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PROGRAMME PLANNING

COUNTRY, INTERCOUNTRY AND GLOBAL PROGRAMMES

Assistance for a global project

Strengthening of Primary Health Care: Development of New Tools for Disease Prevention and Control (GLO/90/007)

Recommendation of the Administrator

Estimated UNDP contribution: $6,000,000

Duration: Four years

Executing agency: World Health Organization (WHO)

I. BACKGROUND

1. One of the most cost-effective approaches to controlling major infectious diseases affecting children in the developing world is the extended use of appropriate vaccines. Thus, the establishment of national expanded programmes on immunization (EPI) plays an essential role in the fight against these diseases. National EPI programmes are today providing immunization against six major childhood diseases to more than 50 per cent of infants in developing countries. There is still much more to be accomplished, however. No vaccines exist at present to protect against acute respiratory viral infections, dengue and viral hepatitis, other than hepatitis B, and these are diseases which cause several hundred million cases annually. Currently available vaccines against poliomyelitis, tuberculosis and measles are not optimally adapted to conditions prevailing in developing countries. Vaccines requiring repeated injections, such as those against tetanus, diphtheria, pertussis and hepatitis B, make achievement of complete vaccine

coverage both difficult and expensive. There is also an urgent need to increase the heat stability of all vaccines for current or future use in EPI which at present require a cold-chain system. Solutions to these problems lie in continued research towards developing new vaccines and improving the efficacy of existing vaccines. The development of biotechnology has been until now centred on the interests of developed nations. The stage has now been reached where it is possible to envisage short-term and medium-term benefits from applying biotechnology to health problems of developing countries. It may be expected that within 10 years most current and future vaccines used in EPI will be based on biotechnology. Also by-products of the vaccine development efforts will allow the transfer of new diagnostic approaches to developing countries for diseases in which case-detection is essential for control (e.g., tuberculosis). The resulting improvement in the ease of vaccine delivery will have a very significant impact on reducing the cost of disease prevention and, in the long term, on the economic burden represented by those diseases. While such efforts are under way, more research is needed to improve strategies to reduce the estimated 3 million childhood deaths occurring each year due to the acute respiratory infections (ARI) that are not preventable by existing vaccines. Emphasis must be particularly directed towards developing and improving approaches utilized in the delivery of the ARI case management strategy. This strategy, if appropriately followed when assessing and treating acute respiratory infections, can result in reduced mortality and ensure more effective use of available resources, thus strengthening primary health care.

2. The efforts on the part of the World Health Organization (WHO) and collaborators to develop new vaccines, improve existing vaccines and refine the ARI case management strategy need to be closely co-ordinated. This programme, by identifying research priorities, stimulating initiatives and improving methodologies, will result in a strengthened global research effort. It will support two WHO programmes, namely, the Programme for Vaccine Development and Transdisease Vaccinology (PVD) and the Programme for the Control of Acute Respiratory Infections. The programme will also enhance the capabilities of supported institutions to undertake research. The importance of new and improved vaccines and disease control strategies was stressed during a recent meeting organized by the Task Force on Child Survival entitled "Protecting the World's Children: A Call for Action" (1-3 March 1990, Bangkok, Thailand). Among the participants in the meeting were the heads and other senior officials of the United Nations Development Programme (UNDP), WHO, the United Nations Children's Fund (UNICEF), the World Bank and the Rockefeller Foundation (members of the Task Force) as well as high-level officials from Governments and other agencies.

II. THE PROJECT

A. Programme for Vaccine Development and Transdisease Vaccinology

3. The major emphasis of the Programme for Vaccine Development and Transdisease Vaccinology (PVD) is on the prevention of major killing infectious diseases in developing countries through the development of new vaccines. More than 10 million children still die each year from infectious diseases in the developing world.

Some of these diseases are preventable by vaccination at an early age. This is the case for poliomyelitis, diphtheria, tetanus and measles. The impact of these vaccines largely depends on the extent of the vaccine coverage achieved in populations at risk. Considerable progress has been made in the last 10 years by national EPI programmes. However, there are three main vaccine-related factors which limit the present impact of immunization and for which targeted research has been initiated:

(a) A number of existing vaccines cannot offer optimal protection in the environmental and epidemiological conditions encountered in many developing countries (e.g., measles, poliomyelitis, meningitis, tuberculosis). Measles is still killing 1.5 million children per year, often before the age at which existing vaccines can be given and there is no possible chemotherapy.

(b) No vaccine yet exists to protect against some of the major infectious diseases which prevail in developing countries (e.g., acute respiratory viral infections, dengue, viral hepatitis non-A and non-B). Acute respiratory viruses account for 40 per cent of acute respiratory infections below one year of age and there is no available therapy.

(c) Many existing vaccines require repeated administration, often by injection. This is very costly owing to the need for trained personnel and the appropriate material. It is also a major cause of drop-outs from vaccination programmes. In many areas, between 30 and 50 per cent of children who receive a first dose of vaccine do not complete the course of immunization and are therefore not fully protected.

4. The Programme for Vaccine Development was established in 1984 with the aim of exploiting recent advances in biotechnology and immunology to generate new vaccines and to fill the gap in the prevention of those major infectious diseases for which there was an urgent need for appropriate or improved vaccines. The diseases selected as targets for PVD were chosen because of their importance as public health problems in developing countries and the lack of co-ordinated research efforts towards the development of corresponding vaccines. In 1988, a new component was added to this programme, i.e., transdisease vaccinology: laboratory research directed towards improving the immune response to vaccines, developing single-dose and oral vaccines and improving the heat stability of vaccines. Success in this effort will lead to improved and more effective population coverage by EPI programmes at a reduced cost. The consequent reduction in disease and premature death will ease the disease burden on health authorities in developing countries and eventually contribute to the development process in many countries. The Programme's general approach has been to support basic research, develop new vaccines and improve existing vaccines using the most recent developments in biotechnology and immunology. Specific approaches are adapted to each target disease. Usually, recombinant DNA technology, peptide synthesis and epitope analysis are applied to the isolation, characterization and production of antigens with potential protective value. In parallel, genetic engineering is applied to the generation of live vaccines. By-products of these research efforts are new immunological reagents or nucleic acid probes, which represent useful tools for the rapid diagnosis of these diseases.

5. The Programme is managed by the Division of Communicable Diseases in WHO. For each type of vaccine, research projects are co-ordinated and assessed by independent steering committees and the general orientation of the Programme is reviewed annually by the Scientific Advisory Group of Experts (SAGE). Representatives of UNDP and interested Governments are invited to attend the meetings of SAGE.

6. In July 1989, the research priorities and the achievements of the Programme were assessed by an external review committee. The committee acknowledged the remarkable achievements made during the first phase of the Programme and strongly recommended its continuation at a higher level of funding.

Specific activities and expected impact

7. Specific activities envisaged under the Programme for Vaccine Development and Transdisease Vaccinology, and their expected impact are outlined below.

(a) Selection of priorities. Priorities are selected on the basis of:

(i) Epidemiological studies indicating the major health importance of preventing certain diseases in developing countries;

(ii) The lack of interest on the part of industry in the development of vaccines against certain diseases;

(iii) The cost-benefit and the expected effectiveness of prevention through vaccination as compared to chemotherapy.

(b) Improvement of existing vaccines

(i) In poliomyelitis new vaccines should greatly facilitate the achievement of the goal to eradicate the disease on a world-wide basis by the year 2000. New polio vaccines that will be developed will be more resistant to heat, thus reducing the requirement and cost of cold-chains. They will be more immunogenic and will have a reduced tendency to revert to virulence, thus avoiding the replacement of naturally acquired polio by vaccine-induced polio.

(ii) In tuberculosis the availability of an improved BCG vaccine and of new disease-specific laboratory diagnostic tools will markedly contribute to the control of the infection, which is still killing 3 million persons annually. In addition, a newly engineered BCG would be able to carry additional gene coding for other vaccines and represent an effective multivalent vaccine produced at a low cost.

(iii) The availability of vaccines against bacterial meningitis which would be effective in children under the age of two years would allow for the prevention of epidemics of bacterial meningitis, together with endemic cases which are recurrent in many areas of the developing world. The technology developed for such vaccines would also be applicable to the

prevention of bacterial pneumonia due to Haemophilus influenzae or pneumococcal infections, which represent the major cause of child death in most of the developing world and are of particular concern to the Programme for the Control of Acute Respiratory Infections.

(iv) The development of a measles vaccine effective at one to four months of age would have a profound impact on child survival.

(c) New vaccines against "forgotten" viral diseases to be added to EPI. The Programme is equally involved in the development of new vaccines. Three groups of viral and bacterial diseases, described below, have been given priority in view of their global importance or of their high prevalence in a significant number of developing countries. The general approach used for the development of each vaccine has a number of common features: characterization of the viral genome, definition of molecules appearing as potential protective antigens, production of these antigens by recombinant-DNA technology and engineering of attenuated viruses as candidate vaccines. The development of vaccines against acute respiratory viral infections caused by respiratory syncytial viruses (RSV) or parainfluenza 3 viruses will considerably affect infant morbidity and mortality throughout the world. Vaccines against dengue will have a great protective value for approximately 60 million people each year and would prevent deaths from the dengue-associated hemorrhagic shock syndrome. The impact of development of vaccines against viral hepatitis will also be considered. The lethality associated with enterically-transmitted hepatitis (non-A, non-B) would be decreased by the availability of vaccines against those viral agents. At the time of writing, consideration is being given to the possibility of including diarrhoeal disease vaccine development in PVD.

(d) New vaccine delivery systems to reduce cost and improve coverage of EPI. Neonatal tetanus is still killing 780,000 neonates annually. This disease can be prevented by vaccination of pregnant women or of women of child-bearing age. However, the requirement for repeated injections with the existing tetanus vaccine is a factor particularly limiting the immunization coverage, and the development of a one-shot tetanus vaccine will significantly improve the control of this disease. The same technology will later be used for other vaccines included, or considered for inclusion, in EPI (DPT, poliomyelitis, hepatitis B). This will lessen the number of contacts needed for EPI coverage and therefore result in a decrease in the cost of immunization. On the basis of the data available in 1988, the savings achieved by decreasing the number of injections for one or more vaccines can be estimated to be from $20 million to $95 million annually, on a world-wide basis (developing countries). Finally, by promoting the development and improvement of oral vaccines, it will be possible to change the mode of delivery for current (and future) EPI vaccines from injection to oral administration. Oral vaccines provide a cheaper alternative to injections because there is less need for trained personnel to administer them; no need for a sterilized environment in administration of the vaccine and disposal of the administering equipment (a syringe in the case of injections); no longer a need for certain equipment (e.g., syringes); and fewer complications. Therefore, the extended use of oral vaccines would certainly further reduce the cost of national immunization programmes.

(e) Co-operation with other WHO programmes. The Programme for Vaccine Development and Transdisease Vaccinology (PVD) is closely collaborating with:

(i) Other disease control programmes interested in using the newly developed vaccines: Expanded Programme on Immunization (EPI), Control of Acute Respiratory Infections (ARI) and Diarrhoeal Diseases Control (CDD). Staffs of these programmes are always involved in the selection of priorities and optimal strategies. Similarly, members of PVD are invited to meetings of the EPI research and development group, of CDD and ARI. There is an intra-secretarial committee for the co-ordination of vaccine-related activities throughout WHO.

(ii) Other programmes which have a vaccine development component: the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases, and the Special Programme of Research, Development and Research Training in Human Reproduction. Members of PVD are participating in all meetings related to vaccine research in these programmes.

Results obtained in the first phase of the Programme

8. PVD has been particularly efficient in promoting collaborative research on an international basis, with results of considerable practical importance. Since 1988, the preparatory assistance of UNDP has been of great help to accelerate this progress, as evidenced by the following:

(a) New vaccines have been developed and are already at a trial stage: acute respiratory viruses (phase 1 in humans), and meningitis A-C (pre-clinical trials);

(b) The molecular basis for engineering a new heat-stable and safer polio vaccine has been established;

(c) The elucidation of the fine structure of dengue viruses has opened the way to the preparation of the needed multivalent vaccine;

(d) The preparation of a single-dose, controlled-release, tetanus vaccine is in progress.

B. Programme for the Control of Acute Respiratory Infections

9. The acute respiratory infections (ARI) rank among the most common diseases the world over. Everywhere they represent either the first or the second cause of visits to health services by young children. Their impact, however, is far more serious in developing than in developed countries. While the annual incidence of pneumonia, the most severe manifestation of acute respiratory infections, is 3-4 per cent in children under five years of age in developed countries, levels are as high as 80 per cent in developing countries, especially in rural areas where relevant risk factors such as malnutrition and low birth weight are highly prevalent. Furthermore, in developing countries, pneumonia is mostly caused by

bacteria and is associated with high case-fatality and mortality rates. Of the estimated 15 million deaths occurring each year in children under five years of age, 25-30 per cent are due to acute respiratory infections, and the vast majority of these are caused by bacterial pneumonia. Thus, in absolute numbers, pneumonia accounts for about 4 million childhood deaths annually.

10. The major emphasis of the WHO Programme for the Control of Acute Respiratory Infections is on the proper treatment of all ARI, which should result, above all, in the prevention of death from pneumonia. It should also lead to a more rational use of antibiotics and other remedies for treatment of ARI, since these comprise 30-50 per cent of all drugs used in the public and private sectors. A second emphasis is on the reduction of the incidence of ARI. Both can be achieved through the establishment of well-managed ARI control programmes. Because of their potential impact on mortality in children, programmes for the control of such infections must be an essential part of broad primary health care and child survival programmes. They need to be complemented also by an extensive research and development effort to develop new and improved tools and approaches, which should be closely linked to the goals of national ARI control programmes.

11. The Programme's research priorities were discussed and redefined by the 4th meeting of the Programme's Technical Advisory Group (TAG) in March 1989. The immediate goal of the research component is the development and evaluation of new or improved intervention measures appropriate in reducing morbidity and mortality due to acute lower respiratory infections (especially pneumonia), since these are, in contrast with the upper respiratory infections, the main causes of severe morbidity and mortality. TAG requested that the Programme consider a limited number of focused priorities and address, as a first priority, the important questions that remain with regard to delivery of the ARI case management strategy.

12. The initial contribution by UNDP (1988-1990) to the Programme for the Control of Acute Respiratory Infections played a major part in the development of its research component. It enabled the Programme to convene meetings of experts in various disciplines to establish broad priorities for support of research, to identify institutes in the developing world interested in undertaking this research, to establish a peer review mechanism for reviewing research proposals, and to initiate support for field projects.

Main areas of research

13. The following is a summary of the priority research planned to be supported through the Programme in four main areas: clinical, behavioural, health systems and disease prevention research:

(a) Clinical research will be concerned with the evaluation and development of improved technical guidelines for the clinical management of ARI cases, particularly pneumonia. Studies are under way to determine the most accurate means of counting the respiratory rate in young children; these are critical since rapid breathing is the most important sign of pneumonia and is the basis for the WHO case management protocol. In infants aged less than two months, where ARI mortality rates are highest, studies will be undertaken to determine a simple set of clinical

signs with a high sensitivity, specificity and predictive value for pneumonia or other serious bacterial infection. Aetiological data will also be obtained to determine optimal therapeutic regimens and to direct future vaccine-related research. A multi-centre study to answer these questions will be carried out in 1990-1991 using a common protocol in institutes in the Gambia, Ethiopia, Haiti, the Philippines and Papua New Guinea. Studies will also be initiated to determine: clinical signs of severe pneumonia or other related severe disease which would benefit from hospitalization; clinical signs and aetiologic agents of pneumonia in severely malnourished children; methods of oxygen delivery suitable for district-level hospitals; and treatment of wheezing at first-level facilities. It is of primary interest to conduct evaluations of simplified and shortened antibiotics regimens, to establish the relative efficacy of alternative antibiotics, to determine the efficacy of recommended antibiotics regimens in high risk groups such as very young infants and severely malnourished children, and to study methods to improve mothers' compliance with oral antibiotics administered at home. The outcome of these studies will be simplified and effective guidelines drawn up for treatment of all ARI cases, applicable by staff working in first-level health facilities and district hospitals, as well as by community health workers.

(b) Of critical importance to the case management strategy is the early case detection and prompt treatment of pneumonia cases. Behavioural research is needed to obtain information on mothers' ability to recognize signs of pneumonia, the sequence and timing of their care-seeking and their compliance with treatment advice. It is also required to identify the signs that mothers recognize as severe and to determine their relationship to clinical pneumonia. This information will assist control programmes in designing messages to mothers about effective home care advice; in identifying maternal expectations concerning antibiotic and other drug therapy; in anticipating problems with antibiotic treatment compliance; and in assisting national ARI programme staff and health workers in understanding relevant cultural characteristics and conditions that are likely strongly to influence community responses to programme activities. In order to obtain this information the Programme is developing a rapid ethnographic assessment protocol. This will be field tested in at least five countries during 1990-1991 and then made available to all ARI programmes. In addition, ethnographic studies will be undertaken to identify significant and modifiable behavioural risk factors that influence the incidence, severity and outcome of pneumonia. Such research may provide important information on how pneumonia can be prevented.

(c) Health systems research includes continued development of three types of appropriate technologies important for national ARI programmes, namely, sounding timers, portable oxygen concentrators, and footpump rebulizers. The availability of a reliable, robust and accurate sounding timer will allow health workers to count a child's respiratory rate accurately without diverting attention from close inspection of the child's breathing. The development of a suitable portable oxygen concentrator will save the lives of many children with severe pneumonia who require oxygen in addition to antibiotic therapy. Footpump rebulizers are needed to treat wheezing children more effectively in an outpatient setting with bronchodilators. Within four years all these technologies should be sufficiently developed to be made widely available to national ARI programmes. Health systems research will also include studies that address the feasibility, efficiency and effectiveness of

national ARI programmes. Correct performance will be assessed by systematic use of evaluation instruments being developed for national programmes (e.g., health facility survey, household morbidity and treatment survey) and by special studies and surveillance methods. In order to develop reliable survey instruments, research will be undertaken to validate interview techniques for detecting pneumonia episodes and deaths. These studies will also address the use of antibiotics when given to community health workers specifically for treatment of pneumonia. These will be complemented by studies to determine the simplest method for monitoring antibiotic resistance of H. influenzae and the pneumococcus in the population, since the potential emergence of such resistance is one of the major concerns in allowing these antibiotics to be distributed by community health workers.

(d) It is recognized that certain risk factors of a biological (e.g., low birth weight and malnutrition), environmental (e.g., indoor air pollution) or behavioural nature may determine the incidence and severity of pneumonia. Disease prevention research will assess potentially important risk factors for pneumonia in young children and relate their presence to precisely defined outcome measurements which are congruent with those used in other clinical studies. In addition, beginning in 1990, the Programme will undertake a review of the feasibility and cost-effectiveness of several potential preventive interventions. This will help to identify other areas of research which are likely to lead to the development of feasible programme strategies for the prevention of pneumonia. Disease prevention research will also include support for field trials of available vaccines being developed by PVD against the main cause of lower respiratory tract infections. At present, vaccines against H. influenzae type B and the pneumococcus are the most likely to be available for field testing. Protein-polysaccharide conjugate vaccines against H. influenzae type B have recently become available and shown to be immunogenic in infants in both developed and developing countries. The Programme is now participating in preparation of a formal proposal to initiate surveillance for this disease in the western region of the Gambia in 1990, and plans to support a vaccine trial there using the most suitable candidate vaccine in 1991 or 1992. Developments in the production of pneumococcal conjugate vaccines will be closely followed, with the intention of having a candidate for testing in 1992 or 1993, possibly also in the Gambia.

Training and institution strengthening

14. The strengthening of research capability in vaccinology and immunology of infectious diseases in the Programme for Vaccine Development and Transdisease Vaccinology is based on a training programme comprising:

(a) Two annual 5-8 week courses (one in French, one in English) for 45-50 participants from developing countries, organized in the Geneva/Lausanne WHO Research and Training Centre;

(b) "Refresher" courses at regional level (e.g., 1989 India, 1990 Costa Rica, 1991 Brazil, Gabon);

(c) Follow-up visits by consultants and staff to previous participants in the training programme;

(d) Transfer of technology to developing country laboratories associated with the Programme in Africa, Latin America and Asia (fellowships, site visits); this transfer of technology aims to:

(i) Favour the direct involvement of scientists from developing countries in vaccine development;

(ii) Establish the basis for field evaluations of immunogenicity and protective efficacy of new vaccines;

(iii) Prepare the transfer of vaccine production to developing countries;

(e) The training programme will also strengthen institutions in developing countries through increasing the number of scientists capable of conducting the epidemiological research essential for effective vaccine trials.

15. The Programme for the Control of Acute Respiratory Infections will develop research-capability strengthening activities closely tied in with the above-mentioned training programmes.

Funding

16. In view of the high mortality and morbidity caused by the selected diseases, UNDP and WHO are seeking additional support from other donors in order to speed up the research efforts for the sake of preventing and controlling diseases, saving more lives and lessening sickness as soon as possible. To date, support for vaccine development/transdisease vaccinology has been provided by the following countries and organizations in addition to WHO and UNDP: Australia, Italy and Norway, as well as the Japan Shipbuilding Industry Foundation, the Pew Charitable Trusts, the Rockefeller Foundation and the Swedish Agency for Research Co-operation with Developing Countries (SAREC). Funding for control of acute respiratory diseases has been provided by the following countries and organizations in addition to WHO and UNDP: Australia, the Federal Republic of Germany, Finland, Italy, Japan, the Netherlands, Sweden, the United Kingdom of Great Britain and Northern Ireland and the United States of America, as well as the Arab Gulf Programme for United Nations Development Organizations (AGFUND), the Kellogg Foundation, the Sasakawa Health Trust Fund and the United Nations Children's Fund (UNICEF). Despite this widespread interest from donors, the level of funding is not yet commensurate with the potential impact of these disease prevention and control measures.

Summary

17. The aim of these initiatives is to reduce the very high morbidity and mortality due to infectious diseases, particularly respiratory infections occurring in a considerable number of children in developing countries. Three levels of activities are involved: first, research to develop new and improved vaccines with particular emphasis on those diseases which cannot be treated with antibiotics or antivirals. It will also comprise the development of vaccines easier to deliver than those used at present in EPI; secondly, research on case management of acute

respiratory infections centred on optimal strategies to control those infections and to develop new methodologies in a strengthened global effort; and thirdly, strengthening of research capability in developing countries.

18. Active support will be sought from other bilateral and multilateral agencies, from foundations and from the private sector.

19. The proposed UNDP contribution is $6,000,000 for four years.

III. RECOMMENDATION OF THE ADMINISTRATOR

20. The Administrator recommends that the Governing Council approve the project entitled Strengthening of Primary Health Care: Development of New Tools for Disease Prevention and Control (GLO/90/007).
