faeces is needed. The test should be suitable for use in peripheral health facilities. It would be used to guide the initial treatment of patients with diarrhoea or dysentery.

2.4.3 Entamoeba histolytica

A sensitive and specific assay for the detection of E. histolytica antigens in faeces (trophozoite and cyst antigens) or blood and other tissues (trophozoite antigens) is required. Of particular value would be an assay that could distinguish virulent from avirulent strains in persons with asymptomatic intestinal infection. Candidate assays should be validated by appropriate clinical and field tests.

2.4.4 Assays for rotavirus and rotavirus antibody

Assays for the routine detection of rotavirus in faeces during acute diarrhoea are adequate. Research is required, however, to develop assays with improved sensitivity for the detection of rotavirus in faeces when the viruses are present in very small numbers, such as occurs during asymptomatic infection or following oral immunization with live vaccine.

A simple, serotype-specific serological assay is needed for measuring the IgA or IgM antibody response in serum following rotavirus infection or oral immunization.

2.4.5 Cryptosporidium

A more reliable diagnostic test is required for use in field studies. This should be based on antigen detection and should be compared with established techniques requiring microscopic examination of stained materials.

2.4.6 V. cholerae O1 phage typing

Available phage-typing schemes should be evaluated and improved. The goal is a reproducible, internationally acceptable scheme with stable phages that can type most V. cholerae O1 and which does not assign a large proportion of strains to any single type.

3. CASE MANAGEMENT

Research on improved methods for the treatment of diarrhoea is divided into four major categories: (i) management of acute dehydrating diarrhoea, (ii) management of dysentery (especially shigellosis), (iii) management of persistent diarrhoea, and (iv) dietary management of diarrhoea. Much of the required research will be based in treatment facilities, but some will be community-based.

3.1 Acute dehydrating diarrhoea

3.1.1 Oral rehydration therapy (ORT)

3.1.1.1 Early home therapy

* Early treatment of diarrhoea by mothers at home using available fluids, special home-made solutions or ORS, combined with continued feeding, may prevent dehydration, improve nutritional status, and reduce the demand for facility-based health services. However, these effects have not been fully documented and the optimal approach(es) to early home therapy have not been defined. The questions to be answered include:

- (a) What home-made solutions are most effective, widely available and culturally acceptable for early home therapy?
- (b) To what extent does early ORT at home affect the incidence of clinically evident dehydration and the need and demand for treatment at health facilities?
- (c) What impact does early home therapy with continued feeding have on nutritional status?
- (d) Is Oral Rehydration Salts (ORS) solution appreciably more effective than other home fluids in preventing dehydration when used for early home therapy?

Two classes of solutions should be studied in addition to ORS solution: (i) fluids readily available in the home, such as rice gruel, vegetable soups, etc., and (ii) home-made solutions such as cereal-salt solution. The electrolyte concentrations, carbohydrate content and osmolality of these solutions should be measured and the amounts given determined; home fluids that are hyperosmolar due to an excessive content of salt or sugar should not be studied. Studies should be controlled, give appropriate consideration to the role of diet and breast-feeding in home treatment, and use objective outcome measurements wherever possible. A major goal should be the improvement of guidelines for early home therapy that can be broadly applied in a variety of cultural and regional settings.

3.1.1.2 Flavouring, colouring and packaging of ORS

The standard WHO/UNICEF ORS is unflavoured, uncoloured and packaged for the preparation of 1 litre of solution. In contrast, many marketed ORS products are flavoured and coloured, and some are packaged for smaller volumes. Whether, and to what extent, these features affect the acceptability of ORS and facilitate its effective use are not known. Controlled, community-based studies are needed to determine whether flavouring (or colouring) of ORS, or packaging for a smaller volume (e.g., 200 ml) have either beneficial or adverse effects on the acceptability and effective use of ORS.

3.1.1.3 Development of improved ORS solutions

The WHO/UNICEF ORS solution does not decrease stool volume. It is likely, however, that ORS solutions can be developed which have this effect. Such solutions might be more readily accepted by health workers and mothers because they could be seen to have an antidiarrhoeal effect. Two approaches to developing improved ORS solutions have been taken: (a) the use of defined, actively absorbed organic solutes other than, or in addition to, glucose and (b) the use of whole cereal powders, such as cooked rice powder. Both approaches require further study, seeking an ORS that will achieve a maximum reduction in stool volume during diarrhoea and can be conveniently packaged. The packaged ORS should be inexpensive and stable for at least two years under tropical conditions. Efficacy trials of experimental formulations will be required in adults, young children and infants with acute diarrhoea; controls would receive the standard ORS.

(a) ORS based on defined solutes

- * The possible benefit of replacing glucose with glucose polymers (maltodextrins), so that potentially available glucose can be increased with no untoward increase in osmolality, should be determined. If a benefit is demonstrated, further studies should determine whether the addition of certain amino acids (e.g., l-alanine, glutamine) or dipeptides to maltodextrin-ORS has an even greater beneficial effect. Tested solutions should be nearly isotonic with plasma and contain electrolytes in the same concentrations as in standard ORS. If effective in older children and adults, solutions containing maltodextrins should be studied in infants under 4 months and in malnourished infants and children to determine whether the polysaccharides are adequately digested and absorbed.

(b) Cereal-based ORS

- * Cereals and some other foods when digested yield glucose, amino acids and polypeptides, all of which may enhance the absorption of water and sodium. Clinical trials have shown that an ORS solution prepared from cooked rice powder can appreciably reduce the volume and duration of diarrhoea. Further studies on rice-based ORS solutions are needed to: (i) determine their efficacy in infants under 4 months (who may not digest rice starch efficiently), (ii) compare their efficacy with the most effective ORS composed of defined ingredients, and (iii) determine whether a packaged ORS product can be developed that is stable under tropical conditions and requires no cooking during preparation. Other cereals, such as millet, maize, sorghum and wheat should also be studied as substrates. Each solution should be studied for acceptability and efficacy in hospitalized patients.

Cereal-based solutions that are found to be superior to standard ORS solution should also be modified into cereal-salt solutions and evaluated for their safety and efficacy in early home treatment of diarrhoea (see 3.1.1.1).

(c) Studies in animals and volunteers

Absorption-promoting organic solutes and experimental ORS formulations should be studied in animal experiments which directly measure intestinal absorption of the solutes and associated absorption of water and electrolytes, e.g., by intestinal perfusion techniques. The goal of such studies should be to identify combinations of solutes with additive effects on the absorption of water and electrolytes and to determine the optimal concentrations for obtaining these effects. The results of these studies should guide the development of improved ORS formulations.

3.1.1.4 ORT in severely malnourished children

The efficacy of standard ORS and improved ORS solutions should be studied in severely malnourished children with acute diarrhoea. The risks of overhydration and electrolyte imbalance should be determined and the incidence of malabsorption of glucose and other organic solutes defined. Replacement requirements for potassium, magnesium and other ions should be determined. The objective of these studies is to develop guidelines for ORT in severely malnourished infants and children.

3.1.2 Antidiarrhoeal drugs

(a) Development and testing of anti-secretory and absorption-promoting drugs

The goal is to identify drugs that decrease the rate of diarrhoeal stool output by either of the above mechanisms and are both safe and inexpensive. Existing drugs may be studied when evidence suggests that they act by these mechanisms. Support will not usually be given to studies of new drugs until experimental evidence of antisecretory or absorption-promoting activity has been obtained. Priority will be given to studies of drugs with mechanisms of action that differ fundamentally from those of drugs already studied and found unacceptable. Before being studied in humans, new drugs should be proved safe and effective in animals. In clinical trials the major etiological agents of diarrhoea (e.g., rotavirus, V. cholerae, ETEC) should be determined.

(b) Traditional therapies

Traditional antidiarrhoeal agents that are extensively used and widely considered to be effective should be evaluated in carefully controlled, double-blind trials. In these trials, the agent should be used in the same form and manner as when used by traditional practitioners. If the agent is effective, efforts should be made to identify and purify the active ingredient.

3.2 Dysentery and shigellosis

There is a need to define simple, practical and effective approaches to the management of patients with acute (bacterial) dysentery, both at the community level and in treatment facilities. Two types of studies are needed: descriptive research (often community-based) and clinical trials of antibiotic therapy. Epidemiological research topics relating to dysentery and shigellosis are described in Sections 4.3.1 and 4.3.3.2.

3.2.1 Descriptive studies on acute bacterial dysentery

- * The greatest need is for information that can be directly used to develop guidelines for the early management of cases at the community level, where the diagnosis is made on clinical grounds and the etiological agent is not likely to be known. Specific questions to be answered are:
 - (a) What proportion of acute diarrhoeal episodes in children of various ages are, or become, dysenteric (i.e., develop visible blood, with or without mucus, in the stool, usually with fever and abdominal pain)?
 - (b) What are the etiological agents of acute dysentery in children of different age groups and how does etiology relate to severity of illness?
 - (c) What are the minimum clinical criteria that would allow dysentery to be diagnosed sufficiently early for treatment to be fully effective? Is examination for faecal leukocytes of practical value for early diagnosis?
 - (d) What are the maternal treatment-seeking patterns for children with dysentery? How do these differ from those for children with acute watery diarrhoea?

3.2.2 Treatment of shigellosis

- * An increasing proportion of *Shigella* strains are resistant to the most commonly used antibiotics; this is especially true for *S. dysenteriae* type 1. Clinical trials are needed to identify alternative antibiotics that are safe and effective for use in shigellosis. Such trials should be double-blind studies that compare the efficacy of a new antibiotic with a conventional one, such as ampicillin, naladixic acid or trimethoprim-sulfamethoxazole. Antibiotics that might be evaluated include: (1) pivamidinocillin (pivmecillinam), (2) fluoroquinolones, such as ciprofloxacin, (3) bicozamycin, (4) single, high-dose tetracycline and (5) oral gentamicin. One objective of such studies should be to define the minimum dose and duration of therapy required for full benefit. Such information should also be sought for conventional drugs when it is missing, e.g., for trimethoprim-sulfamethoxazole.

These studies should also be used to develop clinical criteria for assessing the adequacy of response to antibiotic therapy. These would be used by health workers to clinically diagnose treatment failures (due to antibiotic resistance) so that an alternative therapy can be initiated with a minimum of delay.

3.3 Persistent diarrhoea

A proportion of episodes of acute diarrhoea become persistent, i.e., last for more than 14 days. These result in progressive weight loss and malnutrition, and have a substantially increased risk of death. Major research priorities are to determine the incidence of, and risk factors for persistent diarrhoea, determine its causative mechanisms, and develop practical methods for its prevention and treatment. Clinical studies will be the d

responsibility of the SWG on Clinical Management, while epidemiological studies will be considered by the SWG on Epidemiology and Disease Prevention (see section 4.3.2). A review of this topic will be provided to interested researchers upon request.

3.3.1 Clinical studies

Descriptive studies should be done to define the pathophysiology and microbiology of persistent diarrhoea, especially in its early phase, i.e., 14-30 days after the onset of illness. These should include (a) identification and quantification of enteric viral, bacterial and parasitic pathogens in faeces and small bowel fluid, (b) studies of carbohydrate digestion and absorption, (c) nutrient balance studies using defined diets and (d) measurement of faecal protein loss. Where possible, comparable studies should be carried out in healthy controls and/or children with acute diarrhoea.

- * Intervention studies should be carried out in patients with persistent diarrhoea to evaluate the efficacy of specific treatments, including both drugs and selected antibiotics, that might interrupt important pathogenetic mechanisms. Other studies could include treatment with carefully defined dietary regimens. Such studies should be controlled and, if possible, double-blind; the objective should be to modify existing regimens so that they are more effective, more practical, or both. Outcome measurements should include stool losses, duration of diarrhoea and gain in weight and height.

3.4 Dietary management of diarrhoea

- * Research has shown that weight loss due to diarrhoea can be minimized by providing optimal nutritional support during and after the illness; locally available foods should be utilized that are culturally acceptable for feeding during diarrhoea, are readily available and inexpensive, and have adequate caloric, protein, vitamin (especially vitamin A) and mineral content. However, further studies are required: (a) to determine the beneficial effects of certain foods that are widely used in some regions on the clinical course and the nutritional response of children with acute diarrhoea (these include legume-based diets, fermented cereals, fermented milk products, extruded cereals and possibly others) and (b) to demonstrate that oil can be safely and effectively used to enrich low calorie diets traditionally given to children with diarrhoea, and thereby assure adequate caloric intake.

Clinical trials of selected diets should be carried out in hospitalized patients, outpatients and patients treated at home, and should include patients with both acute watery diarrhoea and dysentery. Feeding schedules should provide extra caloric intake during diarrhoea (if possible) and for 2-3 weeks of convalescence to maximize the recovery of lost weight or growth. Controls should receive an adequate, calorie-dense, lactose-free diet; however, in some instances comparison with a traditional diet would be appropriate. Outcome measurements should include dietary intake, duration of diarrhoea and gain in weight; hospital-based studies should also measure stool output and, if possible, the absorption of dietary components using metabolic balance techniques.

Anorexia is often an important obstacle for efforts to provide adequate nutritional intake during acute diarrhoea or dysentery. Research is required to define the pathophysiological determinants of anorexia in these conditions. Based on the findings of these studies, specific treatment designed to reduce anorexia and facilitate early feeding should be evaluated in controlled trials.

4. EPIDEMIOLOGY AND DISEASE PREVENTION

4.1 Introduction

The SWG on Epidemiology and Disease Prevention will support research on the efficacy, feasibility and cost of control interventions, other than case management or specific immunization, aimed at preventing diarrhoea or reducing its severity. Important research issues have emerged from a systematic analysis, still under way, of the cost-effectiveness of non-clinical interventions that have the potential to reduce diarrhoeal morbidity and

mortality (reports of the analyses of several of these interventions can be provided upon request). The interventions that are considered to deserve priority for research with regard to their role in diarrhoeal disease control and the optimal approach to their implementation are described below. Successful conduct of intervention-related research will require expertise in epidemiology and social sciences (especially social anthropology, communications and economics), and possibly other fields, such as nutrition and microbiology.

The SWG will also support descriptive epidemiological research, such as studies to clarify the frequency of, and risk factors for, severe or persistent diarrhoeal illness or severe dysentery, and to determine the transmission routes associated with certain enteric pathogens.

4.2 Intervention-related research

4.2.1 Effect of weaning education on diarrhoeal morbidity and mortality

Poor weaning practices can be identified in many communities in the developing world. They include (a) using contaminated foods, (b) using foods of low energy and nutrient content, (c) feeding at infrequent intervals, (d) introducing weaning foods too early or too late, (e) weaning abruptly, and (f) giving too small a share of the family food. It is known that inadequate dietary intake may lead to impaired nutritional status and thereby increase the severity and duration of diarrhoea attacks and the risk of death. On the other hand, the role of contaminated weaning foods in the transmission of diarrhoeal diseases is poorly understood and the effect of modifying weaning behaviour in order to increase food safety needs to be studied.

4.2.1.1 Risk factor studies

The aim of these studies is to identify the key foods and practices that are associated with high or low levels of faecal contamination. It is suggested that levels of faecal contamination be used here as the main outcome indicator (in preference to rates of diarrhoea) in view of their more proximate relationship to feeding behaviour. Social and cultural factors that affect choice of weaning foods and of preparation, storage and feeding methods should be documented and their effect on the level of contamination of weaning foods determined. Laboratory and field studies should be conducted to assess the effect of specific practices (e.g., use of fermented cereal-based foods, feeding with bowl and spoon) that may reduce bacterial growth in weaning foods and that could be implemented for this purpose. These studies will generate a large volume of samples for bacteriological analysis and will require the participation of an experienced, adequately staffed and well-equipped laboratory.

4.2.1.2 Intervention studies

- * The effect of promoting specific changes in weaning practices that are shown to reduce the level of contamination of food with faecal bacteria (such as offering young children only freshly cooked foods, or feeding with bowl and spoon) on feeding behaviour, diarrhoeal morbidity and growth should be determined. The feasibility, acceptability and cost of the intervention should be documented and methods of promotion should be developed that are effective and feasible for use in national health services.

4.2.2 Effect of personal and domestic hygiene on the transmission of diarrhoeal diseases

A number of control measures based on specific behavioural changes or on simple technologies that can be used in the home have the potential to interrupt the transmission of diarrhoeal diseases. For example, the promotion of hand-washing can reduce the incidence of diarrhoeal diseases in certain settings. More research is needed to define measures to promote personal and domestic hygiene that might usefully be implemented in diarrhoeal diseases control programmes.

4.2.2.1 Risk factor studies

Behavioural and microbiological research is needed to clarify the relationship between specific practices that may promote the transmission of enteric pathogens (such as inadequate hand-washing, careless disposal of young children's stools, or the improper use of containers for water storage in the home) and the risk of diarrhoea. Some studies are also required to determine the effect of different practices (e.g., use of soap or other cleaning aids for washing hands, methods of drying hands) or the use of simple technologies (e.g., for storing water in the home or for disposing of faecal material) on environmental contamination (of hands, foods, water, etc.). It will be necessary to conduct limited research to validate bacteriological methods for assessing the level of faecal contamination of hands, with the aim of using such methods in field studies to define adequate hand-washing practices.

4.2.2.2 Intervention studies

- * Studies should also be conducted in various cultural, socio-economic and environmental settings to measure the impact of carefully designed, culturally appropriate education or promotion programmes. These studies should document the impact on behaviour, as well as on diarrhoeal incidence and severity. In some projects, where the intervention is conducted on a wide scale, it would be sufficient to measure the impact on behaviour. All studies should document the feasibility, acceptability and cost of the intervention, and assess its dependence on pre-existing resources (e.g., abundant water supplies, availability of soap).

4.2.3 Impact of vitamin A supplementation on the incidence and severity of diarrhoea

- * Studies are needed to clarify the relationship between vitamin A status and diarrhoea in view of recent evidence that vitamin A deficiency may be associated with diarrhoeal morbidity and overall mortality among children in areas where vitamin A deficiency is a public health problem. Of highest priority are studies to measure the potential impact on diarrhoeal morbidity of vitamin A supplementation programmes, including the periodic distribution of large doses of vitamin A to children at community level and the selective administration of vitamin A to children attending a health facility for treatment of diarrhoea. Initial studies should be carried out in areas where the prevalence of xerophthalmia and the incidence of diarrhoea are high. Depending on the results of these studies, a trial might be required in an area where the prevalence of xerophthalmia is low but where there is documented evidence of inadequate dietary intake of vitamin A and low serum vitamin A levels. These studies should examine the influence of important confounding variables such as socio-economic conditions and nutritional status. A document describing these research priorities in greater detail is available on request.

4.2.4 Role of zoonotic reservoirs in the transmission of diarrhoeal diseases

The role of domestic animals kept inside and outside the home in the transmission of diarrhoeal diseases needs clarification. There is good evidence, for example, that the presence of domestic animals (especially chickens) in the home is associated with an increased risk of C. jejuni diarrhoea. It is not clear, however, what are the main transmission routes of C. jejuni to man and whether the disease is primarily a zoonosis. Similarly, the role of animal reservoirs of Cryptosporidium as sources of infection for man should be further investigated. The results of these studies should be used to develop and test interventions for preventing the spread of such diseases.

4.3 Descriptive epidemiological research

4.3.1 Risk factors for severe diarrhoeal illness and for diarrhoeal death

Most episodes of diarrhoea are mild and self-limited, even in the absence of specific therapy. However, a number of children with diarrhoea or dysentery develop signs of severe illness, including dehydration and toxic signs, which place them at risk of death. Little is known about the determinants of fatal episodes of diarrhoea. Research

is needed to determine the risk factors for increased severity of illness and death among children with diarrhoea or dysentery. Risk factors to be evaluated are child care practices, including feeding mode and home treatment practices for diarrhoea, low birth-weight and specific etiology. Because of ethical and practical concerns, these studies should use case-control methods. The Programme has developed guidelines on the design of case-control studies for assessing the risk factors of interest which can be provided to interested researchers on request.

4.3.2 Persistent diarrhoea (see also Section 3.3)

- * An initial priority is to define and quantify the problem of persistent diarrhoea and to identify children at high risk, emphasizing community-based prospective studies with active surveillance of diarrhoea and case-control comparisons of children presenting to hospitals or clinics. Risk factors to be evaluated include age, low birth-weight, nutritional status, feeding patterns before and during the acute illness, specific etiology (including enteroadherent *E. coli*), chemotherapy and previous or concurrent illness (e.g., measles). The impact of persistent diarrhoea on subsequent morbidity, growth and mortality should be defined. Eventually, specific interventions to prevent persistent diarrhoea will require testing.

4.3.3 Epidemiology and modes of transmission of important agents of diarrhoeal disease

Descriptive research into the epidemiology and modes of transmission of specific etiological agents of acute diarrhoea will receive support only when it concerns pathogens that make a significant contribution to morbidity and/or mortality and whose main epidemiological features remain unclear. Research to define the importance of recently identified causes of diarrhoea is considered in Section 2.3.

4.3.3.1 Vibrio cholerae O1

Research is needed to clarify the dominant modes of transmission of *V. cholerae* O1 in different settings. Study topics should include the possible role of environmental reservoirs of *V. cholerae* O1. Innovative approaches to interrupt the spread of the disease in endemic and epidemic situations should then be developed and tested.

4.3.3.2 Shigella dysenteriae type 1

Severe epidemics of shigellosis due to multiple drug-resistant organisms (especially *S. dysenteriae* type 1) continue to occur. Studies are needed to determine the dominant modes of transmission of the disease and to evaluate interventions aimed at preventing transmission.