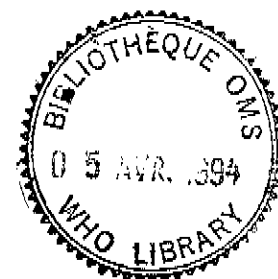


**RESEARCH AND DEVELOPMENT
WITHIN THE EXPANDED
PROGRAMME ON IMMUNIZATION:
THE FIRST FIVE YEARS (1987-1991)**

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1. INTRODUCTION

Research and development have been a part of the Expanded Programme on Immunization (EPI) of the World Health Organization (WHO) since its beginning in 1974. Early on, research efforts focused on supporting the implementation of routine immunization services in developing countries (1). "Research" was a routine part of programme operations, and contributed to the development of methods for monitoring and evaluation. "Research" also led to development of standard EPI quality-controlled equipment for injection, sterilization, and installation and maintenance of the cold chain. With the growth of the EPI, the need for rigorous scientific approaches to problems arising from the field became apparent. In addition, progress toward new vaccines that might ultimately be incorporated in the EPI called for close liaison with programmes working in basic vaccinology. To address these needs, a research and development activity was established in the EPI in 1987, with funds provided by the United Nations Development Programme (UNDP) and the Rockefeller Foundation. A Research and Development Advisory Group was constituted and its first meeting was held in September 1987. In the next few years research and development activities were integrated into the general programme.

Many of the EPI staff have contributed to research projects, although their main efforts continue to be targeted at implementation. In addition, research on applied vaccinology has intensified EPI contacts with other programmes and divisions within WHO.

While a number of specific applied vaccinology objectives can be cited, the over-riding goal of EPI research and development activities has been to improve management of national immunization programmes. In recent years EPI programme performance has improved remarkably. Based on data reported to WHO by September 1993, in 1992 global coverage of children 12 months of age reached 85% for BCG vaccine (against tuberculosis), 79% for a third dose of diphtheria-pertussis-tetanus vaccine; 80% for a third dose of polio vaccine, and 78% for measles vaccine. In contrast, only 43% of pregnant women had received a protective course of tetanus toxoid to prevent neonatal tetanus in their infants.

The vast majority of EPI activities, including its research efforts, are based on collaboration with countries, with other United Nations agencies (including UNICEF, UNDP, and the World Bank), and with bilateral development agencies and nongovernmental agencies (including the Rockefeller Foundation, Rotary International, and Save the Children Fund of the Netherlands, the United Kingdom, and the United States). It is already clear that EPI research activities are attracting additional

resources, most often consisting of donations to countries on a bilateral basis, and in some instances donations directly to WHO/EPI, Geneva. It is anticipated that other donors will become interested in funding EPI research as current projects mature and speak for themselves. This document provides a review of EPI research activities from 1987 through 1991.

2. ESTABLISHMENT OF A RESEARCH AND DEVELOPMENT ACTIVITY WITHIN THE EPI

2.1 Secretariat

In 1987, a research and development activity was established as an integral part of EPI, under the supervision of the Director, EPI in WHO/Geneva. A medical officer serves as the research focal point. Administrative support is provided by general EPI administrative staff. Secretarial support includes one full-time secretary and one half-time secretary. Many of the EPI professional staff contribute to applied vaccinology research on a part-time basis, although their main efforts continue to be targeted at programme implementation. In addition, a number of professionals in other WHO programmes (especially the Division of Communicable Diseases, the Biologicals Unit, the Nutrition Unit, and the Maternal and Child Health and Family Planning Unit) generously provide support on an occasional basis.

Establishing an activity on applied vaccinology within a programme operating in almost every country in the world has offered many advantages. Research activities carried out at the national level have been carefully coordinated with the appropriate WHO Regional Office. EPI staff working at the Regional level have provided consistent support to research activities initiated from EPI/Geneva, as well as to research activities initiated within the Regions. EPI Regional Advisers have been invited to attend one of the EPI Research and Development Group meetings each year. They are requested to propose research issues of particular interest to country programmes in their Regions.

2.2 Advisory group

The Director, EPI is advised by a Research and Development Group, which was constituted in 1987. The Research and Development Group consists of between 5 and 10 members who are not staff members of WHO and who have been selected on the basis of their knowledge of the technical and operational aspects of the EPI (Figure 1). The Chairperson of the Group is appointed for a six-year term by the Director General of WHO. The Chairperson also serves as a liaison member to the EPI Global Advisory Group. To facilitate coordination with the WHO/UNDP Programme for Vaccine Development, the Chairperson of the Scientific Advisory Group of Experts (SAGE) serves as a liaison member to the EPI Research and Development Group.

Figure 1. Members of the EPI Research and Development Group, 1987-1991

<i>Dr W. Foege, Chairman*</i>	<i>Task Force for Child Survival and Development, Atlanta, GA, USA</i>
Dr G. Ada, SAGE Liaison	John Curtin School of Medical Research, Canberra, Australia
Dr I. Arita	Kumamoto National Hospital, Kumamoto City, Japan
Dr F. Deinhardt, SAGE Liaison	Max von Pettenkofer Institute, Munich, Germany
Professor J. Kostrzewski*	National Institute of Hygiene, Warsaw, Poland
Dr J. Kumate	Ministry of Health, Mexico City, Mexico
Professor F.K. Nkrumah	Noguchi Memorial Institute for Medical Research, Legon, Ghana
Dr N. Halsey*	Johns Hopkins School of Public Health, Baltimore, MD, USA
Professor G. Soberon-Acevedo	Ministry of Health, Mexico City, Mexico
Professor J. John	Christian Medical College, Vellore, India
Professor A. Sow	Faculty of Clinical Medicine, Dakar, Senegal

* Member for entire period, 1987-1991.

The Research and Development Group is charged with:

- advising the Director, EPI on research and development priorities in the general field of disease prevention and control through immunization and through interventions which can be appropriately delivered using vaccine delivery systems (such as supplementation with vitamin A or iodine) with primary emphasis on diseases and vaccines currently included within the global programme,
- advising the Director, EPI on the relative priorities of specific research and development proposals submitted for funding from global EPI resources,
- monitoring the progress of research and development activities which have been selected for funding and recommending their continuation, revision, or termination, and
- assisting in the generation of research and development proposals relevant to programme priorities.

2.3 Research priorities

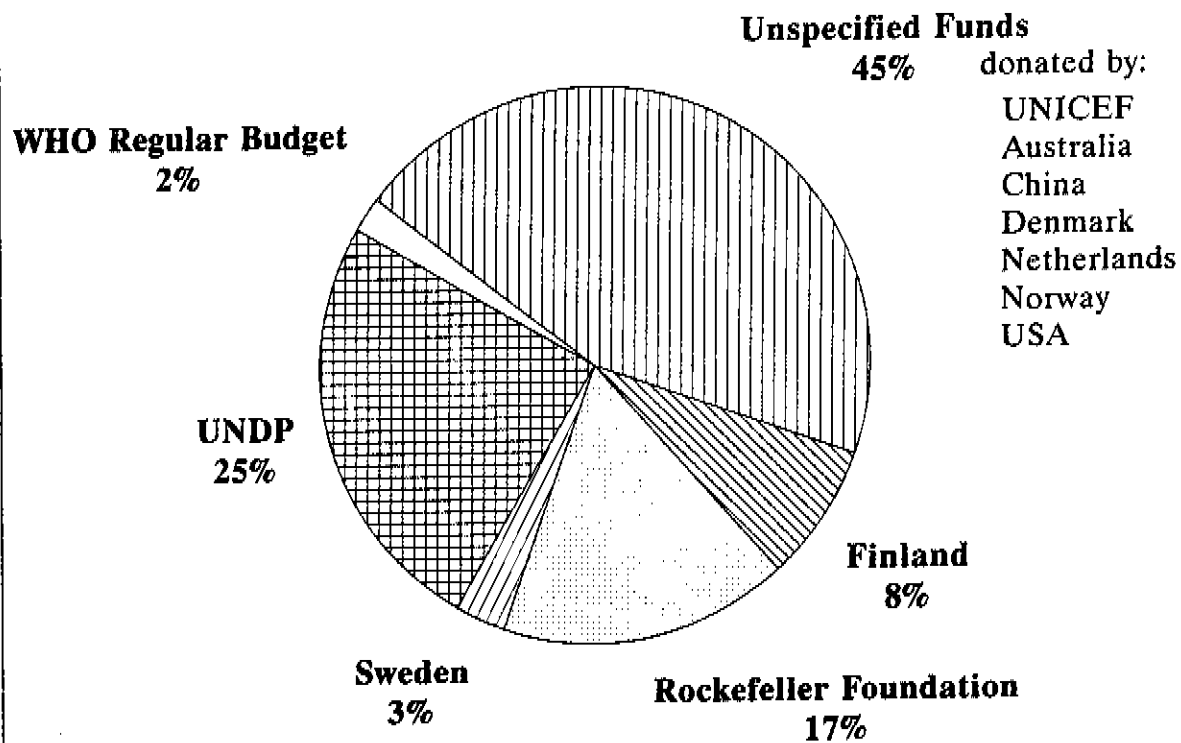
An initial set of research priorities was formulated in 1987. These have been further expanded and revised periodically by the Secretariat in collaboration with the Research and Development Group. In general, the Research and Development Group has preferred not to specifically rank these priorities, so that work on one would not preclude doing work on another, particularly where a major role of WHO was seen to be catalyzing or promoting the work of others. The list of priorities has been widely disseminated outside the WHO to research institutions, funding agencies, and investigators.

In April 1991, the list included 126 different items (2). Persons attending the April 1991 meeting of the Research and Development Group went through a priority setting exercise. Participants were categorized as members of the EPI Research and Development Group, WHO Regional Advisers, WHO Secretariat (Geneva-based), and observers. Results revealed a high degree of consensus among categories concerning the research priorities being promoted by EPI. The highest priority topics were: studies of slow-release tetanus toxoid, follow-up of children immunized with measles vaccine at ages younger than 9 months, strengthening routine surveillance, improving the heat stability of oral polio vaccine, development of diagnostic tests for poliomyelitis, and development and use of surveillance indicators.

2.4 Funding

Although EPI research and development activities receive some financial support from the Regular Budget of WHO (largely in the form of time committed by staff funded from the Regular Budget), most of their support is from extrabudgetary resources (Figure 2). These are available either in the form of unspecified donations to the EPI account of the WHO Voluntary Fund for Health Promotion, which at the discretion of the Director, EPI may be used for research purposes, or in the form of donations to the Fund which are specified for EPI research. Support for EPI research activities has been actively sought. Through 1991, major donors of funds specified for research have been the UNDP, the Rockefeller Foundation, and the Governments of Finland and Sweden. Unspecified funds contributed by UNICEF and the Governments of Australia, China, Denmark, Netherlands, Norway, and the USA were also used in part for research activities.

Figure 2. Funding sources for EPI research and development activities, 1987-1991.



Research expenditures were in the range of US\$ 1 million per year. From the outset, it was recognized that this amount was small in relation to overall programme needs, and that it would be important for WHO to play an active role in facilitating and guiding the research efforts of others. Close working relationships exist with the Canadian Public Health Association, the United States Centers for Disease Control and Prevention and Prevention, the International Children's Center (Paris), the Japan International Cooperation Agency, the London School of Hygiene and Tropical Medicine, the Task Force for Child Survival and Development, UNICEF, the United States Agency for International Development, and many other agencies with strong interests in EPI-related research. Some of these groups have jointly funded projects with EPI. Most have pursued research in EPI priority areas without direct financial support from EPI.

To further promote EPI research priorities, a series of EPI generic protocols was developed. Generic protocols are distributed free of charge to national programme managers through WHO Regional Offices, potential investigators, and collaborating donor agencies. No funding is provided from EPI, but feedback on the methodology and assistance in preparation of publications are offered. The generic protocols have attracted a wide variety of bilateral donors and in some cases investigators have received partial funding from national governments and/or WHO Regional Offices.

The possibility of EPI collaborating with other research-oriented programmes within WHO to support vaccine research centers in developing countries was raised in the 1989 UNDP Project Proposal. While no direct investment in vaccine centers has occurred, EPI was able to initiate studies at research centers developed by others and to share its experience, in turn, with groups seeking to initiate studies. An informal meeting of WHO programmes involved in clinical trials was held in 1991. Since 1987 EPI has provided financial or technical assistance to vaccine trials conducted in Brazil, Gambia, Ghana, Kenya, Ivory Coast, Oman, Rwanda, Senegal, Sudan, Thailand, and the former USSR.

2.5 Mechanisms for generating, reviewing, and supporting research proposals

Formal mechanisms for reviewing applications for research proposals and disbursing research grants within the EPI were developed during 1988 and approved by the Research and Development Group in March 1989. Advice was sought from the directors and administrators of other WHO programmes with long-standing research experience. The system adopted by EPI is not exactly like any other at WHO, but was felt to be appropriate for the types of protocols that would be reviewed.

2.5.1 Generation of research proposals

It was recognized that some of the topics which EPI would seek to study -- preventive health interventions, improved management methods, disease epidemiology and human behavior -- were somewhat different from more basic research of interest to most other WHO programmes. The need for close collaboration with developing country investigators was also recognized as an important aspect of the EPI research process. Therefore four separate mechanisms for generating research proposals have been employed: a network of investigators working collaboratively, development and promotion of generic protocols for adaptation at the local level, commissioned research with assistance in proposal development, and competitive bidding for research funds (Figure 3).

A unique means for promoting operational research has been TECHNET, a worldwide network of about 50 individuals who work on logistics for health and the cold chain. Through extensive communication (by computer bulletin board, facsimile, mail, and meetings) these individuals determine issues to be studied, jointly develop standardized protocols for studies, and then carry them out in several countries simultaneously. Studies reported at the TECHNET meeting in November 1991 included cold chain quality surveys, equipment inventory surveys, and temperature monitor surveys using EPI software. Since then, the TECHNET group has worked on software products for logistics management, guidelines for managers on how to choose the appropriate vaccine vial size, field studies

on whether tetanus toxoid can be used outside the cold chain, and assessing the field performance of low workload jet injectors.

Figure 3. Different methods for generating EPI research proposals

TECHNET	A worldwide interactive network committed to development and testing of cold chain and logistics methods and equipment.
Generic Protocols	Prepared by EPI to provide methods for assessment of management and epidemiological questions. Distributed free-of-charge.
Commissioned Research	For clinical trials of vaccines or other interventions, such as micronutrient supplementation.
Competitive Bidding	To attract protocols addressing basic science questions.

A second method for promoting operational research has been the development and distribution of generic research protocols for specific topics. Generic research protocols have been developed to study missed immunization opportunities, nosocomial measles transmission, measles case fatality rates, efficacy of tetanus toxoid vaccine, rapid assessment of hepatitis B carrier rates, and rapid assessment of serological response to oral polio vaccine. This method has worked very well for operational research projects, but could not be expected to be very efficient for large-scale clinical trials which require intensive coordination of all aspects.

For vaccine trials, most studies have been commissioned in developing countries. EPI has generally assisted promising developing country institutions prepare research proposals which meet the specifications suggested by the Research and Development Group. Investigators are encouraged to suggest improvements to the study design, but a criterion for approval has been the adherence of the proposal to the originally formulated series of questions. Several major clinical trials have involved collaboration between investigators in developing countries and developed countries, and this has led to progressive improvements in the quality and sophistication of the projects undertaken. For most commissioned projects, EPI staff or consultants complete site visits before the project is approved and at least annually thereafter. The ability to establish frequent and clear communication with the study site is a priority; however, experience has shown that communications with developing country study sites is sometimes difficult. Reasons have included poor quality facsimile machines, power failures, poor telephone connections to some countries, prolonged holiday seasons, strikes, and

the Gulf War (which led to extraordinary delays in international shipments).

Competitive bidding for research projects following extensive advertisement in the scientific literature (a more traditional method attracting research proposals) has occurred in some instances. This has been particularly true for basic science questions, such as the development of nonreusable syringes, where the majority of submissions are expected from scientists who do not require assistance in developing their proposals.

2.5.2 Guidelines for writing research proposals

Guidelines for writing research proposals were approved by the Research and Development Group in 1989. Letters of intent are reviewed by the EPI staff member most knowledgeable in the area. If it is felt that the proposal warrants further development, the investigator is asked to submit a detailed proposal on standard EPI forms. When completed, the proposal undergoes formal review by at least two reviewers - one an outside reviewer and the other a member of the Research and Development Group. Proposals where the formal reviews have raised serious questions or where further review is desired can be brought before the Research and Development Group. Prior to awarding of funds, a WHO staff member or a consultant may visit the study site to review operational details of the study with the investigator. Final approval of funding is at the discretion of the Director, EPI.

Any project involving human subjects with financial or scientific input from EPI is required to submit evidence of national and institutional ethical clearances. Such projects must also be approved by the WHO Secretariat Committee on Research Involving Human Subjects.

2.5.3 Disbursing funds

Approved projects are funded entirely or in part through a Technical Services Agreement between WHO and the Institution responsible for the project. Projects not involving human subjects and not requiring more than US\$ 30 000 can be funded through an Agreement for Performance of Work. Projects may be renewed up to a total of three years, subject to satisfactory progress and the availability of funds. A financial report must be submitted annually by the Institution's chief financial officer. In general, funds are not considered for principal investigators or other senior professional staff. Requests for "overhead", "administrative", or "miscellaneous" expenses are not approved. Funds cannot be used for the construction of buildings or attendance at meetings, unless otherwise specified. Travel may be paid from WHO funds only if it is essential to the successful execution of the work and itemized in the budget. In

general, funds are awarded with 50% payment on initiation of the project and 50% on satisfactory completion of the project.

2.5.4 Assessing progress

Detailed annual progress reports are required. For vaccine trials, quarterly reports of study enrollment, drop-outs, and vaccine supplies are also requested. For some laboratory studies, monthly progress reports have been requested, so that EPI is able to monitor the quality of the work. Investigators are expected to notify EPI of any significant delay or difficulties in completing the project. Assistance with data analysis and preparation of material for publication is available through EPI. WHO must review all material before publication and publications are required to acknowledge support provided by WHO. Following discussions with donors in early 1992, every attempt has been made to have acknowledgments also include a list of donors to WHO whose generosity made the WHO funding possible. Preparation of results for publication in peer-reviewed journals is considered an important criteria for judging the success of a project and possible future funding. Publication in local and regional scientific journals is also encouraged.

3. RESEARCH AND DEVELOPMENT PROJECTS SUPPORTED

3.1 Interaction between AIDS and immunization

In October 1986, the EPI Global Advisory Group recommended use of all the EPI vaccines in HIV-infected children, with the exception of BCG, which should not be given to children with symptomatic HIV infection. In 1987, a joint statement of EPI and the Special Programme on AIDS (now called the Global Programme on AIDS) was issued in support of the Global Advisory Group recommendations (3) and several review articles were published (4,5). Subsequently, EPI and the Global Programme on AIDS co-funded a study in Rwanda to examine response to routine immunization in a cohort of HIV-infected children (6-8). That study and others have highlighted the benefits of immunization in protecting HIV-infected children, particularly against measles and the complications of tuberculosis.

In 1989, a joint WHO/UNICEF statement was issued on early immunization for HIV-infected children (9). Because children with known or suspected HIV infection are at increased risk of severe measles, it was recommended that they receive a dose of standard measles vaccine at 6 months of age, followed by a second dose at 9 months of age. The statement also noted that parents of HIV-infected children may be HIV-infected themselves, and have a higher incidence of infectious tuberculosis than the general population. Therefore, the joint statement urged early immunization with BCG for asymptomatic HIV-infected children. EPI and the Global Programme on AIDS continue to monitor the global situation for further reports on the interaction between AIDS and immunization.

3.2 Measles immunization strategies to protect infants under nine months of age

Measles remains the leading cause of death among the EPI diseases, with some 1.2 million deaths estimated to have occurred in 1992. In 1987, EPI posed three questions about measles vaccine strategies, which led to a large number of research activities.

3.2.1 Do newer vaccines offer a significant advantage for developing countries over current vaccines?

Current measles vaccines cannot be successfully administered below nine months of age because of interference of placentally transferred maternal

antibody with the vaccine take. The problems posed by the necessity for this relatively late administration of vaccine are several.

- Clinical measles occurs when maternal antibody drops to unprotective levels, usually around six months of age, and exerts considerable mortality in the period before vaccine can be given with high efficacy.
- The unprotected cohort less than 9 months of age contributes to the spread of measles, particularly in densely populated urban areas where measles is endemic.
- Finally, vaccine coverage decreases with age and the interval between vaccination, so that a measles vaccine that can be administered earlier may be more widely used.

In 1987, preliminary information was becoming available on high titer measles vaccines of different strains, which held promise of being effective when given at 5-6 months of age. However, it was acknowledged that the replacement of the current safe and effective vaccines would require meticulous attention to the safety, stability, and cost of any new vaccines.

Over the next five years extensive evaluation of high titer measles vaccines took place. Two large-scale vaccine studies were funded by EPI, one in Senegal and one in the former USSR. A demonstration project was funded in Kinshasa, Zaire. EPI played an important role in tracking ongoing studies and providing guidelines to investigators for presentation of their data in a standard format. Based on initial positive findings, in 1989 the EPI Global Advisory Group recommended use of high titer Edmonston-Zagreb measles vaccine at 6 months of age in countries where measles before the age of 9 months poses a significant problem (10).

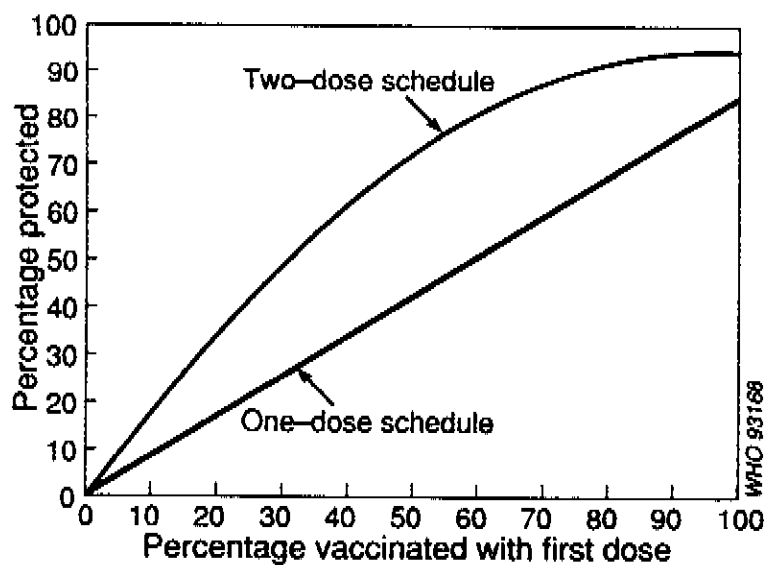
In late 1990, one investigator reported possible decreased long-term survival among children who had received high titer vaccine. Early in 1991, EPI constituted a panel of experts to review data from this and other studies; they found that the data were insufficient to come to any conclusion (11). By late 1991, preliminary data from some other studies showed similar findings. EPI commissioned the London School of Hygiene and Tropical Medicine to examine the data from all known studies on high titer measles vaccines. The EPI panel of experts was re-convened in June 1992 to examine this and other data. This time they concluded that there was decreased long-term survival of infants who received high titer measles vaccines compared with those who received standard titer vaccines (12). This conclusion was reviewed by the EPI Global Advisory Group in October 1992, which recommended that high titer measles vaccines derived from the original Edmonston measles virus isolate should no longer be used in immunization programmes (13).

The needs in this area remain acute, and the EPI will continue to explore the use of some strains of standard titer measles vaccines (including the AIKC strain) before the age of 9 months. Greater emphasis has now been given to basic research aimed at developing new measles vaccines which can be given close to birth (see section 4.3).

3.2.2 Is a two-dose schedule for measles vaccine feasible, cost-effective, and an appropriate strategy for measles control in developing countries?

EPI has monitored the measles experience of countries which have pursued two-dose strategies. Work is ongoing to design a two-dose measles vaccine study where doses would be administered at 6 and 9 months of age. EPI commissioned work on several measles two-dose models (Figure 4) (14). A concern reported by the modelers was lack of sufficiently detailed data from developing countries to allow appropriate projections. Subsequently, data from several countries using different two-dose measles immunization schedules were evaluated (15).

Figure 4. Protection from one-dose and two-dose measles immunization schedules (15).



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3.2.3 What are the most important factors that influence the severity of measles and what factors lead to spread of the disease?

Risk factors for measles were reviewed in two WHO publications (16, 17). More needs to be known about the acquisition of measles and the factors that influence severity of disease. A generic protocol has been developed to explore the role of measles transmission in hospital and clinic waiting rooms. Community-based methods have been encouraged, as it is felt that hospital based data do not sufficiently represent the full spectrum of illness. EPI learned of work in Kampala, Uganda, on a community-based method which was rapid, inexpensive, and could be carried out during measles outbreaks; this work was funded by Save the Children, United Kingdom. To make the method available to other programme managers, EPI facilitated its publication in WHO journals (18, 19).

3.2.4 Other measles studies

The World Health Assembly has called for a 90% reduction in measles cases by 1995, compared with the pre-vaccine era. This led to concerns about the global supply of measles vaccine. Following the recommendation of the Research and Development Group, a consultancy was arranged to investigate difficulties in obtaining measles vaccine. It was determined that standard titer measles vaccines for routine immunization at 9 months of age could be made available in virtually any desired quantity provided 18 months notice was given to manufacturers, along with a commitment to buy those quantities.

A second goal set by the World Health Assembly is a 95% reduction in deaths due to measles by 1995. In collaboration with the Division of Diarrhoeal and Acute Respiratory Disease Control and the Nutrition Unit, EPI is pursuing case management for measles (using vitamin A, oral rehydration therapy for diarrhea, and protocols for respiratory infections). A generic protocol has been prepared to allow programmes to assess the local measles case fatality rate (20).

3.3 Polio eradication

The goal of global eradication of poliomyelitis by the year 2000, which was set by the World Health Assembly in 1988, has strongly influenced research directions pursued by EPI. To sensitize the scientific community of the immediate research needs imposed by polio eradication, a number of articles were published in the scientific literature (21-25).

3.3.1 Optimal use of oral polio vaccine

A major discrepancy exists between the highly successful seroconversion that follows as few as two doses of oral polio vaccine (OPV) in developed

countries and seroconversion rates that appear to be as low as 50% in studies in developing countries after three doses of vaccine. EPI sponsored a review of the global literature on this subject, which was published in 1991 (24). To examine variables that might explain the difference in vaccine performance between developed and developing countries, a number of studies were initiated. A method for rapid serological assessment of response to OPV was developed and promoted in collaboration with the Centers for Disease Control and Prevention, USA (22) (Figure 5).

A study was undertaken by EPI in collaboration with the Medical Research Council Laboratories and the Ministry of Health, The Gambia; the Ministry of Health, Brazil; and the Centers for Disease Control and Prevention, USA to examine whether seroconversion rates could be improved by altering the relative doses of the three strains in OPV.

A study in Ghana which received technical support from EPI and funding from the Japan International Cooperation Agency examined the response of infants given a birth dose of OPV, in addition to the three standard OPV doses. Findings from this study support the WHO recommendation to administer a birth dose of OPV in polio-endemic areas (26).

A study in Cuba, funded by EPI/Geneva and EPI/Region of the Americas, examined the serological profile of children who received up to 8 doses of OPV in mass campaigns (27).

A study in Nashville, USA, compared the response of infants given the USA-formulation of OPV at different intervals (one or two months) between doses. The study also examined patterns of shedding of vaccine virus in these infants. Overall, the response to three doses of OPV was almost 100% for all three serotypes; the interval between doses did not affect the response rate. As a result of these findings, clinical trials are planned to examine the response of children in developing countries to the USA-formulation of OPV.

3.3.2 OPV/IPV combinations

A study in the Ivory Coast which received technical support from EPI examined the responses of children given a supplemental dose of either OPV or inactivated polio vaccine (IPV) at the same time as measles vaccine (28). It appeared that a supplemental dose of IPV might be beneficial in improving seroconversion in selected circumstances, such as providing individual protection in countries where the prevalence of polio antibodies is relatively low despite high coverage with 3 or 4 doses of OPV.

Investigations conducted in Oman during 1989-1990 showed a serious gap in the antibody levels of children to type 3 poliovirus (29). To

address this problem, a study has been initiated in collaboration with the Ministry of Health, Oman, and the Centers for Disease Control and Prevention, USA, to examine the response of children to an extra dose of polio vaccine (trivalent OPV, monovalent type 3 OPV, or IPV) given at the same time as measles vaccine.

Schedules combining multiple doses of OPV and IPV have been used in Denmark, the West Bank, and Gaza, with success. A clinical trial has been organized to assess both serological immunity and intestinal immunity following simultaneous administration of OPV and IPV in the EPI schedule at 6, 10, and 14 weeks of age. The study has enrolled more than 1500 children in The Gambia, Oman, and Thailand; laboratory work is being carried out in The Gambia, Scotland, Thailand, and the USA.

3.3.3 Improving laboratory methods

An immunofluorescent method for the identification of polioviruses has been developed by the Medical Research Council, Gambia, as part of the EPI-sponsored OPV/IPV study (30). This time-saving method has been cited as one of the first breakthroughs in polio diagnosis since the 1950s (31). It is being tested in other laboratories in England, Pakistan, and Scotland, and USA. If these laboratories confirm its utility, the immunofluorescent method will be introduced in the EPI training courses that are now part of the global laboratory network.

Development of IgM capture assays for polio antibodies was reported at an informal consultation sponsored by the WHO/UNDP Programme for Vaccine Development and EPI in June 1991 (32). Investigators from China, Finland, Japan, Netherlands, and USA have worked independently on this method and a collaborative study is underway to further assess its applicability.

Figure 5. Proportion of children aged 7-12 months with polio neutralizing antibody titers 1:8 or higher after 3-4 doses of oral polio vaccine. Three studies based on an EPI generic protocol (22)

	Pakistan	Togo	Uganda
No. OPV doses	3 or 4	4	3
Schedule (age in months)	0/3/5/7	0/2/3/4	3/4/5
No. children tested	36	30	60
Percent with polio neutralizing antibody to:			
Type 1	89	90	90
Type 2	92	100	98
Type 3	94	87	62

The EPI Cold Chain and logistics unit has developed a reverse cold chain to bring specimens from the patient to the laboratory at the proper temperature. Tubes for collecting stool were developed by the cold chain and logistics unit and tested in Colombia, Netherlands, Oman, Thailand, and the USA.

Methods to sample the environment for wild poliovirus will be critical in determining whether eradication has occurred. Considerable efforts have been made in the Region of the Americas to develop and test new methods for environmental surveillance. In Brazil and Colombia the polymerase chain reaction has been explored as a method for examining sewage samples for wild poliovirus. There is also strong interest in the European Region and, as a result of a meeting co-sponsored by WHO and the National Institute for Public Health, Finland, a collaborative group was organized to study methods for sewage sampling and concentrating virus. Other studies on environmental sampling have been conducted during outbreak investigations.

3.4 Technologies and energy management for the delivery of vaccines

EPI activities aimed at the improvement of technologies for the delivery of vaccines fall into two areas: injection equipment and energy management of the cold chain.

3.4.1 Improvement of injection technologies

In 1987, EPI planned work on four different injection technologies: reusable syringes and sterilization, auto destruct disposable syringes, pre-filled devices, and low-cost jet injectors. Work advanced most rapidly on the implementation of steam sterilization and plastic reusable syringes. Investigations were pursued in the laboratory and the field to develop an absorbent pad for the steam sterilizer, which could reduce the tendency for calcium deposition when hard water is used.

After four years of development, auto-destruct disposable syringes which are able to be used only once became commercially available in 1992. The first protocols for this project were reviewed in late 1987 and early 1988 at EPITECH meetings sponsored by EPI. The development of the auto-destruct syringe met with many setbacks and delays due both to the technical difficulty of meeting the WHO/UNICEF specifications and due to larger manufacturers attempting to protect commercial interests. Nevertheless, several models of auto-destruct syringes entered field tests in Pakistan and Paraguay in 1989 and 1990. By late 1990, two manufacturers passed field and laboratory tests and tenders were invited by UNICEF for the first 80 million syringes. In April 1991, the First International Conference on Auto-Destruct Syringes was held at New

York University, USA. The meeting was attended by public health administrators, epidemiologists, inventors, manufacturers, narcotics addicts, and former drug users, who posed many questions about whether the frequency of transmission of HIV, hepatitis B virus, and other pathogens could be reduced by use of the auto-destruct syringe. A brief summary of the conference was published in the *Lancet* (33).

At the same time that the auto-destruct syringes were being developed, EPI developed containers in which used syringes can be stored and subsequently burned. The purpose of the containers is to help avoid accidental needle puncture and to enable used syringes to be incinerated at the point of use without resort to local fuel sources. These containers underwent field studies in Oman and Pakistan during 1989-1990. The development of the third injection technology, the pre-filled device, was taken up by another agency, the Programme for Applied Technology in Health, USA.

Work was delayed in the development of jet injectors due to lack of a reliable method of establishing the risks of cross-infection. Recently, testing methods have been established and it seems likely that cheaper, safer, and more efficient models will become available in the next few years.

EPI has also supported social science research in the area of injection practices (34). In a joint project with the WHO Action Programme on Essential Drugs, research has been initiated in Indonesia, Senegal, and Uganda to examine why individuals choose formal or informal health systems for obtaining injections and to assess the risks associated with each type of service. An anticipated outcome of this project is improved safety of injection delivery through appropriate health education.

3.4.2 Energy management

Energy management in the context of the vaccine cold chain is aimed at making the best use of renewable energies for refrigeration, particularly solar energy. Worldwide, more than 4000 solar refrigerators are now in operation for vaccine storage. EPI has developed training materials on installation and maintenance of solar-powered refrigerators (35). Nine solar energy training courses have been conducted at the inter-regional level (in Colombia, Cyprus, Mali, and Thailand) and five training courses have been conducted at the national level (in Chad, Chile, The Gambia, Indonesia, and Tanzania).

Solar refrigerators are very reliable if the equipment is properly selected and installed in compliance with WHO/UNICEF recommendations and if adequate training is provided to technicians and users. However, in several cases the absence of one of these conditions has resulted in relatively high failure rates. Financial analyses carried out in The Gambia and Uganda indicate that solar refrigeration systems are not competitive in

cost with gas powered systems. Assuming a 10 year life cycle, solar refrigerators cost about twice as much per year as gas refrigerators. For solar refrigerators both capital costs and recurrent costs are high. Nevertheless, in view of the risk of serious and lasting fuel shortages, solar refrigerators are the only viable alternative in certain areas. The decision to use solar refrigerators should be based on multiple factors (including the accessibility of the site, the reliability of alternative fuel supplies, and energy independence), rather than on cost-effectiveness alone.

The introduction of solar technology should be viewed within the broad perspective of integrated efforts towards rural development and primary health care. An EPI-funded demonstration project in Zaire has shown that surplus energy can be sold to the community to fund further development of primary health care (Figure 6) (36,37). The energy can be offered in the form of charging batteries, lanterns, radios, televisions, videos, and other household equipment. This approach was extended to eight other West African countries, with capital investment funds from the *Comite Interetats de lutte Contre la Secheresse dans le Sahel (CILSS)* of the European Economic Community (38).

3.5 Computer software for EPI managers

EPI has created a small revolution in health programme management by developing an innovative software series, specifically tailored to the needs of managers in developing countries. Timing for this project was excellent because managers in most developing countries have recently acquired personal computers. By 1990, four different packages with instruction booklets were available: COSAS for analysis of immunization coverage surveys; EPICost for analysis of costs of immunization programmes; EPIC for analysis of cold chain performance; and CEIS a surveillance and coverage database with special report-generating functions (39-42).

EPI policy is not to purchase computers for programme managers, but to provide software and instruction manuals free of charge. One software item, the EPI information system (CEIS), requires special installation. Once a country has obtained a personal computer and identified personnel willing to use the computer, EPI schedules a consultant visit to install the system and train the staff. EPI policy is synergistic with other donors, who have provided personal computers and/or sponsored software training courses. Epicentre, France; Resources for Child Health, USA; OCCGE, Burkina Faso; the International Children's Center, France; and the United States Agency for International Development have supported a number of special training courses in Africa and South East Asia.

Figure 6. Surplus solar energy from a health project is used to pump water in a village in West Africa.



3.6 Improving disease surveillance

Excellent management skills are critical to effect improvements in surveillance. Disease surveillance is itself an effective management tool to identify areas of greatest need. Effective surveillance is a prerequisite to achieving disease control targets and effectively preventing other infectious diseases as well. In 1990, the EPI Global Advisory Group recommended strengthening routine national systems for surveillance of infectious diseases. This has led to extensive EPI contact with other WHO programmes concerned with disease surveillance in order to coordinate various programmes' needs to collect morbidity data from the peripheral level (43). EPI has proposed that WHO develop a model system for routine surveillance of infectious diseases to demonstrate how relevant data can best be made available. Guidelines have been developed for programme managers and a series of workshops focusing on management and surveillance have been conducted at the regional level (44).

Computerized information systems are tools that are helping many EPI managers use surveillance data for decision making in their own countries. Such systems have now been installed in more than 40 countries and all 6 WHO regional offices. Computerized information systems rapidly

generate standardized reports, tables, graphics, and maps. These reports are forming a common system for use by donor and other operational agencies, including UNICEF and the United States Agency for International Development. Future goals are to extend these systems to other countries and to further develop them into comprehensive monitoring systems for primary health care. This is in recognition that the long-term sustainability of immunization programmes calls for their full integration into primary health care.

Some methods for improving surveillance are developed at the peripheral level by individuals attempting to solve their own managerial problems. When good field methods are identified, EPI has facilitated sharing them with programme managers. Two recent examples can be cited: a method for activating disease surveillance developed in Kinshasa, Zaire (45) and a method for community-based investigation of measles outbreaks developed in Kampala, Uganda (18, 19).

3.7 Strategies to increase immunization coverage

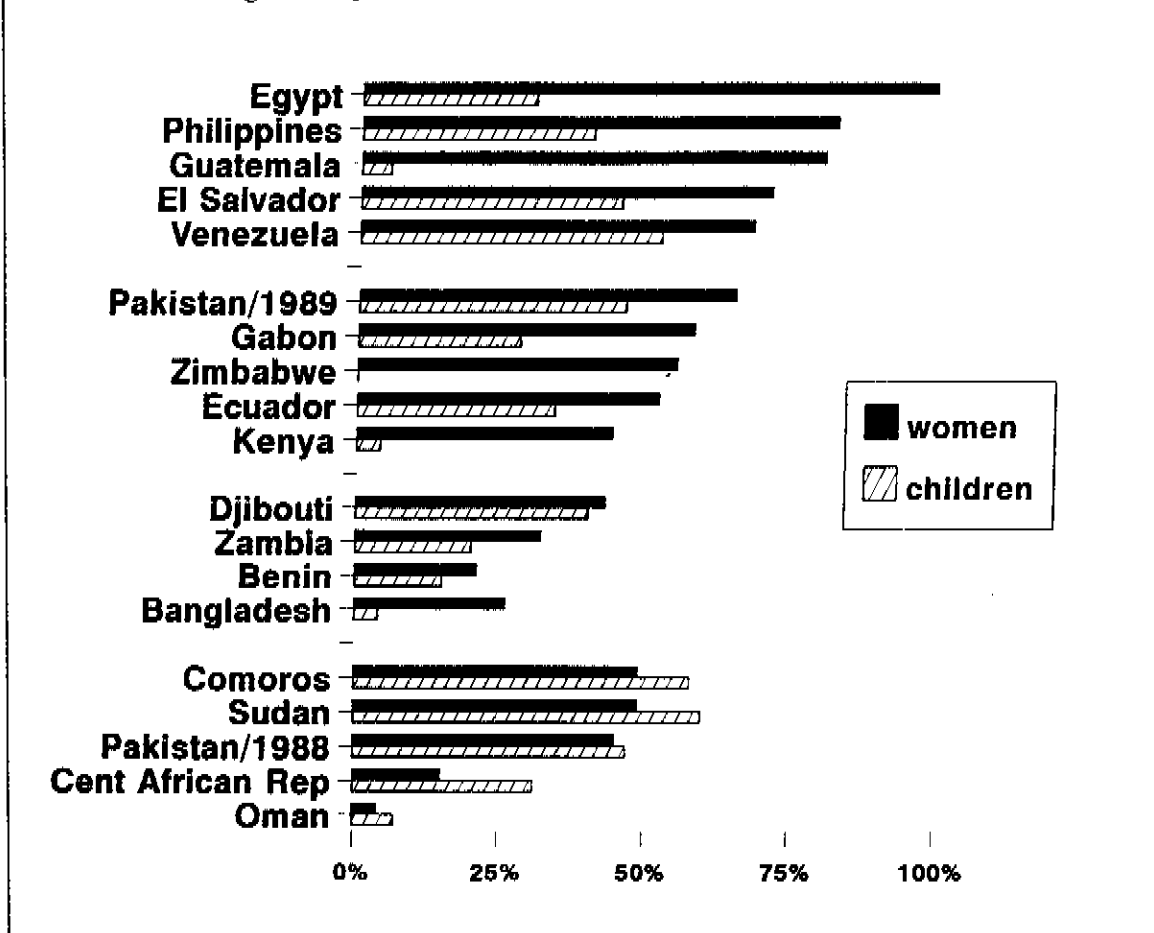
During the second half of the decade of the 1980s EPI focused on strategies to increase coverage. The simplest and most broad-based techniques for operational assessment were welcomed by programme managers: specifically, missed opportunities surveys and EPI software for costing immunization programmes became widely accepted.

3.7.1 Missed opportunities

A simple generic protocol for assessing missed opportunities for immunization was developed and widely distributed by EPI. As countries explored the missed opportunities method and reported results, EPI helped some of these studies reach publication in *EPI UPDATE* and the *WHO Weekly Epidemiological Record* (46-49).

In 1991, EPI reviewed 79 reports of missed opportunities studies from 45 developing and industrialized countries (50,51). A median of 32% of children and women of childbearing age who were surveyed missed an opportunity for immunization during a visit to health services. Among studies which assessed missed opportunities for both women and children, 82% found that missed opportunities for women were several-fold higher than for children (Figure 7). These data reflect the lower coverage among women and also indicate that elimination of missed opportunities could do much to solve this problem. Overall, the most important reasons for missed opportunities were: failure to administer vaccines simultaneously, false contraindications, not opening a multidose vial for a small number of persons to avoid vaccine wastage, and logistical problems, such as vaccine shortage, poor clinic organization and inefficient scheduling.

Figure 7. Missed opportunities for immunization among children aged 0-23 months and women aged 15-44 years. Nineteen surveys based on an EPI generic protocol (50,51).



EPI moved rapidly to develop the missed opportunities method into an EPI training module, which was released in 1991 (52). This new module has been added to the long-standing mid-level series, which is used at the country level to train district health staff. Several thousand persons in developing countries complete EPI mid-level training each year, so the availability of this module will allow rapid introduction of the missed opportunities assessment as a standard supervisory tool.

3.7.2 Mass campaigns

The role of mass immunization campaigns in vaccine policy continues to be refined. Clearly this strategy alone cannot be relied on to build a sustained immunization programme. Studies are underway to examine the effect of immunization campaigns and the ways they can be used to strengthen the whole immunization structure. In 1991, EPI funded a study in Cuba to examine the serological profile of children who received polio vaccine through mass campaigns (27). Countries in the Western Pacific Region have expressed particular interest in examining the

logistical and financial implications of the use of mass campaigns to supplement routine immunization for polio eradication.

3.7.3 Utilizing the private sector



The contribution of the private medical sector in immunization will undoubtedly be important in enhancing immunization coverage, particularly as urban areas grow. Thus far, few methods for involving/assessing private sector input have proved useful. The private sector and the curative care sector need to be brought more into contact with immunization services, either as screening points or as points of delivery. If vaccines are administered, then quality control mechanisms need to be established, including, at a minimum, staff training in service delivery, cold chain, and disease surveillance. Examples of country programmes where this is occurring successfully have been sought and it is planned to share strategies with other programmes, most likely through generic protocols.

3.7.4 Reaching hard-to-reach populations

Different strategies may have to be developed for reaching the increasing urban and periurban populations in the developing world. An issue of *EPI UPDATE* on urban immunization has stimulated interest in this topic (53). More work is needed in this area, including methods for making preventive health services attractive (slum populations are presently more likely to use curative than preventive services), and methods for delivery of other vital primary health care components at the same time as immunizations.

Another population that has proved difficult to reach is women of childbearing age, who should be immunized with tetanus toxoid to prevent neonatal tetanus in their infants. Stronger linkages with maternal/child health programmes are being pursued. The EPI cold chain and logistics unit has developed a "lifetime" immunization card, which is made of durable plastic in the same format as a credit card to ensure that it can be kept throughout the childbearing years (Figure 8).

Figure 8. Model of a plastic EPI immunization card, which is being tested in Central African Republic, Mexico, and Oman.

 CERTIFICATE OF IMMUNIZATION World Health Organization (Name, ID Number, Address)		Fill in:		Date of vaccination in top of box. Vaccine lot number in bottom of box.	
<div style="border: 1px solid black; height: 40px; width: 100%;"></div>		Vaccine type		Dose 1	
TETANUS TOXOID		Dose 2		Dose 3	
Dose Date Given by		Dose 4		Dose 5	
1 <input type="text"/> 4 <input type="text"/>		<input type="text"/>		<input type="text"/>	
2 <input type="text"/> 5 <input type="text"/>		<input type="text"/>		<input type="text"/>	
3 <input type="text"/> 6 <input type="text"/>		<input type="text"/>		<input type="text"/>	
<i>Front of card</i>		<small>This card was provided with the assistance of: Australian International Development Assistance Bureau</small> 		<i>Reverse side (64% reduction)</i>	

3.7.5 Sustainability

The issue underlying sustainability of the EPI is cost. The sustainability of the programme will relate in part to its ability to deliver services in more cost-efficient ways. In 1989, EPI introduced EPICost, a software programme that helps programme managers perform simple and quick cost analyses of their immunization programmes. Programme managers are now requesting that EPICost be adapted to allow more general costing of primary health care. To work towards a primary health care costing programme, extensive collaboration has begun with other programmes in WHO. Countries have also requested help in identifying the key cost items in their programmes, items that require careful management either because of their size or because they are critical for programme impact. New materials will provide guidance on how to budget certain equipment or activities, for example the recurrent costs implications of a new vehicle.

3.8 Immunization contacts for the delivery of other services

3.8.1 Micronutrient supplementation through the EPI

Vitamin A deficiency, iodine deficiency, and iron deficiency affect very large populations throughout the world. Some 14 million preschool-age children in at least 37 countries have eye signs of vitamin A deficiency and 150-190 million children under five years of age at risk of vitamin A deficiency. Studies in Africa and Asia are now beginning to document that supplementation of the diet with vitamin A reduces mortality rates in children due to measles and other diseases. Yet each year 350 000 children are still blinded due to vitamin A deficiency. Iodine deficiency

disorders are a risk for some 1 billion persons globally. Of these, 200-300 million have goiter or other visible signs, and at least 6 million are cretins. Iron deficiency anemia is similarly estimated to involve some 1 billion persons, especially women of childbearing age and children.

Strategies to deal with micronutrient deficiencies include dietary diversification, fortification, and direct supplementation. In practice, effective strategies will depend on a mix of approaches. Using immunization contacts to deliver supplements to both infants and mothers in areas of recognized deficiency has been affirmed as a complementary part of a broad-based approach to deal with some of the worst effects of poverty and malnutrition.

In 1987, a policy on vitamin A for measles was established jointly with the WHO Nutrition Unit and UNICEF (54). During 1988 and 1989, EPI activities focused on advocacy for the feasibility and effectiveness of micronutrient delivery using immunization contacts, development of basic operational guidelines including initiation of training material development, and support for studies on the impact of vitamin A and iodized oil (55,56). In 1990, two joint WHO/UNICEF consultations were supported on vitamin A supplementation and iodized oil. Doses of oral iodized oil have been discussed in several meetings with the International Council for the Control of Iodine Deficiency Disorders. Plans for the delivery of all three micronutrients were presented to the United Nations Sub-Committee on Nutrition at meetings in Paris and New York. A meeting of principal investigators of studies of morbidity and mortality was organized jointly with the WHO Nutrition Unit and the National Eye Institute, USA. A WHO Informal Consultation in July 1992 agreed on recommendations for using immunization contacts to combat vitamin A deficiency. An important outstanding research issue following these recommendations is the impact of vitamin A supplementation on both morbidity and mortality in early childhood.

As WHO/EPI guidelines have become widely disseminated, countries in which micronutrient deficiencies are already identified have begun to take action. Tanzania is already widely using both vitamin A supplements and iodized oil. Mali has used both vitamin A and iodized oil in some areas since 1990. Nepal has used injectable iodized oil widely and is committed to implementing vitamin A supplementation. India has published a policy document on management of vitamin A deficiency and will be implementing countrywide supplementation in high risk areas to children between six months and six years of age. Bangladesh will introduce vitamin A supplementation at immunization contacts from 1993. Indonesia, Mozambique, Nigeria, Thailand, and Zambia are planning vitamin A supplementation. Discussions have been held with Cambodia, Niger, and 13 central African countries.

A pump dispenser for micronutrients has been developed with manufacturers in the United Kingdom and field tested in Bangladesh, Guatemala, Guinea, India, and Malawi. Laboratory Guerbet, France, has collaborated on improved formulations of iodized oil in capsules and dispenser systems. A gastric delivery system for iron has been discussed with the Programme Against Micronutrient Malnutrition, USA, and Hoffmann-La Roche.

EPI has funded laboratory research at the University of Iowa, USA, on potential interactions between vitamin A and iodized oil. Retinyl palmitate, one of the commercial forms of vitamin A, mixed with iodized oil proved to be stable up to 15 days. The National Institute for Public Health and Hygiene, Netherlands has studied reactions between iodized oil and oral polio vaccine in cell culture medium. There was loss of infectivity of the vaccine virus after it had been exposed to iodized oil for more than one hour. EPI commissioned work at the Medical College of Pennsylvania, USA, to review the effects of vitamin A deficiency on immune responses. In experimental animals, vitamin A deficiency has broad effects on the immune system, but it is not yet clear whether the vitamin A status of children at risk of vitamin A deficiency is sufficiently low to compromise their immune responses to vaccines. These findings indicate the need for further research.

3.8.2 Other areas

EPI commissioned work from the London School of Tropical Medicine and Hygiene on ways in which EPI can help the delivery of other health interventions. Suggestions included further development of the EPI programme evaluation method to include other primary health care components, further development of problem-solving operational research methods, improving surveillance systems, developing methods to identify and involve potential public and private resources (especially in periurban areas), ethnographic studies, increased activities in health worker communication, maintenance of equipment and transport. EPI experience in assessing disease epidemiology in developing countries may be applicable for other diseases.

4. PROMOTION OF VACCINE-RELATED RESEARCH OUTSIDE EPI

Many developments are occurring in molecular biology which will impact on immunization. It is considered within the mandate of the EPI to keep abreast of these developments, which include the use of vectors for vaccine delivery, stabilizers, immunomodulators, slow-release vaccines, and vaccines composed of peptides or larger protein subunits of organisms. Simultaneously, there are tremendous advances being made in immunology and molecular pathophysiology which will lead to construction of vaccines that optimally utilize all components of the host immune response, particularly the T-cell immune response. EPI does not directly support research in these areas, although the Secretariat has prepared several extensive reviews on new vaccines and on the stability of vaccines (57-59).

The EPI has attempted to influence directions that are pursued in molecular biology and encourage those that are the most potentially applicable to the programme. Toward this end, the activities within the WHO Division of Communicable Diseases (including the Transdisease Vaccinology Programme, the WHO/UNDP Programme for Vaccine Development, and the Children's Vaccine Initiative) have increasingly emphasized EPI's needs in applied vaccinology. Several examples of these efforts are described below.

4.1 Choice of a vaccine for slow-release technology

In 1988, the EPI Secretariat was consulted by the Transdisease Vaccinology Programme about which vaccine should be developed first in a slow-release form. Diphtheria toxin had been proposed as the initial candidate; however, EPI strongly recommended tetanus toxoid, the sole EPI vaccine delivered to adults and for which coverage remains low, in part because of the need to administer five appropriately-timed doses. EPI staff have attended technical meetings related to development of the slow-release tetanus toxoid and consulted on such matters as what would be the best timing of a pulsed-release product.

4.2 Facilitating development of new polio vaccines

In 1989, the Steering Committee on Polio and Hepatitis of the WHO/UNDP Programme for Vaccine Development met with the EPI Secretariat to request advice on how to further research on recombinant and chimeric polio vaccine candidates. Although scientists in the several countries had developed potential candidates, concerns remained about how to proceed. To facilitate further work in this area, EPI and the

WHO/UNDP Programme for Vaccine Development jointly sponsored a meeting in 1990 to look at the potential use of new polio vaccines. This was an historic occasion, as several of the scientists who studied polio vaccines in the 1950s were introduced to a new generation of molecular scientists. The report of this meeting was subsequently published in the *Bulletin of the World Health Organization* and this was the single most requested EPI publication during 1987-1991 (60).

4.3 Addressing basic science questions on measles

The WHO/UNDP Programme for Vaccine Development did not initially include measles among the diseases for which new vaccines should be considered. In 1990, EPI and the WHO/UNDP Programme for Vaccine Development co-sponsored a meeting to discuss unanswered questions on measles immunology and measles vaccines. Subsequently, a basic research component for measles was added to the portfolio of the Acute Respiratory Viruses Steering Committee of the WHO/UNDP Programme for Vaccine Development.

4.4 Establishing the first Product Development Group of the Children's Vaccine Initiative

During 1989 and 1990 the EPI Secretariat worked with the Steering Committee on Polio and Hepatitis of the WHO/UNDP Programme for Vaccine Development to reassess and revise their research objectives, in light of the polio eradication initiative established in 1988 by the World Health Assembly. It was pointed out that oral polio vaccine is 30 times more heat sensitive than any of the other EPI vaccines. The Steering Committee made development of a more thermostable oral polio vaccine its top priority. In due course, EPI funded a meeting in June 1991 to consider how to proceed toward a more thermostable oral polio vaccine. This meeting recommended a focused research effort and, ultimately, the first Product Development Group of the Children's Vaccine Initiative was established late in 1991 to work on this issue.

5. EVALUATION OF CANDIDATE VACCINES FOR POSSIBLE INCLUSION IN EPI

Within the organization of WHO, most vaccine candidates will not initially be evaluated by EPI, but by other programmes with responsibility for parasitic, enteric, and respiratory diseases. However, promising vaccine candidates will have to be considered in the context of how they might be delivered within the operational framework of EPI. Toward this end, various candidate vaccines have been examined by the Research and Development Group, including hepatitis B vaccine, yellow fever vaccine, rotavirus vaccine, and *Haemophilus influenzae* type b vaccine.

5.1 Hepatitis B vaccine

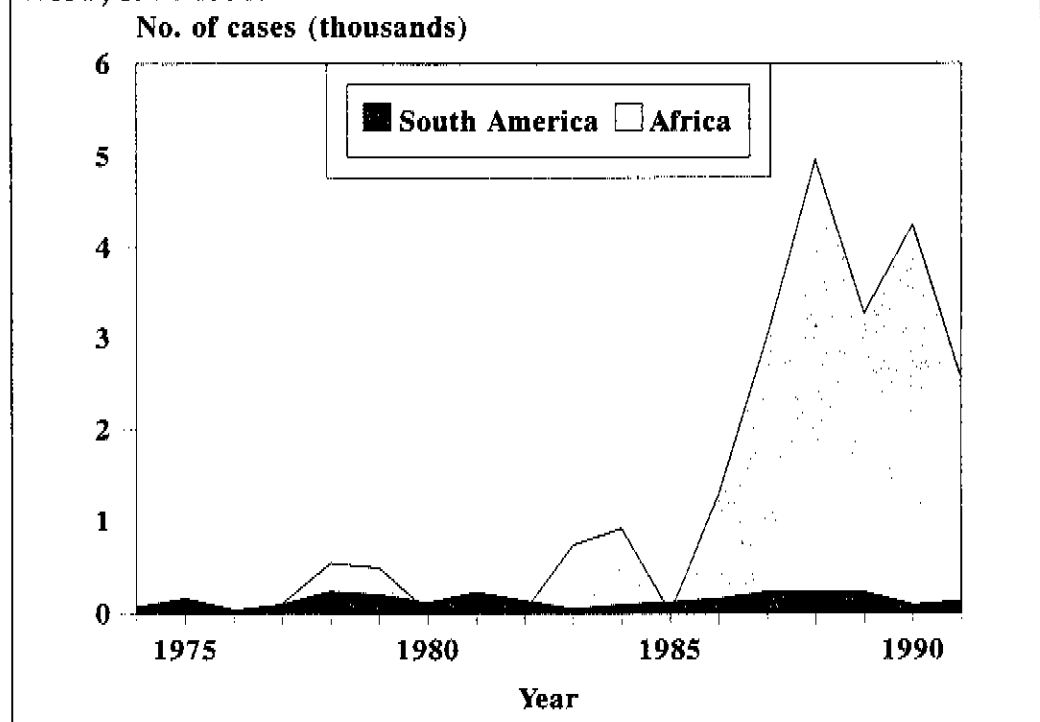
Three-quarters of the world's population lives in areas where the prevalence of chronic hepatitis B virus infection is 2% or more. Chronic infection with hepatitis B virus often leads to cirrhosis or liver cancer. Children are more likely to become chronic carriers and to develop complications as adults. It is estimated that 1-2 million deaths each year are directly related to infection with hepatitis B virus (61,62). Among infants infected at birth, 70-90% will become chronic carriers. Hepatitis B virus infection can be prevented by immunization with hepatitis B vaccine; three doses are needed and the vaccine can be administered at the same time as other EPI antigens. Although the cost of this vaccine has dropped enormously (from US\$ 40 to US\$ 0.65 - 2.25 per pediatric dose), the cost for a full series of three doses is still limiting the number of developing countries which can introduce hepatitis B vaccine as a routine component of the national immunization programme. Various mechanisms, including a revolving fund for vaccine purchase, have been proposed and, since cost can be predicted to be an issue for future new vaccines, a great deal of interest has been expressed in overcoming the price barriers.

The EPI Research and Development Group has reviewed the scientific basis for integration of hepatitis B vaccine in the EPI and concluded that it would be important to add, although countries should not include this vaccine until they are certain they will be able to obtain the vaccine for the long term. The WHO Division of Communicable Diseases now has a full-time staff member working on hepatitis and further progress can be anticipated. In the area of operational research, EPI has made a number of contributions: a generic protocol to assess maternal carrier rates of hepatitis B virus, studies on the temperature stability of hepatitis B vaccine, assessments of the logistical implications of adding hepatitis B vaccine to the EPI, and the use of EPICost software to assess the additional costs of including this vaccine in national immunization programmes.

5.2 Yellow fever vaccine

The status of yellow fever vaccine was reviewed by the Research and Development Group in 1990 and inclusion of this vaccine in the immunization programmes of at-risk countries was strongly recommended. Yellow fever vaccine costs only US\$ 0.25 per dose. It is highly immunogenic, with many studies in developing countries documenting seroconversion rates of 95% or higher in children after a single dose. Antibodies have been documented to persist as long as 40 years following immunization. The missing ingredient for inclusion of the yellow fever vaccine in national immunization programmes has been data concerning the extent that yellow fever affects children. The WHO Division of Communicable Diseases, in collaboration with EPI, assessed available epidemiological data and found that in Africa yellow fever is affecting primarily children (63). This finding, coupled with reports of the highest numbers of cases and deaths due to yellow fever since 1949 (Figure 9), led the World Health Assembly to call for incorporation of yellow fever vaccine in routine immunization programmes of at risk countries by 1993 (64). In support of these recommendations, UNICEF has agreed to purchase yellow fever vaccines in the same way they purchase other EPI vaccines. Yellow fever vaccine coverage and disease surveillance data have been incorporated into the EPI information system.

Figure 9. The resurgence of yellow fever. Official data reported to WHO, 1974-1991.



5.3 Rotavirus vaccine

The Research and Development Group has considered rotavirus vaccine on several occasions. The epidemiology of rotavirus infection and the efficacy of rotavirus vaccines have been evaluated in developing countries, with much of the research being conducted under the auspices of the Division of Diarrhoeal and Acute Respiratory Disease Control. A trial in The Gambia found that rotavirus vaccine may interfere with the response to oral polio vaccine. Preliminary data from a subsequent study in Thailand indicate that there is serious interference between rotavirus vaccine and oral polio vaccine, particularly to types 1 and 3 poliovirus. Although present rotavirus vaccines have performed well in industrialized countries, their performance in developing countries has been disappointing. Future candidate rotavirus vaccines would need to demonstrate immunogenicity, efficacy, and compatibility with the EPI antigens in developing countries before they could be considered for inclusion in the EPI.

5.4 *Haemophilus influenzae* type b vaccine

Acute bacterial meningitis is a potential problem of great severity in developing countries; however, good epidemiologic data from developing countries are lacking. Limited data suggest that rates of meningitis will be as high or higher than those in populations at special risk in industrialized countries (65). One estimate is that as many as 1 in 60 children may die of meningitis in childhood. Those who survive are likely to be left with serious neurological problems, including deafness, seizures, and mental retardation. It is estimated that *Haemophilus influenzae* type b meningitis and pneumonia cause 5% of deaths in children under one year of age in developing countries.

Vaccines for *Haemophilus influenzae* type b have been demonstrated to be effective in industrialized countries; however, studies in developing countries have showed limited immunogenicity of these vaccines. The various vaccines presently available appear to have different degrees of immunogenicity and different durations of protection. These vaccines need to be tested in parallel in several developing countries, with careful assessment of immunogenicity after each dose. Compatibility with the EPI antigens should also be assessed. Further studies are being discussed by various funding agencies and the WHO Division of Diarrhoeal and Acute Respiratory Disease Control. EPI will continue to follow results of these studies as additional data become available.

6. COMMUNICATING RESULTS TO THE SCIENTIFIC COMMUNITY

Communication with different disciplines represented in the scientific community (ranging from basic molecular scientists to solar energy engineers) has been intense and raised enthusiasm for research questions relevant to field programmes. This dialogue has been carried out at scientific meetings, on computer networks, and in the medical literature.

6.1 Scientific meetings

The semi-annual meetings of the EPI Research and Development Group are listed in Annex 1. EPI has also supported technical meetings to review specific issues, establish collaborative studies, share the results of studies, and decide on their implications for further work (Annex 2). From 1987-1991, technical meetings were held in the following areas: bioengineering; HIV and immunization; micronutrient deficiency; computerized information systems and software development; measles vaccine trials and measles diagnostic tests; polio vaccine trials, environmental surveillance, and diagnostic tests for poliomyelitis. Many of these technical meetings were co-sponsored with other WHO programmes or other agencies.

6.2 Other contacts with potential research sites and institutions

Representatives of research institutions in Australia, Canada, Finland, France, Germany, Ghana, India, Ireland, Japan, Mexico, Namibia, Nigeria, Philippines, Poland, Saudi Arabia, Senegal, Sweden, Switzerland, United Kingdom, USA, and the former USSR have attended one or more meetings of the EPI Research and Development Group.

EPI has followed with interest the progress of two epidemiology training programmes aimed primarily at individuals from developing countries: the International Clinical Epidemiology Network (INCLIN) and the Field Epidemiology Training Programme (FETP). EPI staff have attended the annual INCLIN meetings since 1987. At the January 1992 joint INCLIN/FETP meeting there were more than 25 presentations on studies of interest to EPI, in areas described in this report. Both groups have been encouraged to meet with their national EPI managers and seek out areas where research is needed. Investigators from both INCLIN and FETP have been invited to present results of their studies to the EPI Research and Development Group.

To promote potential research contacts, EPI produced a directory of individuals and institutions interested in EPI research, which includes

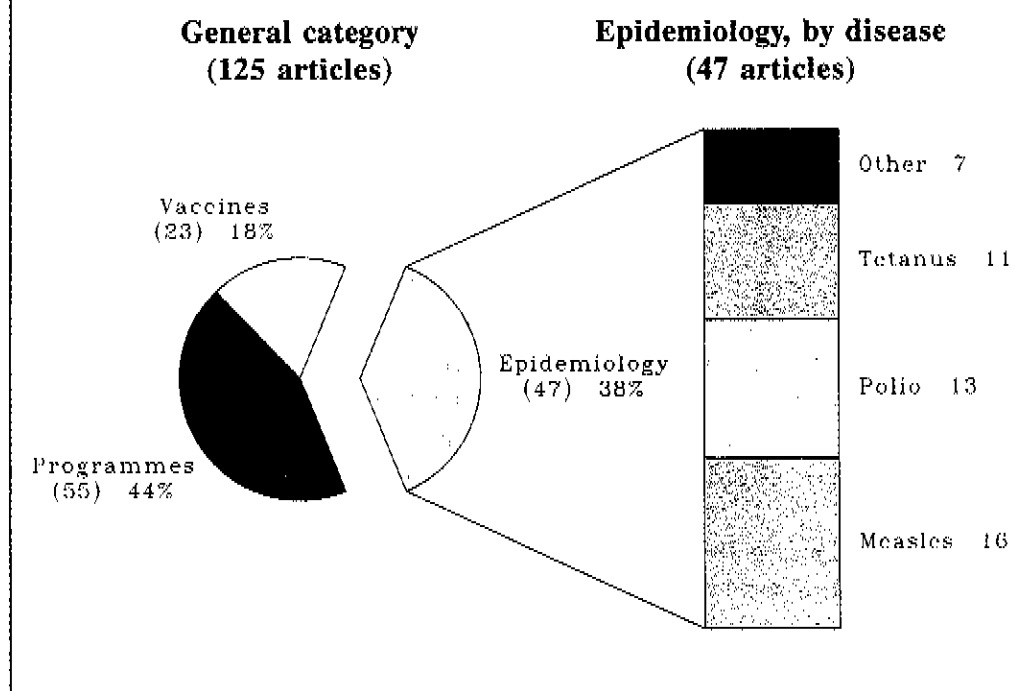
several hundred entries (66). A logistics research computer bulletin board has been established by TECHNET, the logistics and cold chain problem solving group. However, in its first year, some members did not have access to modern communication or could not finance the costs of such communication. Efforts are now being made to facilitate bulletin board access for those individuals.

6.3 Scientific publications

EPI has contributed consistently to the more traditional scientific literature. Through this medium, which is directed at research scientists and academic institutions, EPI is able to promote interest in its research priorities and inform the scientific community of developing country health needs.

EPI has been a major contributor to the WHO *Weekly Epidemiological Record*, a weekly bilingual English/French publication with a distribution of 7500 copies, including Ministries of Health worldwide. From 1987-1991, 125 immunization-related articles (including reports of EPI studies, surveys, and programme evaluations) were published in the *Weekly Epidemiological Record* (Figure 10) (67).

Figure 10. EPI articles published in the WHO Weekly Epidemiological Record, 1987-1991



7. PROVIDING RESEARCH RESULTS TO NATIONAL IMMUNIZATION PROGRAMMES

Continuous efforts have been made to assure that the results from research relevant to the EPI are made available to programme managers. Newsletters and other EPI publications are sent to managers some 4-5 times each year. Training has been a major emphasis of EPI since it began. Operational methods and results have been incorporated into training courses and training materials almost as soon as they become available.

7.1 Newsletters and other EPI publications

EPI produces two newsletters -- *TECHNET News* to cover logistics issues and *EPI ALERT* to provide feedback on surveillance and outbreak investigation. EPI contributes frequently to *World Immunization News* (now called *Child Survival - World Development*), a newsletter published by the Task Force for Child Survival and Development. *EPI UPDATE* is a 6-page color publication issued every 3-4 months, with each issue devoted to a single topic. Issues of *EPI UPDATE* on vitamin A, computer software, communications, surveillance, missed opportunities, yellow fever, hepatitis B, and urban immunization have served to concisely introduce important concepts and recommendations to immunization programme managers.

7.2 EPI training courses

From 1987 to 1991, more than 200 EPI training courses (at the inter-regional or national level) were organized and/or facilitated by EPI. Most of these courses were co-funded and co-facilitated by staff from national and regional levels and by staff from many other agencies.

During the period under review, the entire EPI mid-level training series was revised (68). Changes in this series resulting from EPI research findings included: updated sterilization guidelines; operational methods to increase immunization coverage; use of missed opportunities surveys as a supervisory tool; information about EPI software; and information about how to store and administer hepatitis B and yellow fever vaccines.

During 1990 and 1991 work began on a new EPI series, "The Immunological Basis for Immunization" (69). This series reviews the scientific literature on the EPI diseases, with special emphasis on data from developing countries. It serves as a reference for immunization programme managers, consultants on immunization activities, and

laboratory scientists providing diagnostic or research services for vaccine-preventable diseases. The series is also suitable for medical, nursing, and public health training courses.

8. CONCLUSION

This report documents the first five years of research and development activities within EPI. During this period, EPI sponsored research projects in many countries. In addition, key research issues were identified and shared widely with other institutions and donors. Providing useful information to national programme managers has been an over-riding goal and already many research results have been applied because of the unique linkage of EPI with vaccine delivery programmes worldwide.

EPI research and development activities have now placed the programme as the primary global reference point for immunization questions, particularly but not exclusively questions relating to immunization in developing countries and under-developed areas of industrialized countries. This resource will grow in importance in the future as fruits of more basic research offer a larger array of antigens for use in national programmes, and the needs to simplify immunization schedules and methods of administering antigens intensify.

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ANNEX I

MEETINGS OF EPI RESEARCH AND DEVELOPMENT GROUP, 1987-1991

First Meeting of the EPI Research and Development Group,
22-23 September 1987, Atlanta, USA

Second Meeting of the EPI Research and Development Group,
9-10 March 1988, Geneva, Switzerland

Third Meeting of the EPI Research and Development Group,
13-14 October 1988, Abidjan, Cote d'Ivoire

Fourth Meeting of the EPI Research and Development Group,
13-14 March 1989, Atlanta, USA

Fifth Meeting of the EPI Research and Development Group,
12-13 October 1989, Tokyo, Japan

Sixth Meeting of the EPI Research and Development Group,
15-16 March 1990, Geneva, Switzerland

Seventh Meeting of the EPI Research and Development Group,
10-11 October 1990, Cairo, Egypt

Eighth Meeting of the EPI Research and Development Group,
15-16 April 1991, Geneva, Switzerland

Ninth Meeting of the EPI Research and Development Group,
1-2 October 1991, Geneva, Switzerland

ANNEX 2

TECHNICAL RESEARCH MEETINGS SPONSORED OR CO-SPONSORED BY EPI, 1987-1991

Bioengineering/Logistics

EPITECH Meeting to Review Proposals on Self Destruct Syringes,
23-24 July 1987, Geneva, Switzerland

EPITECH Meeting to Review Proposals on Self Destruct Syringes,
17-18 November 1987, Washington DC, USA

TECHNET: Consultation of Experts in Logistics and the Cold Chain on
Problems Facing the EPI during the 1990s, 12-16 March 1990, Nicosia,
Cyprus

TECHNET: Consultation of Experts in Logistics and the Cold Chain on
Problems Facing the EPI during the 1990s, 18-22 November 1991,
Casablanca, Morocco

HIV & Immunization

WHO Informal Consultation on HIV and Routine Childhood
Immunization, 12-13 August 1987, Geneva, Switzerland

Information Systems

WHO Meeting on Global Strategies for Computerized EPI Information
Systems, 24-26 April 1989, Washington DC, USA

WHO Meeting on Global Strategies for Computerized EPI Information
Systems, July 1990, Geneva, Switzerland

Measles

Meeting on Studies of Alternative Strains of Measles Vaccines,
19-20 September 1988, Washington DC, USA

Informal Meeting on Alternative Routes of Administration of Measles
Vaccine, 20 February 1990, Baltimore, USA

Meeting on the Development of New Vaccines for Measles,
26-27 May 1990, Rolle, Switzerland

WHO Consultation on Studies Involving High Titer Measles Vaccine
before 9 Months, 21-22 February 1991, Geneva, Switzerland

Micronutrients

Joint WHO/UNICEF Consultation on Vitamin A Supplementation
through National Immunization Programmes, and Infant and Young Child
Mortality, 5-6 December 1990, Geneva, Switzerland

Joint WHO/UNICEF Consultation on Elimination of Iodine Deficiency
Disorders - Iodine Supplementation through National Immunization
Programmes, 7 December 1990, Geneva, Switzerland

Polio

WHO Consultation on the Potential Use of New Polio Vaccines:
Biological Requirements, Criteria for Testing, 12-13 March 1990,
Geneva, Switzerland

WHO Consultation on the Creation of a Bank of Wild Poliovirus Strains,
29 May 1990, Geneva, Switzerland

WHO Informal Consultation on New Approaches to Poliovirus Diagnosis
Using Laboratory Techniques, 6-7 June 1991, Geneva, Switzerland

WHO Informal Consultation on Improvement of Thermostability of Oral
Poliovirus Vaccine, 10 June 1991, Geneva, Switzerland

WHO Informal Consultation on Polio Neutralizing Antibody Assays,
5-6 December 1991, Nashville, USA