UNITED NATIONS

DP

Governing Council of the United Nations Development Programme

Distr.
GENERAL

DP/PROJECTS/REC/21
5 November 1986

ORIGINAL: ENGLISH

Special session
February 1987, New York
Item 4 (a) of the provisonal agenda

COUNTRY AND INTERCOUNTRY PROGRAMMES AND PROJECTS

Assistance for a global project

Diarrhoeal Diseases Control Programme: Biomedical and Epidemiological Research Phase III (GLO/86/006)

Recommendation of the Administrator

Estimated UNDP contribution: $US 3,450,000 requested now 1/

Duration: Three years

Executing agency: World Health Organization (WHO)

I. BACKGROUND

1. National health administrations around the world have recognized that the diarrhoeal diseases are a public health problem demanding priority attention. In most developing countries, these diseases are among the leading causes of death and morbidity in children under five years of age. It is estimated globally that every year there are up to one billion episodes of acute diarrhoea in these children, resulting in four to five million deaths. These diseases are also one of the major contributors to malnutrition. Mortality and morbidity among adults is also high, exacting a tragic toll in human suffering, family disruption and economic productivity. The prevalence of acute diarrhoeal diseases also places a serious burden on health facilities in developing countries, often accounting for 30 per cent or more of admissions to children's hospitals as well as a high proportion of visits to out-patient facilities. This represents a serious financial burden on already strained Government health budgets.

2. Against this background WHO established a Global Diarrhoeal Diseases Control (CDD) Programme in 1978, in collaboration with the United Nations Development Programme (UNDP), the United Nations Children's Fund (UNICEF), the World Bank and bilateral organizations. The broad objective of the programme is to reduce mortality and morbidity caused by diarrhoeal diseases, while simultaneously strengthening the capacities of the countries themselves for controlling these diseases. The programme aims to improve the delivery of available strategies for treatment and prevention of diarrhoea through primary health care services and presently supports training, communications, and other activities in national CDD programmes now under way or planned in 102 developing countries, comprising 95 per cent of the global developing world population below the age of five years. In 1984, one third of these children had access to oral rehydration salts (ORS) for treatment of diarrhoea and 12 per cent of diarrhoea cases received oral rehydration therapy (ORT), which probably averted as many as 350,000 diarrhoea deaths. At the same time, through its research component, the programme is supporting the research required to develop more effective control tools. In fact, it was realized from the outset of the programme that such research must form an essential complement to field-oriented activities if any new solutions to this world-wide problem are to be found.

3. At the twenty-sixth session of the Governing Council, held in June 1979, the Council approved a UNDP contribution of $5,200,400 from the global indicative planning figure (IPF) in support of the research component of the programme. In 1982, the Council approved a second UNDP contribution of $4,260,000 from the global IPF. The specific objective of these contributions was to support immunological and other types of research needed for the development of new and improved vaccines and drugs for the treatment and prevention of diarrhoea. Under global projects GLO/78/005 and GLO/81/011 over the past six years, this assistance has made possible the establishment of a major research programme in this area. Following an extensive review of available knowledge, carried out through the convening of nine ad hoc groups involving the participation of 64 scientists from 27 countries, three global scientific working groups (SWGs) were established in 1980 to manage biomedical research in the following areas: bacterial enteric infections; viral diarrhoeas; and drug development and management of acute diarrhoeas. Each group developed a five-year research plan and set research priorities within the plan. Within the management framework provided by these SWGs, research proposals submitted by scientists around the world are assessed and selected for support. As a parallel activity, regional SWGs were established to manage health services research, closely linked to national CDD programmes. The programme has received financial support from 29 contributors, including many multilateral, bilateral and non-governmental agencies. During the 1984-1985 biennium, over $15.5 million was made available to the CDD programme, comprised of approximately $6.5 million from international organizations (UNDP, UNICEF and WHO); $6.5 million from donor and recipient Governments; and the remainder from foundations and other donors. By the end of 1985, a total of 246 biomedical research projects in 56 countries had received support under the global project. Half of these are in developing countries. Beginning in July 1986, the programme reorganized its management scheme to give greater emphasis to epidemiological intervention-oriented research, while at the same time continuing its support of research to develop new and improved vaccines and more effective modes of treatment. This reorganization also called for increased emphasis on strengthening developing country institutions. Highlights of the research currently under way are described below.

4. In the area of immunology, microbiology and vaccine development, 105 projects were active as at 31 December 1985. The main activities of this SWG are directed towards the development and testing of: (a) new vaccines for the prevention of those diarrhoeal diseases which are responsible for a major portion of serious diarrhoea episodes in the first years of life, or are of high epidemic potential; and (b) simple and inexpensive diagnostic methods required for epidemiological studies and research to identify new diarrhoea pathogens. High priority has been given to further development of the new, live, oral enteric-coated typhoid vaccine, which field trials in Chile have been shown to be 55-65 per cent effective after two to three years. A liquid formulation of this vaccine, similar to one which earlier gave 96 per cent efficacy in Egypt, is being evaluated in Chile and Indonesia. Also under development is a second live oral vaccine created by recombinant DNA techniques, a prototype of which has already proven to be effective in preventing salmonellosis in cattle. Another important breakthrough has been the development of an oral cholera vaccine which gave 85 per cent efficacy during the first six months of a field trial in Bangladesh. Studies to determine the duration of the efficacy of this vaccine are continuing and research is under way to simplify its delivery. To prevent dysentery caused by S. dysenteriae type 1 and other types of Shigella, hybrid vaccines are being developed. Field trials of a prototype hybrid will begin shortly. Trials are under way in five countries to evaluate the efficacy of attenuated rotavirus strains as vaccines in young infants. Some of these vaccines have already proven effective and there is good reason to hope that by the end of this decade a highly efficacious and practical vaccine may be available for incorporation into ongoing national expanded programmes of immunization. With regard to diagnostic tests, the programme has supported research which has led to the successful development of a simple test for the detection of heat-liable, toxin producing Escherichia coli (ETEC) and a simple serotyping scheme for Campylobacter jejuni, which are now used world-wide. It has also evaluated diagnostic tests for rotavirus to determine which are best suited for use in developing countries. Under way are studies to develop simplified tests for the detection of the heat-stable toxin of ETEC, the identification of enteropathogenic E. coli (ETEC), the phage-typing of Vibrio cholerae 01, the rapid diagnosis of typhoid fever and the diagnosis of amoebiasis and giardiasis.

5. In the area of case management, 49 projects were being supported by the programme as at 31 December 1985. These have been concerned with development of improved, cost-effective treatment of diarrhoeal disease. A particularly important breakthrough has been the successful development of a more stable ORS formulation containing trisodium citrate in place of sodium bicarbonate. Since such a formulation has a longer shelf life and requires less expensive packaging material, it is easier to produce in developing countries. This has been followed by clinical trials now under way in 15 countries, which should lead to new ORS formulations that can significantly decrease diarrhoea volume and duration, as well as replace the losses of fluid and electrolytes. Such solutions make use of actively absorbed organic solutes (e.g., cooked rice powder); the latter may also be useful as a basis for household ORT solutions. Studies of different home ORT solutions are evaluating their impact on the incidence of dehydration, nutritional status and demand of ORS from the health services; these will provide important information for the operation of national CDD programmes. Research conducted by the programme has shown that diarrhoea patients fed early during diarrhoea have a

much better nutritional outcome than those in whom feeding is initially restricted. Studies are under way to identify locally available foods that are well accepted and adequately absorbed by children with diarrhoea, and thus can lessen the burden of diarrhoeal disease on nutritional status; these should lead to the development of improved guidelines on dietary management of acute diarrhoea. The programme is also evaluating antisecretory agents, antimotility agents, herbs and other traditional medicines with the intent of identifying those that lack efficacy and should not be promoted. For those few diseases where antibiotics or antiparasitic drugs are warranted (e.g., cholera, shigellosis, amoebiasis, giardiasis), simpler dosage regimens are being evaluated in an effort to determine the safest and shortest course of therapy. To help accelerate the clinical research described above, the programme has strengthened three institutes in developing countries that are serving as clinical centres for the testing of suitable compounds and rehydration solutions, and has enlisted the co-operation of the pharmaceutical industry.

6. In the area of epidemiology and disease prevention, 15 projects were under way by the end of 1985. This recently formed SWG supports research to: (a) clarify risk factors and features of transmission of certain diarrhoeal diseases; (b) define the epidemiology of persistent diarrhoea, with the aim of identifying more effective control measures; and (c) examine the efficacy, cost, and optimal methods of delivery of interventions (other than vaccines and case management) that are thought to be either potentially cost-effective or of uncertain effectiveness for preventing diarrhoeal disease morbidity and mortality. Emphasis is placed on interventions suited for implementation through the primary health care approach that can either reduce transmission of the diarrhoea agents or strengthen the ability of the child to cope with the infection and thus reduce the risk of severe disease and death. The outcome of much of this research will enhance the abilities of mothers and other family members to prevent diarrhoeal illness in infants and young children. This area of research is relatively new for the programme. However, studies are already under way or planned to determine the protective effect of breast-feeding and the impact of weaning education on diarrhoea morbidity, the impact of water and sanitation projects and of good personal and domestic hygiene on the transmission of diarrhoeal diseases, the effect of vitamin A deficiency on diarrhoea morbidity and of vitamin A administration during diarrhoea on its reduction, and the effect of low birth weight and malnutrition on diarrhoea morbidity and mortality. To undertake these studies, the programme will strengthen the research capabilities of 6-8 institutions in developing countries that have the potential and interest for this type of research.

7. A number of other research activities have been undertaken, including the organization of scientific meetings to review recent advances and outline research priorities in areas of particular importance, the convening of workshops for principal investigators to design clinical trials and epidemiological research, and the holding of laboratory courses to provide training in up-to-date laboratory techniques for isolation and identification of diarrhoeal pathogens.

II. THE PROJECT

8. The activities and results achieved so far have built a world-wide research programme, which holds the promise of preventing many millions of deaths from diarrhoea in the years ahead. Fundamental research of the type under way is, by its nature, a long and costly effort. The chances for developing effective vaccines, simplified laboratory tests, improved rehydration solutions, more appropriate diets during diarrhoea, new pharmacological agents and more effective means for implementing interventions to prevent diarrhoeal diseases are very promising.

9. The major objectives of the project will be:

(a) To develop new and improved vaccines for the prevention of diarrhoeal diseases and establish guidelines for their use;

(b) To develop improved treatment of diarrhoeal diseases, including more effective ORT solutions, optimal delivery approaches for feeding during and after diarrhoea and new antidiarrhoeal drugs;

(c) To determine the cost and impact of different interventions to diminish diarrhoeal disease mortality, and especially morbidity (other than vaccines or treatment); and to better understand the epidemiology of persistent diarrhoea and of its prevention and treatment.

10. The activities carried out within the framework of this project will be in accordance with the strategic plans of the three global SWGs established within the research component of the CDD programme. About two thirds of the research supported by this project will be carried out in developing countries. Efforts will be intensified to increase the capabilities of developing country institutions to undertake the required research. These will include training fellowships, training workshops, provision of facilities and equipment and support to foster collaboration between developing country institutes and between these institutes and selected centres of expertise in developed countries. The programme will continue to collaborate closely with other WHO programmes. For example, the CDD Programme will: (a) build upon the research strengthening activities of the Special Programme for Research and Training in Tropical Diseases (TDR), of which UNDP is a co-sponsor, by supporting research in institutes supported by that programme; (b) collaborate with the Environmental Health Division in assessing the health impact of water and sanitation projects; (c) collaborate with the Vaccine Development Programme in examining the effects of different adjuvants in increasing the immunogenicity of candidate antigens and evaluating different carrier strains for use in genetically engineered hybrid vaccines; and (d) liaise with the WHO Biologicals Programme in development of cell lines for cultivation and propagation of rotavirus vaccines. The programme will also continue to co-ordinate its support to projects with that of other organizations and agencies supporting research in diarrhoeal diseases (e.g., the International Development Research Centre (IDRC), the Swedish Agency for Research Co-operation with Developing Countries, the United States Agency for International Development (USAID), the Carnegie Foundation, the Thrasher Foundation). Close collaboration will continue with the International

Centre for Diarrhoeal Diseases Research in Bangladesh (ICDDR,B). The scientific research training and extension activities of ICDDR,B are focusing on diarrhoeal diseases and their complex interrelationships with maternal and child health, nutrition, fertility and other aspects of family and community health. The programme will maintain its collaboration with the pharmaceutical industry in the development and testing of candidate vaccines and drugs, including new ORS solutions which will be able to be produced in developing countries. Because of the frequency of diarrhoea and its life-threatening consequences, it is likely that successful products developed by the programme will be widely used. Advances made by the programme in the development of vaccines and the understanding of the immune processes in the intestine will be useful in the development of vaccines against enteric infections in animals and other communicable diseases in humans. Through its mailing list of 6,000 persons and institutes, the programme will continue to provide widespread distribution of new information generated from projects funded by the programme.

11. Since its inception, the programme has had external mechanisms to ensure its monitoring and evaluation. These include a technical advisory group, which annually reviews the scientific and technical content of the programme, a management review committee, which annually reviews the management of the programme and a meeting of interested parties, which meets yearly to review the overall policies and direction of the programme and pledge financial support. UNDP, as co-sponsor of the programme, is a member of the latter two groups and as such has a major voice in the policies, direction and management of the programme. A special external evaluation of the programme, to be conducted in 1987/1988, will examine the overall progress of the programme since 1978 and make recommendations with regard to its future targets and activities.

12. Since 1979, UNDP has provided $7,120,000 for support of programme research in vaccine and drug development. This assistance has been invaluable and is in great part responsible for the success achieved to date in the research efforts of the programme. This project will continue UNDP support for research in vaccine and drug development and will extend this support to the planned epidemiological and intervention-oriented research and associated institutional-strengthening activities. Beyond this period, it is likely that additional UNDP assistance and voluntary contributions from bilateral and multilateral sources may be needed as the programme progresses.

13. The expenditure component of the proposed UNDP contribution is as follows:

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Sub-contract	3 450 000
Total	3 450 000

14. The expenditures under the project will be contained within the IPF available for global projects established by the Governing Council for the fourth cycle.

15. The Administrator recommends that the Governing Council approve this project.

Notes

1/ UNDP support to the programme will be considered for continuation following the results of an external evaluation to be held in 1987-1988. At that time, additional funds of $5 million will be requested for a further two years.
