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THE EVOLUTION OF DIARRHOEAL AND ACUTE RESPIRATORY DISEASE CONTROL AT WHO

Achievements 1980–1995 in Research, Development, and Implementation

DEPARTMENT OF CHILD
AND ADOLESCENT HEALTH
AND DEVELOPMENT

WORLD HEALTH ORGANIZATION

CAH CHILD AND ADOLESCENT HEALTH AND DEVELOPMENT

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Contents

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Introduction

For 15 years, WHO's efforts to combat diarrhoeal disease and acute respiratory infections—two childhood killers—focused on translating relevant research into the practical tools and action needed by countries, then on working with countries to introduce, monitor, and evaluate their use.

In 1990, the WHO Division of Diarrhoeal and Acute Respiratory Disease Control (CDR) was formed and brought together the work of the WHO Programme for the Control of Diarrhoeal Diseases (CDD), established in 1980, and the WHO Programme on Acute Respiratory Infections (ARI), established in 1984.

The experience of the CDD and ARI Programmes provided valuable insight into the process of programme development and, in particular, the cycle of research, development, implementation and evaluation.

The work of these Programmes illustrated a natural and logical thread connecting research to the development and evaluation of priority interventions that can have the most impact in countries burdened by these diseases. The Programmes recognized the need for lessons learned in the field to be incorporated into improved interventions, tools and guidelines, and to guide priority setting for future research.

This document describes how the cycle of research, development, implementation and evaluation has kept work focused on the changing challenges to the prevention and treatment of diarrhoeal disease and acute respiratory infections. As part of this cycle, the Programmes' research agenda underwent a significant evolution between 1980 and 1995. Research activities shifted from a focus on etiology and epidemiology to one that emphasized addressing practical operational problems in order to improve programme implementation and effectiveness, particularly in developing countries.

The research, development, and implementation activities of CDD, ARI, and CDR during the period 1980 to 1995 are outlined in this document. The information presented provides readers with an historical overview of developments in diarrhoeal diseases and acute respiratory infections research, and lessons learned from implementation of national disease control programmes.

The first section summarizes key research findings, achievements and impact up to 1995. Section 2 describes how research management evolved to meet changing needs. Research in epidemiology and disease prevention is presented in section 3, and research in case management is described in section 4. Section 5 provides an overview of activities that applied research findings to support effective programme implementation, including planning and management, training and materials development, and monitoring and evaluation. Finally, the document takes a look at how the WHO Department of Child and Adolescent Health and Development (CAH), formed in 1998, is building upon the work of CDD and ARI to develop innovative new approaches to improving the health of the world's children. One such approach is Integrated Management of Childhood Illness (IMCI), which focuses on the complex health needs of the whole child and the combined treatment of major childhood illnesses such as malaria, measles and malnutrition, in addition to diarrhoea and pneumonia.

1. Summary

1.1 Background

From its start in 1980, the WHO Programme for the Control of Diarrhoeal Diseases (CDD) made a commitment to significantly reducing global childhood mortality. This mandate arose from a resolution of the thirty-first World Health Assembly in 1978, which requested the Director-General:[1]

> "to intensify involvement of Member States in the development of a plan of action for an expanded programme on diarrhoeal disease control...", and specifically, "to promote technical cooperation with and among Member States in programme formulation, implementation and evaluation, and in training health workers at different levels; (and) to accord high priority to research activities for the further development of simple, effective and inexpensive methods of treatment, prevention and control....".

In 1990, CDD and the WHO Programme on Acute Respiratory Infections (ARI), established in 1984, were combined to form the Division of Diarrhoeal and Acute Respiratory Disease Control (CDR). The shared goal of these programmes continued to be the maximum reduction in worldwide childhood mortality.

1.2 Programme Structure

The CDD Programme was the first WHO programme to adopt a structure with two complementary components-health services and research. The health services component focused on incorporating existing knowledge about the prevention and treatment of diarrhoea into the implementation of national primary health care programmes. The research component prioritized support to operational and basic research in order to apply new knowledge to the development of new tools for prevention and treatment.

Linking these two components as integral parts of one control programme ensured that research was directed toward solving problems that emerged during implementation of national CDD programmes. It also ensured that research findings were more rapidly incorporated into programme guidelines.

The Programme's research agenda underwent a significant evolution between 1980 and 1995. Research activities shifted from a focus on etiology and epidemiology to one that emphasized addressing practical operational problems in order to improve programme implementation and effectiveness. There was also an increasing emphasis on research related to case management and treatment and to the evaluation of interventions that prevent diarrhoeal and acute respiratory diseases.

In 1992, management of research and development and implementation activities was integrated to reflect these changes and to ensure that the priority issues for developing countries were addressed.

1.3 Key Research Findings

Diarrhoea and Pneumonia Etiology and Epidemiology

Early on, the CDD Programme focused on the development and evaluation of diagnostic tests for the detection of diarrhoea-causing organisms. CDD also supported a large number of etiological studies.

While there are numerous diarrhoea-causing organisms, the studies showed that the majority of cases in virtually all settings are caused by five organisms: rotavirus, *E.coli*, *Shigella*, *Campylobacter jejuni*, and cryptosporidium. The studies also revealed no cause-specific characteristics of diarrhoea that would significantly influence the approach to case management or prevention strategies. (The exception was the evidence that *Shigella* was the most important cause of bloody diarrhoea.) Because case management of acute diarrhoea was the same regardless of the organism responsible, further studies of diarrhoeal etiology were not required.

[1] Programme for control of diarrhoeal diseases, resolution WHA31.44 (24 May 1978). *Handbook of resolutions and decisions of the World Health Assembly and the Executive Board*, Volume II, 3rd ed., 1973-1978, 1979, p.64.

The ARI Programme also conducted a number of studies in developing countries that confirmed that *S. pneumoniae* and *H. influenzae* are the most common agents of community-acquired pneumonia. This finding supported the Programme's strategy of pneumonia case management using antibiotics. Subsequent research in this category focused on pneumonia etiology in young infants and malnourished children, two groups at high risk of death from pneumonia.

Disease Prevention Research

Research on interventions to prevent diarrhoea and acute respiratory infections was given high priority based on lessons learned from earlier studies.

During the 1980s, the CDD Programme commissioned the London School of Hygiene and Tropical Medicine to conduct in-depth reviews of the potential effectiveness, feasibility and cost of 18 interventions to prevent diarrhoea. The most promising, identified as those with potentially high effectiveness and feasibility, included promotion of breastfeeding, improvement of complementary feeding, improvements in water supply, sanitation and hygiene behaviours, development of rotavirus and cholera vaccines, and measles immunization.

As a result of the reviews, measles immunization was actively promoted as a Programme strategy, the other issues were added to the research agenda, and a large number of related studies were supported.

The ARI programme conducted similar reviews in the early 1990s. Of 28 potential interventions, eight were identified as having the capacity to prevent five per cent or more of childhood pneumonia deaths. Four of these required further research to test efficacy in the field: pneumococcal, Hib and RSV vaccines, and reduction of indoor air pollution. The reviews also suggested that reducing low birthweight and underweight, and promoting measles immunization and breastfeeding, specifically in Latin America, could be effective interventions.

Equally important, the reviews produced no evidence to suggest that childhood death or illness from pneumonia might be reduced by interventions such as use of antibiotics for upper respiratory tract infections, prophylactic use of antibiotics in severely malnourished children, or vitamin A supplementation (with the exception of measles-associated pneumonia).

The conclusions of these reviews significantly influenced future CDD and ARI Programme activities. Research then concentrated on infant and child feeding, vaccines, water supply, sanitation and hygiene behaviour, and indoor air pollution.

Infant and child feeding

Research focused initially on identifying infant feeding practices and their relationship with diarrhoeal illness and death, and on identifying determinants of breastfeeding. Attention then shifted to developing and evaluating interventions to promote breastfeeding and improved complementary feeding.

A number of studies confirmed that exclusively breastfed infants have fewer diarrhoeal episodes and a lower risk of persistent and severe diarrhoea. Studies also found that infants who are exclusively breastfed up to four to six months of age gain adequate weight, and that the introduction of complementary foods before this age does not increase weight gain. Research confirmed risks associated with bottlefeeding, with evidence showing that feeding bottles were often highly contaminated with faecal bacteria.

Based on these findings, the CDD Programme recommended that infants be exclusively breastfed for the first four to six months of life, and discouraged the use of feeding bottles and giving other fluids such as teas or water during this period.

Various studies found that early termination of breastfeeding was associated with delay in starting breastfeeding, breastfeeding on schedule rather than demand, lack of family support, use of estrogen-based contraceptives, pacifier use, and concerns about infant growth.

Research also revealed that mothers commonly begin early supplementation of breastfeeding because of the usually unfounded perception that they are producing insufficient milk. Poor attachment to the breast was also identified as one of the most common obstacles to successful breastfeeding and the main cause of problems such as engorgement and cracked nipples. A breastfeeding counselling training course was developed because of the strong evidence that breastfeeding counselling by health personnel is a highly effective intervention for the promotion of successful breastfeeding. Subsequent research concluded that training in lactation management and effective counselling of mothers can increase exclusive breastfeeding.

A number of studies addressed improved complementary feeding because malnutrition was shown to be associated with increased severity of diarrhoea, pneumonia and measles, and with increased mortality due to these diseases.

For example, early studies indicated that impaired growth in the 6–11 month age period reflects not only the effects of repeated illness but also inadequate energy intake, and that inadequate energy intake may be due to factors such as low

frequency of meals and small size of feeds and not only to low energy density of food. The results of these studies led to interventions developed specifically to address local problems, for example promoting more energy dense foods in Peru and encouraging greater frequency of feeding in Guatemala.

Micronutrients

A study supported by CDR in Brazil found that vitamin A supplementation reduced diarrhoea incidence and severity, especially of highly purging episodes, but had no detectable impact on acute respiratory infections. Another study in India indicated that vitamin A supplementation substantially reduced the severity and persistence of diarrhoeal episodes, but that it may also be associated with increased risk of acute respiratory infections. As a result, further research was initiated to evaluate the benefits and safety of vitamin A supplementation, especially in relation to the risks of acute respiratory infection in young infants.

The Division also supported studies to evaluate the potential benefits of zinc. Results from randomized controlled trials suggest that zinc supplementation may reduce incidence and severity of diarrhoea and acute respiratory infections.

Vaccines

The CDD Programme supported vaccine research for rotavirus, cholera, *Shigella* and typhoid, leading to the development of candidate vaccines for all these major causes of diarrhoea (with the exception of *Shigella*). Field trials were completed and significant results were found for typhoid and rotavirus vaccines.

Vaccine research supported by the ARI Programme focused on the development of vaccines against *H. influenzae* type b and the pneumococcus, the two most important causes of life-threatening episodes of pneumonia in infants and young children. The Hib conjugate vaccines developed have been shown to safely and effectively protect infants and young children in developing countries against Hib pneumonia and meningitis. Wider implementation through national EPI programmes is being evaluated in several countries. The ARI Programme also achieved some degree of success in research to develop a pneumococcal vaccine for safe use in infants. Large-scale efficacy trials are underway in the Gambia to evaluate the safety of pneumococcal conjugate vaccine administration in combination with a liquid Hib/DPT combination product. Results of the first phase of this study are expected by late 1999; the second phase, with the aim of determining the effect of the vaccine on child survival, will commence later the same year, and results should be available after about five years' time.

Water supply, sanitation and hygiene

Community and household interventions were the focus of CDD Programme research related to water, sanitation and hygiene. The finding that water availability is more important than water quality in the prevention of diarrhoea—an adequate quantity of water facilitates hygiene practices—influenced the content of health education messages related to water use.

A Programme consultation in 1992 found that three priority water-related hygiene behaviours had impact on the incidence of diarrhoea: handwashing, sanitary disposal of faeces, and keeping drinking water free from faecal contamination. Of these, handwashing was found to have the most significant effect.

Indoor air pollution

In 1992, studies were initiated to explore how reducing indoor air pollution from biomass fuels could impact on childhood pneumonia incidence. This led to the planning of intervention trials, but they have not been implemented due to funding constraints.

Research in Case Management

A major thrust of CDD and ARI Programme research was how to improve health facility-based case management of diarrhoea, pneumonia, serious bacterial infections, and severe malnutrition, and how to improve care of diarrhoea and pneumonia at home.

CDD priorities included improving oral rehydration salts (ORS) formulations, identifying the most effective dietary regimens for acute and persistent diarrhoea, and assessing the usefulness of drug treatment in acute and persistent diarrhoea and dysentery. Studies supported by the ARI Programme concentrated on validating the use of simple signs to detect pneumonia, on issues related to antimicrobial resistance, and on methods for administering oxygen.

Oral rehydration salts formulations

Citrate ORS was adopted in 1985 as the recommended WHO formula after studies showed it to be considerably more stable than bicarbonate ORS and therefore more simply and cheaply packed. Fifty-four studies since 1984 compared standard

ORS with experimental formulations that might enhance absorption. However, none of the alternative formulations (based on glycine, L-alanine, L-glutamine, maltodextrin, rice and other cereals) was found to have any advantage over standard citrate ORS, except in cholera patients for whom rice-based ORS and amino-acid based ORS reduced stool output. Recent studies show that reduced osmolarity ORS reduces the need for unplanned IV therapy in children but has no benefits for adults with cholera.

Feeding during diarrhoea

A significant finding of research supported by the CDD Programme was that continued feeding, including breastfeeding, during diarrhoea, reduces the adverse effects of the disease on nutritional status. This was in contrast to the common advice to temporarily stop or reduce feeding solids to a child with diarrhoea. Studies in Egypt and Ecuador also showed that, again contrary to earlier advice, there was no need in the majority of cases to dilute milk feeds or to use lactose-free formula during acute diarrhoea. Subsequent studies in Brazil and Guatemala showed that it was safe to give full strength formula to infants under six months of age.

Research on effective approaches to management of persistent diarrhoea became a priority after studies showed that up to 20 percent of diarrhoea episodes last for 14 days or more, and that these cases have a high risk of dying. This research provided clear evidence that patients hospitalized with persistent diarrhoea can be treated successfully with ORS and a reduced lactose diet based on locally available and inexpensive foods.

Drugs in the management of diarrhoea

Concern about the widespread use of drugs to treat diarrhoea prompted the CDD Programme to conduct a review of all common antidiarrhoeals. The review, published in 1990, concluded that none of these drugs should be used in the routine management of diarrhoea as none has been shown to be sufficiently efficacious or free from adverse side-effects.

Research supported by the CDD Programme showed that antibiotics are necessary only in the treatment of severe cases of cholera, and that there is no benefit in routine use of gentamicin or cotrimoxazole for persistent diarrhoea.

The increasing problem of unnecessary prescription and use of drugs in diarrhoea treatment led the Programme to add rational drug use to the research agenda in 1991. Subsequent studies in Guatemala and Nepal found that interventions developed by the Programme significantly improved the dispensing practices of pharmacists and drug sellers.

Evidence that approximately 10 percent of diarrhoeal episodes in children less than five years of age have blood in the stool led the Programme to support research into treatment guidelines for bloody diarrhoea. A significant outcome was that treatment with an antimicrobial known to be effective against *Shigella*, the most important cause of dysentery, leads to clinical improvement in bloody diarrhoea within two days.

Detection and treatment of childhood pneumonia

Studies conducted by the ARI Programme concluded that the case management approach to detection and management of pneumonia could significantly reduce mortality. Initial research also confirmed that counting respiratory rate, for 30 seconds or 60 seconds, was a reliable method of detecting pneumonia, and that sensitivity could be improved by using age-specific thresholds.

The spread of antimicrobial resistance prompted the ARI Programme to support studies examining the impact of resistance on clinical outcome and to develop surveillance methods in collaboration with national programmes.

Research indicated that, even where high *in vitro* resistance rates have been reported, cotrimoxazole treatment of pneumonia usually resulted in recovery. This provided evidence to support the continued use of cotrimoxazole as a first line antimicrobial for pneumonia.

Guidelines and a manual on the methods for surveillance of resistance of the two main pneumonia-causing organisms were also developed, as were simpler approaches to obtaining samples and laboratory methods suitable for developing country settings.

Oxygen plays a critical role in reducing ARI mortality, because hypoxia is a major risk factor for death in children with severe pneumonia or severe bronchiolitis. The ARI Programme devoted considerable efforts to developing and testing oxygen concentrators and methods to deliver oxygen efficiently and effectively. Studies supported by the Programme confirmed that nasal prongs and nasopharyngeal catheter are both effective and efficient methods for administering oxygen to young children who are hypoxic.

Severely malnourished children

Experience since 1980 suggested that diarrhoea may need to be managed differently in severely malnourished children, and the Division's research agenda changed to reflect this thinking. Studies showed it was difficult to detect the presence and severity of dehydration in severely malnourished children, and that full strength ORS should not be used in such children because of major electrolyte abnormalities. Ongoing studies are evaluating the benefits of giving magnesium, zinc and copper to correct deficiencies of these minerals inseverely malnourished children with diarrhoea.

Similarly, research demonstrated that standard definitions of fast breathing and chest indrawing are not sufficiently reliable predictors of pneumonia in malnourished children. However, various studies have confirmed that *S. pneumonia* and *H. influenzae* are the most common causes of pneumonia in both malnourished and well-nourished children, and that the same antibiotics can be used in first-line treatment regardless of the child's nutritional status.

A clinical trial in the Gambia supported by the ARI Programme found that oral cotrimoxazole and oral chloramphenicol were equally effective in the initial management of malnourished children with pneumonia. However, the failure rate in both groups was quite high, suggesting possible absorption problems and that parenteral antibiotics should be considered early in the management of malnourished children.

Integrated management of childhood illness

Research findings that confirmed the overlap in clinical presentation of several major childhood illnesses stimulated a move toward an integrated approach to the management of childhood illness. For example, a study in Malawi in the early 1990s confirmed the overlap in the presentation of malaria and pneumonia.

Research needed for developing a method for integrated case management of ARI, diarrhoea, measles, malaria and malnutrition was completed in 1995. Since then, the method was field-tested and refined, and a training course was designed to teach integrated case management to health care staff.

Priority research topics for the future include malaria diagnosis in low-risk areas, detection and treatment of anaemia, improvements in home case management of child illness, and the management of children hospitalized with severe malaria.

Home care

The success of case management strategies for diarrhoea and pneumonia depends not only on the availability of affordable health services with trained personnel, but also on family behaviour. Thus, the CDD and ARI Programmes devoted considerable effort to identifying interventions to improve home care.

Early CDD studies focused on identifying the types of fluids given at home to prevent dehydration. One conclusion was that cereal-based fluids should be promoted only in areas where they are traditionally used.

The ARI Programme initiated research to identify methods to improve communication with families, recognizing that effective home management requires that families first have adequate knowledge. A focused ethnographic study was developed based on two assumptions: that communication with families would be more effective if health workers used culturally appropriate language and concepts, and that programmes need information about how families manage ARI in order to develop means of improving family practices. The Programme also developed procedures for local adaptation of home care advice, and for assessing understanding of adapted messages.

More recently, CDR initiated work to improve family responses to childhood illness. The new Department of Child and Adolescent Health and Development (CAH) is working toward the development of tools for planning and implementing behaviour change interventions.

1.4 Achievements and Impact

The experiences of the CDD and ARI Programmes over 16 years provided valuable insight into the process of programme development and, in particular, the cycle of research, development, implementation and evaluation. The Programmes succeeded in defining and supporting a research agenda that meets the needs of developing countries, and set a standard for research through collaboration within the scientific community, particularly in the development of clinical guidelines.

The substantial number of studies supported by the Programmes, described in the previous section, led to the development and evaluation of a wide range of interventions and simple techniques appropriate for developing country settings.

Major accomplishments included:

- development of a standardized process of case management in health facilities that involves assessment, classification and treatment, and

that has been shown to be both scientifically acceptable and feasible;
- an increased acceptance of the importance of sound programme management with clearly defined strategies and interventions, target setting, planning, and monitoring and evaluation; and
- development of model programme tools for these activities.

The Programmes' support of effective planning, management, training, and monitoring and evaluation facilitated successful implementation of national programmes. The CDD and ARI Programmes also developed and refined a range of instruments including household surveys, health facility surveys and programme reviews that have enabled national programmes to evaluate their progress and use the results to revise and improve activities.

Improving Management and Training

Thousands of health staff have been trained in the management of programmes to control diarrhoea and acute respiratory disease. Between 1988 and 1995 more than 240 CDD courses were held in over 70 countries. Over 5,600 senior health staff participated in ARI Programme management training during 1990–1995. Training to strengthen supervision in health facilities and the middle level of the health system has covered more than 300,000 personnel.

Training courses and materials were also developed to improve case management. Materials produced by the Programmes include technical guidelines on a wide range of issues such as treatment of acute diarrhoea, communicating with mothers, cholera control, management of acute respiratory infections in small hospitals, and management of fever.

Careful monitoring and evaluation of early case management training revealed that increased emphasis should be given to practice. In response, the CDD Programme encouraged the establishment of Diarrhoea Training Units (DTUs). By the end of 1995, more than 150 of these centres of excellence in diarrhoea case management training were functioning satisfactorily. Seventy of them also provided practical training in ARI case management. In addition, more than 7,300 diarrhoeal disease clinical training courses were held, training over half a million health workers, and more than 250,000 physicians, nurses and other health workers were trained in ARI case management between 1987 and 1995.

Concerns raised and lessons learned over time have helped improve training. For example, including health work-mother communication as part of case management training and establishing formal mechanisms to monitor the quality of training are two recognized needs. In response to the first need, all CDD and ARI case management courses since 1993 contain special exercises aimed at improving health worker-to-mother communication skills.

From 1980 to 1990, the Programmes encouraged and supported primarily in-service training. However, including case management training in medical and nursing schools was a logical next step as it is sometimes more difficult to change health workers' practices after they have been trained. By the end of 1995, more than 152 medical schools in 35 countries had participated in workshops to improve the teaching of diarrhoea case management.

The more recent development of a training course for Integrated Management of Childhood Illness (IMCI) represents a significant achievement, successfully bringing together clinical research, development efforts and systematic pretesting and fieldtesting. IMCI training also takes into account the lessons learned from past experience including the importance of follow-up and support to reinforce health workers' case management skills after they return to their facilities. The next important step is to help countries implement IMCI. Lessons learned from early experiences should help improve programme management and implementation elsewhere.

Measuring Success

Research suggests that the practices of health personnel and families are influenced by extensive promotion and distribution of technical guidelines, promotion of ORS, widespread training of national staff in clinical management, and community level promotion of more effective approaches to management of diarrhoea and ARI. Still, it has been more difficult to assess progress towards achievement of the global goal of reducing childhood mortality and morbidity from diarrhoeal diseases and pneumonia.

Management guidelines for national programmes include indicators and targets that provide an indication of achievement in terms of activities. The CDD Programme achieved and surpassed many of the global targets set in 1980 more quickly than originally anticipated.

For example, by 1984 the number of countries with operational CDD programmes had reached 75, although the original target for 1983 was only 35 countries. And by the same year, 1990 targets

for management training and ORS production had already been achieved and were revised upward. Global access to ORS increased from 21 to 63 percent between 1983 and 1989, and ORS use from 4 to 32 percent in the same period. By 1993, more than 60 developing countries were producing ORS of a satisfactory quality. By 1995, access to ORS reached 80 percent and it was estimated that increased fluids and continued feeding were given in 34 percent of diarrhoea episodes. This represents significant advances since the beginning of the decade. And oral rehydration therapy is now the accepted standard practice in the management of diarrhoea by health staff at all levels.

In 1985, the CDD Programme started to estimate impact based on assumptions about the proportion of diarrhoeal deaths caused by dehydration and the effect of oral rehydration therapy (ORT) use on mortality. It was estimated that the use of ORT might have prevented some 350,000 deaths from diarrhoea in 1984, 700,000 childhood diarrhoea deaths in 1986 and 1.1 million in 1988. However, the Programme stopped reporting these estimates because of the complexity and difficulty of measuring the impact of specific disease programmes along these measures.

Indicators were redefined as the Programme evolved to provide more useful measures of progress. For example, in 1988 the indicator "ORS use" was replaced by "correct case management", which includes giving increased fluids and continued feeding. National programmes have encountered problems in measuring access to case management and cases correctly managed in health facilities. Changes in the definition of indicators over time have also made comparison of rates more difficult. And as survey instruments became more complex, they were less easy to use and therefore less likely to be used. Because of these problems, the value of targets and indicators for programme planning and for motivating health personnel was questioned.

Extensive ARI training efforts have ensured that childhood pneumonia is more widely recognized as a major childhood killer. By the end of 1994, 59 of the original 88 target countries had an operational ARI programme. But impact on mortality is only likely to be achieved by more timely care-seeking by families. Because Programme efforts until 1995 focused on improving case management in health facilities, most of the work to achieve impact remains to be done.

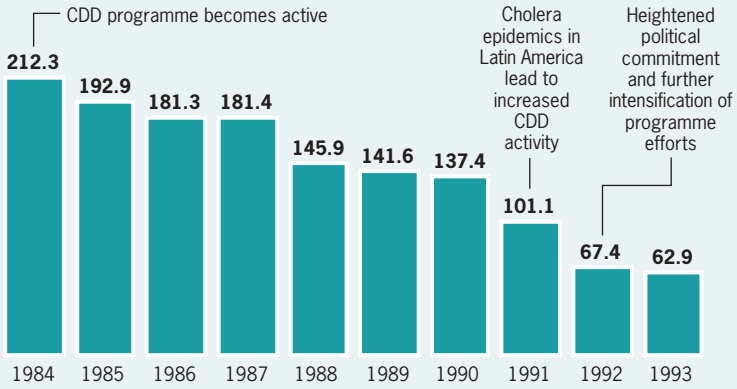
CDR also worked with countries to develop better and easier methods to document mortality decline and to assess programme impact. In Mexico, a focused programme review in 1994 provided the opportunity to evaluate the potential of routine surveillance systems as the basis for documenting mortality decline (see Case Study).

And in north-east Brazil, a variety of program-

CASE STUDY **Documenting success in Mexico**

Reported diarrhoeal disease mortality in Mexican children less than five years of age was reduced by 70% between 1984 and 1993 (see Figure).

Under-five mortality due to diarrhoeal diseases, Mexico, 1984–1993



Source: CONACED, Mexico

In 1994, an external evaluation of diarrhoeal disease control activities was carried out at the request of the Mexican Government. The evaluation methodology was adapted from the CDR focused programme review guidelines. The evaluation team included representatives of the Ministry of Health, other national organizations and a range of institutions and international agencies (ADDR, UNICEF, USAID, U.S. Centers for Disease Control and Prevention and WHO).

Mexico's success in reducing diarrhoea mortality is impressive and has served as a source of motivation for other national programmes. Part of the decline is attributable to overall national development, but the energetic, focused efforts of the Mexican CDD programme led to rapid gains in the proportion of mothers who reported correct home case management, and in the availability and use of ORS both at home and in health facilities. The particularly dramatic declines in diarrhoeal mortality that occurred in 1990–1992 during epidemics of cholera and the intensified efforts against cholera would not have been possible without the prior decade of effort by the national CDD programme. With a solid base of trained health professionals, political commitment and leadership, adequate resources, and intensive use of the existing case management strategy, targets for reduced mortality were achieved and even surpassed. ■

matic and surveillance data sources have been used to document declines in diarrhoea-related mortality and to assess the proportion of the decline that could be attributed to the introduction of oral rehydration therapy. A research study in collaboration with the Ministry of Health in the Philippines was also designed to assess programme impact. This research led to the development of a generic method whereby countries can assess impact. A publication describing the method is now available.

2. Evolution of Research Management

Challenges identified by the CDD and ARI Programmes over the years sparked a significant evolution in research priorities, from a focus on organism-specific research to an integrated approach aimed at strengthening programme implementation. The structure of research management evolved to reflect this new focus.

Initially, Scientific Working Groups (SWG) composed of external experts were created with responsibility for research. Development and implementation activities were managed separately by the Office of the Director and by the Programme's health services component. Since 1992, however, internal working groups have been responsible for both research and development (R&D) and implementation, ensuring that activities are better coordinated and address the priority problems of developing countries.

An overview of the CDD Programme research activities since 1980 (see Table 1) illustrates how these activities adapted to changing needs—from an early focus on etiology and epidemiology to a growing emphasis on research to improve programme implementation. Research on diarrhoea case management and prevention also evolved from basic and descriptive research in the early years of the programme to research directly related to the development and evaluation of priority interventions most applicable to developing country situations.

2.1 Focus on Organism-Specific Research

Three SWGs were initially established to coordinate and manage research on:

- bacterial enteric infections (microbiology, epidemiology, immunology and vaccine development);
- viral diarrhoeas (microbiology, epidemiology, immunology and vaccine development); and
- drug development and management of acute diarrhoea.

The SWGs, each with a steering committee (SC) and composed of experts in relevant fields, set research priorities and solicited and reviewed proposals. The SWGs allocated research funds and monitored the progress of studies in the three areas, with 101, 64 and 69 studies supported respectively between 1980 and 1985. This reflected the strong focus on organism-specific research.

During the same six year period, SWGs established in each of WHO's regional offices to guide operational research supported 122 projects.

In each biennium, around 30 global and regional SWG and SC meetings were held, representing a significant cost but providing an important opportunity to involve a wide range of scientists in the new programme.

2.2 Redefining Research Priorities

Progress made, experience gained and lessons learned from problems in programme implementation led to a redefinition of research priorities and a reorganization of the Programme's research component in 1986. The former SWGs were disbanded and three new SWGs were formed:

- Case management (improving treatment);
- Immunology, microbiology and vaccine development (and technology to support it); and
- Epidemiology and disease prevention (evaluation and implementation of interventions, other than vaccines, to prevent diarrhoeal diseases).

The Programme's Technical Advisory Group (TAG) recommended various changes to the role of the SWGs. The new SWGs were to focus on fewer topics and only those of greatest priority for reducing diarrhoea mortality and morbidity, and to encourage the development of research projects to meet these priorities. Operational research, supported by regional SWGs until incorporation into global activities, increased its focus on solving problems related to programme implementation. Studies to determine the feasibility and impact of preventive interventions delivered by national CDD programmes were given greater attention at the global level.

Table 1 ■ **Research studies supported by the CDD Programme (1980–1993)**[a]

	1980–81	1982–83	1984–85	1986–87	1988–89	1990–91	1992–93
Case management	9	17	38	17	23	20	11
Improved ORS				11	11	8	3
Drugs in the management of acute diarrhoea				4	2	1	
Persistent diarrhoea				2	5	5	1
Dietary management of diarrhoea					5		
Rational use of drugs						2	3
Case management in the home						4	4
Vaccine-related[b]	29	73	51	30	23	5	2
Vaccine development and evaluation				17	16	5	2
Improved diagnostic tests				10	2		
Epidemiology of specific organisms				3	5		
Other preventive interventions	5	14	12	11	11	15	18
Risk factor studies				7	3	2	
Infant feeding (including breastfeeding)				2	3	9	12
Vitamin A and zinc supplementation						2	4
Personal and domestic hygiene				2	5	2	2

[a] More specific topics reflect categories used from 1986 onwards. Earlier programme reports did not provide information summarized in this way. Only main topics of research (around 90% of all projects) are shown.
[b] Including epidemiological and etiological studies and basic microbiological and immunological research, mostly conducted in the first three biennia.

During the 1990–1991 biennium, a panel of expert advisers representing a wide range of disciplines to assist CDR replaced the SWGs. Their role was to:

- review progress and completed research in priority areas;
- define research priorities;
- establish study methods;
- review research proposals; and
- advise investigators on study design, implementation, and data analysis.

In addition to bringing specialized expertise to each project, this new mechanism for research management made proposal development, review and monitoring more efficient.

2.3 Integrated Research and Development to Strengthen Implementation

Starting in 1992, research and development activities related to CDD were managed jointly by internal working groups to ensure that research focused on issues considered the greatest priority for strengthening disease control activities. During 1994–1995, the three working groups focused on:

- case management in the home;
- case management outside the home and national programme management; and
- prevention of disease.

From the start, the ARI Programme had a research management structure similar to that initiated by the CDD Programme in 1990. Research focussed on resolving issues related to case management in health facilities and in the home, behavioural aspects of care seeking, development of appropriate technology, review of preventive interventions and, to a more limited extent, on vaccines and indoor air pollution.

3. Research in Epidemiology and Disease Prevention

There was a logical and necessary progression of the research priorities of the CDD and ARI Programmes. Early research in epidemiology and etiology gave the Programmes a critical knowledge base and the information needed to shape future research as well as programme operations. With this information, the Programmes could then turn their attention to research on preventive interventions—ranging from vaccines and infant and child feeding to hygiene and indoor air pollution—that could have practical impact in the developing world.

3.1 Epidemiology and Etiology

Diarrhoea

Early on, the CDD Programme allocated considerable resources for research to quantify the burden of disease associated childhood diarrhoea. The aim of the research was to demonstrate that, despite some regional differences in etiology, childhood diarrhoea was a global problem warranting a global approach to control.

Table 2 ■ **Development and evaluation of diagnostic tests for enteric pathogens**

Pathogen	Diagnostic test	Outcome
Enterotoxigenic *E. coli*		
• heat-labile toxin (LT)	Gel diffusion (Biken)	Commercial kit
• heat-stable toxin (ST)	ELISA	Commercial kit
• LT and ST	DNA probes	Commercial kit
Enteroinvasive *E. coli*	ELISA DNA probe	Developed Commercial kit
Campylobacter jejuni	Serotyping ELISA (for antibody) Phage-typing	Commercial kit Completed Scheme developed
Vibrio cholerae 01	Co-agglutination assay	Developed
Rotavirus	ELISA Solid phase immune electronmicroscopy	Kit developed Developed
Enteric adenovirus	ELISA	Developed
Calicivirus	RIA	Developed
Giardia lamblia	ELISA	Commercial kit
Entamoeba histolytica	ELISA	Commercial kit

The Programme focused on developing and evaluating diagnostic tests to facilitate detection of diarrhoea-causing organisms (see Table 2). Research initially supported by the Programme led to commercial development and distribution of practical diagnostic kits, the most important of which diagnosed various types of enterotoxigenic *Escherichia coli* and rotavirus. Diagnostic tests were also needed for epidemiological studies to establish the burden of disease caused by specific pathogens and for use in vaccine trials.

Between 1981 and 1985, 40 studies on the etiology of acute diarrhoea in infants and young children were supported. Four-fifths of these were conducted at hospitals, leading to a consequent bias of information towards cases of severe diarrhoea requiring treatment from a major medical facility. Five of these hospital-based studies—in China, India, Mexico, Myanmar and Pakistan—used a standard protocol.

While there are numerous diarrhoea-causing organisms, the studies showed that the majority of cases in virtually all settings are caused by five organisms (see Table 3).

- Rotavirus was shown to be the only frequently isolated viral enteropathogen.
- Enterotoxigenic *E.coli*, *Shigella* and *Campylobacter jejuni* were the most frequently isolated bacteria.
- Cryptosporidium was the most frequent protozoa cause of diarrhoea.

The epidemiology of specific organisms was also studied in a large number of countries. Overall, these studies revealed no cause-specific characteristics of diarrhoea that would significantly influence the approach to case management or preventive strategies. The exception was the evidence that Shigella was the most important cause of bloody diarrhoea.

In 1986, the CDD Programme decided that further descriptive epidemiology and etiology studies were no longer justified. Attention turned to specific strategies for preventing and reducing the severity of diarrhoea. As described in Section 2, the scientific working groups (SWG) on bacterial

Table 3 ■ **Proportional distribution of pathogens isolated in children with acute diarrhoea seen at treatment centres in developing countries**

	Pathogen	Percentage of cases
Viruses	Rotavirus	15–25
Bacteria	Enterotoxigenic *Escherichia coli*	10–20
	Shigella	5–15
	Campylobacter jeuni	10–15
	Vibrio cholerae 01	5–10[a]
	Salmonella (non-typhoid)	1–5
	Enteropathogenic *Escherichia coli*	1–5
Protozoa	Cryptosporidium	5–15
No pathogen found		20–30

[a] The percentage may be higher in endemic areas during epidemics.
Source: *Readings on diarrhoea.* Geneva, WHO, 1992.

and viral diarrhoeas were replaced with new SWGs as part of the reorganization of research management.

Acute Respiratory Infections

When the ARI Programme became operational in 1984, its strategy and clinical guidelines were based on the best and most current information available on the etiology of pneumonia in children in developing countries.

This information was obtained through blood cultures in conjunction with chemotherapy trials, surveillance of bacterial drug resistance, and studies related to vaccine trials. Information collected consistently confirmed that most pneumonia were bacterial in origin and that *S. pneumoniae* and *H. influenzae* are the most frequent agents of community-acquired pneumonia (see Table 4). This supports the Programme's strategy of pneumonia case management using antibiotics.

Table 4 ■ **Bacteria isolated from lung aspirates of 1,120 children with pneumonia in 15 studies in developing countries[a]**

Bacteria isolated	61%
S. Pneumoniae	30%
H. Influenzae	27%
S. Aureus	16%
Other bacteria	27%
No bacteria isolated	39%

[a] Compiled in 1991 from the following sources: Shann: *Paediatr Inf Dis* 1986:**5**:247. Wall: *Bull WHO* 1986: **64**:553. Ikeogu: *Arch Dis Child* 1988: **63**:1266. Children included in studies had not received antibiotics.

Nonetheless, the ARI Programme supported pneumonia etiology research in young infants and malnourished children because more information was needed about these two high-risk groups.

3.2 Preventive Interventions

Reviews of Preventive Interventions

Research on interventions to prevent diarrhoea and acute respiratory infections was a priority for the Programmes. During the 1980s, the CDD Programme commissioned the London School of Hygiene and Tropical Medicine to conduct in-depth reviews of the potential effectiveness, feasibility and cost of 18 interventions to prevent diarrhoea. The most promising, identified as those with potentially high effectiveness and feasibility, included promotion of breastfeeding, improving complementary feeding, improvements in water supply, sanitation and hygiene behaviours, development of rotavirus and cholera vaccines, and measles immunization. As a result of the reviews, measles immunization was actively promoted as a Programme strategy, the other issues were added to the research agenda and a large number of related research studies were supported.

The ARI programme conducted similar reviews in the early 1990s. Of 28 potential interventions, eight were identified as having the capacity to prevent five percent or more of childhood pneumonia deaths. Four of these required further research to test efficacy in the field: pneumococcal, Hib and RSV vaccines, and reduction of indoor air pollution. The reviews also suggested that reducing low birthweight and underweight, and promoting measles immunization and breastfeeding, specifically in Latin America, could be effective interventions.

These reviews significantly influenced the direction of CDD and ARI Programme activities. Research subsequently concentrated on studies related to infant and child feeding, vaccines, water supply, sanitation and hygiene behaviour, and indoor air pollution.

Diarrhoea

In 1982 the CDD Programme identified 18 interventions, other than case management, that might play a role in diarrhoea control, and commissioned the London School of Hygiene and Tropical Medicine to coordinate a series of in-depth reviews. The reviews examined all available information to assess the effectiveness, feasibility and cost of these interventions (see Table 5) and were published as individual articles, mostly in the *Bulletin of the*

World Health Organization (1). More detailed cost-effectiveness analyses were undertaken for the most promising interventions (2).

Pneumonia

Because of the positive experience with the reviews of diarrhoea prevention interventions, a systematic and comprehensive study was carried out from 1991–1995 to identify interventions likely to be effective, feasible and affordable for the prevention of childhood pneumonia. This study was also conducted in collaboration with the London School of Hygiene and Tropical Medicine, building on the methodological experience gained earlier (3).

Three different clusters of preventive strategies were considered:

- immunization;
- case management/chemoprophylaxis of high risk children; and
- strategies based on the modification of factors that place a child at increased risk of pneumonia incidence or death.

The last cluster was further subdivided into four intervention categories: improving nutrition, reducing environmental pollution, reducing transmission of pathogens, and improving childcare practices. Twenty-eight potential interventions were then identified among the resulting six clusters. Reviews of each were commissioned from international experts.

A detailed review was also carried out to describe the etiology of acute lower respiratory infections among young children in developing countries, which was essential background for the reviews relating to vaccines.

The reviews first considered the causality between the risk associated with the intervention area and increased pneumonia incidence or case-fatality. If causality was considered to be possible, the reviews assessed, for each risk category, how widespread it is, by how much it increases the incidence of pneumonia morbidity or mortality, and by how much it might be feasible to decrease the prevalence of the risk category.

These parameters were then used to model the potential impact of interventions according to the following broad categories:

- High effectiveness, potential impact >10%
- Medium effectiveness, potential impact 5–10%
- Low effectiveness, potential impact <5%;
- No impact likely
- Insufficient evidence to assess potential impact
- Inconclusive evidence; doubts exist about causality, and evidence is inconclusive/contradictory concerning an increased relative risk.

It is essential to take into account the fact that not all risk categories operate uniformly through-

Table 5 ■ **Outcome of the review of interventions to prevent diarrhoea (1982–1986)**

Conclusions	Interventions	Implication for CDD Programme
High effectiveness and feasibility	Promotion of breastfeeding Improving weaning practices	Added to or maintained on research and development agenda
	Improving water supply and sanitation Promoting personal and domestic hygiene	Messages included in early health education activities
	Rotavirus immunization Cholera immunization (in some circumstances)	Maintained on research agenda
	Measles immunization	Actively promoted as a programme strategy
Uncertain effectiveness, feasibility or cost	Preventing low-weight births Using growth charts	No action taken as being addressed by other programmes
	Increasing child spacing	Training module prepared with MCH Unit
	Vitamin A supplementation	Added to research agenda
	Improving food hygiene	Maintained in the research agenda
	Epidemic control	Incorporated into CDD
	Control of zoonotic reservoirs	No further action taken
Ineffective, limited feasibility or high cost	Enhancing lactation Supplementary feeding programmes Chemoprophylaxis Fly control	No further action taken

out the first five years of childhood and that 75 percent of pneumonia deaths occur during the first year of life, 58 percent of them within the first six months. This is in contrast to the pattern for diarrhoea deaths, where the comparable figures are 50 percent and 36 percent respectively. Pneumonia prevention interventions that address risk factors important early in life are therefore likely to have the greatest potential impact.

Eight interventions were identified with the potential to prevent 5 percent or more of childhood pneumonia deaths (see Table 6). However, four of these—pneumococcal, respiratory syncytial virus (RSV) and Hib vaccines, and the reduction of indoor biomass pollution—were based on theoretical calculations. Their efficacy is still to be established in field trials. Of the remaining four, reducing the prevalence of underweight and low birthweight was considered to be potentially highly effective. Increasing measles immunization coverage and increasing breastfeeding (in Latin America only) were found to be of potential medium effectiveness. Important regional differences for the three nutritional interventions are shown in Table 7.

Table 6 ■ **Outcome of review of interventions to prevent childhood deaths from pneumonia (1991–1995)**

High effectiveness (potential impact >10%)
- pneumococcal vaccines
- respiratory syncytial virus (RSV) vaccines
- reduction of indoor biomass pollution
- reduction of low birth weight
- reduction of underweight

Medium effectiveness (potential impact 5–10%)
- increase in measles immunization
- *H. influenzae* type b (Hib) vaccine
- increase in breastfeeding (Latin America only)

Table 7 ■ **Regional differences in expected reductions in pneumonia mortality from different nutritional interventions**

	Percent reduction in pneumonia deaths due to 40% decrease in prevalence of risk factor		
Region	**Low birth weight**	**Under-weight**	**Non-breastfeeding**
Sub-Saharan Africa	9.0	10.0	0.5
Middle East and North Africa	6.5	7.0	4.3
South Asia	14.0	13.3	2.2*
East Asia and Pacific	6.9	9.1	
Latin America and Caribbean	6.9	5.1	7.0
All less developed countries	10.1	10.7	3.3

* Available data for non-breastfeeding were not sufficient for separating the two Asian regions

Some interventions showed no evidence of impact on pneumonia mortality or morbidity; this information is equally important for policy formulation. These interventions included:

- use of antibiotics for upper respiratory tract infections (although such use is widespread);
- prophylactic use of antibiotics in severely malnourished children;
- vitamin A supplementation (except in relation to measles-associated pneumonia);
- treatment of helminth infections; and
- reduction of environmental tobacco smoke (although this is clearly implicated in other acute respiratory infections and childhood asthma in developed countries).

Preventive Intervention Research

The reviews described above significantly influenced the direction of CDD and ARI Programme activities. A number of interventions with the potential to effectively prevent diarrhoea and pneumonia deaths were identified and research was supported in the following key areas:

- infant and child feeding (promotion of breastfeeding, improving complementary feeding, micronutrient intake);
- vaccines (rotavirus, cholera, pneumococcal, *H. influenzae* type b);
- water supply, sanitation and hygiene; and
- indoor air pollution.

Infant and child feeding

Research focused initially on identifying infant feeding practices and their relationship with diarrhoeal illness and death, and on identifying determinants of breastfeeding. Attention then shifted to developing and evaluating interventions to promote breastfeeding and improve complementary feeding.

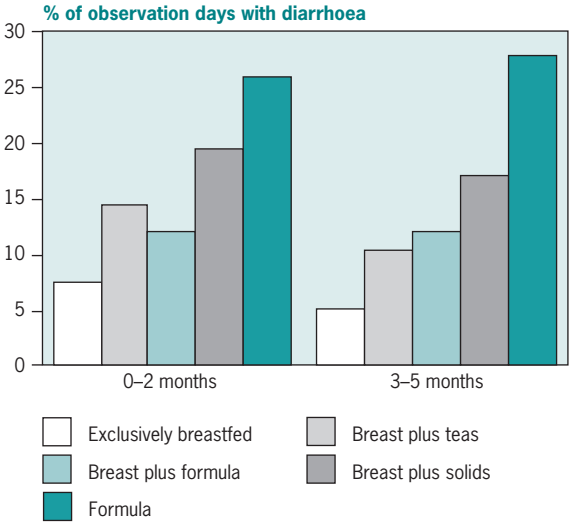
Promotion of breastfeeding

Infant feeding practices

In 1984–1985, the CDD Programme supported studies of the impact of feeding practices during early infancy on diarrhoea incidence in Brazil, Burma, Guatemala, Iraq, Kenya, Peru and Turkey. The Peru study showed that exclusively breastfed infants had the lowest prevalence of diarrhoea (see Figure 1) and the Brazil study showed that exclusively breastfed infants had a lower relative risk of severe and persistent diarrhoea (see Figure 2).

Figure 1

Prevalence of diarrhoea by feeding mode, Peru



Ref: Brown KH et al. Infant-feeding practices and their relationship with diarrhoeal and other diseases in Huascar (Lima) Peru. *Pediatrics*, 1989; **83**:31–40

Studies in the Philippines and Peru examined the risks associated with bottle-feeding. In the Peru study, 35 percent of bottle nipples and 23 percent of bottles were contaminated with faecal bacteria. In the Philippines study, around 90 percent of bottle-feeds were similarly contaminated.

On the basis of these and other subsequent studies, the CDD Programme in 1988–1989 recommended that:

- breastfeeding should be the exclusive mode of feeding during the first 4–6 months of life;
- use of teas and water during this period should be discouraged;
- use of feeding bottles should be strongly discouraged; and
- breastfeeding should be continued for as long as possible, at least for the first year of life.

Determinants of breastfeeding

CDD also supported studies of the determinants of breastfeeding. A Brazilian study in 1988–1989 showed that early termination of breastfeeding was associated with a delay in initiation of breastfeeding (12 hours or more after birth), lack of family support in the first two weeks after delivery, breastfeeding on schedule rather than on demand, the use of estrogen-based contraceptives, and the mother's perception of unsatisfactory growth of the infant. There was no association with the working status of the mother (4).

Interventions to promote breastfeeding

By 1990, the benefits of breastfeeding, particularly exclusive breastfeeding in the first 4–6 months of life, were well established. The focus of research then shifted to studies of interventions to promote breastfeeding.

The national programme for promotion, protection and support of breastfeeding in Guatemala was assessed, and studies in Peru and the Philippines examined community-based approaches to improving breastfeeding practices. CDD, however, continued to concentrate on assessing health facility-based activities in order to develop interventions that could complement ongoing activities to improve diarrhoea case management. By 1993, the positive impact of lactation management training for health workers and breastfeeding counselling for mothers had been demonstrated in Brazil (5) and Pakistan. In Pakistan, for example, 69 percent of infants whose mothers received counselling in an Islamabad lactation management clinic were exclusively breastfed at three months compared with 19 percent in a comparison group.

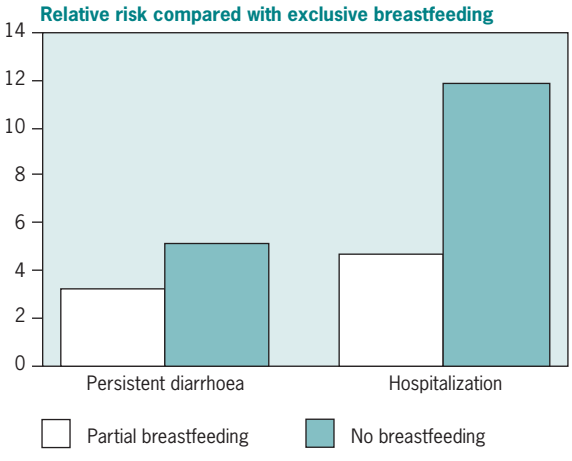
Improving interventions and their implementation

Studies supported by CDR during 1994–1995 focused on ways to improve the design and implementation of health facility-based interventions to promote breastfeeding practices. Research was conducted to:

- improve the content of interventions;
- assess potentially effective ongoing interventions; and
- develop and test new interventions.

Figure 2

Relative risk of persistent and severe diarrhoea among infants under 3 months of age, by feeding mode,* Brazil



* Age at one week

Subjects studied included the ideal duration of exclusive breastfeeding, and whether there are nutritional risks associated with the promotion of breastfeeding beyond the first year of life. Results from studies in Brazil and Honduras, supported in collaboration with the Thrasher Research Fund, UNICEF, La Leche League and USAID, indicated that exclusive breastfeeding can lead to adequate weight gain up to six months of age. The Honduran study suggested that the introduction of complementary foods at four months does not lead to increased energy intake, due to a concomitant reduction in intake from breastmilk (6), nor does it have long-term benefits in terms of weight gain. Infants who started supplementation at four and at six months had similar weight gains in the second semester of infancy (between 6–12 months of age) (7).

Breastfeeding improves nutritional status in young infants, but increased rates of malnutrition have been reported among children breastfed into their second year of life. A study in Peru that examined the association between breastfeeding practices and linear growth in children aged 12–15 months concluded that poor growth determined the continuation of breastfeeding rather than vice versa.

Other studies examined the determinants of breastfeeding in greater depth in order to guide the design of appropriate interventions. In particular, studies addressed the most common problems that lead to early termination or supplementation of breastfeeding, and other practices such as giving prelacteal feeds.

Results from earlier studies identified a strong association between pacifier use and risk of early termination of breastfeeding. Infants who used pacifiers were three to four times more likely to stop breastfeeding in the first six months of life than non-users (8,9). Further research was undertaken to determine whether this relationship was causal or due to confounding or reverse causality before deciding whether pacifier use should be addressed by an intervention.

A study in rural Guatemala found that more than half of the sample used prelacteal feeds—which increase the risk of infection—during the first two days after birth. Beyond the first two days, non-nutritive liquids were frequently given in addition to breastfeeding, for reasons that included feeding the child, quenching thirst or curing colic and stomach aches. There was no association between reports of insufficient milk and assessments of milk intake or child's weight-gain. Problems with attachment and positioning were observed mostly during the first week after delivery but tended to disappear after that. Complaints of sore nipples were most frequent in the second week.

Data collected at the lactation management clinic of the Children's Hospital in Islamabad, Pakistan, identified the most common breastfeeding problem to be inadequate attachment to the breast. According to mothers attending the clinic, the most common reason for supplementation was their perception of insufficient milk. More than two-thirds were diagnosed as mothers whose infants had problems with attachment to the breast. Poor attachment was responsible in most cases for other difficulties reported by mothers, such as breast engorgement and cracked or sore nipples. Correction of the attachment difficulty was associated with return to exclusive breast-

Malnutrition and breastfeeding beyond 12 months in Peru

A quantitative analysis was conducted on data from 134 children living in a poor, peri-urban community of Lima, Peru. The following potential predictors of length at 15 months were examined:

- Length at 12 months
- Time between length measurements
- Breastfeeding frequency
- Complementary food and animal protein intakes
- Diarrhoeal incidence between 12 and 14.9 months.

Lower linear growth was associated with increased breastfeeding frequency when diarrhoeal incidence was high and complementary food intakes were low.

To determine if this negative association reflected reverse causality, logistic regression was used. This showed that when diarrhoeal incidence was high, there was a significant decrease in probability of stopping breastfeeding at age 14 months when weight-for-age and food intake in the previous months were low.

Results from in-depth interviews with 36 mothers conducted in 1993–1994 supported the logistic regression results. Although maternal well-being was a primary reason for stopping breastfeeding, child health had a modifying effect. Termination of breastfeeding was delayed for ill or malnourished children. Mothers reintroduced breastfeeding after attempting weaning if the child adapted poorly, which is more likely with sick malnourished children.

The study concluded that the negative association between continued breastfeeding and slower growth in length, under poor dietary and health conditions, was probably because poor growth determined the continuation of breastfeeding and not vice versa. Breastfeeding in this community continues to have an important positive role in child health after the first year of life and should be promoted. ■

feeding and resolution of breast problems in over two-thirds of the cases.

These results suggested that training health workers to assess adequate attachment to the breast and to help mothers correct problems are key skills for the promotion of breastfeeding through health care services. These skills have been included in *Breastfeeding Counselling* and *Integrated Management of Childhood Illness* training courses.

CDR, in collaboration with the ICDDR,B, in Bangladesh, also supported the development and testing of a hospital-based breastfeeding counselling intervention for mothers of very young infants admitted to hospital. Results indicated that counselling had a very strong effect on feeding behaviour. The prevalence of exclusive breastfeeding two weeks after hospital discharge was approximately seven times higher among infants whose mothers had received counselling than among those who had received more generic health care advice.

Complementary feeding

Global estimates indicate that malnutrition is an underlying factor in approximately 55 percent of childhood deaths. Malnourished children face a risk of early death that is almost three times higher than among those who are well-nourished. Malnutrition is associated both with increased severity of diarrhoea, pneumonia and measles, and with increased mortality due to these diseases. For ex-

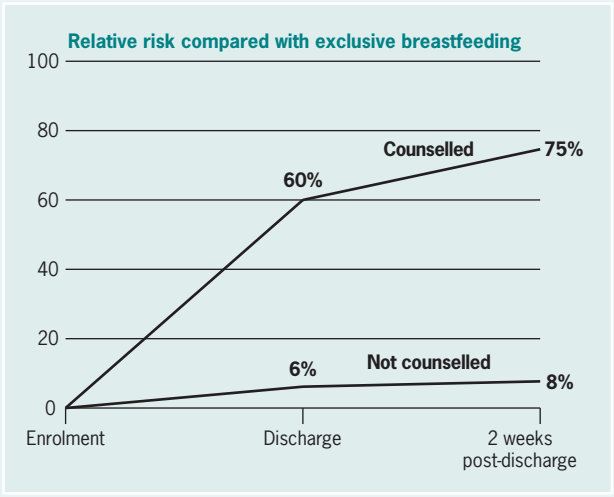
Pacifier use and duration of breastfeeding, Brazil

The association between pacifier use and duration of breastfeeding was assessed in southern Brazil through visits to a population-based cohort of 650 mothers and infants shortly after delivery, and at one, three and six months. Pacifier use was very common, with 85 percent of the infants using them at one month of age. Those who had recently stopped breastfeeding were highly likely to subsequently use a pacifier. Excluding all infants who were not breastfed at one month of age and those who reportedly had breastfeeding problems, data for 450 infants was analysed. Intense pacifier users (children who used the pacifier during most of the day and at least until falling asleep) at one month of age were four times more likely to stop breastfeeding by six months of age than non-users. Pacifier users also had fewer daily breastfeeds than non-users. Several potential confounding variables were assessed but after adjustment through logistic regression, pacifier use was still associated with an odds ratio of 2.5 (95 percent confidence interval 1.40 to 4.01).

A sub-sample of 80 mothers and infants was selected for an ethnographic study that included in-depth interviews and participant observations. Analysis showed that pacifier use was widely regarded as a positive behaviour and mothers often strongly stimulated the infant to accept a pacifier. While few mothers openly admitted that pacifiers might shorten breastfeeding, a considerable number used pacifiers to terminate or space feeds. Pacifiers may thus be an effective weaning mechanism used by mothers who have explicit or implicit difficulties in breastfeeding. Promotional campaigns to reduce pacifier use will fail unless they also support women in breastfeeding. ■

Helping mothers of hospitalized infants to breastfeed exclusively

A 1994 prospective study in Bangladesh assessed whether exclusive breastfeeding can be achieved and sustained in partially breastfed infants admitted to hospital with diarrhoea. One hundred partially breastfed young infants (up to 12 weeks) were identified and randomized to the intervention group or control group and given treatment for dehydration. Mothers in the intervention group were counselled individually by trained lactation counsellors during their hospital stay and again at home one week after discharge. Mothers in the control group were also followed up at home but were not given individual breastfeeding counselling. A physician who had not been involved in the counselling assessed both groups at home two weeks after discharge. The effects of lactation counselling on exclusive breastfeeding are shown below.



Baseline characteristics and feeding histories of the two groups of mother-infant pairs were comparable on admission to hospital. On discharge, however, the rate of exclusive breastfeeding in the counselled group had risen to 62 percent (31/49) but was only 4 percent (2/49) in the non-counselled group. Large differences were still observed two weeks after discharge, with 77 percent (33/43) of the infants in the intervention group exclusively breastfed, compared with only 9 percent (4/43) of infants in the control group ($p < 0.0001$).

These results suggest that, with adequate breastfeeding counselling and support, it is feasible for the majority of mothers of very high-risk infants to be converted to exclusive breastfeeding during their hospital stay and to sustain this practice at home for a period of at least two weeks. ■

Use of research in the promotion of breastfeeding (1984–1995)

1984
Review suggests the importance of promotion of breast-feeding as an intervention for control of diarrhoea (a).

1985–1987
Breastfeeding significantly reduces the risk of diarrhoea mortality, the severity of diarrhoea and the incidence of severe shigellosis (b-e).

1988–1990
Importance of exclusive of breastfeeding: even additional water feeds double the risk of diarrhoea; breastfeeding protects against severe diarrhoea up to age of three years; protection by breastfeeding is higher where maternal literacy is lower or sanitation is worse; breastfeeding is important in the management of current diarrhoea episodes (it protects against the adverse nutritional effects of diarrhoea, shortens duration of episodes and is associated with lower mortality among hospitalized cases). Health care services' practices confirmed as important determinants of breastfeeding (f-o).

- CDR decides to start implementation of breastfeeding activities and hires staff for this purpose.
- WHO and UNICEF state 10 Steps to Successful Breastfeeding and launch the Baby Friendly Hospital Initiative.
- Innocenti Declaration calls for training of health workers to support breastfeeding.

1991–1993
Breastfeeding counselling is a highly effective intervention for the promotion of breastfeeding (p,q).

- CDR completes the development of *Breastfeeding Counselling: a Training Course*.
- CDR convenes meetings of experts to define indicators for assessing breastfeeding practices at the community level and health facility practices that affect breastfeeding.
- CDR incorporates breastfeeding indicators into household survey manual.

1994–1995
Research confirms breastfeeding counselling effectiveness and explores approaches to deliver the counselling intervention (r,s). Protocol for the evaluation of CDD's breastfeeding counselling training course is developed.

- Breastfeeding counselling is incorporated in the WHO/UNICEF course *Integrated Management of Childhood Illness*.

(a) Feachem RG et al. Interventions for the control of diarrhoeal diseases among young children: promotion of breastfeeding. *Bulletin of the World Health Organization*, 1984, **62**:271–91.

(b) Victora CG et al. Evidence for protection of breastfeeding against infant deaths from infectious diseases in Brazil. *Lancet*, 1987, **330**:319–22.

(c) Habicht JP et al. Does breast-feeding really save lives, or are apparent benefits due to biases? *American journal of epidemiology*, 1986, **123**:279–90.

(d) Briend A. et al. Breastfeeding, nutritional state and child survival in rural Bangladesh. *British medical journal*, 1988, **296**:879–82.

(e) Clemens JD et al. Breastfeeding and determinants of severity of shigellosis. *American journal of epidemiology*, 1986, **123**:710–20.

(f) Brown KH et al. Infant feeding practices and their relationship with diarrhoeal and other diseases in Huascar (Lima), Peru. *Pediatrics*, 1989, **83**:31–40.

(g) Popkin BM et al. Breastfeeding and diarrhoeal morbidity. *Pediatrics*, 1990, **86**:874–82.

(h) Victora CG et al. Infant feeding and deaths due to diarrhoea. A case-control study. *American journal of epidemiology*, 1989, **129**:1032–41.

(i) Clemens JD et al. Breastfeeding and the risk of severe cholera in rural Bangladeshi children. *American journal of epidemiology*, 1990, **131**:400–411.

(j) Martines JC. *The interrelationships between feeding mode, malnutrition and diarrhoea morbidity in early infancy among the urban poor in southern Brazil* (PhD Thesis). London, University of London, 1988.

(k) Habicht JP et al. Mother's milk and sewage: their interactive effects on infant mortality. *Pediatrics*, 1988, **81**:456–61.

(l) Rowland MGM et al. Impact of infection on the growth of children from 0 to 2 years in an urban West African community. *American journal of clinical nutrition*, 1988, **47**:134–8.

(m) Brown KH et al. Effect of common illnesses on infants' energy intakes from breast milk and other foods during longitudinal community-based studies in Huascar (Lima), Peru. *American journal of clinical nutrition*, 1990, **52**:1005–113.

(n) Dickin KL et al. Effect of diarrhoea on energy intake by infants and young children in rural villages in Kwara State, Nigeria. *European journal of clinical nutrition*, 1990, **44**:307–17.

(o) Chalmers I et al. *Effective care in pregnancy and childbirth*. Oxford, Oxford University Press, 1989.

(p) Pérez-Escamilla R et al. Effect of the maternity ward system on the lactation success of low-income urban Mexican women. *Early human development*, 1992, **31**:25–40.

(q) Pérez-Escamilla R et al. Infant feeding policies in maternity wards and their effect on breastfeeding success: an overview. *American journal of public health*, 1994, **84**:89–97.

(r) Valdez V. The impact of hospital and clinic-based breastfeeding promotion programme in a middle-class urban environment. *Journal of tropical pediatrics*, 1993, **39**:142–51.

(s) Haider R. et al. Breastfeeding counselling in a diarrhoeal disease hospital. *Bulletin of the World Health Organization*, 1996, **74**(2):173–179.

ample, in malnourished children diarrhoeal episodes last longer and may be more frequent than in well-nourished children.

Since the reviews of preventive interventions linked improved complementary feeding to significant reductions in the prevalence of malnutrition and its associated morbidity and mortality (10), the CDD Programme supported a number of studies to improve complementary feeding (previously called weaning practices).

Safety and energy density of foods

Early studies confirmed that impaired growth in the 6–11 month age period reflected not only the effects of repeated illness, but also less than adequate energy intake. Subsequently, the importance of specific nutrient content has been emphasized, and research since 1988 has included a number of studies on the safety of complementary foods and how to increase energy intake.

A literature review examined the potential of traditional technologies such as malting and fermentation to increase the energy density and safety of weaning foods. Although malting can increase energy density, it was not shown to increase energy intake. And while fermentation may limit bacterial contamination, it is unlikely to affect energy density substantially. Neither approach was considered to have sufficient benefit to warrant promotion in areas where they are not already traditionally practiced.

Studies in Guatemala, Peru and the Philippines demonstrated that poor energy density of food and low frequency and small size of feeds are all important factors in inadequate energy intake, but that their relative importance varies from place to place. In Guatemala, for example, children aged 6–24 months whose energy intake was below the mean were consuming food of equal energy density to those whose energy intake was higher. They were, however, fed smaller meals and less frequently. This tendency was even greater during diarrhoea (see Table 8). In contrast, in Peru, energy density of foods was too low, with soups being the most frequent component of meals.

Interventions to improve complementary feeding practices

During 1994–1995, CDR supported the development and testing of interventions to promote improved complementary feeding practices. In Guatemala and Peru, studies used the findings reported above to develop appropriate interventions. The intervention developed in Guatemala focused on increasing food consumption by promoting higher frequency of feeding (five times per day) and encouraging mothers to take a more active role in stimulating children to eat (see results in box below). In Peru, the intervention focused on the promotion of thicker, more energy dense foods, and results indicate a nearly four-fold increase (from 12 percent to 45 percent) in the proportion of children aged 6–12 months receiving energy-dense complementary foods twice a day.

Improving micronutrient intake

The preventive intervention reviews identified a lack of information on the effectiveness of vitamin A supplementation. Vitamin A studies were added to the research agenda in 1990 (11) after accumulated evidence suggested a major impact on mortality. From 1992–1993, research on zinc supplementation was also carried out after published studies showed positive effects on diarrhoea and growth.

Vitamin A

In 1990, the CDD Programme supported two randomized, double-blind, placebo-controlled trials of vitamin A supplementation in Brazil and India.

In north-eastern Brazil, 1,200 children aged 6–36 months were supplemented with either 100,000–200,000 IU of vitamin A or a placebo every four months and followed prospectively for one year through thrice-weekly home visits. Results indicated that vitamin A supplementation reduced the overall incidence of diarrhoea by 6 percent. Its protective effects were particularly strong in relation to episodes with six or more diarrhoeal

Table 8 ■ **Feeding characteristics of 26 children aged 6–24 months by total energy intake level, Guatemala**

		Children with total energy intake:	
Characteristic of feeding	**Health status**	**Above mean**	**Below mean**
Frequency (meals/day)	Healthy	4.7	4.0
	During diarrhoea	3.9	2.8
Energy density (kcal/g)	Healthy	0.97	0.93
	During diarrhoea	1.0	0.97
Quantity consumed (g)	Healthy	699	347
	During diarrhoea	639	199

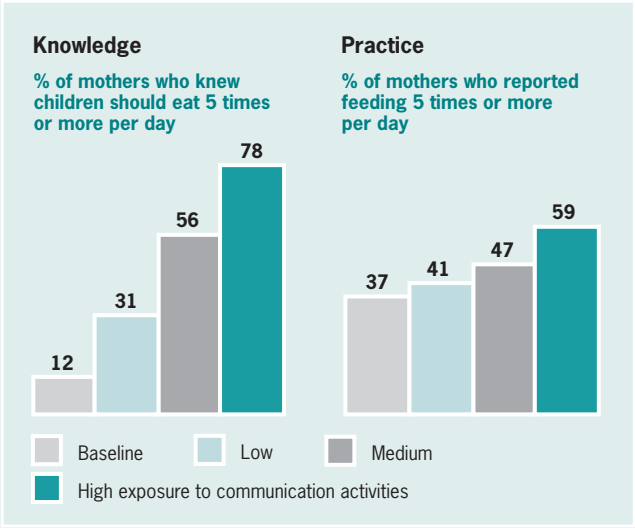
Source: Rivera J et al. Report to CDR.

Promotion of increased frequency of feeding in rural Guatemala

The year-long intervention was implemented in nine communities in rural Guatemala and was directed to mothers of children aged 6–24 months. Secondary audiences included fathers, schoolchildren and health care providers. Health personnel, schoolchildren, posters, talks, games, and health fairs were used as communication channels. Promotional materials developed included a lottery game and educational materials for schoolchildren, health care providers and health promoters.

The figure below shows the impact of the intervention on mothers' knowledge and practice. Knowledge of how frequently children should be fed increased according to exposure to communication activities. Among the group of mothers with the greatest level of exposure, 78 percent responded correctly to the question compared to 12 percent at baseline.

The percentage of mothers who reported feeding five or more times a day also increased with exposure to the intervention, reaching 59 percent from 37 percent at baseline among those with the highest exposure. Observational studies validated the reported behaviours, indicating a high degree of association between reported and observed behaviours (sensitivity 76 percent, specificity 75 percent, and positive predictive value 78 percent). ■



Source: River J et al. Report to CDR

stools a day, with a 23 percent reduction in the prevalence of such high purging episodes. The protective effect was greater in the first month after supplementation and tended to decrease over time until it almost disappeared four months after supplementation (see Figure 3). No effects of supplementation were detected in the incidence or severity of respiratory infections (12).

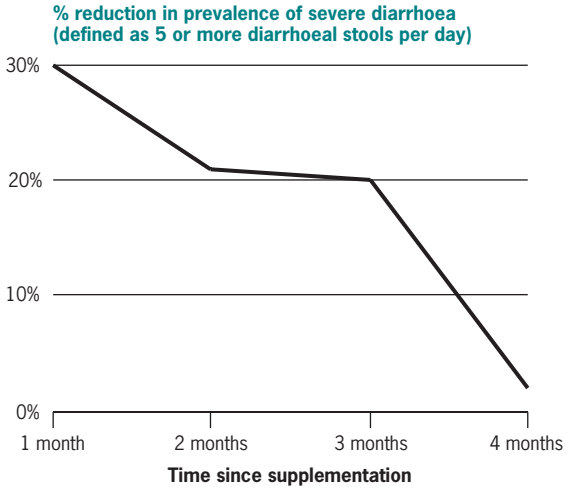
In 1990 in India, 900 children aged 12–36 months attending a health facility for the treatment of diarrhoea received 200,000 IU of vitamin A or a placebo. The children were followed for 90 days after the end of the episode through twice-weekly home visits. Analysis of data during 1994–1995 showed substantial reductions in severity and persistence of diarrhoea episodes among non-breastfed children who received vitamin A supplementation (see Figure 4).

The ARI programme undertook a meta-analysis of available information after the initial results from the India study indicated that vitamin A supplementation may increase the risk of acute respiratory infections in young children (13). The findings from this analysis did not exclude the possibility of supplementation leading to an increased risk of mortality in younger children and its association with increased risk of pneumonia (14).

The results of the India study and of the meta-analysis prompted CDR to initiate a multicentre

Figure 3

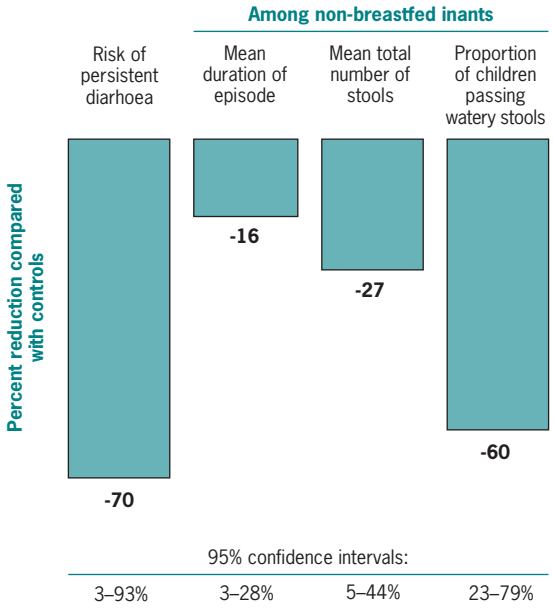
Protective effect of vitamin A: Reduction in diarrhoea prevalence by time since supplementation



trial to examine the safety and benefits of vitamin A supplementation and the efficacy of linking delivery of supplements to immunizations in early infancy. A randomized, double-blind, placebo-controlled study was implemented in collaboration with the Ghanaian Ministry of Health, All India Institute of Medical Sciences, Instituto de Investigacion Nutricional in Peru, Johns Hopkins University, U.S., London School of Hygiene and

Figure 4

Effect of vitamin A supplementation during acute diarrhoea on severity and persistence, India, 1990



Tropical Medicine, and USAID.

The intervention consisted of maternal supplementation of 200,000 IU of vitamin A within the first four weeks after delivery and infant supplementation of 25,000 IU of vitamin A at each of the recommended immunization contacts (at six, 10, 14 weeks and nine months). The study involved follow-up of approximately 10,000 infants through monthly home visits from birth to nine months. Results indicate that early supplementation is safe, but has no benefits in terms of reducing morbidity, and its effect on vitamin A status is limited and short-lived.

Since earlier findings suggested that supplementation may interfere with immune response, substudies are examining the effects of vitamin A supplementation on the response to measles and polio immunizations. A sub-study has also been supported to examine whether the presentation of bulging fontanelles, a potentially common side-effect of vitamin A supplementation, is associated with impairments in psychomotor development.

Zinc

In collaboration with the Thrasher Research Fund, CDR supported a randomized, double-blind, placebo-controlled trial of zinc supplementation during diarrhoea (15). Results from this 1995 trial in India indicate significant benefits from supplementation (see Figure 5). Continued supplementation for six months following the enrolment episode reduced by 49 percent the incidence of persistent diarrhoea among children older than 11 months, and by 43 percent the incidence of radiologically confirmed pneumonia.

Another randomized, double-blind, placebo-controlled trial has been completed in rural Mexico, in collaboration with the Applied Diarrhoeal Diseases Research Project (ADDR), to examine the effects of improving zinc intake on appetite, food consumption and growth. This study showed that supplementation among infants 8–14 months was associated with significant increases in longitudinal growth. Supplemented infants also displayed significantly increased appetite (measured as active search for food).

Vaccines

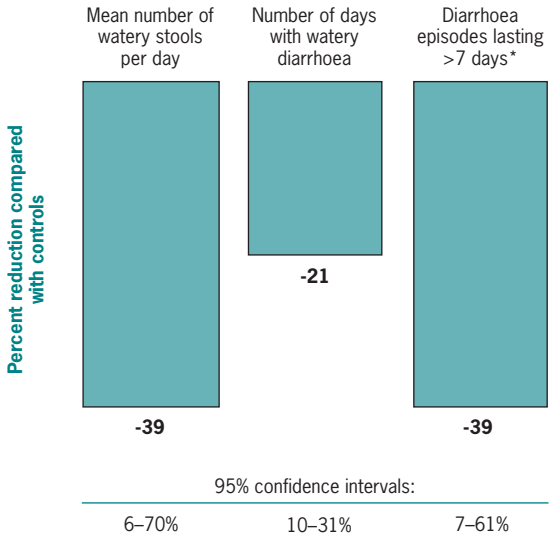
From the beginning, both the CDD and ARI Programmes supported research related to candidate vaccines for the leading causes of acute diarrhoea and pneumonia, including rotavirus, *Vibrio cholerae*, *H. influenzae* type b and *Streptococcus pneumoniae*. Achievements in vaccine research are summarized below. Shigella vaccine research has also been supported but is not included in this section, as studies did not lead to the development of a candidate vaccine.

Rotavirus

Research has focused on developing a safe and effective vaccine for young infants in developing

Figure 5

Effect of zinc supplementation during acute diarrhoea on severity and persistence, India, 1995



** When zinc started within 3 days of onset of diarrhoea*

countries that protects against illness caused by the four important serotypes of rotavirus. Such a vaccine could possibly be given together with oral polio vaccine.

Between 1983 and 1987, the CDD Programme supported studies of several candidate vaccines. Trials were conducted on three vaccines based on bovine or rhesus rotaviruses. Evaluation of a tetravalent rhesus-human vaccine, the approach that now appears most promising, was also begun. The tetravalent vaccine consists of rhesus rotavirus (RRV) containing RNA that encodes the production of the VP7 serotype proteins of human rotavirus. RRV-tetravalent (TV) vaccine consists of rhesus-human reassortant viruses for serotypes 1, 2 and 4, and RRV for serotype 3.

Studies in the United States, supported by the vaccine manufacturer, Wyeth-Ayerst Laboratories, have shown that three doses of RRV-TV vaccine containing 4x105 pfu provide up to 80 percent protection against severe rotavirus diarrhoea. On the basis of this information, the company recently licensed the vaccine in North America and Europe.

It remains uncertain, however, whether the same level of protection can be achieved in developing countries, where rotavirus is the most important cause of dehydrating diarrhoea in infants. In trials in Brazil (16) and Peru, three doses of RRV-TV (4x104 pfu) provided only 20–50 percent protection against all episodes of rotavirus diarrhoea during the first year after immunization and little or no protection in the second year. It is hoped that a vaccine dose of 4x105 pfu would provide a higher level and longer duration of protection. CDR supported a trial of 2,500 infants using this dose in Venezuela. The trial was designed to assess vaccine-induced protection against severe rotavirus diarrhoea. During the three years of surveillance, 221 episodes of serious rotavirus diarrhoea were detected, which should provide definitive information.

The results of this study showed that immunization with RRV-TV significantly reduced the incidence of all episodes of rotavirus diarrhoea. The greatest impact was on admission to hospital for rotavirus diarrhoea and on the occurrence of clinically severe illness. These encouraging results show that the vaccine is as effective in this population as in the United States, and suggest that it could be used in developing countries with socioeconomic conditions similar to those of Venezuela. Further evaluation of the vaccine may be needed, however, to determine its efficacy in poorer countries where earlier candidate vaccines performed poorly.

Cholera

When the CDD Programme began in 1980 there was no effective vaccine against cholera. The Programme supported research into the development of vaccines using both killed antigens and living avirulent bacterial mutants given orally. The two candidate oral vaccines that emerged as most promising were evaluated in large-scale trials in populations with endemic cholera, as described below.

With the emergence in late 1992 of a new cholera-causing strain of *Vibrio cholerae*, designated *Vibrio cholerae* O139, attention turned to developing vaccines against both the O1 and O139 serotypes. A field trial of a candidate combined vaccine is ongoing in Viet Nam.

CAH and WHO's Department of Vaccines and Other Biologicals (VAB) are collaborating to develop recommendations on the use of the new vaccines to prevent and control cholera. Guidelines have been developed on their use in emergencies, such as refugee crises or natural disasters, and on their use to control endemic cholera.

Killed oral whole-cell/recombinant B-subunit (WC/rB) vaccine

In collaboration with researchers in Bangladesh, Sweden and the U.S., the Programme supported evaluation of an oral vaccine produced by the Swedish Bacteriological Laboratories and Institut Mérieux, France, composed of killed *Vibrio cholerae* O1 and purified non-toxic B subunit of the cholera toxin (WC/B vaccine).

The first trial took place in Bangladesh between 1985 and 1988. Results are shown in Table 9 (17,18). Three doses of WC/B vaccine gave 85 percent protection against cholera for six months and an average of 50 percent protection in all ages over three years. The decline was due largely to the brief duration of protection in young children.

Vaccine containing only killed whole bacteria (WC) was less effective during the first six months, but had similar efficacy over three years. The trial also showed that vaccine efficacy was reduced in persons with O blood group or infection caused by the El Tor biotype of *V. cholerae* O1.

Following this trial a modified vaccine was developed in which natural B subunit was replaced by a recombinant B subunit (WC/rB), which facilitated large-scale production at lower cost.

Three efficacy trials were started in Peru after trials supported by the CDR Programme in Colombia and Mexico showed the modified vaccine to be safe and immunogenic. The Peru trials sought to confirm the safety and immunogenicity of a modified vaccine containing recombinant B subunit, to

Table 9 ■ **Efficacy of oral whole-cell/B-subunit (WC/B) cholera vaccine and whole-cell (WC) vaccine alone, Bangladesh**[a]

Period of surveillance	Age	Vaccine efficacy (percent)[b] WC	WC/BS
6 months		58	85
12 months	> 6 years	66	76
	< 6 years	31	38
36 months		52	50

Notes:
[a] Three doses of vaccine were given at 6-week intervals
[b] Protection against cholera presenting for treatment

evaluate this vaccine using modified immunization schedules, and to assess protection where O blood group is predominant and where all cholera is caused by the El Tor biotype.

The first was a small trial conducted in healthy young men given two doses of vaccine at one to two-week intervals. In this trial, supported from other sources, the vaccine provided 86 percent protection for 4–6 months (after which the trial was ended), showing that two doses of vaccine are as effective as three. The second trial, also supported from other sources, assessed vaccine efficacy over two years using an initial two-dose immunization followed by a single booster dose after one year. A third trial, supported by CDR and the WHO Regional Office for the Americas, involved 90,000 persons aged 2–60 years who were also given two doses of vaccine. This trial, however, was inconclusive owing to too few cases of cholera in the year following immunization.

Live oral vaccine CVD 103-HgR

The Programme first supported evaluation of live oral vaccine CVD 103-HgR in 1988. The vaccine consists of a strain of *V. cholerae* O1, classical biotype, which lacks the genes that encode the toxic A subunit of cholera toxin, although production of B subunit is normal. Vaccine safety and immunogenicity were studied in trials in North and South America and Asia, some of which were supported by CDR (19). Studies in volunteers have also shown that single-dose immunization gives high-level protection against cholera introduced in experimental conditions. Protection is established within eight days and lasts at least six months. In contrast with WC/rB vaccine, immunized volunteers did not shed V. cholerae O1 in their faeces, which suggests that the vaccine might interrupt the spread of infection.

In collaboration with the vaccine manufacturer, Swiss Serum and Vaccine Institute, CDR helped develop and support the first field trial of this vaccine. The trial in Indonesia in 1993, involving 66,000 adults and children, showed that a single dose of the vaccine failed to give significant protection. An oral vaccine based on *El Tor* strains from the current pandemic could possibly prove effective, and such vaccines are being developed.

Typhoid fever

The traditional parenteral vaccine for typhoid fever is effective, but frequent side-effects prevent wide adoption for public health use. Between 1981 and 1990, the CDD Programme supported the evaluation of two new vaccines that were essentially free of side-effects.

The first, a live oral vaccine designated Ty21a, is based on an avirulent mutant of *Salmonella typhi*. Trials showed that the formulation being marketed in 1981 was ineffective. Subsequent trials evaluated modified formulations designed to protect the vaccine—enteric-coated capsules or dissolved in a buffer solution—during passage through the stomach. When at least three doses were given, substantial protection developed and lasted for at least three years (20,21) (see Table 10). The liquid preparation gave greater protection than did capsules.

The second is an injectable vaccine containing the purified Vi capsular polysaccharide antigen of *Salmonella typhi*. Studies supported by other sources showed that a single dose of this vaccine gave substantial protection for at least two years. Studies supported by the Programme to determine whether the vaccine might be effective in infants or young children, showed that the vaccine reduced immunogenicity in infants, as did other polysaccharide antigens. However, significant responses in one-year-old children suggest the vaccine would be effective in this age group.

Haemophilus influenzae type b

Haemophilus influenzae type b (Hib) causes 5–10 percent of life-threatening episodes of pneumonia

Table 10 ■ **Efficacy of live oral Ty21a typhoid vaccine**

Location	Immunization schedule	Age (years)	Vaccine formulation	Vaccine efficacy[c]
Indonesia	3 doses, 7-day intervals	3–14	liquid	53
			capsule	42
		15–44	liquid	64
			capsule	58
Chile	3 doses, 2-day intervals	5–14	liquid	77
			capsule	33

[c] After 30–37 months of follow-up

in infants and young children in developing countries. It is also the leading cause of bacterial meningitis in young children. Studies in Finland, Iceland and the U.S. have shown that Hib vaccines, composed of the purified capsular polyribose-phosphate (PRP) antigen of Hib conjugated to a protein carrier, are highly effective for preventing Hib meningitis in infants. These vaccines also prevent nasopharyngeal carriage of Hib, which plays an important role in transmission of infection from person to person. Hib meningitis has virtually disappeared in developed countries where the vaccines have been widely used.

CDR helped to organize and support the first trial to evaluate the efficacy of Hib conjugate vaccine in preventing pneumonia and meningitis in a developing country setting. The trial in the Gambia used a Hib vaccine containing PRP conjugated to a tetanus toxoid carrier (PRP-T), supplied by Pasteur-Mérieux Vaccines of France. The trial was supported by other agencies including the UK Medical Research Council, USAID, U.S. National Vaccine Programme, UNICEF, UNDP and the CVI.

Infants were given three doses of PRP-T (or a placebo) mixed with standard diphtheria-pertussis-tetanus (DPT) vaccine at two, three and four months of age. The trial was completed at the end of 1995 and results showed that the vaccine was highly protective against pneumonia caused by Hib and against all invasive Hib disease (chiefly pneumonia and meningitis). The vaccine's immunogenicity and safety was confirmed. It also reduced asymptomatic nasopharyngeal colonization with Hib in vaccinated infants, suggesting that it might evoke significant herd immunity, as occurs in developed countries.

These results provide strong support for use of the vaccine in EPI programmes in developing countries, possibly in combination with DPT. CAH is collaborating with VAB to implement the vaccine in several developing countries and to evaluate effectiveness of the vaccine when delivered by national EPI programmes. Preliminary results from an ongoing trial in the Gambia have shown a decrease in the incidence of Hib-related disease by two-thirds, and a decrease in carriage of the organism from 8–15 percent to 3.3 percent.

Pneumococcal vaccines

Streptococcus pneumoniae causes more than half the episodes of life-threatening pneumonia among infants and young children in developing countries. Development of an effective pneumococcal vaccine for use in infants has been a high priority.

About 70 percent of invasive pneumococcal infections in children are caused by nine common serotypes of the organism. Immunity appears to be largely mediated by antibody to the type-specific capsular polysaccharide antigen. Success with Hib conjugate vaccines prompted efforts to develop a pneumococcal vaccine for infants, which is also based on capsular antigens conjugated to protein carriers. One U.S. manufacturer has developed a nine-valent vaccine with support from the National Institutes of Health. Similar vaccines are being developed by two other manufacturers and through a collaborative effort involving the Nordic countries and the Netherlands.

In 1993, the Division organized a meeting to agree on the objectives and basic design of trials of pneumococcal vaccine safety, immunogenicity and efficacy. One outcome was agreement to standardize serological testing procedures to facilitate comparison of the results of different studies. Comparison of existing assay methods in 26 laboratories was then completed and a subsequent meeting concluded that a single standard assay would give the best results. A standard assay has been designed and is now being evaluated.

One or two initial large-scale efficacy trials of the new vaccines in developing countries are required. Smaller trials are also required to address questions such as vaccine safety and immunogenicity related to immunization schedules, combining pneumococcal vaccine with other EPI vaccines, and vaccine efficacy in different populations. In collaboration with the U.S. National Institutes of Health and USAID, the Division developed a large-scale efficacy trial. A second trial is ongoing in South Africa with support from one of the vaccine manufacturers.

Water supply, sanitation and hygiene

Improving water supply and sanitation, and promoting personal and domestic hygiene were identified as highly effective, feasible interventions to control diarrhoea. The CDD Programme focused on examining associated risk factors, determinants and interventions at the community and household level.

Quantity versus quality of water

Early studies in Nicaragua and Nigeria indicated that water availability was more important than water quality in the prevention of diarrhoea, probably because an adequate quantity of water facilitates hygiene practices. This finding influenced the content of health education messages related to water use.

Hygiene practices and handwashing

Descriptive studies of hygiene-related practices were carried out in Nigeria, Papua New Guinea and the Philippines. In the Nigerian study, handwashing was observed to occur before food preparation and child feeding in only 1 percent of instances. In the Philippines, children living in environments with the worst score on a group of hygiene indicators were six times more likely to be hospitalized with diarrhoea than those living in highly rated environments, even after controlling for potential confounding variables.

Further studies were conducted in Guatemala, Pakistan and Peru in 1989–1990 to identify specific hygiene-related practices associated with increased or decreased diarrhoea as a basis for defining interventions to be tested.

In Guatemala, small tilting plastic water containers ("tippy taps") were introduced along with intensive interpersonal health education to encourage handwashing. Although the study was disrupted by a cholera outbreak, the limited data available suggested a positive impact, and no cholera cases occurred in the study households.

A randomized controlled trial in Peru examined the impact of the following interventions: handwashing with soap before eating, before cooking and after defecation; reducing the contact of young children with human and animal faeces by using playpens and corralling animals; and reducing the contamination of the external water source and household water containers. Only handwashing (in isolation or in combination with the other sets) had a significant effect on reducing the incidence of diarrhoea.

Based on these findings, the Programme strongly emphasized handwashing with soap in its preventive health education messages.

Priority hygiene behaviours

In May 1992, a consultation was held jointly with WHO's Community Water Supply and Sanitation Unit (CWS) to identify key hygiene behaviours for the prevention of diarrhoea and to review available information on approaches to promoting behavioural change. Three sets of hygiene behaviours were identified as being of highest priority:

- Sanitary disposal of faeces (with emphasis on faeces of young children and babies, and of people with diarrhoea);
- Hand-washing (after defecation, after handling babies' faeces, before preparing food, and before feeding and eating); and
- Maintaining drinking water free from faecal contamination (in the home and at the source).

CWS subsequently coordinated hygiene-related research within WHO and the CDD Programme focused its attention on nutrition-related preventive interventions and vaccine trials.

Indoor air pollution

The review of interventions to prevent pneumonia suggested the need for more information on the impact of reducing indoor air pollution.

Research studies, initiated by CDR in 1992, have focused on establishing the level of reduction in air pollutants required to achieve a significant impact on pneumonia mortality and morbidity, and the potential impact of reducing indoor air pollution on the incidence of low birthweight, thought to be related to maternal respiratory morbidity.

Intervention trials have been developed, in collaboration with the International Development Research Centre (IDRC), Canada, to assess the impact of reducing indoor air pollution from biomass fuels on the incidence of pneumonia in childhood, on low birthweight, and on maternal respiratory morbidity.

Preparatory studies have been conducted in Guatemala to validate methods of measuring key air pollutants and to explore behavioural factors that will be important in the implementation of the trials. Implementation of a study in South Africa is under preparation.

4. Research in Case Management

Over the years, case management became an increasingly important focus of CDD and ARI Programme research. Research efforts followed two tracts: the improvement in case management of diarrhoea, acute respiratory infections, serious bacterial infections and severe malnutrition at *health facilities*; and the improvement in case management of diarrhoea and of acute respiratory infections in the *home*.

CDD priorities included developing improved oral rehydration salts (ORS) formulations, identifying the most effective dietary regimens for acute and persistent diarrhoea, and assessing the usefulness of drug treatment in acute and persistent diarrhoea and dysentery. ARI studies concentrated on validating the use of simple signs to detect pneumonia, on issues related to antimicrobial resistance, and on methods for administering oxygen.

Findings from case management research also provided the basis for Integrated Management of Childhood Illness (IMCI), which is described in this section as well.

4.1 Case Management in Health Facilities

Diarrhoea

Since 1980, the CDD Programme gave highest priority to research efforts to improve the management of diarrhoea by:

- developing improved ORS formulations;
- defining appropriate dietary regimens and assessing the usefulness of drugs for *acute diarrhoea*;
- defining appropriate dietary regimens and assessing the usefulness of antibiotics in the management of *persistent diarrhoea*; and
- developing treatment guidelines for *dysentery*.

ORS formulations

By the time the CDD Programme was formed in 1980, the standard formula for ORS had already been determined at a meeting in 1978, based on research results available at that time.[2] Studies in many countries between 1980 and 1986 demonstrated the efficacy and safety of standard ORS, including in young infants and in malnourished children.

Improved stability

Studies supported by the Programme in 1983–1984 compared standard ORS containing sodium bicarbonate with a new formulation containing trisodium citrate, dihydrate. A series of eight studies was undertaken, five supported by the Programme in various countries and three by the International Centre for Diarrhoeal Disease Research, Bangladesh, (ICDDR,B). Citrate ORS[3] was adopted in 1985 as the recommended WHO formula after studies showed it to be clinically as effective as bicarbonate ORS and considerably more stable, and therefore more simply and cheaply packed.

Enhanced absorption

ORS solution works through the coupled active transport of sodium and glucose across the brush border membrane of the enterocyte, which results in passive absorption of water and other electrolytes from the small intestine. Glucose is not the only water-soluble organic molecule that can enhance the absorption of sodium from the small intestine. Two groups of organic solutes are absorbed efficiently and relatively independently of each other by the small intestine and enhance the absorption of sodium and water:

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[2] The following composition of oral rehydration fluid (in g/l) was recommended: sodium chloride – 3.5; potassium chloride – 1.5; sodium bicarbonate – 2.5; glucose – 20. The composition resulted in the following concentrations (in mmol/l): sodium – 90; potassium – 20; chloride – 80; bicarbonate – 30; glucose – 111.

[3] The new formulation of oral rehydration fluid (in g/l) was: sodium chloride – 3.5; potassium chloride – 1.5; trisodium citrate, dihydrate – 2.9; glucose – 20. This composition resulted in the following concentrations (in mmol/l): sodium – 90; potassium – 20; chloride – 80; citrate – 10; glucose – 111.

- D-hexoses—oligosaccharide mixtures (several grades of maltodextrins also called glucose syrup solids or corn syrup solids) and polysaccharides (starch from rice or other cereals).
- Amino acids—glycine, L-alanine, L-glutamine and dipeptides of neutral amino acids.

Since 1984, research focused on these two groups of organic solutes. The aim was to develop and test improved ORS formulations that could not only successfully replace the deficit of salts and water during diarrhoea, but also actively induce the reabsorption of intestinal secretions, which would reduce the volume and duration of diarrhoea. A total of 54 studies were supported comparing standard WHO ORS solution with experimental formulations (See Table 11).

Glycine was studied first because of its low cost and low toxicity. The Programme supported 12 studies on **glycine-based ORS** formulations, but the results published in 1990 showed that these formulations offered no clinical advantage over WHO ORS for acute non-cholera diarrhoea. (22).

In 1986, it was discovered that L-alanine could enhance sodium transport across the brush border more efficiently than glycine. Studies on **L-alanine-based ORS**—initiated in patients with cholera in Bangladesh—showed the formulation to be superior to WHO ORS for patients with cholera. Six subsequent studies, conducted from 1988 to 1992, showed no comparable benefit in patients with acute non-cholera diarrhoea (23,24,25).

In 1988, L-glutamine was shown to enhance absorption of sodium and chloride. It was also identified as the principal metabolic fuel of the small bowel mucosa and essential in the repair of mucosal damage. Based on these findings, **L-glutamine-based ORS** was developed and tested. The results of these studies, which became available in 1992, showed similar clinical effectiveness to that of L-alanine based ORS. For patients with cholera, L-glutamine-based ORS formulation was found to be superior to WHO ORS. For acute non-cholera diarrhoea, no clinical advantage over WHO ORS was found (25,26).

Encouraging results with **rice powder-based ORS** formulations in Bangladesh (1982) led to another hypothesis: that ORS formulations would be hypotonic when glucose (20g/l) was replaced by increased amounts of complex carbohydrates (50g/l). Such formulations would not only prevent osmotic diarrhoea, but would also yield sufficient glucose to promote the reabsorption of intestinal secretions, thus reducing the volume and duration of diarrhoea. However, in these early studies, the rice used had to be cooked just before it was used and the salts added just after cooking.

Believing this would limit the widespread use of this type of ORS solution, the Programme developed a packed rice-based ORS. Because it did not require prior cooking and dissolved readily in cold water, it would be as easy to use as the standard WHO ORS and would still retain the potential

Table 11 ■ **Clinical trials on improved ORS (1982–1995)**

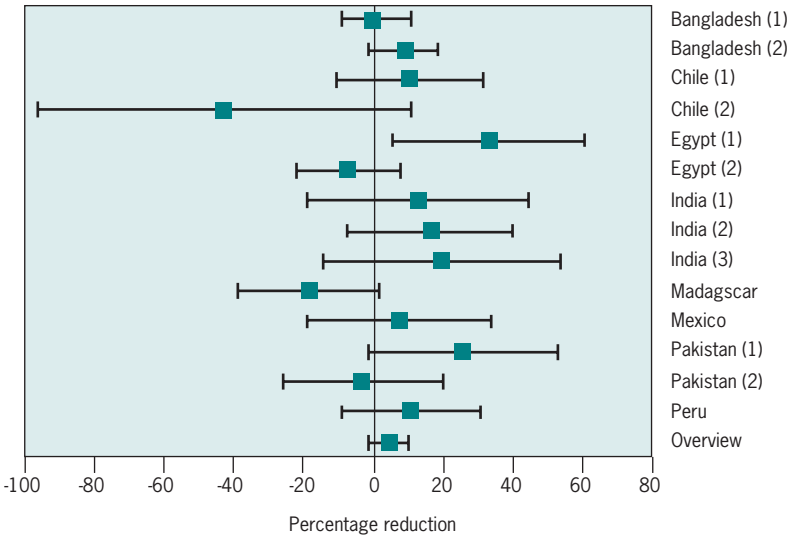
Organic solutes	Amount per litre (g)	No. of Studies	Sites
1. Glucose plus glycine and/or glycyl-glycine	12–20 8	5	Costa Rica, Indonesia, Peru, Philippines, Thailand
2. Maltodextrin (MD25) plus glycine and/or glycyl-glycine	20 8	7	Egypt[a], India[b], Myanmar, Nigeria,
3. Maltodextrin (MD02)	50	4	Bangladesh, Egypt, India, Indonesia
4. Glucose plus L-alanine	16 8	4	Bangladesh, India, Philippines
5. Glucose plus L-alanine	16 5	2	Bangladesh, Philippines
6. Glucose plus L-alanine	9 5	1	Egypt
7. Glucose plus L-glutamine	16 13	1	Indonesia
8. Glucose plus L-glutamine	9 7	2	Brazil, India
9. Rice powder	30	1	Senegal
10. Rice powder	50	10	Bangladesh, Chile, Egypt, India, Indonesia, Madagascar, Mexico, Pakistan, Peru
11. Mung bean powder	50	1	India
12. Sorghum powder	50	1	Rwanda
13. Maize powder	50	1	Cameroon
14. Reduced glucose[c]	13	5	Brazil, Egypt, India, Mexico, Peru
15. Reduced glucose[c]	13.5	9	Bangladesh, Brazil, Egypt, India, Indonesia, Peru, Viet Nam

Notes:

[a] One study evaluating two solutions
[b] Two studies were conducted in this country with this formula
[c] Sodium content is reduced to 1.75g/l

Figure 6

Mean percentage reduction in 24 hour stool output in children with non-cholera diarrhoea given rice-ORS*



** Compared with standard WHO-ORS. Lines represent 95% confidence intervals.*

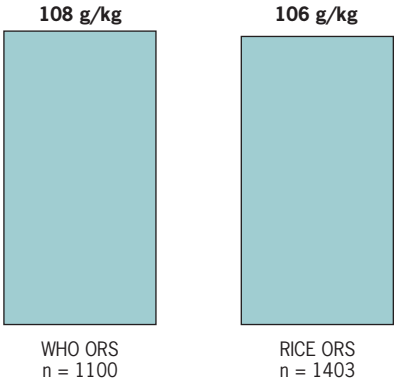
benefits of rice powder ORS. The first formulation developed and evaluated was a maltodextrin-based ORS. However, a 1992 analysis of 11 completed studies showed that **maltodextrin-based ORS** had no clinical advantage over WHO ORS for patients with acute non-cholera diarrhoea (25,27,28,29).

In 1987, the Programme developed a pre-cooked rice-based ORS solution in collaboration with Galactina SA, Belp, Switzerland. The efficacy of this solution was evaluated in 10 clinical trials supported by the Programme. A 1992 meta-analysis on the available findings from all studies of rice-based ORS was revised in 1996 when results of recently completed trials of rice-based ORS were available (30). The results of the revised meta-analysis indicated that, for cholera patients, rice-based ORS solution reduced stool output compared with WHO ORS, but that the rice-based formulation was not superior for the majority of non-cholera childhood diarrhoea cases. (See Figures 6 and 7).

A few studies on other **cereal-based ORS** formulations (sorghum, maize) showed that the efficacy of these ORS formulations was similar to that of rice-based ORS. For this reason, no further research with other cereals was supported.

Figure 7

Mean 24 hour stool output in children with non-cholera diarrhoea: meta-analysis of 14 studies



Reduced osmolarity

A 1990 meta-analysis of glycine-based ORS studies clearly showed the impact of small differences in ORS osmolarity on stool output (22). A clinical trial of maltodextrin-based ORS conducted in Egypt in the same year revealed a high incidence of osmotic diarrhoea due to transient glucose malabsorption in children treated with standard WHO ORS (29). These findings prompted the Programme to evaluate the efficacy of various formulations of reduced osmolarity ORS solutions (31,32,33). Based on the results, a joint WHO/ICDDR,B consultative meeting in 1994 concluded that:

- Reduced osmolarity ORS solution—when compared to standard WHO ORS solution—causes clinically important decreases in stool output and reduces the need for unplanned intravenous infusion in both cholera and non-cholera diarrhoea.
- There were insufficient data to reach firm conclusions on possible risks and benefits of reduced osmolarity ORS for treatment of patients with cholera.
- Before recommending the use of such solutions, additional studies should be conducted in patients with both cholera and non-cholera diarrhoea with a single reduced osmolarity ORS solution containing (in mmol/l): glucose 75, sodium 75, potassium 20, chloride 65, and citrate 10 (total osmolarity 245 mosmol/l).

Following these recommendations, a workshop

was held in Dhaka, Bangladesh, in March 1995 to develop two multicentre studies to evaluate the efficacy and safety of reduced osmolarity ORS solution in children with acute non-cholera diarrhoea and adults with cholera. The paediatric trial took place in Bangladesh, Brazil, India, Peru and Viet Nam, and the adult trial in Bangladesh and Indonesia.

Results of these studies indicate that:

- In the paediatric trial, use of reduced osmolarity ORS solution is associated with a 40 percent reduction in the need for unscheduled IV therapy while having no apparent effect on stool output and illness duration.
- In adults with cholera, there is no difference between reduced osmolarity ORS and standard WHO ORS solutions with regard to stool output or need for unscheduled IV therapy.
- In combined studies, use of reduced osmolarity ORS solution is associated with a significantly higher incidence of biochemical hyponatremia; the risk being higher for patients with cholera. A significant reduction in incidence of unscheduled IV therapy with reduced osmolarity ORS solution applies for children but not for adults with cholera.

Flavouring and colouring

The potential benefits and risks associated with the flavouring and colouring of many commercially available ORS brands have also been questioned. A CDD-supported study in Egypt (1988–1989) showed that, in a hospital setting, there were no adverse effects of flavouring, including over-consumption. A subsequent study, conducted in health centres in the Philippines, compared flavoured ORS with standard ORS and rice-based ORS. No difference in the amounts consumed was observed between the three groups. No further research on flavoured ORS has been undertaken.

The addition of flavours and colouring substances to ORS shows no benefits and is considered unnecessary. Manufacturers should adhere strictly to international guidelines on the use of such additives because intake of large volumes of ORS, for example in the management of cholera, may result in a total intake of additives above the recommended levels.

Feeding during diarrhoea

A significant finding of CDD-supported research was that continued feeding, including breastfeeding, during diarrhoea reduces the adverse effects on nutritional status. Research also found that there was no need to dilute milk feeds or give lactose-free formula during most cases of diarrhoea. Both findings were contrary to advice commonly given.

In the past, doctors commonly advised mothers to temporarily stop or reduce feeding solids to a child during diarrhoea. Because of the precarious nutritional status of many children who have frequent diarrhoea, the CDD Programme initiated studies to demonstrate that such practices were unnecessary. In 1984–1985, a study in Burma showed lower stool losses in children who continued breastfeeding during diarrhoea than those who stopped (34).

Many studies have proven that continued feeding will not adversely affect the course and outcome of diarrhoea. By 1986–1987, there was sufficient evidence to show that the adverse nutritional consequences of acute diarrhoea could be minimized or prevented by continuing to feed a nutritionally balanced diet, including breastmilk for nursing infants, during diarrhoea. Studies had also demonstrated that nutrients, including animal fats and vegetable oils, are absorbed during diarrhoea and that giving potassium-rich foods compensates for losses during the episode.

Lactose intolerance

Research in Ecuador and Egypt showed that dilution of milk feeds during diarrhoea is unnecessary. These studies found that true lactose intolerance was rare and demonstrated that full-strength cow's milk formula was safe and nutritionally beneficial in non-breastfed children older than six months of age with acute diarrhoea. A multi-centre study in Brazil and Guatemala supported by the Programme showed that it was also safe to give full-strength formula to infants under six months of age who are receiving exclusively or mainly animal milk (35). A review of all the literature on feeding of milk during diarrhoea commissioned by the CDD Programme in 1992–1993 confirmed that there is no need to dilute milk feeds during diarrhoea or to use lactose-free milk formulae (36).

Drugs in the management of acute diarrhoea

Concern about the widespread use of drugs to treat diarrhoea prompted the CDD Programme to conduct a review of all common antidiarrhoeals. The review, published in 1990, concluded that none of these drugs should be used in the routine management of diarrhoea as none has been shown to be sufficiently efficacious or free from adverse side-effects.

The widespread problem of unnecessary prescription and use of drugs in diarrhoea treatment led the Programme to add rational drug use to the research agenda in 1991. Subsequent studies in Guatemala and Nepal found that interventions developed by the Programme significantly improved the dispensing practices of pharmacists and drug sellers.

Antidiarrhoeals

In the early years of the CDD Programme a number of randomized controlled trials were conducted to test existing antidiarrhoeal drugs and to develop and assess new ones, especially those that might affect intestinal secretion and absorption.

Loperamide hydrochloride, chlorpromazine, cholestyramine, Bioflorin (a live culture of *Streptococcus faecium*), berberine and other compounds were studied in Bangladesh, Egypt, Denmark, Italy, Netherlands, Sweden and the U.S. Traditional remedies were studied in Bangladesh, China, Madagascar and Viet Nam. None of these studies identified a drug of sufficient efficacy and freedom from adverse side-effects to recommend its use (37,38,39,40,41).

A study of smectite (attapulgite), a kaolin like substance, jointly supported by the manufacturer and the Programme, was completed in Egypt in 1990. Smectite had a modest impact on duration of diarrhoea but no effect on total stool output, and is not recommended for the routine management of diarrhoea in children (42).

In 1990, a review of all commonly used antidiarrhoeal drugs was published. The review concluded that none of the common antidiarrhoeals should be used in the routine management of childhood diarrhoea. Some were shown to be harmful, even potentially fatal, and use of any of them is likely to divert attention away from life-saving prevention or treatment of dehydration (43).

Antibiotics

Research provided the basis for recommending that use of antibiotics in the management of acute watery diarrhoea should be restricted to severe cases of cholera. The safety and efficacy of single-dose doxycycline in the management of cholera was demonstrated by a study conducted in Bangladesh in 1990 (44).

Evidence that approximately 10 percent of diarrhoeal episodes in children less than five years old have blood in the stool led the Programme to support research into treatment guidelines for bloody diarrhoea. A significant outcome was that treatment with an antimicrobial known to be effective against *Shigella*, the most important cause of dysentery, leads to clinical improvement in bloody diarrhoea within two days; this became a Programme recommendation.

Rational drug use

Rational use of drugs was added to the research agenda in 1991, and studies in Guatemala and Nepal examined patterns and determinants of drug use. In 1993, based on available knowledge, the CDD Programme produced a guide for developing interventions to change the dispensing practices of pharmacists and licensed drug sellers. Experience in several countries has shown that these interventions can significantly improve dispensing practices and advice.

Management of persistent diarrhoea

In 1986–1987, epidemiological studies of diarrhoea in Brazil, India and Peru showed that up to 20 percent of episodes may start acutely but last 14 days or more. An episode lasting 14 days or more became the accepted definition of persistent diarrhoea (previously it had been 21 days or more). Taking an active interest in the topic, the CDD Programme devoted research efforts to identifying the most effective approach to management of persistent diarrhoea (45). This research showed that that there is no benefit in routine use of gentamicin or cotrimoxazole for treating persistent diarrhoea, and provided clear evidence that patients hospitalized with persistent diarrhoea can be treated successfully with ORS and a reduced lactose diet based on locally available and inexpensive foods.

Feeding

Initial studies of the management of persistent diarrhoea focused on the effect of **reducing the lactose content** of the diet. A study in Algeria showed a better outcome in children fed a yoghurt-based diet than in those receiving cow's milk formula (see Table 12), confirming the value of reducing the lactose content of the diet during persistent diarrhoea (46).

Two studies reviewed the role of **dietary fat** during persistent diarrhoea. Research in Peru in 1990–1991 showed no advantage in substituting vegetable oil for animal fats during the management of persistent diarrhoea. And a 1993 study in Bangladesh found that use of a diet rich in medium-chain fatty acids in the management of persistent diarrhoea had no beneficial effect on fat absorption, energy intake or nutritional status.

Table 12 ■ **Impact of milk and yoghurt diets on clinical and nutritional outcomes of persistent diarrhoea in non-breastfed children aged 3–36 months, Algeria (1989–1990)**

Outcome	Milk (n=35)	Yoghurt (n=28)	
Mean total diarrhoeal stool output (g)	1341	762	p<0.01
Percentage of episodes that lasted more than five days after initiation of diet	46	11	p<0.01
Mean weight gain on discharge (as percent of admission weight)	1.5	2.3	ns

By 1991, considerable experience had been gained in the management of persistent diarrhoea in the centres where research on other diarrhoea-related topics was being carried out. This experience was summarized at a meeting in Mombasa, Kenya, convened by the Applied Diarrhoeal Disease Research Project (ADDR). A clinical management algorithm was developed based on:

- oral rehydration therapy;
- locally available and inexpensive diets with specified nutrient content;
- vitamin and mineral supplementation; and
- selective use of antibiotics to treat associated infections.

To test this algorithm, a joint ADDR/CDD Programme multicentre cohort study was undertaken in 1992–1993 using a standard protocol (47). Some 460 children aged 4–35 months were enrolled at collaborating centres in Bangladesh, India, Mexico, Pakistan, Peru and Viet Nam. All had diarrhoea of at least 14 days duration and associated malnutrition, dehydration or infection of sufficient severity to require hospitalization. Fifty-two children were excluded because of the presence of another severe condition requiring specialized care.

The study population was young (mean age 11.5 [SD 5.7] months), malnourished (mean weight-for-age z-score 3.03 [SD 0.86]) and associated conditions were common (45 percent of the children required rehydration or treatment for a serious infection on admission).

Patients were initially given diet A, containing cereal, vegetable oil and a reduced amount of animal milk or yoghurt (lactose < 3.7 g/l). In some centres this diet also contained sugar, lentils or soy flour. Diet B, given to those patients who did not improve with the initial regimen, was lactose-free and used simple sugar to partially replace the energy lost by the eliminated milk products.

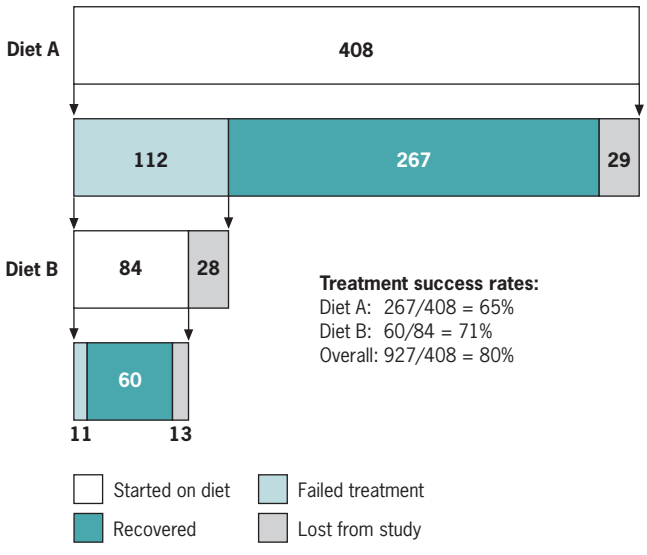
The overall success rate of the treatment algorithm was 80 percent (95 percent confidence interval 76–84%). For children receiving only diet A, the recovery rate was 65 percent (95 percent confidence interval 62–70%). For those receiving diet B, it was 71 percent (95 percent confidence interval 62–81%) (see Figure 8). This study, analysed in 1994, showed that most patients hospitalized with persistent diarrhoea can be treated safely and effectively using an algorithm based on locally available foods and simple clinical guidelines. The results have provided the basis for simple, rational and effective treatment for persistent diarrhoea, which have been incorporated into revised diarrhoea treatment guidelines and in Integrated Management of Childhood Illness in referral facilities.

Another joint ADDR/CDD Programme multicentre cohort study evaluated a similar treatment algorithm, adapted for use in outpatient settings. Results indicated that:

- the treatment success at day seven was about 60 percent;
- the risk of treatment failure, defined as inad-

Figure 8

Assessment of an algorithm for in-patient management of persistent diarrhoea, 6 countries, 1992–1993



equate weight gain or delayed recovery, was increased three-fold by low compliance with taking prescribed micronutrients (95 percent CI 1.5 –6.5, $p < 0.001$) and two-fold by the presence of fever (95 percent CI 1.1–3.6, $p < 0.03$);
- the use of animal milk was not associated with increased risk of treatment failure;
- the reported number of feeds offered were adequate, but the amounts and the energy density of the food offered were insufficient leading to low energy intakes;
- mothers correctly recalled messages related to energy dense foods and the number of feeds to be given, but very few recalled the portion size to be given at each meal.

Drugs

Studies in South Africa and the U.S. showed significant clinical improvement in persistent diarrhoea in children following treatment with gentamicin. This prompted the Programme to support two further trials in Guatemala and India in 1988–1989, however, neither study showed gentamicin to improve clinical outcome (48,49).

A double blind clinical trial to evaluate the efficacy of cotrimoxazole, an absorbable combined antibiotic, in the treatment of persistent diarrhoea was conducted in Peru. A total of 148 children with persistent diarrhoea were included in the study (74 in each treatment group). There were no statistically significant differences between the treatment groups in the main outcome variables: stool frequency, ORS solution intake, duration of diarrhoea, proportion of patients cured on day six after admission, calorie intake, and weight gain. Although the treatment success rate was slightly higher in the group of children receiving cotrimoxazole (70 percent) than in those given the placebo (60 percent), this difference was not statistically significant, suggesting that there is no benefit in the routine use of cotrimoxazole in the treatment of persistent diarrhoea.

Management of dysentery

Epidemiological studies supported by the Programme in the 1980s showed that around 10 percent of diarrhoeal episodes in children under five years of age have visible blood in the stool, and are therefore defined as cases of dysentery. This 10 percent of episodes causes about 15 percent of diarrhoea-associated deaths in the under fives. *Shigella* is the most important cause of bloody diarrhoea, accounting for about half of all episodes and nearly all episodes that are clinically severe or fatal. In contrast, *Entamoeba histolytica* usually causes less than 2 percent of episodes of bloody diarrhoea in this age group.

Antimicrobial treatment

The increasing resistance of *Shigella* organisms to the most affordable antibiotics prompted CDD to initiate studies to determine the safety and efficacy of other antimicrobials to treat shigellosis in children. A study completed in Guatemala in 1992 showed **pivmecillinam** to be as effective as **cotrimoxazole** in treatment of shigellosis in children (50). More recently, the safety and efficacy of short course treatment with **ciprofloxacin** is being studied in Durban, South Africa and Harare, Zimbabwe.

In 1994–1995, CDR developed treatment guidelines that reflected the most recent research on the management of bloody diarrhoea in children[3] and emphasized that:

- Treatment should include an oral antimicrobial known to be effective against most *Shigella* isolated in the area. The most widely used antimicrobials are cotrimoxazole and nalidixic acid. Pivmecillinam and fluoroquinolones are also effective, although the latter are not formally approved for children.
- An effective antimicrobial leads to clinical improvement within two days, characterized by less fever, fewer stools, less blood in the stool, less pain, improved appetite and increased activity.
- Children not improving after two days should be given a different antimicrobial, also effective against most local *Shigella*. Those at high risk of death should be referred to hospital. These include children under 12 months of age who presented with dehydration or who have had measles in the past six weeks. Children with severe malnutrition should be referred when first seen.
- Treatment for amoebiasis (metronidazole) should not be given routinely. It is appropriate only when trophozoites of *E. histolytica* containing red blood cells are seen in faeces or when consecutive treatments with two different antimicrobials for *Shigella* have not led to improvement.
- All children with bloody diarrhoea should be given appropriate fluids, to treat or prevent dehydration, and nutritious foods. Breastfeeding should continue.

[4] *The management of bloody diarrhoea in young children*. Geneva, World Health Organization, 1994 (Document WHO/CDD/94.49).

During 1994–1995, CDR revised its guidelines on the control of epidemics due to *Shigella dysenteriae* type 1.[5]

Acute Respiratory Infections

In 1984, when the WHO ARI Programme became operational, a working group established a simple approach to detection and case management of pneumonia, based on two key signs: chest indrawing and counting the respiratory rate (51).

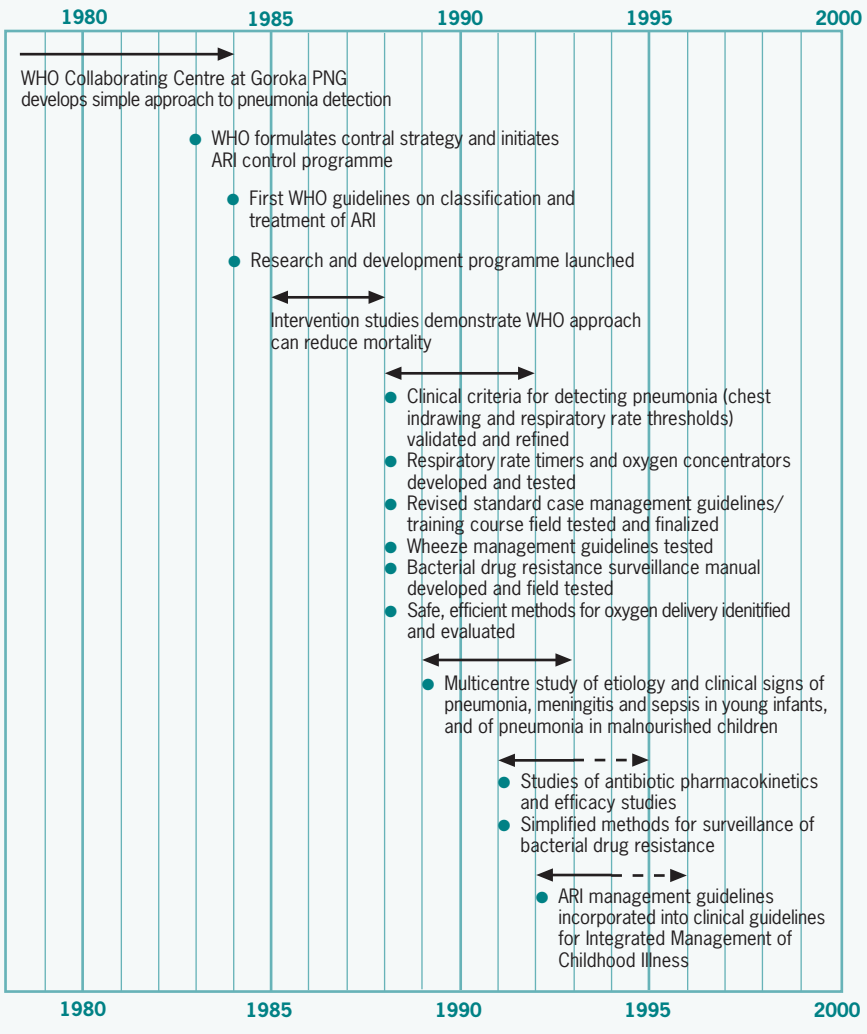
Initial research focused on evaluating the impact of this approach and validating the use of clinical signs for diagnosis (52,53,54,55). Subsequent research covered other aspects of case management including intervention studies (56,57,58,59, 60,61,62,63), oxygen therapy (64), the pharmacokinetics of antibiotics, and management of ARI in young infants and severely malnourished children (65,66). An overview of ARI research and development is provided in Figure 9.

Studies concluded that the case management approach to detection and management of pneumonia could significantly reduce mortality. Initial research to validate this approach also confirmed that counting respiratory rate was a reliable method of detecting pneumonia, and that using age-specific thresholds could increase sensitivity.

The spread of antimicrobial resistance prompted the ARI Programme to support studies examining the impact of resistance on clinical outcome and to develop surveillance methods in collaboration with national programmes. Research indicated that cotrimoxazole treatment of pneumonia usually resulted in recovery, even where high *in vitro* resistance rates have been reported.

Figure 9

ARI case management research and development milestones



Intervention studies

Five research projects to evaluate the impact of the ARI control strategy on childhood mortality began in 1985. Further studies were conducted with and without ARI Programme support over the following years. The results of seven studies, available by 1988, confirmed a significant impact on mortality through pneumonia detection and management, in most cases by community health workers. A meta-analysis of the results of all available studies in 1992 showed an overall reduction in infant mortality of 15.9 deaths per 1,000 live births (95 percent confidence interval 10.6–

[5] *Guidelines for the control of epidemics due to* Shigella dysenteriae *type 1.* Geneva, World Health Organization, 1995 (Document WHO/CDR/95.4).

21.1). For infant mortality due to acute lower respiratory infection, a reduction by 10.7 (4.8–16.7) deaths per 1,000 live births was found. Mortality among children under five years was reduced by 36 deaths per 1,000 live births (67). The pooled estimates of relative risk are consistent with a 20 percent reduction in infant mortality and a 25 percent reduction in under-five mortality.

Validation of respiratory rate to detect pneumonia

The ARI Programme supported studies to examine the reliability of counting respiratory rate, given its importance in the procedure to detect pneumonia. Five studies showed acceptable reliability using either a 30-second or a 60-second count. Studies in the Philippines and Swaziland showed that the sensitivity of respiratory rate in detecting pneumonia could be improved by having age-specific thresholds: more than 50 breaths per minute for infants 2–11 months and more than 40 for children 1–4 years (52).

Further studies of the reliability of the assessment process were conducted in two groups at particularly high risk of mortality due to pneumonia—infants less than two months of age and severely malnourished children (55). Results from these studies are reported in the section on pneumonia, sepsis, and meningitis in young infants.

Pharmacokinetics of cotrimoxazole and chloramphenicol

Standard management of pneumonia, sepsis and meningitis in young infants requires hospitalization and parenteral administration of penicillin and gentamicin. However, in many developing countries, young infants suffering from these serious infections cannot be hospitalized and must be treated at home. Oral medication is often the only feasible option in these circumstances. Although parenteral cotrimoxazole has been used successfully to treat severe bacterial infections in young infants, including Gram-negative infections, there was little information on the oral administration of cotrimoxazole in this age group.

Pharmacokinetic studies in young infants and in malnourished children were therefore initiated in 1992 because of concerns about antibiotic absorption and metabolism in these two patient groups. A multicentre study to determine the pharmacokinetics of cotrimoxazole in infants age three months and younger with sepsis or other serious infection was carried out in Guatemala and Viet Nam. Blood samples were collected and these are being analysed at the laboratory of the Children's Hospital, Helsinki University, Finland.

Further pharmacokinetic studies are also being designed to explore whether raising the dose of cotrimoxazole is a safe and efficacious response to increasing bacterial drug resistance. The studies are being carried out in children aged two months to five years with pneumonia, using the standard dose twice daily and a double dose divided into two or three intakes a day.

Oral chloramphenicol is recommended for severe pneumonia and very severe disease in children aged two months to five years when referral is not possible and parenteral antibiotics are not feasible. However, malnutrition may adversely affect the intestinal absorption of oral chloramphenicol.

The results of a study on the pharmacokinetics of oral chloramphenicol in the Gambia in 1993 suggested that absorption might be erratic in both well-nourished and malnourished children. To confirm these results, the study was repeated in the Gambia and in Pakistan using the same protocol. The concentrations of chloramphenicol in plasma have been measured at the Pediatrics Department, Infectious Disease Division, Southwestern Medical Center, University of Texas at Dallas. This study found that the absorption of oral chloramphenicol is acceptable in well-nourished children. However, newborns and malnourished children should not be treated with oral chloramphenicol, but should be treated with injectable instead.

A protocol was also developed for a study to determine the pharmacokinetics of amoxycillin twice a day, with and without probenecid. The study is being carried out in Brazil and Pakistan, with the University of Texas Pediatrics Department acting as the reference laboratory.

Antimicrobial resistance

WHO was already concerned with the issue of antimicrobial resistance before the ARI Programme became operational in 1984. Since then, the Programme has supported studies to examine the impact of resistance on clinical outcome and to develop surveillance methods.

Clinical importance

It is relatively easy to establish the relationship between *in vitro* resistance to an antimicrobial and failure of treatment with that drug in bacterial infections such as meningitis, where the organism causing the infection can be isolated. With most cases of pneumonia, however, the offending organism cannot be isolated. Furthermore, many children, particularly those with mild pneumonia,

would probably recover without appropriate antibiotics, and thus, the clinical impact of resistance may not be obvious.

Reports from Spain and South Africa have indicated that adults with pneumococcal pneumonia caused by penicillin resistant pneumococci still do well if treated with intravenous penicillin (68). In Pakistan, where high *in vitro* cotrimoxazole resistance rates were reported in 1990, paediatricians have noted that use of cotrimoxazole for the treatment of pneumonia usually resulted in recovery.

To examine this further, the ARI programme supported a study in Pakistan in which 587 children with pneumonia had blood cultures performed, were randomized to receive cotrimoxazole or amoxycillin, and were then observed in hospital. Analysis compared the outcome between the two groups. A separate analysis was performed for the 147 children whose blood cultures were positive for *S. pneumoniae* or *H. influenzae*. All isolates were tested for resistance to cotrimoxazole or amoxycillin. Very few of the isolates were resistant to amoxycillin, but cotrimoxazole resistance was demonstrated in about half of the isolates from children who had been randomized to receive cotrimoxazole.

Overall, the rate of clinical failure was higher in the children with severe pneumonia who were randomized to receive cotrimoxazole, and especially in those who were bacteraemic. In bacteraemic children, the failure rate was 50 percent for cotrimoxazole compared with 10 percent for amoxycillin. There was no difference in the failure rates between the two groups for non-severe pneumonia.

The Pakistan study also showed no relationship between clinical performance of cotrimoxazole and the level of *in vitro* resistance, suggesting that surveillance for resistance to cotrimoxazole is of very limited value.

Surveillance

In 1984, the Programme prepared preliminary guidelines on surveillance of *S. pneumonia* and *H. influenzae* resistance to antimicrobials. These guidelines were subsequently developed into a collaborative study on surveillance methods within national ARI control programmes.

The development of a manual on epidemiological and microbiological methods for surveillance of resistance of the two main pneumonia-causing organisms was initiated in 1988, a project undertaken in collaboration with the U.S. Centers for Disease Control. Studies in Pakistan served to explore and refine the proposed methods such as the suitability for surveillance purposes of nasopharyngeal isolates (69). Data from two studies indicated that nasopharyngeal swabs taken from children with signs suggesting pneumonia could be used to estimate the prevalence of antimicrobial resistance among strains causing invasive disease.

Consensus was reached in 1990 on the many questions that had been raised about the feasibility and reliability of various methods in developing country laboratories. In 1991–1992, the manual was fieldtested in Egypt and Pakistan. Following a meeting in August 1992 to review and improve the bacteriology methods, further fieldtesting was conducted in Thailand and Viet Nam in 1993–1994. The box summarizes some of the results from fieldtesting in the four countries. Common problems encountered during fieldtesting were:

- difficulties in transport of nasopharyngeal specimens from rural health centres to the local laboratory and of bacterial isolates from local laboratories to the central laboratory (where the resistance tests are performed);
- contamination of culture media;
- variations in the rates of isolation of *S. pneumoniae* and *H. influenzae* from nasopharyngeal swabs between participating laboratories in the same country; and
- discrepancies between the results of locally performed disc diffusion tests and mean inhibitory concentration (MIC) determinations.

Even laboratories considered among the best qualified for bacteriological work in developing countries had some problems in producing reliable sensitivity tests. In 1994, the manual was revised to address these problems and work continues to try to identify simpler approaches to obtaining samples and laboratory methods.

Obtaining samples

Under investigation is an approach to estimating bacterial drug resistance that involves taking a large number of samples from sick children in inpatient and outpatient clinics over a single two-week period. This short timeframe allows the laboratory procedures to be carefully overseen by a special team.

One study of antimicrobial resistance among nasopharyngeal isolates of *S. pneumoniae* and *H. influenzae* took place in Bangui, Central African Republic, in January–February 1995. Enrolled in this study were 371 children 2–59 months of age, 138 of whom had pneumonia. One objective

Selected results from fieldtesting in four countries of the WHO/CDC Manual for National Surveillance of Antimicrobial Resistance of *S. pneumoniae* and *H. influenzae*

Resistance of *S. pneumoniae* and *H. influenzae* isolated from nasopharyngeal cultures to cotrimoxazole by MIC determination

Study	Laboratory	Number of strains	Resistance %
Streptococcus pneumoniae			
Egypt	CDC, Atlanta	655	6.0
Pakistan: Urban	CDC, Atlanta	276	77.5
Rural		132	40.2
Thailand	Bangkok	104	19.0
Viet Nam	Hanoi	74	25.6
Haemophilus influenzae			
Egypt	CDC, Atlanta	600	6.0
Pakistan: Urban	CDC, Atlanta	196	45.9
Rural		111	12.6
Viet Nam	Hanoi	44	9.1

Cotrimoxazole resistance of *S. pneumoniae* and *H. influenzae* isolated from the blood from children with pneumonia, Pakistan, 1991–1992 (per cent)

	S. pneumonia	*H. influenzae*
Number of strains	48	78
Sensitive (MIC <1)	31.2	43.5
Partially resistant (MIC 1 to <4)	23.0	35.8
Fully resistant (MIC 4+)	45.8	20.7

Resistance of *H. influenzae* isolated from nasopharyngeal cultures to ampicillin by MIC determination

Study	Laboratory	Number of strains	Resistance %
Egypt	CDC, Atlanta	600	7.0
Pakistan: Urban	CDC, Atlanta	196	4.1
Rural		111	0.0
Thailand	Bangkok	109	17.0

Resistance of *S. pneumoniae* isolated from nasopharyngeal cultures to penicillin by MIC determination

Study	Laboratory	Number of strains	Resistance %	
			Intermediate	Fully resistant
Egypt	CDC, Atlanta	655	25.0	0.0
Pakistan: Urban	CDC, Atlanta	276	12.3	0.0
Rural		132	6.8	0.0
Thailand	Bangkok	104	36.0	3.0

of the study was to determine whether it is necessary to sample only children with pneumonia. Nasopharyngeal swabs were taken from each child and cultured for *S. pneumoniae* and *H.influenzae* using standard methods. *S. pneumoniae* and *H. influenzae* were isolated from 23 percent and 72 percent respectively of children with pneumonia, and from 18 percent and 74 percent of children with other conditions. Resistance rates to common antibiotics are summarized in Table 13.

Based on these findings, the investigators concluded that sampling all children presenting to a clinic, rather than only those with pneumonia, provides a reasonable estimate of the prevalence of resistant organisms. Training of staff is simpler and the required information can be obtained in less than half the time.

Laboratory methods

To simplify the laboratory requirements of surveillance, the ARI Programme supported a laboratory study in the Philippines of transport media for bacterial isolates. The results showed that a commercially available dehydrated medium (Columbia Agar Base), when supplemented with activated charcoal and blood and then chocolatised, preserves the viability and type integrity of both *S. pneumoniae* and *H. influenzae* at room temperature (23.5–25.0 °C) and *S. pneumoniae* at 36.0 °C, for at least 11 weeks (70). The medium is inexpensive and simple to prepare.

Lyophilization is the most effective method of storing isolates of bacteria for later use at the same laboratory or for transportation. However, the technology required for the process is complex and expensive. A simplified, fairly inexpensive lyophilizer for use in developing countries, developed by the University of Alabama, was evaluated in early 1995 at the Papua New Guinea Institute of Medical Research. Effective use of the apparatus was shown to be feasible, although the initial experiments with *S. pneumoniae* were disappointing, as many of the

Table 13 ■ **Percentage of nasopharyngeal isolates of respiratory pathogens resistant to common antibiotics**[a]

Antibiotic	Pneumonia	No pneumonia	All Children
S. pneumoniae			
Cotrimoxazole	7.1	5.8	6.4
Penicillin	6.1	10.4	8.8
Chloramphenicol	14.1	6.4	9.2[b]
H. influenzae			
Cotrimoxazole	12.5	12.2	12.3
Ampicillin	3.1	0.0	1.4

Notes:

[a] Based on samples from children presenting with pneumonia versus those presenting with other conditions

[b] p=0.05

strains were not viable at the end of the procedure. By modifying the procedure and increasing the inoculum, the yield was improved so that all eight isolates in the final experiment could be recovered after one week at room temperature. Work to improve this system is continuing and further evaluation is required to determine whether the lyophilized isolates are viable for longer periods of time, and whether the procedure is appropriate for organisms other than *S. pneumoniae*.

Results from various laboratories indicate that the E-test represents a reliable method for determining the level of resistance of *S. pneumoniae* and *H. influenzae* to penicillin or cotrimoxazole, and could replace disc and MIC determinations. Fieldtesting in developing countries is needed to make sure use of the test-strips will provide valid results outside a laboratory setting.

Oxygen therapy

After antibiotics, oxygen is the most important case management intervention to reduce ARI mortality. This is because hypoxia is a major risk factor for death in children with severe pneumonia or severe bronchiolitis. A study showed that the case fatality rate was significantly higher in young infants with serious bacterial infection in the presence of hypoxia (71).

To improve the provision of oxygen in small hospitals in developing countries, ARI Programme research focused on the development and testing of oxygen concentrators and methods for delivering oxygen efficiently.

Oxygen concentrators

In 1989, specifications were drawn up for an oxygen concentrator that would perform well in the adverse environmental conditions of small hospitals in developing countries. More than 20 manufacturers were invited to submit machines for testing. Four did so, and three—DeVilbiss, Healthdyne and Puritan Bennett—successfully met all the laboratory quality control requirements specified by WHO.

Fieldtesting in Egypt, in collaboration with the USAID-sponsored Child Survival Project, assessed the performance of the oxygen concentrators in small hospitals with no oxygen supplies, the way in which the concentrators are used and maintained by hospital staff, and the costs of providing oxygen by this method.

The study involved 29 oxygen concentrators in 12 hospitals that have very challenging environmental conditions: high temperatures, high humidity, high levels of dust pollution, and wide variations in the voltage of the electricity supply. ARI Programme consultants trained doctors in the use of the concentrators and the recording of data, and trained six technicians on preventive maintenance procedures. During the first year of fieldtesting, 27 of the 29 concentrators functioned well. Final results proved that this method was successful and cost-effective in providing oxygen therapy.

Oxygen analysers

An oxygen analyser is an essential tool to check the oxygen concentration delivered if the concentrator is not equipped with an oxygen indicator. For this reason, the ARI Programme also carried out a laboratory evaluation of portable oxygen analysers in collaboration with Ashdown Consultants in the UK.

Administration of oxygen

Oxygen is expensive in developing countries and it is important that the limited supplies available are used efficiently. Nasopharyngeal catheters and nasal prongs are economic methods of administering oxygen, and the ARI programme supported studies in Ethiopia and the Gambia to evaluate the efficacy, safety and flow rates required for delivering oxygen by these two methods (64).

Children aged between seven days and five years admitted to hospital with an acute lower respiratory infection and with an oxygen intake of less than 90 percent saturation (measured by pulse oximetry) were randomly assigned to one of the two methods. Oxygen flow rates, oxygen saturation and respiratory rate were recorded every two hours.

In the Gambia, the oxygen flow requirements for the nasal prongs to obtain a saturation of 95

percent ($p < 0.001$), were slightly higher than those for the nasopharyngeal catheter. The flow rates for both systems, however, were very low, with most children in both groups needing flow rates of less than one litre per minute. The nasopharyngeal catheter requires dedicated nursing care to prevent complications: the oxygen should be humidified, the catheter must not be pushed in too far and must be taken out and cleaned at least twice a day, and the flow rate must not be greater than two litres per minute. In both studies, the nostrils were blocked with mucus more commonly in children treated with the nasopharyngeal catheter and these children required more frequent suction. In the Gambia, complete nasal obstruction was observed in 25 percent of child-days in the nasopharyngeal catheter group and in 7 percent of child-days in the nasal prong group ($p < 0.001$).

A similar study, conducted in a high altitude setting in Addis Ababa, Ethiopia, showed that flow rates required were similar in the two groups, with most children being adequately oxygenated with one litre per minute of oxygen. But complications, particularly nasal blockage and nasal ulceration, were more common in those receiving oxygen by the catheter method.

These two studies confirm both the effectiveness and efficiency of nasal prongs and nasopharyngeal catheters, the two methods of oxygen delivery recommended by WHO for use in children who are hypoxic due to lower respiratory tract infection. Although the materials required for the catheter method (nasogastric tubes) are more readily available, the studies reinforce doubts about the safety of this method, particularly because the studies were conducted in settings where nursing care is likely to be better than in most hospitals in developing countries.

Standard reading of chest radiographs

Between 1989 and 1996, the ARI Programme radiology working group developed, standardized and utilized a recording instrument specifically designed for reading paediatric chest radiographs from a variety of developing countries without the assistance of clinical information. This has enabled the results to be used as independent outcome indicators in a variety of clinical studies. The group also studied inter-observer agreement in the interpretation of paediatric chest x-rays, and evaluated the utility of a lateral chest film in the diagnosis of pneumonia.

Pneumonia, Sepsis and Meningitis in Young Infants

To better understand the pathophysiology of pneumonia, sepsis and meningitis in young infants, and to improve case management guidelines for their care in both outpatient and inpatient settings, a multicentre study was conducted in four countries with high infant mortality rates: Ethiopia, the Gambia, Papua New Guinea and the Philippines. The study took place from 1990 to 1992.

Out of a total of 8,418 young infants brought for primary care in the four sites, the study enrolled 4,552 who had symptoms or signs reported by the mother or observed by the health worker. These 4,552 infants received a full physical examination by an expert clinician and pulse oximetry. Of these, 2,398 were found to have a clinical sign or overall impression suggesting serious bacterial infection (pneumonia, sepsis or meningitis) and received a full laboratory work-up. In addition, 176 infants with no clinical signs or symptoms (the control group) received a full laboratory work-up. Among the 2,457 children in whom a blood culture was successfully obtained, the positivity rate was 7.2 percent. Of these 2,457 infants, 249 died, a case-fatality rate of 10 percent. The case-fatality rate was substantially higher in those with a positive blood culture and in the first weeks of life. Almost half the deaths occurred within two days of admission.

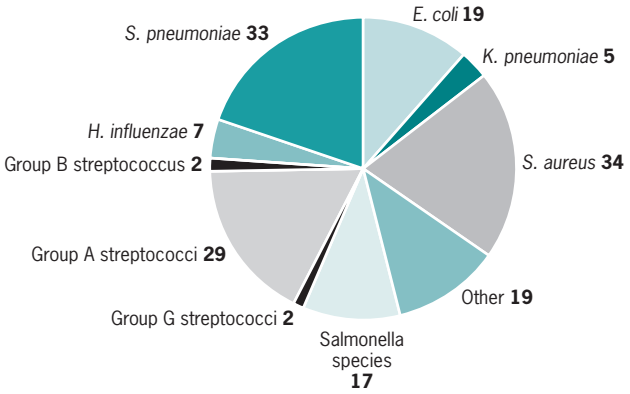
The blood culture results (excluding *Staphylococcus epidermidis* isolates), summarized in Figure 10, showed that:

- gram-positive cocci, especially streptococci and *Staphylococcus aureus*, were the most common isolates, followed by Gram-negative rods;
- pneumococcus was the most common organism in the second and third month of life and an important pathogen in the first month;
- group A Streptococci were frequently isolated, and this may relate to the global resurgence of invasive streptococcal sepsis; and
- group B beta-hemolytic streptococci, which are still common neonatal pathogens in developed countries, were rarely isolated.

Strong clinical predictors of serious bacterial infection include age, temperature, respiratory rate, weight-for-age Z score, signs of increased respiratory effort (lower chest indrawing, grunting, nasal flaring or central cyanosis), crepitations, problems feeding (by history or observed difficulty sucking), a history of crying more or sleeping less, and a cluster of signs related to drowsiness (decreased movements, appears drowsy, weak cry, or history

Figure 10

Multicentre study of pneumonia, sepsis and meningitis in young infants: Distribution of 167 bacterial isolates from blood



of less activity or difficulty waking the infant).

A full multivariate analysis using these signs is highly predictive of the risk of serious bacterial infection. Results from completed analyses have already been used to finalize the guidelines for the management of young infants in the *Integrated Management of Childhood Illness* training course. Further analysis of the clinical predictors of serious bacterial infection is ongoing.

Severely Malnourished Children

Management of diarrhoea

Experience since 1980 suggested that diarrhoea may need to be managed differently in severely malnourished children, and the Division's research agenda changed to reflect this thinking.

Clinical signs

Many of the signs normally used to assess dehydration are unreliable in a child with severe malnutrition, making it difficult or impossible to detect dehydration reliably or to determine its severity. Dehydration is therefore frequently over-diagnosed and its severity over-estimated in such children.

Treatment

Full strength ORS solution should not be used because of the major electrolyte abnormalities found in severely malnourished children. Total body potassium is low and total sodium is high, so the rehydration solution should contain less sodium (45 mmol/l) and more potassium (40 mmol/l) than standard WHO ORS. Magnesium, zinc and copper should also be provided to correct deficiencies of these minerals. Studies to evaluate this new treatment approach are planned.

Management of pneumonia

Pneumonia is more frequent and severe, and more likely to result in a fatal outcome, in malnourished children than in well-nourished children. Research demonstrated that standard definitions of fast breathing and chest indrawing are not sufficiently reliable predictors of pneumonia in malnourished children. However, various studies have confirmed that *S. pneumonia* and *H. influenzae* are the most common causes of pneumonia in both malnourished and well-nourished children, and that the same antibiotics can be used in first-line treatment regardless of the child's nutritional status.

A clinical trial in the Gambia supported by the ARI programme found that oral cotrimoxazole and oral chloramphenicol were equally effective in the initial management of malnourished children with pneumonia. However, the failure rate in both groups was quite high, suggesting possible absorption problems and that parenteral antibiotics should be considered early in the management of malnourished children.

Clinical signs and etiology

Between November 1990 and June 1994, a detailed study of pneumonia in malnourished children in the Gambia (55,66) compared the clinical and etiological aspects of pneumonia in malnourished children with those in well-nourished children. The clinical signs of pneumonia were evaluated in 487 malnourished children (less than 70 percent of the median weight-for-age) and 255 well-nourished children aged three months to five years who presented to the outpatient department with cough or difficult breathing. Pneumonia (defined as definite radiological pneumonia or probable radiological pneumonia associated with "crackles" on auscultation) was present in 30 percent of the malnourished children and 26 percent of the well-nourished children.

- The sensitivity of **fast breathing** (respiratory rate of 50 or more per minute in children under 12 months, and 40 or more in children 12 months to five years) as a predictor of pneumonia was 79 percent in well-nourished children and 61 percent in malnourished children (specificity of 65 percent and 79 percent respectively). A comparable sensitivity

and specificity in malnourished children could be achieved using a respiratory rate cut-off of approximately five breaths per minute less, because it seems that their malnourished state prevents them from responding adequately to the stress of pneumonia.

- **Intercostal indrawing** was more frequently found in malnourished children with pneumonia (71 percent) than in well-nourished children with pneumonia (48 percent).
- **Lower chest indrawing**, the more specific sign of severe pneumonia used in the WHO guidelines, was less common in malnourished children (17 percent) than in well-nourished children (27 percent).

These findings indicate that the definitions of fast breathing and chest indrawing recommended by WHO are not sufficiently reliable as predictors of pneumonia in malnourished children, and support the recommendation to refer severely malnourished children with an acute illness with cough to hospital for empiric antibiotic therapy.

In the same study, 159 malnourished children with radiological evidence of pneumonia were investigated to determine the etiology of their pneumonia (66), as were a control group of 119 well-nourished children admitted to hospital with pneumonia during the same period. Bacteria were isolated from the blood, lung or pleural fluid of 28 (18 percent) malnourished children and 42 (35 percent) well-nourished children.

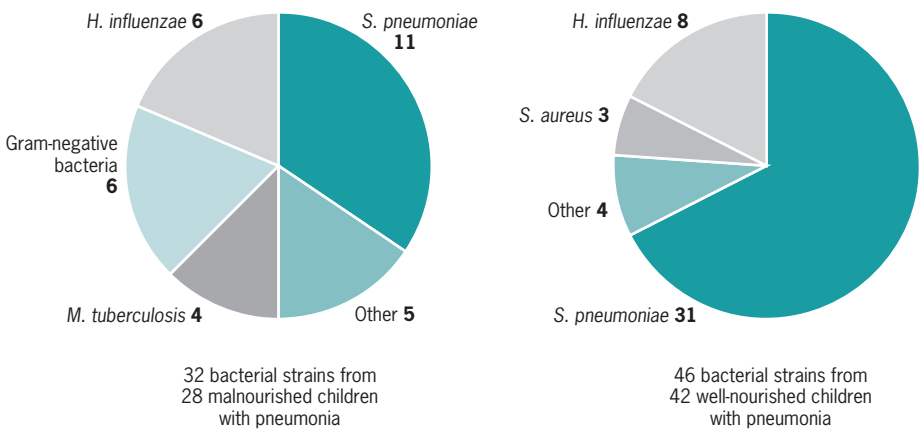
Blood cultures were positive in 9 percent of the malnourished and 18 percent of the well-nourished children. Lung aspiration was carried out in 35 malnourished and 59 well-nourished children in whom radiography showed a well-defined area of pulmonary consolidation adjacent to the chest wall. Lung aspirate cultures were positive for bacteria in 31 percent of the malnourished and 51 percent of the well-nourished children. The distribution of bacterial isolates is shown in Figure 11.

- *S. pneumoniae* and *H. influenzae* represented 85 percent of all the pathogenic organisms identified in well-nourished children, but accounted for only 53 percent of the strains isolated from malnourished children.
- Almost one-third of the strains isolated from malnourished children were Gram-negative bacteria such as Salmonella spp, *E. coli* and *Klebsiella pneumoniae* (19 percent).
- *Mycobacterium tuberculosis* (12.5 percent) was identified in four lung aspirate specimens obtained from malnourished children.

The study showed that *S. pneumoniae* and *H. influenzae* are the most important causes of pneumonia in young children, regardless of nutritional state, and that the same antibiotics can be used as first-line treatment of community-acquired pneumonia in malnourished and well-nourished children. However, other causes of pneumonia, including tuberculosis, are more likely in malnourished children. When these children do not respond to first-line antibiotics, other causes of pneumonia should be considered and these children should be referred to hospital. Finally, the study confirmed that finding a virus in a child with pneumonia does not rule out the possibility of a bacterial etiology; in many cases a combination of pathogenic viruses and bacteria may cause clinical pneumonia.

Figure 11

Study of pneumonia in malnourished children: Distribution of bacterial isolates from blood, lung or pleural tissue



Treatment

A clinical trial evaluated cotrimoxazole and chloramphenicol, two antibiotics frequently used to treat community-acquired pneumonia in malnourished children (65). The trial enrolled 144 Gambian children who presented for the first time with malnutrition and who had clinical or radiological evidence of pneumonia. They were randomized to receive:

- oral cotrimoxazole suspension (40 mg of sulfamethoxazole/200 mg trimethoprim for children under 12 months of age and 60 mg of sulfamethoxazole/300 mg trimethoprim for children over 12 months of age)

OR

- chloramphenicol palmitate suspension (25 mg/kg every eight hours).

The study was double blind with each child receiving both a placebo and an antibiotic, administered for a week along with oral metronidazole, vitamins and standardized nutritional therapy. There were no differences between the treatment groups in the clinical indicators of severity, etiology or radiological findings.

Treatment failure was defined as:

- death

OR

- the need for change to parenteral antibiotics during treatment

OR

- failure to respond to a week of treatment with the study drug

OR

- relapse during the following two weeks.

Four cotrimoxazole recipients and eight chloramphenicol recipients died. Thirty-three children were excluded from the analysis because of tuberculosis, inappropriate enrolment or inadequate follow-up. Data was analysed for the remaining 111 children. Of the 56 children in the group who received cotrimoxazole, 16 (29 percent) failed treatment. Of the 55 who received chloramphenicol, 16 (29 percent) failed treatment. Clinical failure was not related to *in vitro* antimicrobial resistance in the 20 cases in which invasive bacterial isolates were obtained. Those who failed treatment were more likely to have had lower chest wall indrawing and positive bacterial cultures than those who were successfully treated.

Oral cotrimoxazole and oral chloramphenicol were shown by the trial to be equally effective in the initial management of malnourished children with pneumonia. However, the failure rate in both groups was high, possibly because of absorption problems, suggesting that parenteral antibiotics should be considered early in the management of malnourished children with pneumonia, particularly for those with signs of more severe disease such as lower chest wall indrawing.

Prophylactic antibiotic treatment

Empiric antibiotic treatment of severely malnourished children with cough or difficult breathing and the prophylactic use of antibiotics in preventing pneumonia in these children have also been explored. A review of the literature and of expert opinion on this subject concluded that these high-risk children should be treated empirically with antibiotics when admitted with an acute respiratory infection or for nutrition therapy, because they are at particular risk of pneumonia. However, it was also concluded that prophylactic antibiotics in severely malnourished children without signs of ARI were not justified beyond the initial course, as there is no direct evidence that prophylactic antibiotics would reduce pneumonia incidence or mortality.

Some clinicians believe that empiric treatment with metronidazole reduces the risk of systemic infection arising from the overgrowth of anaerobic bacteria in the small intestine, but the available evidence does not support this.

In addition to research on management of diarrhoea and pneumonia in severely malnourished children, CDR collaborated with the WHO Nutrition Programme to develop a document titled *Management of severe malnutrition*, and with the London School of Hygiene and Tropical Medicine to develop guidelines for referral level care of severely malnourished children.

Integrated Management of Childhood Illness

Common management of the CDD and ARI programmes since 1988 raised the possibility of developing an integrated approach to the management of sick children. This idea was stimulated by research findings that showed an overlap in clinical presentation of several major childhood illnesses.

For example, a study in Malawi conducted in 1990–1991 confirmed the overlap in the presentation of malaria and pneumonia. Of 1,605 children enrolled in the study with either cough or fever in the past 48 hours, 63 percent had both cough and fever, 35 percent had parasitaemia, 7 percent radiographic evidence of pneumonia, and 3 percent both pneumonia and parasitaemia. Ninety-six per cent of the children who met the clinical definition of pneumonia also met that for malaria. Subsequent studies in Malawi and in the Gambia showed that cotrimoxazole, the oral antibiotic of choice for treating pneumonia, was also an effective antimalarial treatment.

In 1992, in collaboration with other WHO pro-

grammes and based on available information, CDR developed the first draft of a chart for the integrated case management of ARI, diarrhoea, measles, malaria and malnutrition. In some areas, existing knowledge was inadequate and two studies were commissioned during 1992–1993. These studies at the Medical Research Council (MRC) in the Gambia and in Siaya, Kenya (with CDC Atlanta and the Kenya MRC) evaluated the performance of health workers trained to use the draft chart for Integrated Management of Childhood Illness.

The assessments carried out by the health workers were compared with an expert paediatrician's clinical assessment, supported by otoscopy, haemoglobin determination, blood smear, and chest x-ray. Other laboratory tests including blood culture and lumbar puncture were carried out when indicated. The sensitivity and specificity of the health workers' assessment for various sections of the protocol are summarized in Table 14. Following these studies, lack of specificity in the clinical predictors of malaria in a low-risk area was partially remedied by changing the clinical criteria. The detection of severe anaemia was also a particular concern. In some malarious areas, severe anaemia is a significant contributor to mortality that could be reduced by prompt referral of children with signs of respiratory distress to a hospital for urgent blood transfusion.

To assess whether particular clinical signs have adequate sensitivity for the detection of children with severe anaemia, a multicentre effort to collect relevant data was organized by CDR and the Special Programme for Research and Training in Tropical Diseases (TDR) with collaborating investigators in Siaya and Kilifi, Kenya, Bangladesh, the Gambia and Uganda. Data collected suggested that **severe** palmar pallor could be used as an indicator for referral while children with **some** palmar pallor could be treated with oral iron. In Siaya, Kenya, referral based on severe palmar pallor or cough or difficult breathing plus chest indrawing had a sensitivity of 84 percent and a specificity of 92 percent in detecting severely anaemic children. Lower sensitivity was found in the Gambia. The chart was modified, therefore, using palmar pallor to improve the detection of severe anaemia with decompensation (marked by dispnoea, venous engorgement, cyanosis and edema) while reducing the rate of unnecessary referral.

During 1994–1995, the research needed for the development of the case management guidelines was completed. A training course on Integrated Management of Childhood Illness was developed and implementation has begun in over 60 countries in all WHO regions.

A number of important research questions remain. CAH continues to maintain and update a list of global research priorities related to the management of childhood illness. The list is circulated periodically, and reviewed in meetings with collaborating agencies and institutions, in an effort to ensure that research remains focused on the most important and urgent questions. Of particular note has been the successful collaboration between CAH and TDR Sick Child Task Force/Malaria. This task force has concentrated on malaria diagnosis in low-risk areas, detection and treatment of anaemia, home case management of the sick child, and the management of children hospitalized with severe malaria. CAH and TDR also collaborated in adapting the Integrated Management of Childhood Illness guidelines in some countries in Asia. In addition, the performance of the adapted fever guidelines, modified to include dengue haemorrhagic fever, are being studied in areas of high and low risk for malaria in Viet Nam.

Table 14 ■ **Health workers using integrated management guidelines versus expert clinician/laboratory**

	Sensitivity (%)	Specificity (%)
Pneumonia		
Gambia	78.0	90.0
Kenya	98.0	62.0
Malaria by history of fever		
Gambia (low risk)	100.0	1.3
Kenya (high risk)	96.0	21.0
Malaria by T >38 °C or splenomegaly		
Gambia (low risk)	81.0	50.0
Ear infection		
Gambia	39.0	97.0
Kenya	51.0	88.0
Malnutrition		
Kenya	95.0	78.0
Anaemia by eyelid pallor		
Hgb<6—Gambia	33.0	85.0
Hgb<6—Kenya	70.0	89.0
Hgb<4—by eyelid pallor	100.0	45.0

4.2 Case Management in the Home

The WHO guidelines for standard case management of diarrhoea, ARI and IMCI include components on essential home management. The success of case management strategies depends not only on the availability of health services with trained personnel and affordable treatment, but also on

family behaviour such as effective home care, utilization of appropriate services by families of children who require care, and correct implementation of prescribed care.

Diarrhoea

Identification of home fluids

Early studies of diarrhoea management in the home focused on identifying the types of fluids given to prevent dehydration. In 1984–1985, studies in Bolivia, India and Thailand showed that rice-water was a widely used and acceptable fluid for home management of diarrhoea (72). Further studies of cereal-based fluids in Kenya, Pakistan, Philippines, Thailand and Sudan (73) contributed to the formulation of country-specific messages on home care. It was concluded that, where cereal-based fluids were traditionally used, they should be promoted as one option for early home management of diarrhoea, but that where they were not used, promotion of special preparation of such fluids was unlikely to be effective without sustained input.

Acceptability and use of home fluids

Later research in 1994–1995 focused on the identification and use of acceptable home fluids and on the evaluation of methods for obtaining data on caretaker behaviours with respect to fluids and foods. Research methods had evolved considerably since 1984 and research was more precisely targeted at obtaining information of use in communication with families.

In Kenya, a study among Abaluyia speakers used qualitative and survey methods to determine the acceptability of *uji* (a porridge that is traditionally prepared at different dilutions from thick to thin) for children with diarrhoea. In a household survey, more than two-thirds of the mothers interviewed responded that *uji* was "acceptable" during diarrhoea. However, in-depth interviews revealed that a number of factors affected whether *uji* would be used in a particular episode. These related to the type of *uji* (ingredients and preparation) and the type of diarrhoea the child was thought to have. The study results not only have implications for the design of communication messages, but also provide one explanation for discrepancies between survey reports and household behaviours.

A qualitative study in the Philippines examined the acceptability of *am* (rice-water) as a recommended home fluid during diarrhoea. Small samples of 20 mothers each in an urban and a rural area were asked to compare a number of different foods and fluids, using a simple rating technique that had been validated as a research tool in previous anthropological studies. In the urban area, *am* was ranked just below *Oresol* (ORS) as the preferred fluid. In contrast, the rural mothers ranked *am* first, followed by thin rice porridge, banana and *Oresol*. Water, tea, and other fluids were given progressively lower ratings.

However, stated beliefs and attitudes are not necessarily a good predictor for behaviour, as shown by results from a 12-hour observation period in the home of children (ranging in age from six to 24 months) who had been experiencing diarrhoea for between 48 hours and three days at the time of the observation. In the urban area, the most common foods and fluids given were cereals (breads, biscuits), water, and chocolates and other sweets. Half of the children received cooked ground rice or *am*. In the rural area, boiled rice, water, candies, soups and cereals were the most common foods and fluids given. Only three of the 20 children were given *am*.

A study in Bangladesh evaluated the relationship between caretaker reports of increased fluid intake during diarrhoea and actual intake, to assess how well caretakers perceive changes in fluid intake and how actual changes in intake compare with reported changes. Findings suggest that responses of caretakers to simple questions on children's fluid intake during diarrhoea appeared consistent with children's observed intake of fluids.

Community-based support for home management

A number of countries have tried different community-based interventions—ranging from simple holders of stocks of ORS, to mothers trained in ORS preparation to community oral rehydration units—to support home management of diarrhoea.

The latter were the subject of a study in Peru in 1990–1991 and in Colombia in 1993–1994. The Peru study found that 74 percent of the community oral rehydration unit (CORU) volunteers had adequate knowledge of ORT procedures and 85 percent knew which cases required referral. The study in Colombia showed that while the CORU performed well, utilization of their services was low. Only 2 percent of 533 diarrhoea cases were taken to a CORU. It was found that 70 percent of mothers did not know the service existed. Of those who did know, 28 percent had sought help and 89 percent of these were satisfied and said they would use the CORU again. These findings suggested that CORUs can provide a useful complementary service but need to be actively promoted in the community.

The focused ethnographic study (FES)

In 1990, a draft manual was prepared to obtain social and cultural data on ARI household management and a description of the local health system. However, it became clear from the first field studies that it was not feasible in a timeframe of four to six weeks to obtain adequate information about both household management and the health system.

Consequently, the study protocol was revised to be "focused" on obtaining information about those aspects of household management that facilitate or constrain desired caretaker behaviours, about the language and concepts that could provide the basis for sensitive communication, and about common practices that have positive or negative consequences for the outcome of respiratory infection—hence, the emphasis on "ethnography". Since obtaining such data requires a systematic approach, using qualitative research techniques, it was appropriate to label it a "study." Thus, the phrase "focused ethnographic study" was coined to emphasize these key elements.

The FES has a set of specific procedures, which are described in a manual. For each procedure, the manual includes a discussion of its objective, preparation of materials for interviewing and observation, forms for data recording and analysis, suggestions on how to present the procedure to respondents, and detailed instructions on analysing the results. To facilitate use of the results by programme managers, the final section of the manual provides investigators with suggestions about how to write the report.

The study uses several ethnographic methods:

- Open-ended interviewing of key informants.
- Interviews with mothers of young children at home using a structured interview schedule that includes asking about a recent past ARI event; presentation of a set of hypothetical cases ("scenarios") on which they are asked to give advice; simple sorting exercises in which they match signs and symptoms with illness ("diagnostic") terms and indicate their relative severity; questions about their choices among local health care alternatives and an inventory of the household "medicine cabinet".
- A videotape shown to mothers with clips of children with ARI signs, including children with pneumonia of varying severity, as well as with mild upper respiratory infections. Questioning frames provide an opportunity to verify terms used for signs and symptoms, as well as to assess the respondents' recognition of signs of pneumonia.

Another component of the study involves:

- Interviews in health facilities with mothers and other caretakers of sick children, using a structured interview with questions about caretakers' interpretation of signs and symptoms. A brief physical examination is conducted to assess the state of the child and to establish the physical correlates of the signs reported by the caretaker.
- Interviews with community practitioners to elicit their perceptions about community language and practices.
- Presenting pharmacists with a "case" for which their advice is sought, to obtain a picture of pharmacists' practices. ■

Care-seeking

Findings from studies of patterns and determinants of care-seeking for diarrhoea emphasized the need for specific adapted messages to mothers on this aspect of home care. This critical area is discussed further in the sections on ARI and Integrated Management of Childhood Illness.

Acute Respiratory Infections

Standard case management of ARI requires complementary roles for health workers and caretakers. The role of health workers is to provide effective case management and advice. Caretakers must provide safe home care and, in more severe cases, seek care promptly from an appropriate practitioner and follow advice given. Caretakers must recognize which of their children's many respiratory infections are potentially life-threatening, take rapid action if a child has pneumonia, and overcome the many social, economic and cultural constraints to obtaining care.

Collecting information to improve communication with families

In 1989, the ARI Programme focused on ways to promote appropriate household behaviours to complement health worker training efforts. Effective home management requires that families know what to do. Thus, the Programme began by identifying methods for improving communication with families. During 1991–1993, a qualitative, ethnographic protocol and a manual for a focused ethnographic study were developed to obtain cultural data on community beliefs and practices. This was based on two main assumptions: that communication with families would be more effective if health workers used culturally appropriate language and concepts; and that programmes need information about how families manage ARI in order to develop means of improving family practices (74).

In addition to providing information that could be used to improve the content and language of home care advice, the FES was also designed to provide information about caretakers' recognition of signs of pneumonia, perceptions of health care alternatives within the community, household decision-making with respect to ARI episodes, and constraints to care-seeking (75).

It was envisaged that national programmes would use the findings to support health workers with materials that would enable them to use the local vernacular for respiratory signs and symptoms, recommend locally acceptable safe remedies

for soothing the throat and cough, to advise caretakers to use foods and fluids that are locally available and acceptable, and warn them to avoid dangerous practices that were common in the community.

Local adaptation of home care advice

The literature on medical anthropology of diarrhoea and early FES studies of more than one ethnic group contributed to the hypothesis that underlying patterns of household management tend to be similar across broad culture areas (76). However, how to address the linguistic and cultural diversity within countries was a major concern of the ARI Programme in its efforts to develop effective communication with caretakers.

Because of this concern, a protocol was developed for local adaptation of ARI home care messages. The procedures were first used by researchers in the Philippines, who compared the results with those from full FES studies. The second stage, which was carried out in 1995, was a fieldtest of the protocol, *Procedures for local adaptation of ARI home care advice*, which describes simplified procedures based on experience with the research study. It is designed to be used by individuals with health education training and experience, and can be administered in less than a week. The fieldtest was conducted in two locations by the national ARI programme in Pakistan with excellent results.

The protocol, which has been finalized and is available from CAH, uses a videotape of children with ARI signs and symptoms to elicit local vocabulary and treatment practices. The two-stage process begins with interviews of individual mothers to obtain information to design a provisional set of messages. The appropriateness of these messages is then confirmed or modified through focus group discussions.

Assessing mothers' understanding of messages

The ARI programme also developed a protocol for testing message comprehension, as many factors other than message content are involved in transmission and interpretation of verbal information. The first step, during 1994–1995, was a series of studies on caretaker comprehension of ARI home care messages in the Philippines and Viet Nam.

The Philippines study examined the comprehension of mothers of children with non-pneumonia ARI. Consultations were observed to determine whether specific messages on danger signs and supportive home care had been given to the mothers. The mothers were interviewed twice—once on leaving the clinic and once at home a week after the clinic visit. Non-prompted recall showed that while message recall was generally quite low, messages on supportive home care appeared to have more salience than messages on danger signs indicating when to return. Recall of messages on continued feeding and feeding more after illness was greater at one week than at the exit interview. The explanation for improved recall over time may be that the exit interview reinforced the initial message. The Viet Nam study showed high salience of messages about extra fluids (based on exit interviews), but that recall of some messages tended to decline with time, even with prompting (see Table 15).

Following fieldtesting, the protocol was developed into a tool that can be used by national ARI programmes.

Why local terms matter

Messages must be understood if they are to be acted on by families. Home care advice is unlikely to be fully understood if advice is delivered in unfamiliar terms or only with the help of a translator. The purpose of local adaptation is not just to identify words caretakers understand, but to also identify meaningful concepts.

The difference between understanding words and understanding concepts is illustrated by the results of a study of message comprehension in Viet Nam. Researchers compared caretakers' recall of the danger sign of "fast or difficult breathing" after:

- giving the message as "fast or difficult breathing" in a direct translation;
- giving the message as "strong or tired breathing" using local cultural terms or concepts.

Although the caretakers understood the literal translation into Vietnamese, only 12 % of the mothers who were told this version of the message remembered the warning. Caretakers who were given the message using the local terms were more likely to remember the warning; 27 % of these caretakers recalled the message.

The difference between the two groups was statistically significant ($p<.009$) and the results of this comparison indicate that understanding the words is not enough. Caretakers are more likely to pay attention to messages that are culturally meaningful. ■

Using ethnographic data

Between 1992 and 1994, 24 FES studies were undertaken in 19 countries. But despite efforts by the global Programme to increase awareness of the value of ethnographic data (75), application of the findings by national ARI programmes was slow.

Table 15 ■ **Proportion of ARI home care messages recalled with prompting on exit and at one week follow-up in two provinces in Viet Nam**

Message	percent of caretakers recalling prompted message			
	Province 1		Province 2	
	On exit	After one week	On exit	After one week
Offer extra fluids	86	56	100	100
Increase breastfeeding	100	100	100	100
Clear nose if it interferes with feeding	100	100	78	47
Soothe throat/relieve cough	100	91	100	56
Increase feeding after illness	32	21	100	50
Continue feeding	33	60	81	63

This was due in part to problems in making the transition from research to action, despite collaboration between programmes and research institutions. National programmes were therefore encouraged to conduct FES as part of communication action plans. Following requests from national programme managers for assistance with carrying out ethnographic studies and with using the results, the global ARI Programme concluded that:

- Many public health programme managers have little or no prior experience with using community-based information for communications planning, and inputs from consultants with skills in this area were necessary.
- An explicit framework for reviewing results, examining their implications, prioritizing problems, and developing a plan of action is an important tool in developing a communication plan.
- A two-stage process is an effective approach to organizing the planning exercise (see example of Pakistan). First, a workshop brings together core programme staff and ethnographers to reach a consensus about the implications of the study results and to outline a general plan of action. The second stage

Developing an ARI communication plan for Northwest Frontier Province, Pakistan

The process of developing a communication plan, using ethnographic data, is illustrated by the example of Northwest Frontier Province in Pakistan. In 1993, WHO held a workshop at the request of the national ARI programme, to train anthropology graduates, social workers and medical staff from the national programme to use the focused ethnographic study manual. The seven-day workshop included two days of practice interviewing in a nearby rural area.

Studies were then conducted in two ethnically distinctive communities in Northwest Frontier Province, one Hindko- and the other Pushto-speaking. The results showed many commonalities in home management but also identified differences that had implications for programme planning. In one community, for example, opium is a traditional remedy for suppressing coughs, but this potentially harmful practice appears to be uncommon in the other ethnic group. Differences between the two communities in the use of the public health system also had implications for the potential effectiveness of health facility-based interventions.

In 1994, a workshop attended by national and provincial programme staff and the ethnographers who carried out the study reviewed the study results in detail. A "problem list" was drawn up concerning household behaviours, health worker behaviours, and clinic and community conditions that are not supportive of positive outcomes for child health. For problems that could be addressed through improved communication with families, the participants drafted messages phrased in local dialect and based on local concepts, and developed a plan for preparation and testing of various materials for conveying these messages, including counselling cards, flyers, posters, and scripts for health workers.

Immediately following the workshop, a seminar was held with individuals from several national and provincial government units, clinical and health education professionals and representatives from international agencies. After presentation of the results of the studies and the workshop, seminar participants focused on problem-solving: to define potential actions to address the problems, make an inventory of resources that could be mobilized to undertake these actions, and outline an operational plan for exploring the feasibility of the proposed activities.

Various specific actions emerged from the exercise including: preparing adapted mother counselling cards for distribution to local health centres; establishing ARI communication units in teaching hospitals in the province; adapting national training materials for a large-scale community health programme; using locally appropriate messages in a mass media health education campaign that was already being planned and in preparing an ARI module for a set of health education videos for the province; and adding an ARI component to a health education curriculum for school teachers.

The national programme has subsequently been working in the province to follow-up on the action plan and has secured funding to administer the local adaptation protocol in other provinces so that all major linguistic groups in the country are covered. ■

brings together a larger group, representing other regional and national government units, within and outside the ministry of health, and other key players whose skills and resources can be used to advance the action agenda.

Improving Family Response to Childhood Illness

Throughout the world, the actions families take when a child is sick range from those that are highly beneficial, to others that have no effect, to a few that are dangerous. Reducing childhood death and illness requires finding ways to help families respond effectively to all illness, by taking appropriate action in the home and seeking appropriate care outside the home for potentially life-threatening disease.

In early 1994, the working group on case management in the home carried out a review of current knowledge about the determinants of household management of acute illness, and made an inventory of social science approaches to behaviour change. In October that year, a meeting was held in collaboration with the BASICS project in Washington, D.C., with social scientists representing several disciplines concerned with behaviour change. The meeting reviewed action required by child health programmes to plan and implement interventions aimed at improving family responses to illness. Two areas were identified as needing attention: procedures to evaluate existing information and decide what additional formative research was needed; and procedures to assist programmes in using formative research results to select and implement interventions.

In response, CDR initiated work to develop tools for planning and implementing interventions, including a series of technical manuals on specific interventions, to complement existing manuals such as the CDD *Radio Guide*. These technical manuals are intended to strengthen implementation of a range of strategies including health education, counselling family members, and materials production, and their use is compatible with the planning process developed for IMCI.

At a meeting in September 1995, a group of experts in the behavioural sciences considered ways in which practical and effective interventions could be used to apply the principles of behaviour change. An important outcome of the meeting was a practical framework for analysing desired behaviours and developing possible interventions that would improve the quality of national and local efforts.

5. Programme Management and Implementation

The CDD and ARI Programmes consistently emphasized the importance of effective planning, management, and evaluation for successful implementation of national diarrhoea and ARI control programmes.

Research supported by CDD and ARI led to the development of a wide range of interventions, management tools and training courses to ensure the success of such programmes in developing country settings.

CDD and ARI also recognized that lessons learned in the field could translate into improvements in national programmes. For example, key lessons from monitoring of training included the need to emphasize practical clinical skills more, improve communication between health workers and mothers, and encourage pre-service as well as in-service training.

This section describes activities and materials to support national diarrhoea and ARI control programmes.

5.1 Programme Management

Management Training Courses and Materials

CDD programme management

The CDD training course *Programme Management* was first fieldtested in 1980 and made available for use in May 1981. The course was held 37 times between 1981 and 1985. In 1985, the course underwent major revisions. It was fieldtested in Nairobi at the end of 1987 and issued in 1988. This revised course focused on ways of improving and expanding existing programmes and provided more information on home treatment for the prevention of dehydration, on interventions for the prevention of diarrhoea, on programme indicators and evaluation methods, and on communication activities. The revised course, with selected modules updated in 1993, had been used more than 240 times in 70 countries by the end of 1995.

Supervision

There was early recognition that supervision needed to be strengthened at the middle level of the health system and within health facilities.

A *Supervisory Skills Training Course* was developed in 1981–1982 and fieldtested and finalized in 1983. The course was held over 250 times in 98 countries, with more than 10,000 participants, between 1983 and 1987. The course was extensively revised during 1986–1987, just as the programme managers course had been. The new course was supplemented with a module on the management of the child with an ARI. More than 300,000 supervisory staff participated in this course, but it has been difficult to demonstrate subsequent improvement in supervisory practices. In 1995, the Programme decided to develop different approaches to improving supervision.

ARI programme management

In 1988, *ARI Programme Management: a training course* was developed. Parallel to the course developed to train CDD managers, this had modules covering national policies, national targets, planning and monitoring activities and evaluation, as well as facilitators' and directors' guides. More than 5,600 senior health staff participated in ARI programme management training from 1990, when the course became available, until the end of 1995.

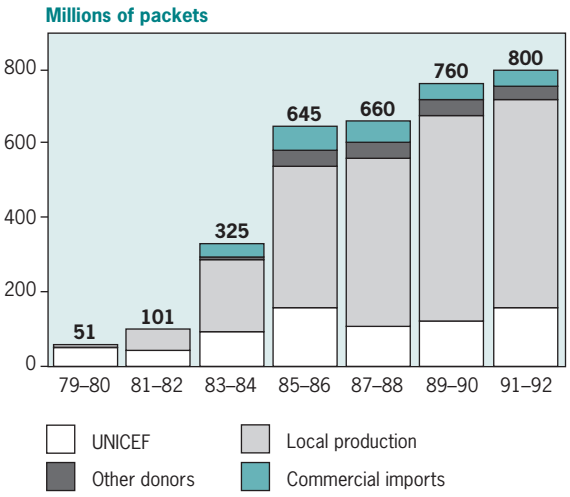
Integrated programme management

With greater integration of CDD and ARI Programme activities, a combined programme management course was developed from existing materials in 1994. Guidelines and training for an integrated approach will be needed as vertical programmes find new ways to work together and systems increasingly decentralize, and as Integrated Management of Childhood Illness at country level is increasingly emphasized.

CAH is monitoring the introduction of IMCI in selected countries to document the management challenges and the solutions developed. This descriptive case study investigation of policy and

Figure 12

ORS supply in developing countries, 1979–1992



programme change in a limited number of countries is providing an unusual and rich database on health system change. On the basis of this descriptive work, guidelines on planning IMCI have been developed.

ORS Production, Supply and Cost-effectiveness

The CDD Programme initially devoted considerable attention to the development of ORS production facilities and, later, to ensuring adequate ORS availability. Figure 12 shows the trend in ORS supply. In 1993, approximately 60 developing countries were producing ORS of a satisfactory quality, and available information from UNICEF suggests that these levels are being maintained.

Guidelines for the production of oral rehydration salts were issued in 1980 and then again in 1985 following extensive revision. In 1988, guidelines titled *Estimating costs for cost-effectiveness analysis* described ways of assessing whether the introduction of ORT in districts and hospitals, or the local production of ORS, would be cost effective. The guidelines, developed to assist programme managers, have been used in China, Indonesia, Lesotho, Mexico, and Philippines.

5.2 Training Courses and Materials for Case Management

From the start, the CDD and ARI Programmes demonstrated a strong commitment to developing methods and materials to improve case management.

The supervisory skills training course

Aimed at all middle and lower-level supervisors of health services, this course presents general principles of supervision that are applicable to any health programme and uses examples that are relevant to diarrhoeal diseases control. The course comprises seven modules as follows:

Community involvement: Participants learn how to define and calculate access to health services, how to find out about those services and the health problems of the community, and how to work with the community to plan improvements.

Treatment of diarrhoea: All aspects of diarrhoea case management are covered, namely, educating family members, assessing and treating cases, and recording data. Exercises with cases are included.

Prevention of diarrhoea: This module describes seven interventions for the prevention of diarrhoea and teaches participants how to assess community practices and decide which preventive activities need to be emphasized.

Targets: Participants learn how to estimate the past use of health services, consider ways of increasing use, set targets for the coming year (particularly for use and access rates), and estimate the supplies needed.

Planning and monitoring: The planning, scheduling, and monitoring of health workers' activities and performance are covered in this module. It also deals with problem solving and feedback to health workers.

Training: A simple approach to task analysis is presented along with a selection of methods for training, and for the planning and evaluation of such activities. The module explains the need for all training to include information, demonstration and practice.

Evaluating progress: This module describes methods of collecting data to monitor health services and provides guidelines for summarizing and analysing data on their use each month and taking appropriate follow-up action. It also discusses the annual calculation of use rates and their comparison with targets, and the reassessment of community health problems and needs. The module concludes with guidelines for using the evaluation findings to plan services in the coming year. ■

Without clear technical guidelines and high quality training materials, little of the knowledge accumulated through research would be translated into action at country level. An enormous number of documents and training materials were produced in English, French and Spanish by the CDD and ARI Programmes between 1980 and 1995, and many have been translated into other languages. Guidelines reflected the state of knowledge at the time and revisions were made periodically to reflect new research findings.

Table 16 ■ **Milestones in the development of CDR programme management tools**

	Programme managers	Supervisors	Technical support	Milestones
1980	CDD Programme Management: a training course		Guidelines for the production of oral rehydration salts	*Components of a CDD Programme described, with a training tool to help establish a national programme, and ORS standards set*
1981	Manual for the planning and evaluation of national diarrhoeal disease control programmes (revised in 1984)			*First guidelines for planning and evaluation produced*
1983		CDD Supervisory Skills training course		*First tool developed to strengthen supervision of health facilities and case management*
1985	(Major revision of programme managers training course started)		Oral rehydration salts: planning, establishment, and operation of production facilities	*Practical guidance provided to help countries become self-sufficient in the production of ORS*
1988	CDD Programme Management: A training course (revised)	Module on management of the child with cough added to the Supervisory Skills Training Course, for use by ARI programmes	Estimating costs for cost-effectiveness analysis: guidelines for managers of diarrhoeal diseases control programmes	*Case management of ARI added to supervisory skills, compatible with CDD materials*
1989	ARI Programme Management: a training course			*Major CDD programme components and strategies adopted by the ARI Programme, permitting greater collaboration*
1991	CDD/ARI Programme Management: a training course (selected modules for joint courses, updated in 1993 and 1995)			*Materials revised to support joint CDD and ARI programme management training*
1999	Planning guidelines for Integrated Management of Childhood Illness			*CDD and ARI experience serve as basis to the development of materials to support IMCI*

Diarrhoea

Technical guidelines

Management of diarrhoea

Guidelines for trainers of community health workers on the treatment and prevention of acute diarrhoea, produced in 1980, described the simple approach to assessment and treatment of dehydration that still underlies the guidelines used today. They introduced the use of three categories to classify hydration status: no dehydration, some dehydration and severe dehydration, and related treatment plans (designated as A, B and C).

These guidelines soon became the approach recommended for first level health facilities. Two revised versions were published incorporating the latest research findings: *Treatment and prevention of acute diarrhoea: Guidelines for the trainers of health workers*, 1985; and *The management and prevention of diarrhoea: Practical guidelines*, 1993.

A manual for the treatment of acute diarrhoea, including more information on the use of drugs, was first issued in 1980 for use by physicians and other senior health workers.[6] It was revised in 1984, 1990, and most recently in 1995. This most recent

[6] *The treatment of diarrhoea: a manual for physicians and other senior health workers*. (Document WHO/CDR/94.48).

revision took into account experience gained in the management of persistent diarrhoea.

Other technical documents produced on important aspects of the management of diarrhoea include *The selection of fluids and food for home therapy to prevent dehydration from diarrhoea: Guidelines for developing a national policy* (1987, revised 1993), and a WHO booklet *The rational use of drugs in the management of acute diarrhoea in children* (1990).

Communication

Evaluations of case management in health facilities revealed that health workers' communication of essential information to caretakers of sick children was frequently deficient. The CDD Programme developed *Advising mothers on management of diarrhoea in the home—a guide for health workers* in 1993 to improve the communication skills of health workers. The content of this guide, and its companion for training course facilitators, was subsequently incorporated into clinical training courses and materials. The process and skills taught to improve health worker-mother communication have since been incorporated into Integrated Management of Childhood Illness training.

The *Radio guide: a guide to using radio spots in national CDD programmes*, completed in 1995 in collaboration with UNICEF and USAID, has been used to train consultants and has been utilized in nine countries covering three WHO regions. The format of the guide allows it to be adapted for ARI and other health problems.

Dysentery and cholera

In 1994, the CDD programme recognized the need for more detailed guidance on the management of dysentery and issued *The management of bloody diarrhoea in young children*.[7]

Guidelines on cholera control, first issued in 1980, were revised substantially before being issued as a WHO document in 1993. Several complementary documents were also produced in 1991–1992 including *Management of the patient with cholera* and a guide to formulation of national policy on cholera control.

Earlier *Guidelines for control of epidemics due to* Shigella dysenteriae *type 1* were extensively revised and reissued in 1995.[8]

[7] *The management of bloody diarrhoea in young children*. (Document WHO/CDD/94.49).

[8] *Guidelines for the control of epidemics due to* Shigella dysenteriae *type 1*. (Document WHO/CDR/95.4).

Training courses and materials

The CDD Programme devoted considerable resources to the development of training materials to give health workers the essential knowledge and skills related to case management (see Table 17).

Case management

Early on, case management training for health workers relied on the skills of those providing the training to adequately prepare and conduct it, and a large amount of training took place without adequate attention to practice.

For example, the *Supervisory skills* course in 1984 was the first training course to incorporate the case management guidelines and was designed to teach the basics of case management for supervisory staff, but did not include hands-on practice.

To overcome this problem and stimulate centres of excellence in diarrhoea case management training, the Programme developed a package called *Diarrhoea training unit (DTU): Director's guide and training materials* in 1986. The criteria established for an effectively functioning DTU required that it:

- receive regularly a sufficient number of diarrhoea cases for teaching purposes, both as outpatients and inpatients;
- have at least one senior physician who has adequate experience in treating acute diarrhoea according to WHO guidelines, especially using ORT;
- regularly hold training courses on the treatment of diarrhoea for health workers. Such courses should be designed according to the principles in the *Diarrhoea Training Unit—Director's Guide* and should include clinical demonstrations and hands-on practice by participants in treating diarrhoea cases;
- make educational materials available to the participants for use both during and after training; and
- assist in follow-up activities to help trainees set up a diarrhoea treatment or training unit in their own facility.

By the end of 1994, 420 DTUs had been established, but not all satisfied these criteria. A year later, 156 DTUs, including 70 that were also ARI Training Units, were considered to be functional based on these criteria.

The Programme developed *Guidelines for conducting clinical training courses at health centres and small hospitals* in 1990 after recognizing that DTUs could not cover all of the training needs of countries and that the potential trainers who partici-

Table 17 ■ **Development of CDR training tools for case management**

	CDD	ARI	IMCI	Milestones
1980	Guidelines for trainers of community health workers on the treatment and prevention of acute diarrhoea (revised in 1985 and 1989 for all health workers)			*First description of assessment, classification, and treatment of dehydration; the beginning of the Division's commitment to a simple approach to case management*
1984	Supervisory skills course, with module on treatment of the patient with diarrhoea (revised in 1989, 1992)			*First materials for inservice training of health workers in case management*
1985		Management of the child 1) with cough, and 2) with ear, nose, or throat infections (for use with the supervisory skills course, revised in 1990)		*First description of management of ARI, for use in inservice training*
1986	Diarrhoea training unit (DTU)—Director's guide and training materials			*First major intervention to strengthen clinical practice in model inpatient and outpatient facilities*
1990	Guidelines for conducting clinical training courses at health centres and small hospitals (revised in 1992)	Management of the young child with an acute respiratory infection		*First clinical course designed to be held in any facility with cases*
1992	Strengthening of the teaching of diarrhoeal diseases in medical schools	Outpatient management of young children with ARI: A four-day clinical course Treating children with cough or difficult breathing: A course for community health workers		*First attempt to improve the curriculum and clinical practice in the basic training of doctors*
1993	Advising mothers on management of diarrhoea in the home—A guide for health workers Clinical skills: A self instructional course			*Increased emphasis on importance of communication between health worker and caretaker; also new attempt to reach peripheral workers*
1994	Strengthening the teaching of diarrhoeal disease in basic training programmes			*Process described for improving the basic training of nurses and other health workers*
1995			Integrated Management of Childhood Illness—A WHO/UNICEF training course for first-level facility (outpatient) health workers	*Introduction of the guidelines for Integrated Management of Childhood Illness with training materials*
1997			Drug supply management	*Course to support the management of drugs at health facilities for use in treating childhood illness*
1999			Referral-level IMCI guidelines	

pated in DTU courses themselves needed materials to facilitate the training of others. These have been used since then, with some revisions in 1992, as the basis for inservice training of health staff.

Overall, more than 7,300 courses were held and more than 570,000 health workers were trained through the end of 1995, representing approximately 38 percent of health workers who regularly treat children with diarrhoea. Because the quality of these courses was not always known, and thus some of these staff may not have been adequately trained, the Programme undertook steps to formally monitor and ensure the quality of courses.

Distance learning

To further extend training and to cater for those health workers unable to attend a formal training course, the Programme developed guidelines for distance learning titled *Clinical skills: a self-instructional course*. This allows health workers to learn about diarrhoea case management in their own health facility with support through correspondence or visits from a tutor. This course became available in 1993 but experience with its use has been very limited due to resource constraints.

Pre-service training

Although inservice training was the main focus of training during the first 10 years of the CDD Programme, considerable effort since 1990 went toward improving teaching in medical schools and other training institutions for health professionals. A package of materials titled *Strengthening the teaching of diarrhoeal diseases in medical schools* became available in 1992–1993, and a set of materials with a similar aim for schools of nursing and other health professional training institutions was developed in 1994–1995.[9,10]

By the end of 1995, 152 medical schools in 35 countries had participated in workshops to plan improvements to teaching of diarrhoea management to medical students (see Figure 13). A subsequent review of progress in three countries (Bangladesh, Ethiopia, and Myanmar) confirmed that the schools assessed were giving more time to teaching on diarrhoeal diseases, were using the case management chart to teach students, and were placing more emphasis on clinical instruction and interactive teaching.

[9] *A manual for instructors of nurses and other health workers*. (Document CDD/94.2).

[10] *Workbook on management and prevention of diarrhoea*. (Document WHO/CDR/95.7).

Components of a package to strengthen the teaching of diarrhoeal disease in medical schools

Student Text Readings on Diarrhoea (i)
Contains key information on the etiology, epidemiology, pathogenesis, management, and prevention of diarrhoea. It is intended to be read by each student when he or she is learning about diarrhoeal diseases. By assigning units in the book as homework, it is possible to use classroom time normally devoted to lecturing for other teaching methods in which students are more actively involved.

Instructors Manual (ii)
Designed to assist faculty in planning how to teach the topics covered in the student text. Emphasis is given to the use of a variety of teaching methods, especially ones that require active student participation, and to ensuring that students gain competence in specific clinical skills.

References on Diarrhoea (iii)
A collection of original references on diarrhoeal diseases for students or faculty who wish to study in greater depth any of the topics presented in the student text.

Guide to Student Evaluation (iv)
Describes methods that can be used to evaluate a student's knowledge and skills. It also contains a collection of nearly 100 questions for use during written or oral examinations. The questions are especially designed to assess the student's ability to use knowledge rather than simply restate memorized facts.

Workshop Director Guide (v)
For use by directors when planning and conducting workshops on strengthening the teaching of diarrhoeal diseases in medical schools. It provides a sample agenda and detailed guidelines on how to conduct each activity in the workshop.

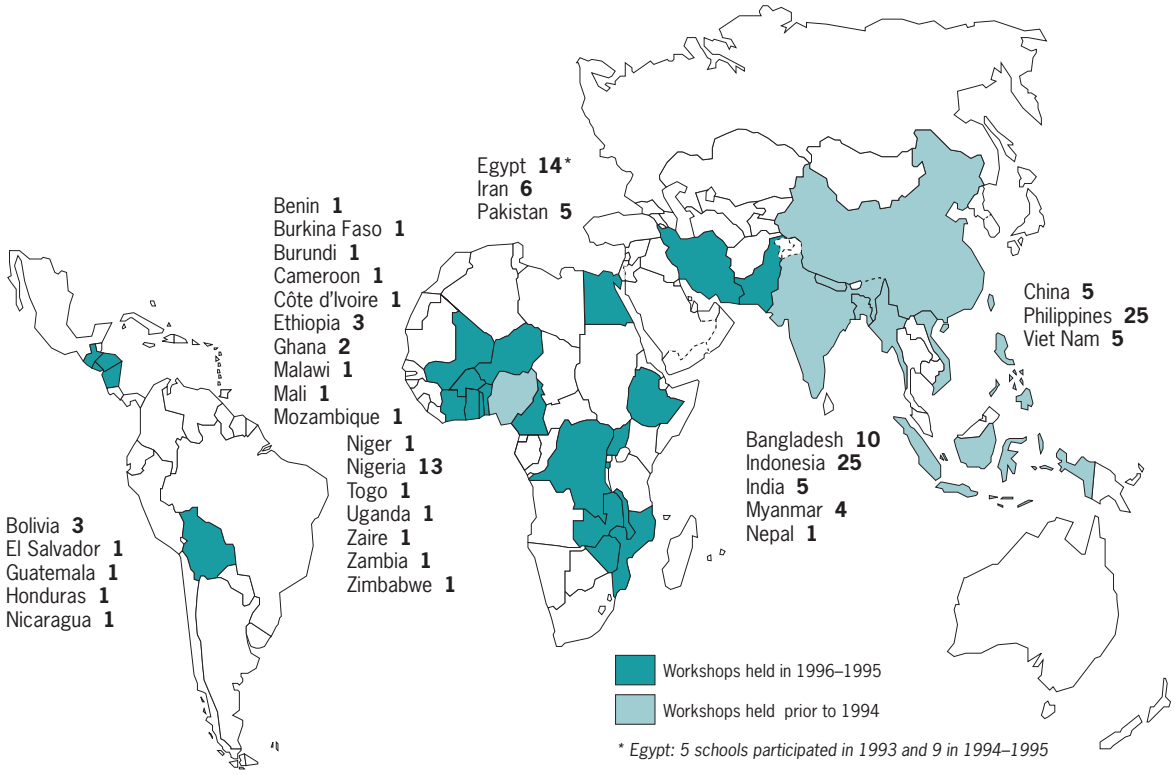
Workshop Participant Manual (vi)
Contains background information, instructions and work sheets for workshop participants. ■

Pharmacists and drug sellers

In 1993, the CDD Programme produced a *Guide for improving treatment practices of pharmacists and licensed drug sellers*. The guide was designed to help plan and implement interventions that could improve the prescribing practices of pharmacists and drug sellers because of their considerable influence on the way diarrhoea cases are managed. The guide was used and fieldtested in Kenya, Indonesia and the Philippines. As with the *Clinical Skills* course, resource constraints have not permitted more extensive use of this guide, one of the few specifically intended for use with service providers in the private sector.

Figure 13

Countries participating in workshops for medical school teachers



Acute Respiratory Infections

Technical guidelines

The first WHO ARI case management guidelines, developed and issued in 1985, classified the child with cough as having either mild, moderate or severe ARI and suggested appropriate treatment for each category. These guidelines were used as the basis for training in early programme development in countries and for the case management strategy evaluated in a number of intervention studies.

During 1988–1989, two existing training modules—one on management of the child with cough and one on management of the child with ear, nose and throat infections—were combined into a single module *Management of the young child with an ARI*. Revised in 1991, this module has since served as the basis for guidelines on outpatient case management of ARI. It was complemented by a training video, which showed the main signs of pneumonia and included exercises for trainees, and by a *Clinical instructor's guide* to improve the practical component of training.

In 1990, the ARI Programme issued a manual for doctors and other senior health workers called *Acute respiratory infections in children: case management in small hospitals in developing countries*. Beginning that same year, the ARI Programme produced a series of technical documents that described the rationale for various aspects of the case management approach including:

- Antibiotics in the treatment of acute respiratory infections in young children.
- Technical basis for the WHO recommendations on the management of pneumonia in children at first-level health facilities.
- Oxygen therapy for acute respiratory infections in young children in developing countries.
- Bronchodilators and other medications for the treatment of wheeze-associated illness in young children.
- The management of fever in young children with acute respiratory infections in developing countries.

Training courses and materials

Although the module on ARI case management was originally designed so that it could be used as part of the CDD Programme *Supervisory skills* course, there was a need for a more comprehensive training course on ARI case management. Consequently, the ARI Programme developed and fieldtested two sets of training materials: *Outpatient management of young children with ARI: a four day clinical course*, and *Treating children with cough or difficult breathing: a course for community health workers*. These materials are still being used by national ARI control programmes.

Specific guidelines for developing ARI Training Units, or for introducing ARI into medical and nursing schools, were not developed. However, adaptations of the CDD versions of such guidelines were used in a number of countries, and there were 191 active ARI Training Units in 1995.

Between 1987 and 1995, over 250,000 physicians, nurses and other health workers received training in ARI case management. As with CDD training, it is not clear to what extent adequate training methods were used, and in particular, the inclusion of sufficient hands-on practice.

Integrated Management of Childhood Illness

Training for health workers at first-level facilities

The training course *Integrated Management of Childhood Illness: A WHO/UNICEF training course for first-level facility (outpatient) health workers* was completed in 1995 in close collaboration with UNICEF and with other Programmes within WHO. This course represents an important achievement, successfully bringing together clinical research, development efforts and systematic pre-testing and fieldtesting. The box below describes the integrated case management process taught by the training course.

In mid-1994, the draft modules of the IMCI first-level facility course for case management of children aged two months to five years were pretested in Gondar, Ethiopia. Based on the pretest results, the course materials and methods were revised. In February and March 1996, the course was fieldtested in Arusha, Tanzania.

To be used effectively, the IMCI first-level course needs to be adapted to reflect the situation in each country, national guidelines and policies, and the epidemiology of common, serious childhood illnesses. The guidelines on counselling mothers should reflect local terminology and locally available foods and fluids.

In most countries, some research will be required to collect the information needed for course adaptation. Guidelines have been developed to guide this adaptation process, including protocols for research to obtain information about feeding practices, to validate local illness terms and to pretest the adapted mother's card.

The availability of a training course for health workers in Integrated Management of Childhood Illness is an important first step. However, continued research will be necessary to ensure that this tool is as useful and effective as possible, to determine the extent to which course adaptation is necessary for specific country or regional settings, and the most efficient methods for collecting the information necessary to do this.

To achieve long-term change in national programmes, efforts must go beyond the in-service training of health workers to address the basic teaching institutions that prepare medical professionals. IMCI can contribute much more if it is an accepted part of initial training for nurses, physicians and other health professionals. For physicians, experience with pre-service training in diarrhoeal diseases is being formally evaluated as

Case management process

- The health worker is taught to first **assess the child**, asking questions, examining the child and checking immunization status.
- Then the health worker is taught to **classify the child's illness**. The classification of illness is based on a colour-coded triage system with which many health workers are already familiar through use of the WHO case management guidelines for diarrhoea and acute respiratory infections. This classifies each illness according to whether it requires: urgent referral; specific medical treatment and advice; or simple advice on home management.
- After classifying, **specific treatments are identified**. If the child is being referred urgently, health workers learn to give only the urgent treatments before departure.
- Practical **treatment instructions are provided**, including how to teach the mother to administer oral drugs, to increase fluids during diarrhoea, and to treat local infections at home. The mother is advised on the signs that indicate the child should immediately be brought back to clinic and when to return for follow-up.
- Feeding is assessed (in children less than two years and those who are malnourished), any feeding problems are recorded, and **counselling on feeding problems provided** (summarized on the chart *Counsel the mother*).
- **Follow-up instructions** for the various conditions are provided on the chart *Treat the child* and explained in a module.

Fieldtest of the training course on management of childhood illness, Arusha, Tanzania

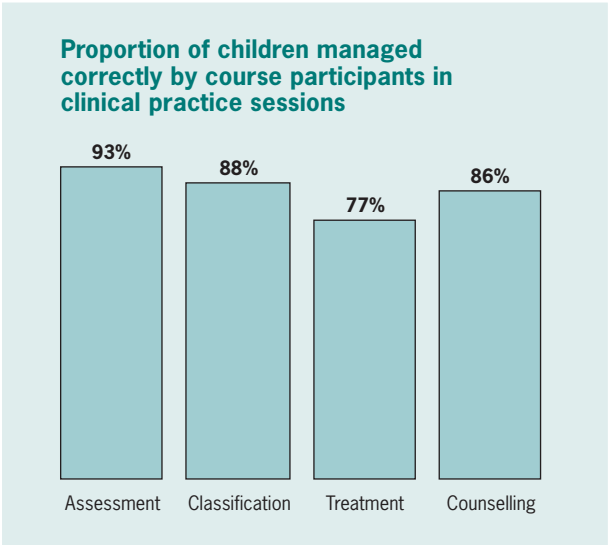
Objectives: To estimate the competence of participants in correct case management of the sick child; and to identify possible improvements in course materials or teaching procedures.

Participants: Three different categories of health workers participated in the course:

- 8 medical assistants who had completed 11–13 years of school and could read English easily.
- 8 rural medical aides (RMA) who had completed 9–13 years of school and could read English with some difficulty.
- 7 MCH aides who had completed seven years of schooling and who had considerable difficulty in reading English.

Methods: All course materials were in English, and had been partially adapted for use in Tanzania. Participants' ability to assess, classify and treat children and counsel their mothers during the clinical sessions was evaluated and recorded by facilitators as a regular part of course implementation. In addition, each exercise was evaluated and the results recorded by facilitators. Facilitators and observers identified revisions needed to improve the clarity of text of the materials. They also identified changes in teaching procedures that would improve instructional effectiveness or efficiency.

Results: The proportion of children for whom specific parts of case management were performed correctly by course participants during clinical practice sessions are presented in the figure. Medical assistants performed better than RMAs or MCH aides in assessment, treatment and counselling.



The course, in its fieldtest version, was effective in training medical assistants to assess, classify, treat and counsel mothers, using the training methods as recommended in the course facilitators' guide. These health workers were able to read the modules without difficulty and completed the whole course within the scheduled 11-day period. The two groups of health workers with lower levels of English literacy had considerable difficulty reading the course materials. To compensate for this, methods not described in the course facilitator guide were used and these participants were able to learn the case management process and perform adequately in clinic.

The fieldtest led to substantial improvements in the course materials and methods including significant simplification of the charts and modules and improvements in the visual aids. In addition, more drills were added to the methods used in the course, the standard definitions for selected signs were clarified in the course materials, and the sequence of topics improved. ■

the basis for developing a strategy to introduce integrated management into medical schools. A panel of senior medical professors has been convened to assess the potential benefits and challenges of developing pre-service training for physicians.

For health assistants and nurses, a field trial based on the existing in-service course materials will be supported in Ethiopia. After minimal adaptation, these materials will be used as the basis for a three-week rotation during the final year of training for clinical nurses. Careful observation of this trial will determine further research and development needs.

Case management at referral-level facilities

Improving case management at first-level outpatient health facilities will contribute significantly to the reduction of child mortality. Further reductions can be achieved if effective care for children with severe disease is provided at referral level facilities such as hospitals. The criteria for referral are clearly defined in the guidelines for managing childhood illnesses at first-level facilities and the following products are being developed and tested:

- Studies of the factors influencing mortality and severe morbidity associated with referral facilities (unpublished report, completed December 1998—observational studies on the relative importance of factors such as failure

to seek care, delays in seeking care, inadequate clinical skills, lack of drugs, and inadequate facility management).

- *Management of severe malnutrition: a manual for physicians and other health workers* (completed November 1998)—guidelines to improve clinical management of severe malnutrition in district hospitals.
- *Management of the child with a serious infection or severe malnutrition* (projected date October 1999)—primarily a treatment manual, covering the following conditions: emergency treatment, diarrhoea, respiratory problems, fever, bacterial infections in a young infant, severe malnutrition, breastfeeding problems. Short introductory sections on triage, history, examination and diagnosis are also included. A pocket on-the-job version of the manual will also be available.
- *Training material on triage/emergency care* (projected date October 1999)—studies of both the validity and the feasibility of the clinical guidelines under development, followed by the development of training materials.

Additional products will be developed including a "diagnostic kit" to enable countries to assess the relative importance of the factors impeding quality care, guidelines on interventions to address factors other than clinical skills, and further clinical training material.

Monitoring and reinforcing skills

After health workers complete clinical training, they often find it difficult to maintain their skills when they return to their health facilities. A follow-up visit is now seen as important to reinforcing the skills of facility staff recently trained in Integrated Management of Childhood Illness. In addition, information collected during follow-up can help countries monitor the progress of implementation activities.

The main purpose of the visit is to help health workers transfer their newly acquired case management skills to clinical work in the facility. During the visit, the supervisor observes the health worker managing a case, gives feedback on the care given, and provides practice to strengthen and reinforce the health worker's skills. Facility activities and the availability of drugs and other supplies needed to correctly manage sick children are reviewed. The supervisor helps the clinic staff identify and solve problems that may be preventing trained health workers from implementing IMCI.

New programme indicators of Integrated Management of Childhood Illness are being developed using data that can be collected through health facility and household surveys. Visits can also occur periodically to evaluate the quality of efforts to implement IMCI and help countries review priorities for planning programme activities.

5.3 Monitoring and Evaluation

To support effective monitoring and evaluation, the CDD and ARI Programmes developed and refined a range of instruments including household surveys, health facility surveys, and programme reviews. These tools have enabled national programmes to evaluate their progress and use the results to revise and improve programme activities.

The importance of evaluation was identified in the first CDD programme management course in 1980. New programmes developed national plans that set targets and subtargets, identified how these were going to be achieved, and proposed indicators to describe progress in implementing programme strategies. The course module on evaluation presented ways to measure programme indicators based on available information on mortality and on case management in the home and in the health facility.

Summary of the development of Integrated Management of Childhood Illness (1990–1995)

1990–1991
Studies in Malawi and the Gambia show overlap in presentation of pneumonia and malaria and that cotrimoxazole can be used to treat both. Accumulating experience shows the importance of dietary management of persistent diarrhoea.

1992
EPI programme seeks CDR collaboration in developing guidelines on the management of measles. CDR initiates a working group involving 10 WHO programmes and UNICEF to work on integrated management of the sick child.

1993
Draft guidelines on management of childhood illness at first-level health facilities prepared. Research to validate and improve clinical criteria for classification of illness, especially malaria and anaemia.

1994
Pretest of IMCI training course modules for managing illness in children two months to five years, Gondar, Ethiopia.

1995
Fieldtest of full IMCI course for first-level health staff, Arusha, Tanzania. Finalization of generic course materials.

In 1981, a *Manual for the planning and evaluation of national diarrhoeal disease control programmes* was issued. Subsequently revised in 1984, the manual included a simple method for mortality, morbidity and treatment surveys. It also emphasized the need for clearly stated programme objectives and strategies, for the calculation of realistic targets and subtargets for the main objectives and activities to achieve them, for scheduling and monitoring of activities, and for periodic evaluation. In these early guidelines, the Programme described the target setting process in terms of:

- establishing a baseline;
- describing change interventions and activities;
- estimating the likely extent of use of activities and interventions; and
- estimating impact of use of interventions on baseline.

Evaluation Tools

Household surveys

In 1984, the CDD Programme developed *Guidelines for a sample survey of diarrhoeal disease: morbidity, mortality and treatment rates*. This manual provided instructions for conducting household surveys and represented an important methodological advance from the earlier household survey method included in the 1981 manual of operations. The 1984 version provided the core for the revised CDD surveys of 1986 and 1989.

Based on the success of the CDD household survey, the ARI Programme adopted this method in 1994 to collect information on caretaker knowledge and practices, and on the incidence of disease.

The most recent household survey manual combines measures for diarrhoea and ARI, and also includes optional sections on measuring breastfeeding indicators, drug utilization rates, and access to ORS.

The increasing complexity of succeeding versions of the household survey guidelines meant that they required greater resources. As a result, only 12 surveys were conducted in 1994–1995, whereas 350 surveys were carried out between 1980 and 1988, and 76 between 1989 and 1993.

Because measuring diarrhoea mortality proved to be less reliable through the household survey, the 1994 survey manual dropped the procedures for collecting mortality data. CDR collaborated with UNICEF and the London School of Hygiene and Tropical Medicine to identify simple, but relatively reliable, methods for measuring trends in childhood mortality. The preceding birth technique was introduced through *A manual for the measurement of childhood mortality with simple surveys*. Although the methods described in this manual did not permit reliable measurement of cause-specific mortality, and thus were not used by CDR, they are likely to be important for IMCI, which is concerned with overall mortality from all causes.

Health facility surveys

To evaluate the quality of care children receive from health workers and to identify the conditions that affect it, the CDD Programme introduced the *Health facility survey manual: diarrhoea case management* in 1988. A similar manual on the management of ARI followed in 1994, and both were revised at that time to ensure that the survey procedures, forms, and training were compatible.

The surveys collect information to measure facility-based indicators on the quality of case management, and access to required drugs and trained workers. During visits to health facilities, surveyors also give immediate feedback to health workers to improve their skills and help them solve problems in the organization of facility activities, the availability of supplies, and other barriers in providing care.

During 1989–1993, 29 CDD health facility surveys were carried out using the original methodology. Using the revised methodology, 13 CDD and 16 ARI surveys were carried out during 1994–1995.

This method is now being adapted for use during follow-up visits to health workers trained in IMCI.

Programme reviews

The need for periodic evaluation of activities became evident as national programmes progressed. *Guidelines for conducting a comprehensive review of a diarrhoeal disease control programme* were developed in 1986 to help review teams examine all components of a national programme. During 1981–1993, approximately 120 programme reviews were carried out, half of which used the formal methods described in these guidelines.

The experience gained from these reviews taught CDD that the reviews would be more helpful if they concentrated on solving a few problems identified by the national programme. As a result, the *Guidelines for conducting a focused programme review* (CDD) replaced the larger comprehensive review in 1990. Materials for the focused programme review were then adapted for use by the ARI Programme in 1994. Sixteen CDD and two ARI focused programme reviews were carried out up to1995.

Guidelines for conducting a short programme

review, became available in 1996 to help CDD and ARI programmes review and replan their activities. This method is for more routine use, when an in-depth review of specific problem areas is not needed.

To meet an increasing demand for *joint* in-depth reviews, the CDD and ARI programme review guidelines were combined in a new version that became available in 1997.

Using Evaluation to Support Planning and Programme Management

The tools developed by CDR described above help countries evaluate their progress and use the results to improve plans and programme activities. The figure and text overleaf illustrate how the major components of evaluation support planning and programme management.

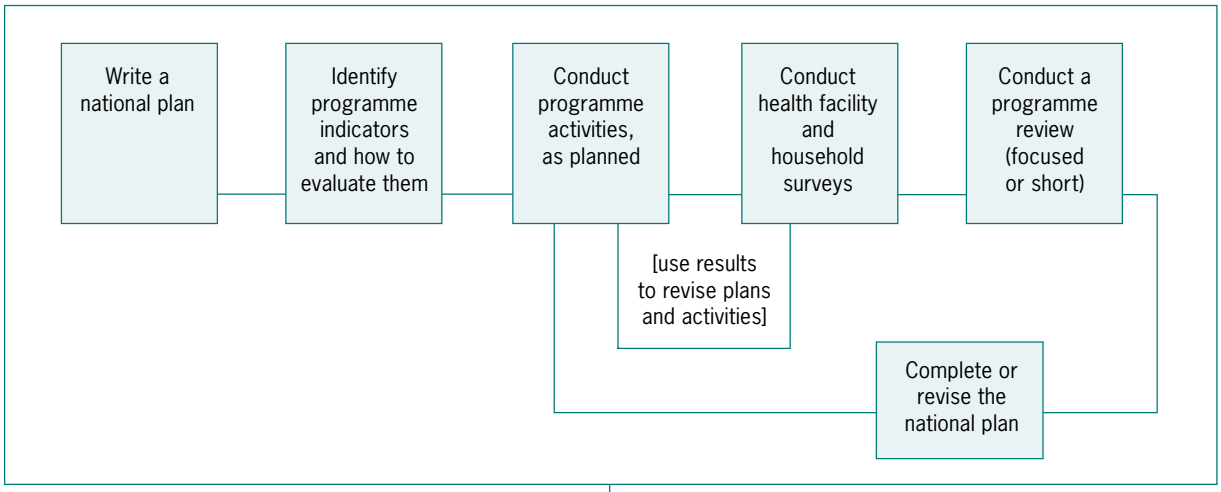
Programme indicators suggest or indicate programme achievements and provide a standardized description of how well programmes have been able to implement the most important control strategies.

Surveys measure programme indicators and provide feedback to national programmes and health workers.

- *Health facility surveys* collect data used to measure WHO/UNICEF facility-based indi-

Table 18 ■ **Milestones in the development of CDR evaluation tools**

	Programme management tools	Household-based tools	Health facility-based tools	Milestones
1980	CDD Programme Management: a training course, with module on evaluation (revised in 1988)			*Evaluation activities described as a component of a CDD Programme*
1984		Guidelines for a sample survey of diarrhoeal disease morbidity, mortality and treatment rates		*Tool to measure incidence of disease, and programme indicators related to home practices (household-based)*
1986	Guidelines for conducting a comprehensive review of a diarrhoeal disease control programme	Household survey manual: diarrhoea case management, morbidity and mortality (revised in 1989)		*First programme review tool (replaced by the focused programme review in 1990)*
1988			Health facility survey manual: diarrhoea case management (revised in 1990 and 1994)	*First tool to evaluate health worker performance and measure facility-based indicators*
1989	ARI Programme Management: a training course, with module on evaluation			*Evaluation activities described as a component of an ARI programme*
1990	Guidelines for conducting a focused programme review (CDD, revised in 1994)	A manual for the measurement of childhood mortality with simple surveys—UNICEF/ WHO/London School of Hygiene and Tropical Medicine		*Introduction of the preceding birth technique to measure childhood mortality (household-based)*
1994	Guidelines for conducting a focused programme review (ARI)	Household survey Manual: diarrhoea and acute respiratory infections	Health facility survey manual: case management of acute respiratory infections	*First combined CDD and ARI evaluation tool (household-based), the survey stopped measuring disease-specific mortality*
1996	Guidelines for conducting a short programme review (ARI and CDD)			
1997	Guidelines for conducting a focused programme review (ARI and CDD combined)			



cators. They assist programme managers in using the results to identify and address weaknesses in the quality of care in health facilities.

- Through interviews with caretakers, *household surveys* identify the quality of case management in the home and provide information to measure the WHO/UNICEF home and community-based indicators. Programme managers use the results of these surveys to identify the knowledge of caretakers about when to seek treatment for the child, treatment practices in the home, breastfeeding practices, and the availability of ORS in the community.

The results of surveys provide focus for future programme reviews and planning, as well as provide information that can be used immediately to revise programme activities. *Programme* reviews use indicators and other survey results to identify progress, and help programmes develop more effective national plans to address identified problems.

- *Focused programme reviews* help countries review their efforts in relation to selected problems. The review team begins with an analysis of survey results and programme indicators, and a qualitative review of efforts to complete programme activities. This information is used to identify and address programme issues such as difficulties in providing effective case management. An in-depth investigation into selected problems provides the basis for a work plan to address them.
- The *short programme review* process also begins with an analysis of survey results and indicators, and a review of activities planned and conducted. Although it does not allow time for an in-depth investigation of problems, the results of the short review enable programmes to complete or revise their national plans.

Integrated Management of Childhood Illness

Sound management of IMCI will require the availability of timely information about the implementation and effectiveness of programme activities. Continued refinement and extension of evaluation tools is planned.

Two specific research activities have been conducted to refine and validate existing tools. The first, in the Philippines, assessed the impact of national programme activities on morbidity and mortality. Measurement of impact continues to be a challenge for most national programmes, and this activity validated a protocol for the evaluation of programme impact using routine data sources. The resulting document, *Evaluating the impact of national CDD programmes* (WHO/CHD/97.2), provides guidance on the main steps involved in carrying out such an evaluation.

Second is research that assessed the validity of maternal reports of fluid and food intake by children during illness. Further validation is both urgent and essential as such reports are used in household surveys to determine the effectiveness of numerous health system and community-based interventions.

Indicators and Targets

Management guidelines for national programmes include lists of recommended indicators for countries and methods for establishing and measuring targets. The global CDD, ARI and CDR Programmes also used indicators and targets to measure global achievements.

- An "indicator" is defined as a number, proportion, or rate that suggests or indicates the extent of some programme achievement or the level of some condition in the population.
- A "target" is defined as a level of achievement of an indicator to be reached by a specified time.

In recent years, indicators and targets have been divided by level, with "activity" indicators (e.g., proportion of staff trained) leading to "programme" indicators (e.g., proportion of cases correctly managed), and then to "health" indicators (e.g., reduction in mortality).

The CDD Programme achieved and surpassed many of the global targets set in 1980 more quickly than originally anticipated. By 1984, the number of countries with operational CDD programmes had reached 75, although the original target for 1983 was only 35 countries. And by the same year, 1990 targets for management training and ORS production had already been achieved and were revised upward. Global access to ORS increased from 21 to 63 percent between 1983 and 1989, and ORS use from 4 to 32 percent in the same period. By 1993, more than 60 developing countries were producing ORS of a satisfactory quality. By 1995, access to ORS reached 80 percent and it was estimated that increased fluids and continued feeding were given in 34 percent of diarrhoea episodes. This represents significant advances since the beginning of the decade. And oral rehydration therapy is now the accepted standard practice in the management of diarrhoea by health staff at all levels.

In 1985, the CDD Programme started to estimate impact based on assumptions about the proportion of diarrhoeal deaths caused by dehydration and the effect of ORT use on mortality. It was estimated that the use of ORT might have prevented some 350,000 deaths from diarrhoea in 1984, 700,000 childhood diarrhoea deaths in 1986 and 1.1 million in 1988.

With regard to ARI, extensive training efforts have ensured that childhood pneumonia is more widely recognized as a major childhood killer, and by the end of 1998, 59 of the original 88 target countries had an operational ARI programme. But impact on mortality is only likely to be achieved by more timely care-seeking by families. Since Programme efforts until 1995 focused on improving case management in health facilities, most of the work to achieve impact remains to be done.

CDD indicators and targets: 1980–1990

Early targets and definitions

The first **indicator** used by the global Programme was the number of countries with "well formulated plans." This was defined as a plan "with well-defined objectives, strategies, targets, activities, a budget and a plan for evaluation." The number of countries achieving this increased from 8 in 1980, to 24 in 1981, to 55 in 1982, to 72 in 1983.

At this stage, a country was defined as having an "operational CDD programme" when it had a CDD unit or manager at the national level, implementation of some of the activities in the plan, a monitoring system, and ORS available at some health facilities. The number of countries meeting these criteria increased from 37 in 1982 to 75 in 1984.

The first set of global **targets** established in 1980–1981, to be achieved by 1990, related to country programme planning, training and evaluation (see Table 19).

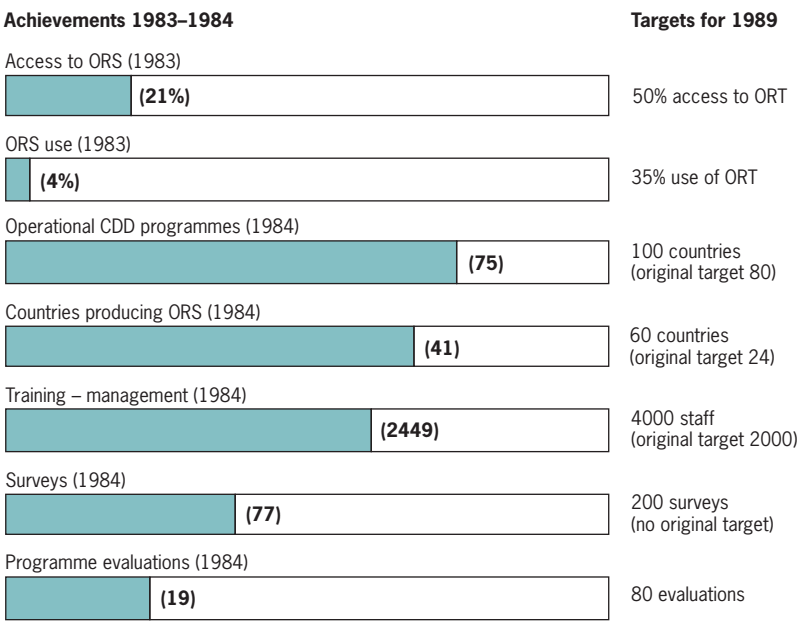
Initially, the global Programme focused on managerial training. Case management training was limited to national programme managers, hence the modest target of training only 520 staff in case management during the decade 1981–1990.

Table 19 ■ **Targets and achievements of the CDD health services component**

Targets	1983	1990
Planning		
Number of countries with operational CDD programmes	35	80
Number of subregional and national ORS production centres	15	24
Training		
Total WHO-sponsored courses/number of staff trained:		
• senior level management (programme management)	10/300	24/720
• mid-level management (supervisory skills)	8/320	22/980
• technical (for trainers)	12/240	26/520
Number of regional and subregional training centres	6	10
Number of countries with training and health education materials	35	80
Evaluation		
Number of country programme evaluations	20	175
Achievements		
Childhood diarrhoea cases with access to oral rehydration therapy	25%	50%
Childhood diarrhoea cases receiving oral rehydration therapy	12.5%	37.5%
Diarrhoea deaths averted (estimation based on ORT use rates)	not measured	1 million

Figure 14

Targets and achievements



Access to and use of oral rehydration therapy referred only to ORS:

- "Access" was defined as "reasonable geographical access (considering both distance and time) to a supply of ORS," and no standardized method for measuring access was used beyond reporting estimates provided by countries.
- "Use" was defined as "the proportion of diarrhoea episodes in children under five years of age actually treated with ORS," measured through household surveys (as described above).

Revised targets and definitions

By 1984, targets related to numbers of operational programmes, management training and ORS production had been met or surpassed, and new targets were established (see Figure 14).

By 1985, the number of countries with well formulated plans increased to 104, and 80 of these programmes were considered to be operational. Factors that prevented the shift from planning to implementation included inadequate political commitment, lack of financial resources, failure to designate a national programme manager, overemphasis on cholera control, and poor coordination between and within ministries.

The growing recognition that dehydration could be prevented through the use of fluids other than ORS prompted the Programme to modify its definitions of access and use:

- "ORS access" was redefined as "reasonable access to a provider of ORS who is trained in its use," actually an indicator of access to correct case management.
- "ORT use" was redefined as "treatment with ORS or sugar/salt solution."

In 1984, global ORS access was estimated to be 33 percent and ORT use 12 percent. Thus, the 1989 targets for these indicators were increased, from 50 percent to 80 percent and from 35 percent to 50 percent, respectively. Access to ORS had increased to 59 percent by 1986 and the definition of ORT was expanded to include "recommended home fluids" other than sugar-salt solution. ORT use rates had increased to 23% by 1986 and to 38% by 1991; it is estimated that this may have resulted in 1.1 million diarrhoea deaths being averted that year.

Country programme indicators

In 1987, the Programme Management training course was revised. One important aspect was inclusion of a set of recommended country programme indicators. The 13 indicators selected were:

- **Training coverage rates:** (i) Proportion of current health staff with supervisory responsibilities who have been trained in supervisory skills; (ii) Proportion of current health staff with responsibility for treating diarrhoea cases who have been trained in diarrhoea case management, where training includes actual practice.
- **ORS access rate:** Proportion of the population less than 5 years old with reasonable access to a provider of ORS who has been trained and receives adequate supplies.
- **ORS use rate:** Proportion of all cases of diarrhoea in children less than 5 years old treated with ORS.
- **ORT use rate:** Proportion of all cases of

diarrhoea in children less than 5 years old treated with ORS and/or a recommended home fluid.

- **Increased fluid intake rate:** Proportion of cases of diarrhoea in children less than 5 years old to whom an increased amount of fluid (ORS or recommended home fluid) has been administered.
- **Continued feeding rate:** Proportion of cases of diarrhoea in children less than 5 years old given normal or increased amounts of food during diarrhoea.
- **Households with correct knowledge of when to seek treatment outside the home:** Proportion of caretakers who knew when to seek treatment outside the home for a child with diarrhoea (according to the national recommendation).
- **Households able to prepare ORS correctly:** Proportion of caretakers who could demonstrate the correct method of preparing ORS.
- **Households able to prepare the recommended home fluid correctly:** Proportion of caretakers who could demonstrate the correct method of preparing a recommended home fluid.
- **Cases correctly assessed:** Proportion of diarrhoea cases among children less than 5 years old treated at health facilities that were correctly assessed.
- **Cases correctly rehydrated:** Proportion of diarrhoea cases among children less than 5 years old treated at health facilities that were correctly rehydrated (orally or IV).
- **Cases whose caretakers were correctly advised on treatment at home:** Proportion of diarrhoea cases treated at health facilities whose caretakers were given advice on treatment at home, including continued and compensatory feeding, ORT and when to seek further treatment.
- **Dysentery cases given appropriate antibiotics:** Proportion of dysentery cases among children less than 5 years old treated at health facilities who were given appropriate antibiotics.

1989 targets relating to the number of operational programmes, programme reviews, and countries producing ORS were exceeded. However, achievements related to the proportion of staff trained in supervision and case management, and those related to ORS access and ORT use fell significantly short. Case management training was reported to be up to 11 percent in 1989. ORS access rates increased only slightly, from 58 to 63 percent between 1986 and 1989, while ORT use increased from 23 to 32 percent during 1986–1988.

By 1988, there was growing recognition that it was important to measure more than ORT use. For example, "correct use of ORT" should be emphasized, including correct preparation of the fluid and giving increased fluid plus continued feeding, not

Table 20 ■ **Programme status and targets**

	Status (%)		Target (%)	
Selected key indicators[a]	**1989**	**1991**	**1995**	**2000**
Maternal knowledge of the three rules of home case management—provide increased fluid, continue feeding, seek care from a health facility when appropriate	b	b	80	100
Access to case management through health facilities—a composite of the availability of ORS and antibiotics and observed practices of staff	b	b	80	95
ORS access rate—defined as the proportion of the population with a regular supply of ORS in their community	63	68	80	100
Case management rate (ORT plus continued feeding)—the most important indicator for assessing likely impact on mortality	19	21	50	80
Other indicators				
ORT use rate	36	38	c	c
Supervisory skills training coverage	17	31	40	d
Case management training coverage	11	19	40	d
Programme reviews	81	98	160	d

a WHO and UNICEF agreed to give priority to cooperating with countries in the measurement of the four indicators.
b Measurement of these indicators began in 1992.
c No targets set for 1995 and 2000 as this indicator is replaced by the case management rate.
d Targets not set for 2000. Targets are now focusing on IMCI.

Following discussions between UNICEF and WHO the 1995 target for case management rate was increased from 50 percent to 80 percent.

just use of an appropriate fluid. Although the Programme continued to report on ORT use after 1989, greater emphasis was placed on the proportion of childhood diarrhoea cases receiving both increased fluid and continued feeding (originally called the "case management rate"). A case management target rate of 50 percent was set for 1995; the rate reported in 1990 was 19 percent.

CDD indicators and targets: 1991–1995

The World Summit for Children in 1990 included among its targets for the year 2000 the reduction of childhood diarrhoea mortality by 50 percent and of diarrhoea incidence by 25 percent. CDR and UNICEF subsequently met to plan the strategy to achieve these targets, and to agree on key indicators and sub-targets (see Table 20). Standardized

Table 21 ■ **Key indicators and targets for CDD programmes in the 1990s**

Indicator	Numerator	Denominator	1995 target	2000 target	Method of evaluation
Access to ORS	Communities where one or more sites has ORS in stock at time of evaluation, and reports that sufficient stock has been available all or most of the time in the past three months to meet the needs of the population	Communities assessed	80%	100%	WHO household survey
Caretaker knowledge	Mothers or other caretakers of children with diarrhoea who know the three rules of home case management (to give increased amounts of fluid; to continue feeding; and to seek treatment outside the home for a child with diarrhoea when appropriate)	Mothers or other caretakers of children with diarrhoea	80%	100%	WHO household survey; UNICEF MICS survey
ORT (increased fluid intake) plus continued feeding	Diarrhoea cases in children less than 5 years who receive increased amounts of fluid and continued feeding	Diarrhoea cases in in children less than 5 years	80%[a]	90%[a]	WHO household survey; UNICEF MICS survey
ORS and/or RHF use (pre-1991 definition of ORT)	Diarrhoea cases in children less than 5 years who received ORS and/or recommended home fluids	Diarrhoea cases in children less than 5 years	80%	90%	WHO household survey; UNICEF MICS survey
Case management training coverage	Facility health workers with responsibility for treating diarrhoea cases who have been trained in standard diarrhoea case management (training must include practice)	Facility health workers with responsibility for treating diarrhoea cases	40%	60%	Routine reports; WHO health facility survey
Supervisory skills training coverage	Health staff with supervisory responsibilities who have been trained in supervisory skills)	Health staff with supervisory responsibilities	40%	60%	Routine reports; WHO health facility survey
Correct case management at health facilities	Diarrhoea cases in children less than 5 years seen at health facilities who receive standard case management. Standard case management includes correct assessment and advice to the caretakers for children who are not dehydrated, and correct assessment and treatment for children who are dehydrated	Diarrhoea cases in children less than 5 years seen in health facilities	No targets set	No targets set	WHO health facility survey

[a] Original 1991 targets for this indicator were 50% for 1995 and 80% for 2000.

definitions of indicators were further refined in 1994 (see Table 21).

Concerns about targets and indicators

Access to case management was never measured and was replaced in 1992 by a different composite indicator, "cases correctly managed in health facilities." Initial results were felt to present an unrealistically negative picture of health worker and facility performance. The indicator was revised again in 1993 to a new "proxy" indicator "cases correctly rehydrated at health facilities". The results from 23 surveys carried out during 1990–1993 showed an increase from 9 percent to 20 percent in this period. But this indicator was quite complex, requiring a high volume of ORS to have been administered, and it was felt to be an overly conservative proxy for estimating case management.

By the end of 1992, ORS access had increased to 73 percent and mother's knowledge of the three rules of home case management had increased to 32 percent. The figure for cases receiving increased fluid and continued feeding, however, declined to 19 percent, based on a revised analysis of survey data.

As survey instruments were revised and became more complex, they were used less and criteria for measuring indicators changed. For these reasons, it was difficult to compare global rates between one period and another. In 1993, for example, while there continued to be a reported increase in ORS access, from 73 percent to 75 percent, and increased fluid and continued feeding increased from 19 percent to 34 percent, mother's knowledge of the three rules was now estimated to be only 11 percent. This was because of very low knowledge of when children should be taken to a health facility, and the rate of 32 percent reported for 1992 was considered to have been a significant overestimate.

In 1992, the Programme began to question whether the targets set in 1991 for the year 2000 were still useful for programme planning and as a source of motivation for health staff, since it was clear that several targets would not be achieved.

Another concern, expressed in the 1994 Interim Programme report, was whether the number of surveys being carried out was too small to allow global estimates to be made. Nonetheless, ORS access was estimated to be approaching, if not exceeding, the 1995 target of 80 percent. A median rate for eight household surveys showed a "caretaker knowledge" rate of 18 percent, far below the target of 80 percent, because of inadequate knowledge of when to seek care outside the home. The median of these same surveys for increased fluids and continued feeding was 43 percent.

In 1994, UNICEF developed the "Multiple Indicator Cluster Survey" (MICS), a much less complex instrument than the revised CDR survey, to measure progress toward mid-decade targets across a variety of programmes. By the end of 1995, 82 such surveys were carried out. The increased fluid and feeding rate, based on measurement in 44 of the surveys, was estimated as 34 percent, significantly short of the 1995 50 percent target originally established and the revised target of 80 percent. This rate is similar to the 36 percent median of 12 household surveys reported by CDR

Table 22 ■ **CDR/UNICEF key programme indicators: targets and levels of achievement (%)**

Indicator	1995 target	2000 target	1989	1991	1992	1993	1994	1995
Access to ORS	80	100	63	68	73	75	80	80
ORT (increased fluid) and continued feeding	80*	90*	19	21** (17)	19	34	43	34 MICS†
Caretaker knowledge of the three rules of home case management	80	100	—	29	32	11	18	24
Access to case management through health facilities (established 1991, not measured)	80	95	—	—	—	—	—	—
Cases correctly managed (established 1992, results not reported)	50	80	—	—	—	—	—	—
Cases correctly rehydrated (proxy for cases correctly managed) (established 1993)	none	none	—	—	9	20	20	20

* Original targets were 50% for 1995 and 80% for 2000
** 21% in Programme Report 1990–1991, 17% in Programme Report 1992
† UNICEF Multiple Indicator Cluster Survey

in the 1994–1995 Programme Report. By the end of 1995, it was also reported that the median rate for caretaker knowledge of the three rules was 24 percent, and the median rate for 13 health facility surveys showed that 20 percent of diarrhoea cases were correctly rehydrated.

The Programme came close to reaching the 40 percent target for case management training, but as already noted, information on the quality of this training was not generally available. Because of the turnover in personnel, fewer than 40 percent of staff currently treating cases can be considered as having been trained.

A summary of achievement of key targets and indicators is provided in Table 22.

Use of indicators and targets by national CDD programmes

A number of individual countries have found indicators and their measurement to be useful, as illustrated by the following examples of two household surveys conducted in 1992 and 1994 in Egypt, and of health facility surveys conducted in Brazil, Jordan and Malawi in 1993. In these examples, measurement of the specific elements included in indicators was found to be more useful than measurement of the overall composite indicators themselves.

ARI indicators and targets: 1987–1995

The ARI Programme took a similar approach to CDD in the selection and use of indicators and targets, both globally and in individual countries.

Concentrating on the 88 countries with an infant mortality rate greater than 40 per 1000, the Programme initially measured the number of countries with well-formulated plans and with operational programmes. An operational programme was defined as one where:

- A programme manager, full- or part-time, is responsible at the national level for the ARI programme;

Household surveys in Egypt

In August 1994, the National Control of Diarrhoeal Disease Programme (NCDDP) and the National Acute Respiratory Infections Programme (NARIP) of the Ministry of Health of Egypt carried out a combined CDD/ARI household case management survey in collaboration with WHO and UNICEF. The primary purpose of the survey was to:

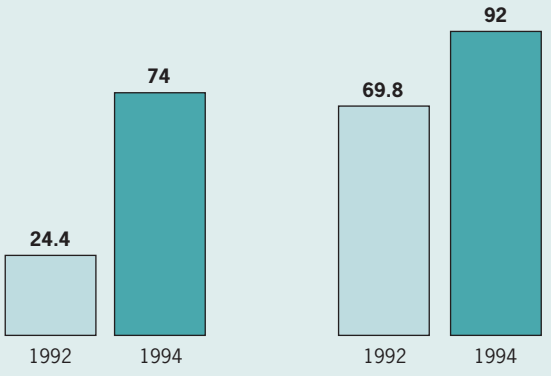
- assess caretakers' knowledge and practices in the home management of diarrhoea and ARI;
- collect information about the use of drugs during episodes of these diseases; and
- collect information about breastfeeding practices.

The survey was conducted in two governorates (Gharbia and Dakahlia) with sampling based on probability proportional to population size. Among the 11,798 children in the survey, 2,044 were investigated for an episode of diarrhoea in the previous two weeks.

Selected survey results for diarrhoea were compared with those collected in a CDD household case management survey conducted in 1992 in the same two governorates. Results showed that a greater proportion of mothers of children with diarrhoea reported giving their child increased fluids and continuing to feed the child during the episode in 1994 than in 1992 (see Figure). The increase was probably associated with the intensive CDD communication and training activities implemented by the NCDDP since 1992. It may also reflect some measurement bias, as the 1992 survey interviewed mothers of children with diarrhoea in the past 24 hours, whereas in 1994 the sample was expanded to include mothers of children with diarrhoea in the past two weeks.

ORT use and continued feeding

Household case management surveys, Egypt 1992 and 1994



The results also showed increased use of inappropriate drugs in the treatment of diarrhoea, with 54.2 percent of children with diarrhoea reported by their caretakers to have been given drugs to treat the disease in 1992, increasing to 76 percent by 1994. Most caretakers had obtained these drugs from private physicians and public health facilities, rather than from pharmacies. Concerned by these findings, the national CDD programme took immediate steps to address the problem, including training physicians in the private sector, with particular emphasis on the appropriate use of drugs, revising the national CDD case management chart to include additional guidance on bloody diarrhoea, and increased efforts to emphasize and promote timely complementary feeding in infants aged 6–9 months. ■

- Technical guidelines for case management (i.e., the diagnosis and treatment of pneumonia and other acute respiratory syndromes at different levels of the health care system) have been approved and issued officially by the ministry of health;
- Programme policies, objectives, strategies, stages, targets for activities, indicators for evaluation, and budget are described in a distinct plan of operation;
- Implementation of a case management strategy that is technically consistent with the national guidelines has started in one or more administrative jurisdictions of the country.

In addition, indicators and targets were established in 1988 for staff trained, access to case management, and treatment of pneumonia cases. From 1988 to 1990 targets were increased (see Table 23).

By 1991, the number of operational programmes had increased to 44. The number of staff trained had risen to 20,000 and so the training targets were increased to 200,000 by 1995 and 400,000 by 2000. Access to case management was still only 6 percent, however, and the Programme recognized that there was no information available on which to base reasonable estimates of the rate of childhood cases of pneumonia treated with recommended antibiotics.

The World Summit for Children in 1990 established a target of a one-third reduction in childhood ARI mortality by the year 2000. It was estimated that this would require a treatment rate of 60 percent, but the baseline information for this estimate—the extent to which pneumonia mortality was currently being prevented through the use of antibiotics—was not available.

By 1992, the number of operational programmes increased to 47, and the number of staff trained in case management increased to 100,000. Although concerned about the quality of much of this training, the Programme used this figure to estimate that access to standard case management had doubled, to 12 percent.

The overall pneumonia treatment rate was replaced by a more measurable indicator, the pneumonia treatment rate among cases seen at health facilities. To link this with a reduction in overall pneumonia mortality would require an indicator for care-seeking, but in the absence of interventions to improve care-seeking other than counselling of families already seeking care, the Programme did not establish such a target.

Because of serious concern about the likelihood of achieving the ARI mortality reduction target set by the Summit, WHO and UNICEF developed new indicators to measure essential steps in achieving such reductions. These included:

- the proportion of mothers who know the signs indicating that a child with ARI should be taken to an appropriate provider of care (*maternal knowledge of when to seek care*);
- the proportion of children with ARI needing assessment, or ANA, who are taken to an appropriate provider of care (*care-seeking for ANA*);
- the proportion of all health facilities that are able to give correct pneumonia case management (*health facility capability*), defined as facilities with at least one health provider adequately trained in standard case management and regularly supplied with free or affordable antibiotics for the home treatment of pneumonia; and

Table 23 ■ **ARI programmes in countries with an infant mortality rate greater than 40/1000:[a] Progress and targets**

	Status in		Status in/Targets for		Targets for
Category of target	**1984**	**1990**	**1995**		**2000**
Programme					
Countries with operational[b] ARI control programme:	3 %	39 %	67 %	100 %	100 %
Training					
Facility-based staff trained in case management:	—	0.5 %	4 %	5 %	15 %
(total number 2 million)	1 000	10 000	80 000	100 000	300 000
Access					
ARI standard case management access rate:[c]	—	5 %	40 %	50 %	75 %
Use					
Childhood pneumonia cases managed correctly:	8 %	12 %	31 %	40 %	60 %

[a] Source: United Nations Population Division, World Population Chart 1988, United Nations, New York.
[b] In 1988, 88 countries had an infant mortality rate greater than 40/1000 live births. Status in 1984 and 1990 is calculated using this denominator which may change in future years.
[c] The ARI standard case management access rate was defined as access of the population to a provider (health staff or community-based practitioner) who is adequately trained in the correct case management of pneumonia and who is regularly supplied with free or affordable antibiotics for the treatment of pneumonia. Access and use, or treatment, were not measured directly, but extrapolated from the estimated numbers of staff trained.

- the proportion of pneumonia cases seen in health facilities who receive standard case management (*pneumonia case management*).

A fifth indicator, developed to monitor achievement of training targets, is the proportion of facility-based staff trained in case management.

No targets for these indicators were set, given the absence of information on current levels, and previous targets for access and treatment were dropped. The Programme did, however, modify its household and health facility surveys manuals in order to measure the new indicators.

By the end of 1994, 59 of the original 88 target countries were considered to have operational ARI programmes, 20 of these were carrying out activities nationwide, and approximately 200,000 staff had been trained in case management.

The ARI Programme management training course, which became available 1990, recommended the following country indicators:

- **Health facilities with trained health staff:** Proportion of health facilities with at least one health worker trained in standard ARI case management (training must include practice on cases).
- **Antibiotic availability in health facilities:** Proportion of health facilities with a regular supply of the antibiotic(s) recommended for home treatment of pneumonia in stock.
- **Health facility case management capability for ARI:** Proportion of facilities with at least one health worker trained in standard case management (where training includes practice) and with a regular supply of the antibiotic(s) recommended for the home treatment of pneumonia in stock.
- **Severe cases correctly treated:** Proportion of children with very severe disease or severe pneumonia seen in a health facility who are correctly referred or admitted to hospital by the health worker.
- **Pneumonia cases correctly treated with an antibiotic at home:** Proportion of children with pneumonia seen in a health facility who are given an appropriate antibiotic by the health worker.
- **Cases whose mothers were correctly advised on home care:** Proportion of children with ARI seen at health facilities and not referred or admitted to the hospital by the health worker whose caretaker receives appropriate home care advice.
- **ARI cases correctly managed:** Proportion of children classified with very severe disease, severe pneumonia, pneumonia, and no pneumonia (cough or cold) who are correctly managed by the health worker.
- **Care-seeking for ARI needing assessment (ANA) outside the home:** The proportion of ANAs for whom care was sought outside the home. ANAs are defined as cases with cough who have rapid or difficult breathing.
- **Care-seeking for ARI needing assessment from appropriate providers:** The proportion of ANAs for whom care was sought from providers who have been trained in standard ARI case management and supplied with appropriate antibiotics, or other providers expected to deliver good case management.
- **Caretaker knowledge of when to seek care for ARI:** The proportion of caretakers who know when to seek care from a health worker for a child with cough. In order to be counted as having correct knowledge, caretakers must mention at least one of the following signs: fast breathing, difficult breathing, or a local term concordant with fast or difficult breathing or pneumonia.

Lessons Learned About Use of Indicators and Targets

As described earlier in this section, there are several challenges to using global indicators and targets. However, there are a number of valuable lessons to be learned for future public health strategies such as Integrated Management of Childhood Illness:

1. Global indicators and targets are only appropriate when resources (including funding, large-scale country commitment and the active support of international agencies) permit implementation of global activities.
2. Indicators chosen should reflect an understanding of the strategic approach to reducing mortality or morbidity. For ARI, where antibiotics were already being used extensively, the major step required to reduce mortality was improvement of timely care-seeking.
3. Indicators are most useful at country level and should include specific, rather than composite measures. Indicator selection should emphasize issues that are needed to sustain programme commitment, and which measure achievement of intended results.

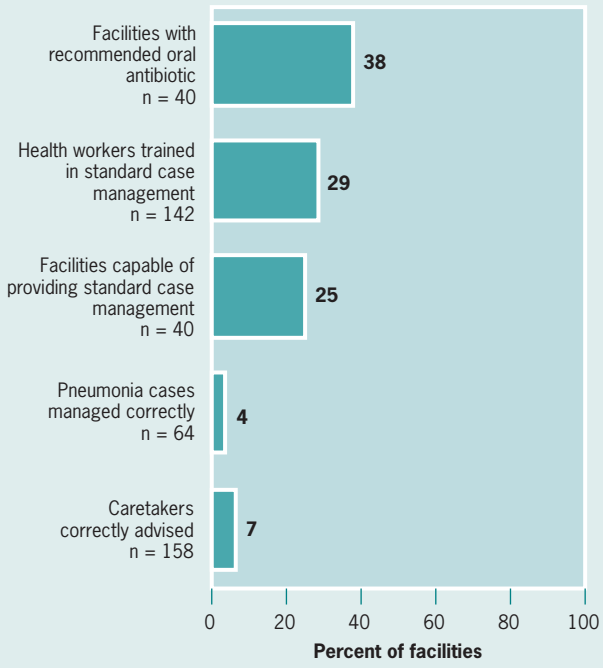
The ARI health facility survey in Pakistan

Pakistan's national ARI programme conducted a health facility survey in January and February 1994. The survey was carried out in collaboration with WHO and UNICEF, using the guidelines developed by WHO.

A random sample of health facilities was drawn from 11 divisions in three provinces and the Central District. The facilities surveyed included 11 hospital outpatient departments, 15 rural health centres and 14 basic health units. Each facility was visited by a team of trained surveyors. In the course of one day at each facility, surveyors observed the case management practices of health workers, conducted independent assessments of children presenting with cough or difficult breathing, interviewed caretakers and health workers, and assessed facility equipment and drug supplies. The surveyors observed the case management of 281 children with cough or difficult breathing by 64 health workers (mainly physicians).

Indicator levels as estimated by the survey are summarized in the figure. Other important findings included the fact that health workers trained in standard case management perform better than untrained health workers in the assessment of danger signs, in the classification of disease, and in assessments of their knowledge about standard ARI treatment. In the treatment of severe disease, severe pneumonia, and pneumonia, however, the training status of the health worker made no difference. One explanation for this finding is that both trained and untrained workers usually prescribed antibiotics for children with pneumonia. Unfortunately, however, both groups also prescribed antibiotics for children without severe disease or pneumonia, although trained workers did so less often than untrained workers (for 31 percent and 67 percent of cases, respectively). Proper instructions on antibiotic treatment and advice on home care were seldom given to caretakers, and performance in this area did not vary by training status. In addition, the antibiotics recommended for the treatment of ARI were frequently not in stock in the facilities assessed. Although these drugs are widely available from private outlets, they may not be affordable to the majority of families.

The quality of ARI case management in Pakistan, ARI health facility survey, 1994



The results from this survey showed a need for urgent action to improve several components of the programme's activities. The Federal ARI Cell responded rapidly. Directives were sent to facility directors requesting that they purchase only recommended antibiotics. To encourage improved communication with mothers, new materials were produced including a mother's card, home care posters, a flipchart, and folding ARI case management charts. Supervisory skills courses for district health officers and other supervisory staff are now being carried out on a regular basis. Refresher training is used to improve clinical monitoring and evaluation of service delivery in peripheral health facilities. ■

4. Target setting, whether at global or country levels, needs to be based on clear baseline information, specific interventions and realistic estimates of the extent and likelihood of change. Setting realistic goals can help avoid gaps between planned activities and targets. Achieving major stated targets can motivate programmes and health workers.

Conclusion

As WHO's approach to improving child health evolved through the 1980s and 1990s, diarrhoeal disease and acute respiratory infections remained high priorities for the Organization.

Diarrhoea and pneumonia cause millions of deaths each year, primarily in the developing world. The WHO Programme for the Control of Diarrhoeal Diseases (CDD), the WHO Programme on Acute Respiratory Infections (ARI), and then the subsequent Division of Diarrhoeal and Acute Respiratory Disease Control (CDR), defined and supported a research agenda that led to the development of practical tools and guidelines for use by national programmes to improve children's health in countries most burdened by these diseases. Experience gained from the use of these tools then helped define future research priorities, resulting in a seamless cycle of research, development, action, evaluation and further research priority setting.

In 1996, CDR became the Division of Child Health and Development (CHD) and in 1998, was incorporated into the Department of Child and Adolescent Health and Development (CAH) as part of the new Director-General's reorganization of WHO programmes. CHD took advantage of the expertise developed through experience in the disease control programmes for diarrhoea and acute respiratory infection. Research and development activities were expanded to address the causes of most deaths of children under five years of age—malaria, measles and malnutrition, in addition to pneumonia and diarrhoea. CAH is, in turn, building on this work to develop a more comprehensive approach to child and adolescent health and development.

At the core of CAH's efforts as they relate to young children is an innovative strategy that focuses on the child as a whole, rather than on a single disease or condition. The strategy—Integrated Management of Childhood Illness, or IMCI—ensures the combined treatment of the major childhood illnesses, prioritizes treatment of the most seriously ill children, and emphasizes prevention of disease through immunization, improved nutrition and exclusive breastfeeding.

There are three components to CAH's work on IMCI:

- Improving health workers' skills, through both in-service and pre-service training, so that the integrated approach is used effectively to improve case management;
- Strengthening health systems to support IMCI, including improvements in the organization of services, referral practices, the availability of drugs and supplies, and the supervision of health staff; and
- Improving family and community practices, including helping parents recognize illness and seek appropriate care, and community promotion of immunization, good feeding practices, and improved hygiene.

Evidence from those countries already implementing IMCI is encouraging, and the list of countries wishing to start the implementation process is growing rapidly.

To provide the best possible leadership to countries, CAH continues to maintain a balance between research, development, and technical support to countries. Although reducing child mortality remains a key objective, CAH continues to be concerned with the prevention of disease, and is defining a role in addressing the psychosocial development and the rights of children. With continuing research, development and action, CAH and its partners are radically changing the way child health is approached in the developing world.

Annex 1. Glossary

ADDR	Applied Diarrhoeal Disease Research Project
ARI	Acute Respiratory Infections
CAH	Child and Adolescent Health and Development
CDC	Centers for Disease Control
CDD	Control of Diarrhoeal Diseases
CDR	Diarrhoeal and Acute Respiratory Disease Control
CHD	Child Health and Development
CVI	Children's Vaccine Initiative
CWS	Community Water Supply and Sanitation
DTU	Diarrhoea Training Unit
EPI	Expanded Programme on Immunization
FES	Focused Ethnographic Study
GPV	Global Programme for Vaccines and Immunization
ICDDR,B	International Centre for Diarrhoeal Disease Research, Bangladesh
IMCI	Integrated Management of Childhood Illness
SWG	Scientific Working Group
TAG	Technical Advisory Group
TDR	Special Programme for Research and Training in Tropical Diseases
UNDP	United Nations Development Fund
UNICEF	United Nations Children's Fund
USAID	United States Agency for International Development
VAB	Vaccines and Other Biologicals
WHO	World Health Organization

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