

State of the world's vaccines and immunization



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Front cover photo: An eight-year-old girl shows her immunization card at a health centre in Guinea-Bissau. [UNICEF/Giacomo Pirozzi (C-94)]

Back cover photo: Luis Fermin Tenorio—the last polio case in the Western Hemisphere. [WHO/PAHO/A. Waak]

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Foreword

by Carol Bellamy, Executive Director of the United Nations Children's Fund (UNICEF)

and Dr Hiroshi Nakajima, Director-General of the World Health Organization (WHO)



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This report highlights many of the successes and challenges in our global efforts to protect children from the vaccine-preventable diseases. Over the past two decades, a public health revolution has quietly taken place. Immunization services that were virtually non-existent in developing countries in the mid-1970s now reach almost 80% of children before their first birthday—preventing over three million needless deaths every year. During this same period WHO and UNICEF have forged a partnership for health that has worked well and benefited hundreds of millions of children around the world. This partnership has brought together governments, non-governmental organizations, vaccine manufacturers, and researchers.

As national immunization programmes have grown, there has been a corresponding radical change in attitudes towards preventive health care. Only a few years ago, expenditure of around one billion US dollars a year by the developing countries themselves on immunization services would have been unthinkable.

Immunization is now entering a new era. Advances in technology are enabling the development of a whole range of both new and improved vaccines. Currently, new vaccines are being developed against more than 60 different diseases. Until recently, only the most visionary researcher would have considered some of these diseases to be vaccine-preventable.

These new and improved vaccines are not put into general use as fast as they could be. One of the major concerns is that price is still considered to be a major obstacle. There is a need to work closely with the vaccine industry to ensure that commercial interests are carefully balanced against the need to provide equal access to vaccines for all the world's children.

The issue is not only the price of vaccines but their enormous value for children, families, and society in averting premature death or the huge costs of lengthy hospitalization.

If our organizations and our partners can give the world a better understanding of the value of vaccines and immunization, the success of the past twenty years in saving millions of children's lives will be dwarfed by the successes of the next two decades.



Carol Bellamy
Executive Director of the United Nations
Children's Fund (UNICEF)



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Photo: UNICEF



New vaccines under development could save the lives of up to 8 million children a year.

Photo: WHO/EPI

The vaccine challenge

Introduction

Two hundred years after the discovery of the first vaccine—against smallpox—the world is on the threshold of a series of major scientific developments that will change the face of preventive health care for children. Over the next 5-15 years a new generation of vaccines will come on line that could save the lives of up to 8 million children a year. Dramatic advances in molecular biology and the use of genetic engineering techniques have produced a raft of candidate vaccines that will simplify immunization, improve the performance of existing vaccines, and protect children against diseases for which no vaccines currently exist. In addition, some of these vaccines will increasingly become the first line of defence against a range of diseases that are fast becoming untreatable due to rapidly increasing microbial resistance to antibiotics.

Since 1980 a total of 14 new or improved vaccines have become available. Today many more are in the pipeline—undergoing tests in animal models or being tested in humans. Scientists are studying a range of potential new vaccines against over 60 different diseases. They include vaccines against the major child killers—diarrhoeal diseases, acute respiratory infections, and malaria. In addition, millions of adult lives could be saved through childhood immunization against diseases that can remain dormant and strike in adulthood. Vaccines such as hepatitis B—already on the market but not universally accessible—and new vaccines under development against major killers such as tuberculosis and AIDS.

But there is a catch. The new generation vaccines are expected to be many times more expensive than those in use today. Vaccines are likely to cost not cents but dollars a dose from now on. Research and development costs today for a single vaccine can range from

Over 12 million children die every year—3 million of them before they are even a week old.

US\$ 50 million to US\$ 200 million. On top of that, new vaccines will be constrained by a web of intellectual property rights—each adding a fixed percentage to the price of a single dose as well as potentially restricting its manufacture elsewhere.

It is significant that—despite a 1992 recommendation by WHO that hepatitis B vaccine should be added to the six vaccines currently available through the Expanded Programme on Immunization (EPI)—no new vaccines have been made universally accessible through the EPI since its launch more than two decades ago. As donor funding for immunization shows signs of declining, will governments be willing—or able—to pay for the new vaccines? Can they afford not to?

Over 12 million children under five die every year—3 million of them before they are even a week old. As many as 2 million of those deaths are from diseases that could be prevented by the vaccines already on offer through the Expanded Programme on Immunization. They occur for two main reasons: because not all existing vaccines are 100% effective and because each year about 20% of the world's children are not fully immunized during their first year of life with the basic six EPI vaccines—against diphtheria, tetanus, whooping cough, polio, tuberculosis, and measles. Work is now under way to boost immunization coverage rates and cut delivery costs through simplifying immunization—cutting down on the number of contacts needed and developing new vaccines that can be given at an earlier age. This would help protect children against diseases such as some acute respiratory infections which can strike before they are old enough to be immunized, as well as reaching more children with vaccines before they lose contact with the health care system. The new vaccines include vaccines that can be inhaled, single-dose vaccines with built-in slow-release booster shots, and conjugate vaccines in which new antigens are combined with a “vaccine carrier” such as tetanus toxoid.

The two-pronged approach to transform immunization—boosting coverage through improving existing vaccines and immunization and adding a range of new vaccines against diseases that are not yet vaccine-preventable—will be a severe test on immunization finance

and delivery systems. But, perhaps more importantly, the new approach will require a fundamental rethink of the value of disease prevention through immunization. What is a vaccine really worth?

The availability of new, more expensive vaccines will focus attention increasingly on the relative value of alternative disease-prevention measures. The cost-effectiveness of each possible intervention—whether immunization, efforts to improve sanitation and hygiene, environmental protection, or the adoption of a healthier lifestyle—will need to be carefully weighed to ensure that the choice is based on the most effective and efficient use of the resources available from individuals, governments, and donors. But even at a higher price, vaccines will remain one of the most cost-effective means of preventing disease and avoiding treatment costs.

The Expanded Programme on Immunization (EPI)

In 1974, when the Expanded Programme on Immunization was launched by the World Health Organization (WHO), less than 5% of the world's children were immunized against the initial six target diseases—diphtheria, tetanus, whooping cough, polio, measles, and tuberculosis—during their first year of life. By 1990 and again in the most recent statistics (after a slight interim drop in coverage), almost 80% of the 130 million children born each year were immunized before their first birthday. An achievement involving over 500 million immunization contacts with children throughout the year. Within two decades the EPI was preventing the deaths of at least 3 million children a year. In addition, at least 750,000 fewer children were blinded, crippled, mentally retarded, or otherwise disabled.

A global coalition of partners—governments, WHO, UNDP, UNICEF, bilateral development agencies, major development banks, and nongovernmental organizations such as the Rockefeller Foundation, Save the Children Fund, Médecins sans Frontières and Rotary International—have helped bring this about. The involvement of political, religious, and community leaders amounted to what has been described as the greatest social mobilization effort in peacetime. Behind the scenes, millions of health workers have been trained and millions more volunteers mobilized, a cold chain established to



Immunization has opened up the opportunity for routine health checks.

Photo: UNICEF/Frank Charlton (DO195-0128)

ensure the safe storage and transport of vaccine, global vaccine supply and quality control mechanisms developed, and laboratory networks and disease surveillance systems put into place.

The immunization contacts have also opened up opportunities for other primary health care interventions—health education for mothers, vitamin and mineral supplements for children who need them, and routine health checks. In the Americas, a study on the impact of the EPI/polio eradication effort on health care systems in six Latin American countries—the *Taylor Commission Report* (1995)—found that it had helped to strengthen health systems and established a “culture of prevention” among health workers, politicians, and community members. “It is very likely that the health systems of the Americas would not have had the capability to respond as they did to the cholera epidemic [of 1991] without the EPI/polio experience.”

During 1995, in addition to the over 500 million routine immunization contacts with children under one, a record 300 million children throughout the world—almost half the world’s children under five—were immunized during mass campaigns against polio. By the year 2000 polio is expected to be eradicated—saving governments over US\$ 1.5 billion a year once immunization is no longer needed. But will that money find its way back into immunization services—to help increase immunization coverage with existing vaccines or fund the introduction of new ones?

While the war against polio is being won, the battle against other vaccine-preventable diseases has a long way to run. In 1994 over a million children died from measles, almost 500,000 from neonatal tetanus, and almost 400,000 from whooping cough. These were the children who slipped through the EPI net—among them some of the poorest and most disadvantaged children in the world. They included children caught up in wars, children on the move who were never in the right place at the right time to be immunized, children who had some but not all the doses of vaccine needed for full protection, children in sub-Saharan Africa where less than 60% of children are immunized. The effort not only to sustain current levels of immunization coverage but also to reach out to more children—meeting the global target of 90% immunization coverage by the year 2000—is a major challenge, especially at a time of shrinking donor resources.

The EPI Plus

In its 1993 World Bank Development Report, *Investing in Health*, the World Bank maintained that in developing countries an EPI “package” that also incorporated vaccines against hepatitis B and yellow fever together with supplements of vitamin A and iodine (the “EPI Plus”) would have “the highest cost-effectiveness of any health measure available today”—an assertion few would dispute. Yet neither hepatitis B nor yellow fever vaccine is available today in many of the countries in greatest need. The poorest countries are still having difficulty attracting donor funding. In addition, vitamin A and iodine supplements are not widely available where they are needed.

Of the 33 countries in Africa considered high risk for yellow fever, two-thirds are classified by UNICEF as needing continuing external support to obtain vaccines. But as donors have shown little interest in supporting the cost of yellow fever vaccine, few of these countries can afford to buy the vaccine today—even at the UNICEF discounted price of US\$ 0.17 for the single dose needed for 10-year and probably lifetime protection against the disease. Instead, expensive mass immunization campaigns are mounted to control the increasing number of yellow fever epidemics as they occur—an illustration of how funds can be mustered for emergency efforts to contain the spread of disease but not for its prevention. Yet a 1993 cost-effectiveness study showed that routine delivery of the vaccine through the EPI would be seven times as effective as mass immunization campaigns in reducing the number of cases and deaths.

Hepatitis B vaccine has not fared much better. The availability of the first plasma-derived hepatitis B vaccine in 1982 and a second generation recombinant vaccine four years later marked the beginning of a new era for vaccine development. But it also opened a Pandora’s box—the implications of which are not yet fully understood. The dilemma lies in finding ways of ensuring that new vaccines are made available—right from the outset—to children in developing countries who are also at risk. The experience with hepatitis B vaccines has not been a very encouraging start. Today, 14 years after the first vaccine came on the market, millions of children throughout the world still do not have access to hepatitis B vac-

cine—despite a dramatic drop in price. Allowing vaccines to slowly filter down to children in the poorer countries over 10-20 years is neither just nor equitable.

Vaccine prices

Vaccine prices are “tiered” with prices tailored to different markets. As a result, UNICEF is able to procure vaccine at a low price for use in the poorest developing countries—offset by the far higher prices that manufacturers charge for vaccines in the industrialized countries. The arrangement suits both parties: UNICEF secures cheap vaccines while manufacturers profit from a guaranteed market of millions of doses of vaccine—albeit at low-tier prices—and gain a potential foothold in other developing country markets. Over the 10-year period to August 1995, UNICEF—which handles over a fifth of the volume but less than 5% of revenues from the US\$ 3 billion global vaccine market—brokered the supply of 8 billion doses of vaccine for over 100 countries.

At today’s prices it costs no more than US\$ 1 altogether for the original six EPI vaccines (at UNICEF-discounted prices), and an additional US\$ 14 for the other programme costs involved in fully immunizing a child—the cost of laboratories, transport, the cold chain, personnel, and research, for example. Little wonder that the World Bank Development Report describes immunization as one of the most cost-effective public health interventions. But the availability of low-cost vaccines through the UNICEF system is double-edged. The world has become inured to the topsy-turvy notion that, while antibiotics may be expensive, vaccines should come cheap. The development of a second generation hepatitis B vaccine in 1986—the world’s first genetically engineered vaccine—signalled that the days of cheap vaccines are over. Initially marketed at US\$ 150 for three doses—150 times the cost of all 6 EPI vaccines combined (at UNICEF-discounted prices)—by 1994 this one vaccine alone accounted for almost a third of the turnover from the global vaccine market, placing it firmly in the multi-million dollar drugs league.

There is little to suggest that other new vaccines will be marketed—initially at least—with a much less expensive price tag. For a start, the technological processes involved are far more sophisticated than

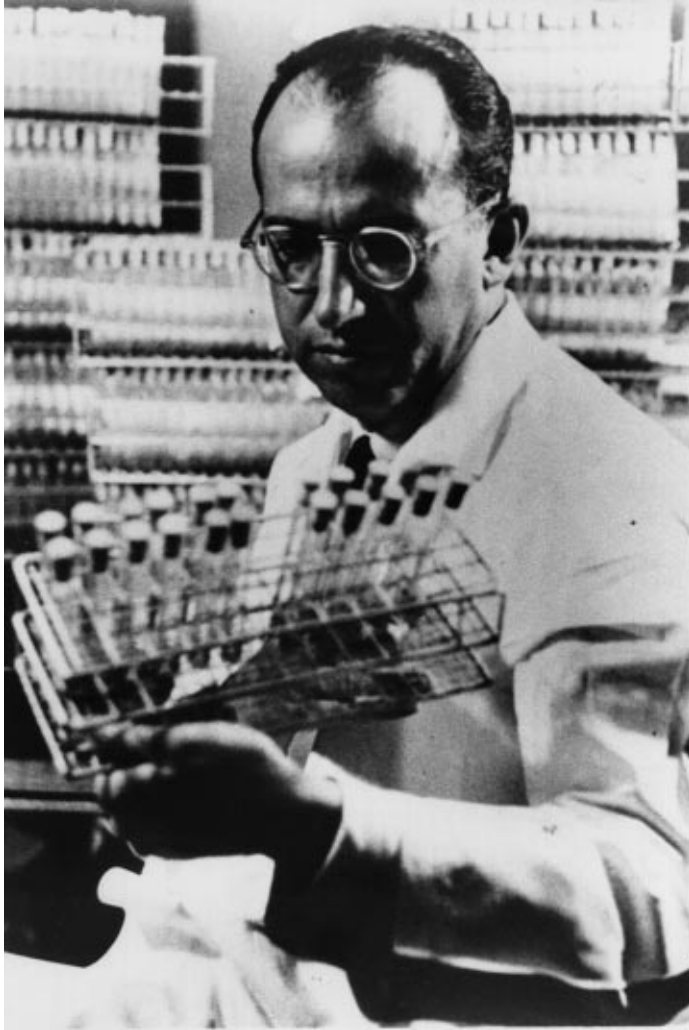
The World Bank maintains that immunization is one of the most cost-effective public health interventions.

those required for the manufacture of the previous generation of vaccines. In some cases they may entail years of research to identify and manipulate the genetic sequence of pathogens, for example, or to devise novel techniques for the production of single-dose vaccines with built-in slow-release booster shots. And while rapid advances have been made in vaccine development, major scientific hurdles remain. No one knows yet, for example, exactly which immune responses correspond with protection against diseases such as tuberculosis, AIDS, or malaria.

Research efforts are also hampered by the lack of suitable animal models that can be used to test vaccines and study immune responses to disease. In some cases researchers have succeeded in genetically engineering “transgenic” mice that can be successfully infected with some of the bacteria, viruses, and parasites that cause disease in humans—polio, measles, and malaria, for example. But for other diseases, such as AIDS, there is still no reliable animal model.

Intellectual property rights

In addition, each stage of the complex manufacturing process and each component is likely to be patented—a necessary stimulus and reward for innovation but also adding a fixed percentage to the final price in the form of royalties as well as potentially restricting its manufacture elsewhere. In the 1950s Dr Jonas Salk waived all intellectual property rights to his polio vaccine. To do otherwise would be like patenting the sun, he declared. More recently, in May 1995 Dr Manuel Patarroyo granted WHO an exclusive worldwide royalty-free licence to the patent and know-how for his candidate vaccine against malaria. If the vaccine—SPf66—proves to be successful, the licence gives WHO the right to develop, manufacture, distribute, and sell it for public sector use in developing countries. But things are changing. Today vaccines belong not, as Salk resolutely maintained, to “the people” but to a complex web of biotechnology companies, universities, public and private sector research institutes, and pharmaceutical companies. The economics of vaccine production are such that patent holders need to guard their intellectual property in order to stay competitive in the marketplace. Royalties are a way of recouping the high costs involved in the research, development, and regulation of new vaccines. Patents command a



In the 1950s Dr Jonas Salk waived all intellectual property rights to his polio vaccine.

Photo: WHO/USIS

royalty fee—normally recouped as a fixed percentage of the final price of the vaccine. The more expensive the vaccine, the higher the cost of the royalties to be added on. Royalties account for about 6% of the price of acellular pertussis vaccines, 2¹/₂% of the price of Hib conjugate vaccines, and 13% of sales of recombinant hepatitis B vaccine.

For developing countries that produce their own vaccines, intellectual property rights will complicate and could prevent the transfer of new vaccine technology. Developing country producers need to be prepared to negotiate a licensing agreement with the patent holders or embark on joint ventures with vaccine manufacturers in the industrialized countries. For their part, pharmaceutical companies would need financial incentives as well as assurances that developing country manufacturers would produce quality vaccine and not encroach on their more profitable markets. One possible option (first mooted at a workshop on intellectual property rights organized by the Children's Vaccine Initiative in Brazil in 1995) would be the introduction of a tiered royalty system—modelled on the tiered pricing system for vaccines—in which a lower royalty rate is negotiated between the manufacturer and the patent holder for vaccines supplied to the poorer countries through the UNICEF system.

The spectre of vaccines that are unaffordable outside the wealthier countries is one of the reasons cited by several vaccine manufacturers for dropping out of the race to develop a vaccine against HIV. Adverse publicity surrounding the expensive anti-AIDS drug AZT has made some manufacturers fearful of the political fallout from ending up with sole rights to a vaccine that is affordable for the industrialized countries but way beyond the price range of developing countries where most HIV infections are occurring.

New strategies are now needed to ensure that these newer, more expensive vaccines will be accessible from the outset for children in developing countries. In its 1995 report, *The State of the World's Children*, UNICEF noted that—as a result of an unprecedented social mobilization effort over two decades—immunization is the only medical breakthrough that has been made available not to 10% or 20% but to the vast majority. But will it remain so?

The Children's Vaccine Initiative (CVI)

The Children's Vaccine Initiative was launched at the World Summit for Children in New York in 1990. Since then it has set out a radical agenda aimed at improving the global supply and quality of existing vaccines, orchestrating a dialogue between the public and private sectors on the research and development of new vaccines, and developing strategies to ensure that these vaccines will be affordable for use in developing countries.

Originally the brainchild of five sponsoring agencies—UNICEF, UNDP, the Rockefeller Foundation, the World Bank, and WHO—the CVI has built up a global forum that includes development agencies, governments, donors, commercial and public sector vaccine manufacturers, vaccine researchers, and national immunization programme managers. Through establishing a dialogue between all the key players in the “vaccine continuum”—from research, testing, licensing, and production to quality control, vaccine procurement, and delivery—the CVI is able to pinpoint the weaknesses and potential bottlenecks in the global vaccine system and seek workable solutions.

In addition to its role as a global think tank for vaccines and immunization, the CVI has worked closely with WHO's Global Programme for Vaccines and Immunization (GPV) and UNICEF to broker concrete solutions to some of the problems it has identified. They include action to improve the quality of vaccine production and control mechanisms in developing countries, and efforts to coordinate and speed up the research and introduction of priority new vaccines.

New initiatives

In the wake of the 1990 World Summit for Children and the launch of the Children's Vaccine Initiative (CVI), a range of new initiatives has been developed to ensure that children in developing countries will have rapid access to new and improved vaccines at affordable prices.

The establishment in 1994 of the Global Programme for Vaccines and Immunization (GPV) within WHO was a reflection of the new priorities identified by the CVI. The new integrated programme wedded two operational units: the Expanded Programme on Immunization (EPI) and the Vaccine Research and Development Unit (VRD), and created a third—the Vaccine Supply and Quality Unit (VSQ). The programme incorporates each stage in the life cycle of a vaccine: from research and development to vaccine quality control and supply and the delivery of vaccines. The EPI defines global immunization policy and provides technical support to countries through the regional offices of WHO, while the Vaccine Research and Development Unit stimulates and supports the research and development of new and improved vaccines. Meanwhile the work of the Vaccine Supply and Quality Unit with countries, donors, and vaccine manufacturers has been crucial in upgrading the quality and long-term viability of vaccine production and ensuring that governments have the capacity to accurately forecast and finance their vaccine supply needs. A new training network has been set up to provide training for vaccine producers and national control authorities and laboratories in developing countries. This is intended to pave the way for the establishment of a new vaccine production consortium to help improve the quality of vaccine production in developing countries and foster the exchange of information on vaccine production—part of an overall policy to sustain immunization and secure vaccines for the world's children.

Another crucial innovation is a global vaccine targeting strategy devised by UNICEF and WHO to promote the sustainability of vaccine financing in individual countries. The aim is to encourage countries that can afford to pay for their own vaccines to do so and, at the same time, to focus limited donor assistance to fill the gaps in the world's poorest countries. However, under the new system even the poorest countries are expected to establish a budget line and start financing 10-25% of their vaccine needs. In order to identify the countries that need continuing donor support and those that need short-term assistance to become self-sufficient in buying vaccines, UNICEF and WHO grouped countries into four bands on the basis of their wealth and population size and total GNP. For those countries in transition to self-sufficiency, other forms of assistance have been devised, including training in vaccine procurement and a new financial mechanism—the Vaccine Independence



The Viking ship Gaia promotes the message of the 1990 World Summit for Children.

Photo: UNICEF/Ruby Mera (4813/91)

Initiative. Under this scheme, countries are required to rigorously plan for their vaccine needs and corresponding vaccine budget over a two- and five-year period—an exercise that some countries were failing to perform. Countries can then procure vaccines through UNICEF, which allows them to pay for vaccines in hard or local currency, and to pay either in advance or after receipt through the use of a revolving fund mechanism.

The vaccine targeting strategy will also be applied to the introduction of new vaccines to national immunization programmes—depending on the availability of donor funding. The poorest countries in band A will be offered donor assistance for the purchase of priority new vaccines. The more than 40 countries in band B will continue to have access to the UNICEF procurement system (be able to buy vaccines at UNICEF discounted prices) and be offered time-limited donor assistance to help phase-in the cost of new vaccines. From then on they will have to shoulder the cost of new vaccines themselves. However, UNICEF has also made it clear that support for new vaccines for countries in bands A and B will not be automatic. Priority will be determined on the basis of four main criteria: financial need, the magnitude of the health risk, the ability of the national EPI to deliver other vaccines, and government commitment to sustain their national immunization programme. Moreover these criteria will each be weighed according to the specific vaccine and its potential impact in the country involved. The purchase of yellow fever vaccine, for example, will be supported for all high-risk countries, while purchase of hepatitis B vaccine will be restricted to high-risk countries that also have high rates of immunization coverage for other vaccines. For hepatitis B vaccine, the criteria are a hepatitis B carrier rate of over 5% of the population plus immunization coverage of not less than 70% coverage with three doses of DTP vaccine.

The remaining countries in bands C and D, which have demonstrated their ability to become self-sufficient in financing their vaccine needs, will be expected to go it alone—negotiating directly with vaccine manufacturers to obtain an “affordable” tiered price for new vaccines. UNICEF and WHO maintain that this new independence will give these countries total control over their immunization programmes—and free them from the constraints of dependency on the changing focus of donor support.

This new pragmatic approach to vaccine financing—narrowing down support to the neediest countries—has been accompanied by a commitment to obtain new vaccines. In the past, vaccine manufacturers have been unwilling to offer UNICEF low prices for new vaccines due to resentment over the UN agency's procurement of discounted-price vaccines for countries they believed could afford to pay more. The new understanding has been translated into recent offers for new vaccines, including one—a DTP-hepatitis B combination—that is not yet licensed. Major vaccine producers have demonstrated a willingness to provide multi-tiered pricing for new vaccines, as they do for existing EPI vaccines, tailored to each band of countries—provided development agencies and donors recognize and support a system of market segmentation. If they don't, UNICEF will find itself unable to negotiate a low price for the neediest countries. In this situation, the wealthier developing countries would be able to access the new vaccines, while the poorest—especially those in Africa—would be forced to wait 10-15 years.

The need to lower the overall cost of immunization is also being addressed by vaccine researchers. It has been estimated that efforts to combine several vaccines in a single dose, use less expensive vaccine technology, and combine booster doses with the initial vaccine dose could reduce vaccine delivery costs by up to 50%. However, these savings would be slashed when new, more expensive vaccines alter the balance between vaccine and delivery costs. Research is also under way into the development of potentially less expensive vaccine technologies, such as DNA vaccines, and vaccines that use a common antigen—against *Streptococcus pneumoniae*, for example—instead of combining antigens from a wide range of different serotypes of the pathogen involved.

The missing links

A range of additional measures is now needed to ensure that new and improved vaccines will be rapidly introduced in developing countries.

For a start, a lot more groundwork needs to be done in developing countries to assess the burden of disease and estimate the cost-effectiveness of introducing a new vaccine. One extreme example is rubella vaccine which has been on the market for almost 30 years

Rubella vaccine has been on the market for 30 years but is still used mainly in the industrialized countries.

but is still used mainly in the industrialized countries. Only recently—in 1995—was a major survey launched to establish the incidence of rubella in developing countries, determine how many countries are already using rubella vaccine and assess the impact of this on the incidence of congenital rubella. A similar study is now under way to help determine whether Hib vaccine should be recommended for use in the EPI in developing countries. Studies of disease burden and estimates of cost-effectiveness are of key importance in bringing a new vaccine onto the market. This crucial information would help governments and donors prioritize in choosing between a new vaccine, alternative preventive measures, or treatment, for example. It would also help manufacturers keep down the cost of the vaccine through advance knowledge of the size of the potential market in developing countries. This information would enable them to determine the right size production plant, for example.

At present, most vaccine development takes place within the private sector in the industrialized countries—where the most profitable vaccine market exists. As a result, most vaccines are tailored to diseases that occur in the industrialized countries among otherwise healthy children. But these diseases also occur in developing countries and may take a more severe form when they affect children who may also be suffering from malnutrition and from other diseases. Hib vaccine, which has been on the market now for six years, has been highly successful in reducing the incidence of Hib meningitis among children in the industrialized countries. But until recently, no one was sure whether it would be equally successful in lowering the estimated 550,000 annual death toll from Hib meningitis and pneumonia among children in developing countries. However, the results of a recent study in the Gambia by the UK Medical Research Council indicate that Hib vaccine is also effective when used in a developing country. Meanwhile new vaccines against rotavirus have reached an advanced stage of development in the United States without being extensively tested in developing countries—where most rotavirus deaths occur. When children in Thailand were given a candidate vaccine against cholera in a limited trial it was discovered that they needed a dose at least 10 times greater than the level needed to protect a child in the United States. Earlier studies in developing countries would help reduce the delay in getting new vaccines into use worldwide.



Most vaccines are tailored to diseases that occur in the industrialized countries but these diseases may take a more severe form among children in developing countries.

Photo: UNICEF/Giacomo Pirozzi (DO192-0102)

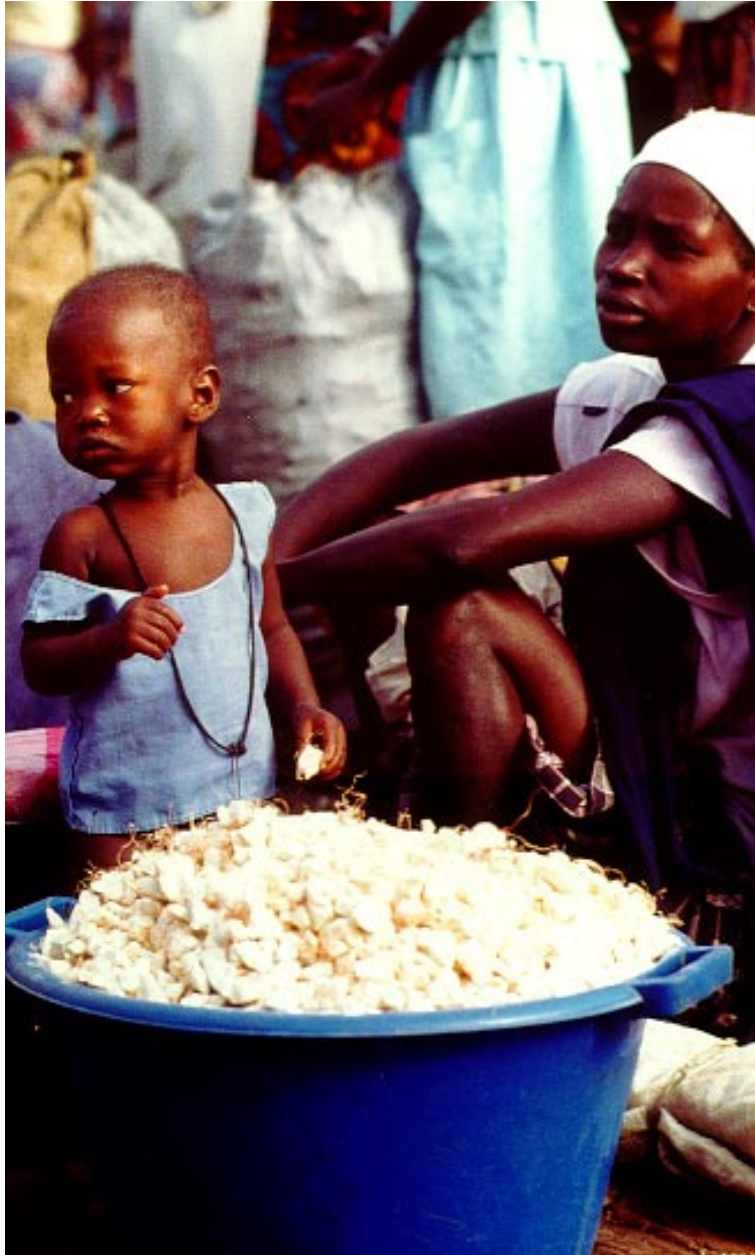
Greater advocacy is needed to ensure that vaccine research and development is driven not only by commercial interest but by public health goals as well.

Another handicap is the genetic diversity and geographical distribution of some of the organisms that cause disease. Individual organisms may have a wide range of serotypes and the ones that predominate in the industrialized countries may not be the same as those implicated in diseases in the developing countries. Since vaccine manufacturers in the industrialized countries tend to focus—understandably—on the development of vaccines against diseases that occur largely on their own doorstep, different vaccines may be needed to protect children in developing countries against diseases caused by the same or a genetically similar pathogen.

One example is the development of a vaccine against pneumococcal disease. In developing countries more than a million children a year die from pneumonia caused by the bacterium *Streptococcus pneumoniae*. More than 83 serotypes of this bacterium can cause disease, of which about 10 are implicated in up to 70% of cases involving children. But the predominant serotypes vary between industrialized and developing countries and between different forms of the disease, such as pneumonia, or otitis media (inner ear infection)—which can result in hearing loss. Until recently, pneumococcal vaccine research was driven—not by the death toll from pneumonia in developing countries—but by the bacteria's role in the increasing incidence of inner-ear infections in the industrialized countries. However, new vaccines are now under development that are also designed to protect against pneumonia in developing countries.

AIDS vaccine research is similarly hamstrung. Efforts to produce a vaccine against HIV-1 have so far concentrated almost exclusively on just one of the 10 sub-types of the virus. This sub-type occurs mainly in the industrialized countries but not in most developing countries where the incidence of HIV is highest.

Greater advocacy is needed to ensure that vaccine research and development is driven not only by commercial interest but by public health goals as well. However, vaccine manufacturers must have financial incentives—such as the guarantee of a large market in developing countries—to develop vaccines for the less profitable markets. WHO has worked closely with vaccine manufacturers to help steer the development of meningococcal vaccines, for example—providing incentives through organizing and funding clinical trials of the vaccines in the Gambia and Niger. And in response to the re-emergence of tuberculosis, linked to the spread of HIV



UNICEF continues to provide vaccine for children in the world's poorest countries.

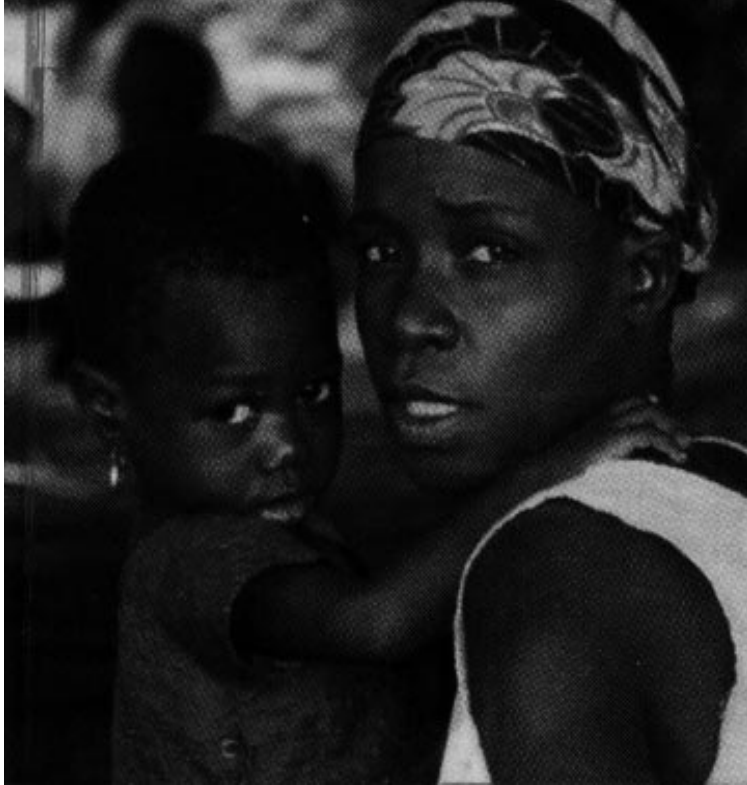
Photo: UNICEF/Giacomo Pirozzi (C-94)

infection, and the increase in drug-resistance, WHO has provided seed money for research—at a time when there was little interest and even less funding available for development of a new vaccine against tuberculosis. More importantly, WHO has helped coordinate and focus research—generating interest in a crucial but neglected area. Meanwhile, over the past two decades the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) has coordinated international efforts to control the major tropical diseases, including efforts to develop vaccines against diseases such as malaria, leishmaniasis, leprosy, and schistosomiasis (bilharzia).

The major stumbling block to the introduction of new vaccines in developing countries will undoubtedly be the availability of sustainable funding. Efforts by WHO and UNICEF to ensure that the majority of governments assume responsibility for funding their own vaccine needs will release donor funds that can be redirected to the neediest countries (in band A). The problem is that, after shifting responsibility for the vaccine needs of 90% of the world's children, donor funding is still insufficient—at today's level—to provide the remaining 10% of the world's poorest children with new vaccines in addition to existing ones.

By 1998, UNICEF and WHO aim to ensure that up to 90% of the world's children will have access to vaccines financed by their own governments. The remaining 10% will continue to receive most of their vaccine needs through donor support—both for new and existing vaccines. According to recent estimates, this means that by 1998, donor funding for the six original EPI vaccines in band A countries will be about US\$ 21 million—without allowing for the extra cost of supplementary immunization with oral polio vaccine. The addition of hepatitis B vaccine for the highest risk countries would add an estimated US\$ 25-35 million.

The funding crisis is twofold. If donors are to fund both new and existing vaccines, they will need to guarantee a hefty increase in future in the overall amount currently provided for vaccines—even though only the neediest countries will qualify for assistance from now on. Most governments, on the other hand, are being asked to assume responsibility for their own vaccine funding—at the very time when the newer, more expensive vaccines become available.



Donor funding is insufficient to provide the poorest 10% of the world's children with new vaccines in addition to existing ones.

Photo: WHO/Maria Santamaria

Other financial mechanisms are needed to ensure that new vaccines are accessible to children in developing countries.

If UNICEF and WHO are to hold the line on targeting vaccine support to only the poorest countries, they will need firm political support from both donors and development agencies. If this strategy fails, there are fears that the existing tiered price structure could collapse—and with it all hope for the foreseeable future of access to new vaccines for these countries. Unless vaccine manufacturers are convinced that today's discounted-price vaccines are being procured for only the neediest countries, there is little hope that new vaccines will be made available to UNICEF at discounted prices.

WHO, UNICEF, and the CVI will continue to work with vaccine manufacturers and policy-makers to develop a strong multi-tiered pricing system so that new vaccines can be made available from the outset at prices tailored to a country's ability to pay. Efforts will also be continued to strengthen the viability of vaccine producers in developing countries—by providing technical assistance to improve the quality of vaccine, for example—so they can attract partners and have access to new vaccine technology and products.

Other financial mechanisms will be needed if new vaccines are to be widely accessible to children in developing countries. Otherwise the history of the introduction of hepatitis B vaccine is likely to be repeated. At a CVI workshop on financing the introduction of new vaccines in Brazil, in October 1995, participants suggested a range of possible options including: financial incentives by donor governments—such as tax concessions—to encourage manufacturers to supply the new vaccines at discounted prices to the poorest developing countries; sustainable high-profile fund-raising initiatives such as regular lotteries or other fund-raising events; special fund-raising for new vaccines by UNICEF through its supplementary funding mechanism for specific projects; and the establishment of a vaccine fund in which money is pooled and targeted to the countries in greatest need.

In the meantime, a concerted effort is needed to elevate the status of vaccines within the public health sector. This will entail efforts to change public perception of what is an “affordable” price to pay for a vaccine—by providing tools to evaluate the cost-effectiveness of vaccines in relation to other national health concerns. The laudable efforts of the public sector to obtain very low vaccine prices for the benefit of the world's poorest nations have had an unfortu-

nate knock-on effect. While governments and individuals are prepared to allocate large sums of money for hospitalization and high-cost treatment with drugs such as antibiotics, they now balk at the idea of having to pay out comparable amounts for a vaccine that can provide lifetime protection against disease—avoiding the costs of treatment and days lost at work. One of the most serious obstacles to the provision of new vaccines to children in developing countries is that the higher cost of vaccines may not be weighed against the potential cost benefits. Governments and donors need to undertake rigorous cost-benefit analyses in order to make difficult choices within limited health budgets. The danger is that, unless there is a fundamental shift in understanding of the immeasurable value of vaccines, countries which have recently become self-sufficient in providing the EPI vaccines will not be prepared to fund the newer, more expensive vaccines. Each of which is likely to cost several times as much as the cost of all six EPI vaccines combined.

The outcome of efforts to finance new vaccines will hinge on the success of four key strategies:

- targeting donor support to the neediest countries;
- tiered pricing by manufacturers;
- a commitment by governments and donors to increase the amount they now spend on vaccines; and
- advocacy to encourage governments, donors, and the general public to recognize the value of vaccines on the basis of their health impact in individual countries.

Although undoubtedly a herculean task, changing attitudes to vaccines would not cost large amounts of money. In the long run, treatment to save the lives of children not immunized against vaccine-preventable diseases and the legacy of disabled children will cost a lot more—both in money and needless suffering for children and their families.



Dreaming of a world in which children will no longer die from diseases such as diarrhoea, pneumonia or malaria.

WHO-TDR/Reile

The value of vaccines

Dr Scott B. Halstead, *Scientific Director for Infectious Diseases at the US Naval Medical Center, and a founder member of the CVI, maintains that society mistakenly places a higher value on curing the sick than on preventing sickness.*

The achievement of national immunization programmes over the past two decades has allowed families, rich and poor alike, to dream of a new world in which their children would no longer die from diseases such as diarrhoea, pneumonia, or malaria. Vaccine scientists know this to be a realistic dream. Excellent new vaccines already on the shelf could save children from diseases such as hepatitis B, cholera, typhoid fever, and Hib disease. These vaccines are available to children in industrialized countries but not yet to those in poor countries. With more investment in research, scientists will be able to make new vaccines against other killer diseases.

Only one barrier prevents this dream from becoming reality—money.

Money can put vaccines into the arms and mouths of children; money brings new vaccines into clinics. But WHO, UNICEF, and other donors are already stretched to the limit to achieve the goals of the Expanded Programme on Immunization (EPI) to immunize 90% of the world's children and to eradicate polio by the year 2000. These donors have struggled mightily to cap the cost of vaccines. Ironically, their efforts to hold the line on prices may have been counter-productive. The vital investment which is needed to produce new vaccines may have been inhibited by the artificially low price of vaccines imposed by well-meaning donor agencies.

What is to be done? The solution, strangely enough, may simply be one of attitude. A single antibiotic tablet may cost many times more than multiple doses of vaccines. When a life is to be saved, no cost is too much. A curious

inversion of values has become all-pervasive. An antibiotic is a drug of great value since it saves a patient once an infection begins. But a vaccine which could have prevented the same disease in the first place is worth only pennies.

How did vaccines, these “miracles of prevention”, come to be worth less than miracle drugs? Perhaps it is because vaccines were originally developed and produced in public sector laboratories, often using simple, inexact and inexpensive production methods. The costs of research and development were heavily subsidized by governments, and governments themselves became major purchasers.

Vaccines were either free or available at prices far below production costs. Drugs, on the other hand, largely emerged from private sector research and have always been associated with doctors, hospitals, and pharmacies—institutions widely regarded as valuable and expensive.

The distorted attitude of placing a higher value on curing the sick rather than on preventing sickness sends out all the wrong messages to customers and businesses. Can cheap goods ever be regarded as having high value? Can an authentic vaccine market ever emerge unless vaccines are sold at prices which reflect their true cost?

We must instil energy, enthusiasm, and idealism into leaders everywhere to help guide parents to a paradigm shift which redefines the value of vaccines. Our generation must conquer the fear of saying out loud the truth about vaccines: that they have immense value.



The Expanded Programme on Immunization prevents the deaths of at least 3 million children every year.

Photo: UNICEF/Adrian Pennink (93-BOU1104)

Vaccines used in the Expanded Programme on Immunization

Introduction

In 1994, almost 80% of children under one throughout the world were immunized against six diseases—diphtheria, tetanus, whooping cough (DTP), measles, polio (OPV) and tuberculosis (BCG)—through the Expanded Programme on Immunization (EPI). In some countries children were also immunized against hepatitis B and yellow fever. Elsewhere, failure to immunize has highlighted the vulnerability of the achievements of the EPI and led to the re-emergence of diseases such as diphtheria (in Eastern Europe) and yellow fever (in Africa).

Although the six vaccines are highly effective against childhood diseases—preventing an estimated 3 million deaths a year—in some cases alternative vaccines are now needed. Improved vaccines would help extend protection to at least 90% of children under one and slash the number of deaths (2 million a year) still occurring from vaccine-preventable diseases.

One of the key goals is to reduce the number of contacts needed to immunize a child, another to develop vaccines that can be given at an earlier age when take-up rates are highest. At present five contacts are needed during the first year of life (at birth, 6 weeks, 10 weeks, 14 weeks, and at 9 months) and in many countries coverage rates decline progressively. Measles vaccine (at 9 months) has the lowest take-up rate of the original six EPI vaccines. One solution is to find ways of combining both the initial dose of vaccine and the booster doses in a single dose. Efforts are under way to develop a new single-dose tetanus vaccine, for example, in a bid to increase coverage among women of child-bearing age. If drop-out rates could be lowered, many of the almost 500,000 deaths a year from neonatal tetanus could be prevented. Meanwhile, new vaccines are now be-

ing developed based on DTP combined with a fourth or fifth antigen in a single shot. A DTP- Hib conjugate vaccine and a DTP-IPV-Hib conjugate vaccine are both on the market and combinations including hepatitis B and inactivated polio vaccine (IPV) are also in the pipeline.

The development of new vaccines that can be given at an earlier age would help reduce the number of child deaths in two ways—by reducing the number of drop-outs when vaccines are given later in life and by protecting children at a vulnerable age. Several candidate measles vaccines are being studied that could be given at an earlier age. One option under consideration is a vaccine that could be directly inhaled. This kind of vaccine would be particularly useful in mass immunization campaigns as it would dispense with the need for sterile injection equipment.

Another priority is the development of a more effective vaccine against tuberculosis—a re-emerging disease that kills 3 million people a year. Ironically, BCG vaccine is the most widely used of all the EPI vaccines—with almost 90% coverage among children under one during 1994. But there is an urgent need to develop a new vaccine that is not only more effective in preventing childhood forms of the disease but also extends protection into early adulthood when most TB cases occur. Meanwhile, a new acellular pertussis (whooping cough) vaccine has been developed—genetically engineered to prevent some of the side-effects associated with the use of whole-cell vaccines. This vaccine will be more expensive than existing whole-cell vaccines and it is not yet known whether the new vaccine technology can—or should—be transferred to developing countries where over 60% of pertussis vaccine is currently produced.

So far only two new vaccines, hepatitis B and yellow fever, have been recommended for inclusion in the EPI globally since its launch 22 years ago. The experience with both vaccines has been a sobering one for public health planners. The problem is that many of the highest-risk countries are among the poorest in the world and the ones with the least developed immunization programmes. While yellow fever vaccine is relatively cheap, hepatitis B vaccine costs at least one and a half times the total cost of the six EPI vaccines—despite a dramatic drop in price. Donor reluctance to provide fund-

ing for these vaccines does not augur well for the newer vaccines on the way—many of which would have the greatest impact in developing countries.

The immunization schedule for infants recommended by the WHO Expanded Programme on Immunization

Age	Vaccines	Hepatitis B vaccine ¹	
		Scheme A	Scheme B
Birth	BCG, OPV)	HB 1	
6 weeks	DPT 1, OPV 1	HB 2	HB 1
10 weeks	DPT 1, OPV 2		HB 2
14 weeks	DPT 3, OPV 3	HB 3	HB 3
9 months	Measles Yellow fever ²		

¹ Scheme A is recommended in countries where perinatal transmission of hepatitis B virus is frequent (e.g. South-East Asia). Scheme B may be used in countries where perinatal transmission is less frequent (e.g. sub-Saharan Africa).

² In countries where yellow fever poses a risk.

Polio

During 1995 almost half the world's children under five—a record 300 million children—were immunized against polio in a push to eradicate the disease globally by the year 2000. In just two weeks in December over 160 million children were given oral polio vaccine in national immunization days (NIDs) in India and China. A month earlier, in strife-torn Sri Lanka, a one-day truce (called a Day of Tranquillity) was organized to enable children to be immunized against polio.

Meanwhile, in Africa, which has the lowest immunization coverage rates in the world, WHO, Rotary International, and other partners, are to launch a three-year mass immunization campaign, “Kick Polio Out of Africa”. Two national immunization days, one month apart, will be held each year for the next three years.



During 1995 almost half the world's children under five were immunized against polio in mass immunizations.

Photo: WHO/V. Abramov

Polio has been eradicated from the Americas and an increasing number of countries are now reporting zero incidence of the disease. Worldwide the number of reported cases is down by over 80% (from over 31,000 to less than 6,200) since the eradication effort was launched in 1988. Other major areas of the world are becoming polio-free—Western and Central Europe, North, Southern, and East Africa, the Middle East, the Arabian Peninsula, and the Western Pacific.

National immunization days

The number of mass immunization campaigns to halt the circulation of wild poliovirus is increasing rapidly. By the end of 1995, 62 of the countries where polio is endemic had conducted at least one national immunization day (NID). By early 1996 all the polio-endemic countries of Asia and the Middle East—apart from Nepal and Yemen—had organized NIDs. The largest of these was in India which in December 1995 immunized 82 million children under three. India alone accounts for one quarter of the children born in the world each year—and more than half of the reported cases of polio. The campaign is expected to lead to a significant decline in the number of polio cases over the next few years as well as reducing the risk of imported cases of the disease in polio-free areas. The Indian sub-continent has been identified as the source of many of the cases of polio imported into Europe and the Middle East.

In China—a dramatic success story—the number of reported cases dropped from 5,000 in 1990 to zero in 1995 following massively successful NIDs in December 1993 and a month later. Some 83 million children under four were immunized—establishing an immunization world record. Even more ambitious was MECACAR, a co-ordinated campaign of NIDs in 18 adjoining countries from the Middle East, Caucasus, and the Central Asian Republics, which targeted 56 million children. Most of the countries involved succeeded in immunizing more than 95% of children under five. Meanwhile, a further 14 countries organized NIDs to mark World Health Day on 7 April 1995, targeting an additional 42 million children.

The NIDs have also provided the opportunity to immunize children against measles and provide vitamin A supplements. In addition, mothers have been immunized with tetanus toxoid in order to protect any babies from subsequent pregnancies against neonatal tetanus.

Despite these successes, wild polio virus is still circulating in almost 70 countries. And recent outbreaks of the disease involving hundreds of cases in Chechnya in the Russian Federation, Pakistan, and Zaire underscore the obstacles that remain. In many countries there is a desperate lack of infrastructure—often the result of years of war or internal conflict. Roads and clinics, vehicles, and refrigerators for vaccine storage have been destroyed or fallen into disrepair. In 11 countries in Africa less than half of the children born each year are immunized against polio. In war-torn Chechnya the latest outbreak, involving more than 150 cases, followed a three-year gap in immunization. Elsewhere, high population density, refugee movements, and economic migration make it more difficult to organize and follow up both routine immunization and national immunization days (NIDs).

There is an urgent need for improved surveillance and reporting in many countries. During 1994, over 8,600 cases of polio were reported to WHO. But the disease often goes unreported and WHO estimates that more than ten times as many cases are actually occurring (up to 80,000 a year)—two-thirds of them in Bangladesh, India and Pakistan. Global immunization coverage for the three routine doses of oral polio vaccine (OPV) increased slightly from 80% in 1993 to 82% but remains persistently lower than the 85% coverage attained in 1990—the year of the World Summit for Children. And the global figures mask wide discrepancies. In Afghanistan less than 10% of children are immunized against polio and in Chad less than 20% are protected.

In addition to efforts to boost global immunization coverage rates, there is an urgent need to improve disease surveillance systems in many countries. A network of 80 laboratories has been established at national, regional and global levels, to provide rapid case detection, follow-up surveillance and a means of tracking the chains of transmission of the different virus strains as they appear. Effective disease surveillance is crucial in efforts to detect and eliminate the last pockets of poliovirus transmission in countries where only a few cases are occurring. And it is also essential in determining whether transmission of the virus has been successfully interrupted. In the Americas, for example, after the last case of polio in 1991, in a four-year-old boy in Peru, stool samples were collected from about 2,000 paralysed children a year for three years to test whether



National Immunization Days against polio have been massively successful in China.

Photo: UNICEF/Roger Lemoyne (93-COU)

polio was the cause. Eradication could not be officially certified without proof that no more wild poliovirus was circulating in the region.

While immunization experts are confident that polio can be eradicated by the year 2000, there is increasing concern over a shortfall in donor funding. Almost 80% of the resources needed for polio eradication come from the endemic countries themselves. The rest is provided by a global coalition comprising WHO, UNICEF, Rotary International (which has raised over US\$ 250,000,000 and provides volunteers and services through its PolioPlus Programme), major Development Banks, the US Centers for Disease Control and Prevention (CDC), and bilateral donors including the Governments of Australia, Canada, Denmark, Japan, Sweden, the UK, and the United States. Today as the eradication campaign focuses increasingly on the poorer countries of the world, a higher percentage of the costs will have to be met by donors.

WHO estimates that an additional US\$ 100 million a year is needed over the next four years—for vaccine purchase, personnel, training, research, logistics and the cold chain, and the development of a global laboratory network. The United States currently spends more than twice that amount each year to protect children against the possible reimportation of a disease that has already been eradicated in the Americas.

The quest for a more heat-stable polio vaccine

A research project to develop a more heat-stable polio vaccine, using heavy water as a stabilizer, has been discontinued—largely because the research has been outpaced by efforts to eradicate the disease but also because of concern about the possible rejection of the vaccine by parents.

The heavy water-stabilized polio vaccine would extend the current safety margin for vaccine storage to seven days at up to 37 degrees. It was developed to help lower vaccine failure rates and reduce vaccine wastage. But after the disease was eradicated in the Americas—using the existing vaccine—doubts arose about the need for an alternative vaccine. More recently, China is also believed to have eradicated the disease—using a vaccine of even lower thermo-sta-

bility. In tropical countries, WHO now recommends that children should be immunized during the cool, dry season when a higher immune response to the vaccine is obtained.

The case for a more heat-stable polio vaccine was further weakened by the development of innovative vaccine vial monitors—first promoted by the EPI—which enable health workers to check with accuracy whether the vaccines have been damaged by exposure to heat.

Another drawback is that, while the use of OPV is expected to peak over the next two years with a series of national immunization days, the new heat-stable OPV is unlikely to be on the shelf for at least another three years—probably too late to have any real impact.

There is also doubt over public acceptance of the new vaccine, which uses deuterium oxide as a stabilizer. Although safe, the inclusion of an isotope of water—which is non-radioactive but widely used in the nuclear power industry—could lead to a public relations disaster and scupper global efforts to eradicate polio. The human cost of the campaign against whooping cough vaccine in the UK, for example has been measured in a corresponding rise in the incidence of disease.

In October 1995, the Global Programme for Vaccines and Immunization (GPV) announced that it would not recommend the use of the new polio vaccine within the EPI. More recently, in February 1996, the CVI group coordinating the research project recommended that the work should be discontinued, as there is little chance that this heavy water-stabilized vaccine would be accepted by national immunization programmes.

OPV or IPV?

Polio is a viral infection of the nervous system. It affects mostly children and can cause lifelong paralysis, breathing incapacity, sometimes death. Although polio is incurable it can be prevented by immunization. Two vaccines are available—an inactivated injectable polio vaccine (IPV) originally developed in 1955 by Dr Jonas Salk, and a live attenuated oral polio vaccine (OPV) developed by

Dr Albert Sabin in 1961. Both vaccines are highly effective against all three types of poliovirus. But there are significant differences in the way each vaccine works.

The oral polio vaccine is the vaccine of choice for use in the EPI. For a start, it is cheaper (IPV costs five times as much) and easier to administer than an injectable vaccine. But the overriding reason is its ability to induce immunity in the gut—the key site where wild poliovirus multiplies. Although OPV is safe and effective, in about two in every 5 million doses of the vaccine the live attenuated vaccine virus can cause paralysis—either in the immunized child or in a close contact.

Reducing vaccine wastage

The introduction of vaccine vial monitors—together with new rules for handling opened vials of vaccine—is expected to lead to dramatic reductions in vaccine wastage. Today almost 60% of vaccines are thrown away because of doubts about their potency after breaks in the cold chain and possible damage from exposure to high temperatures. Now cold chain experts are predicting that the new device will slash wastage to around 10–15%—saving tens of millions of dollars on vaccine purchase every year.

Vaccine vial monitors—coloured discs calibrated according to the heat stability of each vaccine—change colour when the vaccine has been damaged by heat. As well as indicating the state of unopened vials of vaccine, they can be used to determine whether vaccine that has been opened and stored for several days has been damaged by heat. Until now, opened vials of vaccine were thrown away at the end of an immunization session because their potency could not be guaranteed. While reconstituted measles, yellow fever, and BCG vaccines will still have to be discarded (because of the risk of bacterial contamination), other vaccines such as OPV can be safely kept for several days after the vaccine vial has been opened provided they meet rigorous safety requirements including storage in the cold chain and strict adherence to the expiry date. A full list of these safety requirements was drawn up by WHO in March 1995.

The monitors were introduced on all vials of UNICEF-supplied OPV from 1 January 1996 and will in due course be added to other vaccines. The device could also appear on blood bags.

Inactivated polio vaccine provides individual protection against polio paralysis but is not capable of preventing the spread of wild poliovirus since it induces only very low immunity in the gut. Because of this, IPV cannot be used to eradicate polio. However, IPV does not carry the risk of paralysis associated with OPV and the vaccine may play an increasing role in some industrialized countries once the disease is eradicated.

In the United States, for example, where wild poliovirus has already been eradicated, the only source of the disease is now OPV. Every year from 5 to 10 people become paralysed following immunization with OPV—half of them recently immunized children and the rest non-immunized or partially immunized contacts. In response to mounting public concern, the US Advisory Committee on Immunization Practices decided in June 1995 to draw up new guidelines on polio immunization. In October 1995 the Committee recommended the introduction of a combined IPV/OPV schedule in the United States—an initial two doses of IPV to be followed by two doses of OPV. The new strategy—which will cost an additional US\$ 20 million a year to implement—is expected to prevent polio paralysis in up to five recently immunized children a year.

Public health experts fear the US decision may give the impression that OPV alone is not enough to control polio or that it is an unsafe vaccine. It could also lead to pressure for a switch to IPV in developing countries as well—undermining eradication efforts in areas where polio is still a threat. The use of funds from limited immunization budgets to purchase IPV could even increase the incidence of polio by reducing the number of doses available to the poorest and most vulnerable children. Meanwhile it could also set back the introduction of vaccines against other priority diseases such as hepatitis B.

The members of the US Advisory Committee on Immunization Practices agree. They have underlined that the IPV/OPV schedule applies only to the United States and have strongly endorsed WHO's global eradication strategy. Whether other governments will be convinced remains to be seen. The real test could come in a few years' time when only vaccine-related cases are occurring—even in countries where the disease is now still endemic. Will developing

In the United States, where wild poliovirus has been eradicated, the only source of the disease is now oral polio vaccine.

Transgenic mice

Scientists have succeeded in genetically engineering a mouse susceptible to polio. Once available, the “transgenic” mice will help cut the cost of polio vaccine quality control tests.

For over a decade these tests have been carried out on monkeys—the only available animal model. But there are two major drawbacks to using monkeys: their limited availability (only two species are suitable) and their exorbitant price tag (up to several thousand US dollars for a single animal). At least 20 new monkeys are needed to test each polio virus lot produced. Transgenic mice could be bred and supplied for a fraction of the cost.

The development of transgenic mice—following research initiated and coordinated by WHO—is a major breakthrough which will dramatically reduce the very high costs involved in testing the safety and efficacy of oral polio vaccine (OPV). The mouse model would be especially useful for large state vaccine institutions in countries which currently produce large amounts of OPV for use in mass immunization campaigns. The mice won't replace monkeys altogether but they will help reduce the number of monkeys needed. The mice will be used for initial screening tests to check the consistency of production lots. This will enable producers to step up the size of each vaccine lot—leading to a corresponding reduction in the number of monkeys required.

The transgenic mice were developed following identification of the gene that makes humans susceptible to polio. This gene—encoding for a receptor for polio virus on the surface of a human cell—was isolated from the human genome and inserted into the genome of a mouse.

Six laboratories have been involved in the initial two-year research project. A more extensive follow-up study has now been launched involving additional research laboratories, manufacturers, and vaccine regulation authorities. If the initial promising results are confirmed, the transgenic mice could be available for use by 1998.

Meanwhile the same techniques have been used to develop transgenic mice with human-type red blood cells for use in malaria vaccine research, as well as mice that can be infected with the measles virus.

country governments or donors be willing to fund the purchase of a vaccine that costs five times as much—in order to prevent these cases?

WHO believes that most countries will continue to use OPV to interrupt transmission of the virus.

Measles

Measles remains one of the major childhood killers—accounting for more child deaths than any other vaccine-preventable disease. WHO estimates that in 1994 more than a million children died from measles—more than the total child deaths from all the other EPI vaccine-preventable diseases combined.

Most of the measles deaths—98%—occur in developing countries. Globally the disease accounts for over 10% of deaths among the under-fives—half of them in children under a year old. According to some estimates, the measles virus may be responsible for more child deaths than any other single pathogen—mainly through the complications of pneumonia, diarrhoea, and malnutrition. Measles can also lead to lifelong disabilities—including brain damage, blindness, and deafness—especially in developing countries.

WHO estimates that about 40 million cases of measles occur each year but only a small percentage of these—less than 5%—are ever reported. The disease thrives in cities—especially in deprived urban areas where overcrowding, poor sanitation, and pockets of low immunization ensure the continued circulation of measles and other diseases. Meanwhile, population movements to and from urban centres result in the introduction of the disease into nearby villages and towns.

Before the launch of the EPI in 1974 the death toll from the disease was around 8 million a year and there were an estimated 130 million cases. By 1990 global immunization coverage under the EPI had reached 80%. Since then it has levelled off at 78% although coverage varies greatly. In some developing countries it remains stubbornly below 50% while in others it is already over 90%. Some

In 1994 more than a million children died from measles.

industrialized countries have surprisingly low coverage. In Italy only 50% of infants were immunized in 1994, less than 60% in some regions of France, and less than 70% in Japan (1993 figures).

In 1990 the World Summit for Children established two global targets aimed at reducing the incidence of measles:

- by 1995 a reduction of 95% in the number of measles deaths
- by 1995 a reduction of 90% in the number of measles cases.

Both targets were based on estimates of the number of measles deaths and cases that occurred before the introduction of immunization against the EPI diseases. They were viewed as a major step towards the long-term goal—global eradication of measles.

The EPI added two additional targets to be achieved within the same time-frame:

- measles immunization coverage of at least 90% by one year of age to be achieved at country, district, and community levels
- case fatality rates from measles to be reduced to less than 1% in all countries.

Although none of these targets has been met, there has been a dramatic reduction in the number of measles cases and deaths. By the end of 1994 the estimated number of deaths was down by 85% globally and the estimated number of cases by 78%. It is estimated that by December 1995 just over a third of all countries had achieved a 90% reduction in cases and over half had cut the number of deaths by at least 95%.

However, the global figures mask wide disparities between individual regions and countries. Only two countries in WHO's South-East Asia region and five in the Africa region have succeeded in reducing the number of cases by 90%.

In the Americas, where the WHO Regional Office for the Americas (AMRO) is determined to eliminate measles by the year 2000, transmission has been interrupted in Chile, Cuba and the countries of

the English-speaking Caribbean and the incidence of the disease is the lowest ever. Every country in this region reached the 1990 World Summit targets on time.

The disease is proving difficult to control in many parts of the world. The major problem lies in reaching every child. In Africa, for example, only 54% of children under one were immunized against measles in 1994. Unlike other EPI vaccines, measles vaccine is not given in the first few months of life when mothers and babies have most contact with health services. It is the last vaccine to be given under the EPI schedule. As a result, drop-out rates for measles immunization are high and the vaccine generally has the lowest coverage of all the EPI vaccines for children.

Another drawback is that measles vaccines are less effective before nine months of age. At any earlier age the vaccines may be neutralized by measles antibodies acquired across the placenta from the mother. However, for children at high risk of catching measles—for example, children affected by disaster, in refugee camps, hospitalized or children with HIV-positive mothers—WHO recommends an initial dose of measles vaccine at six months to be followed by a second dose at nine months. The aim is to close the short window of opportunity when the disease may strike a child unprotected by either maternal or vaccine-induced antibodies—the age at which the disease is most likely to be fatal. In July 1994, up to 90,000 Rwandan children at high risk of contracting measles in the massively overcrowded refugee camps in Goma, Zaire, were immunized against the disease as a routine precautionary measure.

Despite these problems, innovative strategies have been developed—based on use of the existing vaccine. These involve efforts to prevent outbreaks or to interrupt transmission of the disease, as in the Americas. These strategies involve the use of mass immunization campaigns to target the age group where most non-immune children have accumulated—usually 9 months to 14 years—coupled with sustained high immunization coverage of each annual birth cohort and the development of an active surveillance system to detect every case of measles.

The EPI strategies for the global control and elimination of measles place increasing emphasis on the need for more effective disease surveillance systems. Surveillance-based measles control and elimination efforts will help sustain the gains made by the polio eradication initiative in establishing national surveillance networks.

Measles vaccine research

Both private and public sector vaccine manufacturers are involved in efforts to develop new measles vaccines. The ideal measles vaccine would be one that could be given at an earlier age, which was non-injectable, thermostable and ready for use without the need for reconstitution.

Testing is now under way in monkeys to evaluate the safety and effectiveness of several measles candidate vaccines. One promising vaccine, known as ISCOM (immune-stimulating complex), combines measles virus proteins with a purified plant extract saponin—derived from a South American tree (*Quillaja saponaria* Molina). Saponin acts by boosting the immune response to the measles antigens. Clinical trials of this vaccine could be under way by 1998. Another candidate vaccine, ALVAC, uses an attenuated canarypox virus (affecting birds but harmless to humans) as a vector for a DNA-derived measles vaccine. The third candidate vaccine is comprised of BCG vaccine and a gene encoding for measles virus N-protein. If successful, this would immunize children at the same time against both measles and the childhood forms of tuberculosis. Meanwhile, studies are also under way to develop a measles nucleic acid vaccine.

Another possible breakthrough is the development of a measles vaccine that can be inhaled. Scientists are looking at the possibility of developing a dry powder vaccine that could be directly inhaled—a method that would be more practical and less expensive to use in mass immunization campaigns.

Efforts are also under way to genetically engineer cheaper animal models for use in vaccine trials and vaccine quality control tests. The gene encoding for one measles virus receptor in humans has already been identified and transgenic mice expressing this receptor have been developed as a potential model system for measles infection.



Measles vaccine generally has the lowest coverage of all EPI vaccines for children.

Photo: WHO/L. Taylor

Preventing epidemics

Analysis of epidemiological data on measles incidence, immunization coverage and patterns of previous epidemics can provide estimates of the build-up of non-immune children and predict the likely date of the next epidemic. These analyses are crucial in efforts to prevent epidemics and eventually eliminate the disease. Mathematical models have been developed to corroborate the data collected from surveillance.

In 1994, public health officials in the UK warned that in 1995 England and Wales faced the most serious epidemic of measles since the early 1980s. As many as 150,000 cases were anticipated with about 50 deaths. This warning was consistent with a marked increase in the number of measles cases being reported as well as changes in the pattern of the disease. The most recent outbreaks had involved more cases and older children were increasingly affected.

In England and Wales a nationwide school-based immunization campaign was planned—targeting every child aged from 5 to 16. A high-profile publicity campaign was launched to ensure blanket immunization coverage. Manufacturers were unable to meet the demand for supplies of UK-acceptable measles/mumps/rubella (MMR) vaccine in time for the campaign and so the UK Joint Committee on Vaccination and Immunisation recommended the use of a measles/rubella (MR) vaccine instead.

The national immunization campaign succeeded in reaching about 8 million children—over 90% of those targeted. The campaign cost about £20 million. According to a cost-benefit analysis, a measles epidemic on the scale predicted would have cost three times as much in health care costs and the value of lives lost, plus an estimated 0.3 million working days lost through parents caring for sick children.

One major innovation expected to be available in the near future is a diagnostic field test for measles which—within minutes—can confirm whether a child is infected. The “immuno-dot” test—using blood—is expected to be ready for field-testing in several developing countries during 1997. The availability of a rapid diagnostic test would help accelerate case investigation and control measures and improve disease surveillance.

Neonatal tetanus

In 1994—a year when 80% of children throughout the world were immunized against tetanus (with DTP) during their first year of life—more than 50% of babies were born unprotected against the disease because their mothers were not immunized with tetanus toxoid.

Almost 500,000 of those babies died during the first three weeks of life because their mothers could not pass on protective antibodies during pregnancy.

And it wasn't just the babies that died. Public health experts estimate that every year 30,000-60,000 mothers die too—victims of tetanus infection during childbirth. In many countries immunization of women is considered a second priority not only by mothers but by health workers as well.

Neonatal tetanus is caused by unclean delivery practices—the introduction of tetanus spores from soil through poor hygiene or the use of unsterile instruments or dressings during childbirth. The disease is usually associated with poverty, lack of education, poor living conditions, and home births supervised by untrained birth attendants.

In high-risk areas, targeted immunization programmes are also routinely supplemented by training birth attendants in safe delivery practices—emphasising the importance of clean hands, clean delivery surface, and clean cord-cutting and care (“the three Cs”). Information campaigns are also used to highlight the hazards of traditional childbirth practices (the use of clarified butter or cattle dung, for example, to “heal” the umbilical stump). In India, a number of NGOs now provide special birth kits with sterile equipment including a razor blade, soap, and a plastic sheet to provide a clean delivery surface. In Nepal, these are now being produced by a women's cooperative for sale at a low price.



All women of childbearing age should be fully immunized with tetanus toxoid vaccine.

Photo: UNICEF/Giacomo Pirozzi (D0194-1187)

Elimination of neonatal tetanus

In 1989 the World Health Assembly committed WHO Member States to achieving the elimination of neonatal tetanus as a public health problem by the year 1995. Elimination is defined as less than one case of neonatal tetanus for every 1,000 live births in each administrative district throughout the world. Once that target is met, WHO estimates that fewer than 150,000 cases will occur globally each year.

While the global target has not been met on time by all countries, almost 60 developing countries have already succeeded in eliminating the disease and about 90 are meeting the WHO target nationwide, if not yet at district level. WHO estimates that in 1994, almost 800,000 deaths from neonatal tetanus were prevented through immunization—most of them in just three countries: Bangladesh, India, and Indonesia.

In Sri Lanka, where over 80% of pregnant women were immunized in 1994, neonatal tetanus appears to have been eliminated. In Latin America, 98% of districts are now reporting less than one case for every 1,000 births. The disease has also been eliminated in Iran. In Thailand more than 80% of provinces are reporting zero cases and in Egypt up to 70% of districts have already met the WHO target of less than one case for every 1,000 live births.

In China, which accounts for almost 20% of the world's neonatal tetanus cases, over 90,000 babies die from neonatal tetanus every year—the majority (80,000) in rural areas. In 1994 only about 10% of pregnant women in China were immunized against tetanus. In October and December 1995, in a mass immunization campaign, women of childbearing age in selected high-risk areas received two doses of tetanus toxoid.

Elsewhere, in Bangladesh, where only 10% of women have access to a clean delivery, the number of cases has plummeted from 41 for every 1,000 births a decade ago to 6 today. A mass immunization campaign was carried out in 130 thanas (sub-districts) during 1995, targeting all women of childbearing age not previously immunized. In war-torn Afghanistan, where only 3% of pregnant women were reported to be immunized in 1994, mass campaigns carried out

In Sudan in 1994 only 2% of women were reported to be immunized with tetanus toxoid.

during Days of Tranquillity in 1995 are expected to boost immunization levels for 1995. And in Indonesia, women in high-risk districts are to be immunized during 1996.

However, in some countries—and more specifically in key pockets within those countries—immunization coverage remains stubbornly low. Eighty per cent of reported cases are now occurring in only 12 countries—Bangladesh, China, Ethiopia, Ghana, India, Indonesia, Nepal, Nigeria, Pakistan, Somalia, Sudan, and Zaire. In five of these (Ethiopia, Ghana, Nepal, Somalia, and Sudan), in 1994, immunization coverage for tetanus toxoid ranged from no more than 2% in Sudan to 14% in Ghana.

But immunization coverage rates can be deceptive. In India, for example, despite high immunization coverage of over 80% in 1994, there were between 40,000 and 60,000 deaths from neonatal tetanus. The reason for this anomaly is that over 70% of these deaths occurred in just four Indian states.

Reporting systems for both tetanus toxoid immunization coverage and morbidity rates are still inadequate in many countries. The problem is that most neonatal tetanus victims die at home in the first few weeks of life. Very few are ever admitted to hospital and many of these deaths go unrecorded.

In an effort to improve reporting systems and gather more accurate data, WHO has issued new guidelines for monitoring immunization coverage at district level and detailed assessments will be carried out during 1996. Meanwhile, UNICEF has launched a study in 70 developing countries to determine the immunization status of women who gave birth in 1995. Combined data from these two studies will help determine to what extent the 1995 targets have been met.

Development of a single-dose tetanus toxoid vaccine

Tetanus toxoid is a detoxified form of the toxin that attacks the central nervous system during tetanus infection. All women of childbearing age should be immunized with boosters at least twice and previously non-immunized women should have five doses of the vaccine to ensure protection throughout the childbearing years.



Immunization campaigns have been carried out in Afghanistan where only 3% of women were reported immunized with tetanus toxoid in 1994.

Photo: WHO

The need for regular booster doses of tetanus toxoid over a number of years is one of the reasons why immunization coverage remains low in some areas. In remote areas with no readily accessible means of transport, for example, there is a high drop-out rate among women scheduled for booster doses. Research is now under way into the development of a single-dose tetanus toxoid vaccine. If successful, the technique will be used to develop single dose vaccines for as many childhood vaccines as possible.

One of the most promising single-dose tetanus toxoid vaccines borrows a technique developed for the timed release of drugs. Tetanus toxoid is microencapsulated in minute bead-like capsules—each primed for controlled release at different time intervals to mimic the effect of phased booster shots. Although initial tests with microencapsulated vaccines produced a stronger priming effect than the first dose of existing tetanus toxoid vaccine, the new vaccine failed to produce subsequent boosting of immunity. In early experiments the microencapsulated TT vaccine was found to be unstable. It primed the immune system well but failed to deliver the booster doses. These problems are now believed to have been resolved. Meanwhile, researchers are now trying to find ways of delivering the vaccine orally instead of by injection.

An alternative candidate vaccine uses a live attenuated bacterium—*Salmonella typhi*—as a vector to carry a non-toxic but protective part of the tetanus toxin gene. Phase I safety trials of this oral vaccine are expected to be carried out during 1996.

Researchers are also looking into ways of improving the existing tetanus toxoid vaccine through replacing the immune-boosting adjuvant (alum) with one that is more effective. A well-tried adjuvant—calcium phosphate—now looks promising for use in a single-dose tetanus toxoid vaccine and will be re-tested in human trials. Research is also under way using another adjuvant—polyphosphazene. All three vaccines are scheduled to undergo final testing in animals during 1996 in preparation for human trials. Elsewhere, several commercial vaccine producers are also developing other candidate single-dose tetanus toxoid vaccines.



In the Americas neonatal tetanus has almost been eliminated.

Photo: WHO-PAHO/C. Gaggero

False claims by anti-abortion groups halt immunization programmes

WHO and UNICEF have strongly rebutted claims by some anti-abortion groups that women in Mexico, Nicaragua, the Philippines, and Tanzania were given tetanus toxoid vaccine with an added component that can reduce fertility.

Tetanus toxoid vaccine is routinely given to women of childbearing age in developing countries to prevent post-natal tetanus infections which entail a high fatality rate for both mothers and babies. Some pressure groups claimed that tetanus toxoid vaccines, with an anti-fertility component, were being secretly used to limit population growth in the target countries. A publicity campaign was launched on the Internet—issued as a press release by Human Life International.

As a result, public confidence in immunization programmes has been badly dented. In the Philippines, where the reports originated, a court injunction succeeded in temporarily halting the use of tetanus toxoid in immunization campaigns. The ban also affected other childhood immunization programmes, including measles, and resulted in lower participation in a national immunization day against polio. In Mexico, the Secretary of Health was accused of genocide, while in Nicaragua, tetanus toxoid immunization was suspended and batches of the vaccine withdrawn for testing.

The action by anti-abortion groups was prompted by reports of clinical trials carried out by scientists in India in 1994 to assess the

effectiveness of a prototype anti-fertility vaccine intended to provide contraceptive protection for 1-2 years. The active ingredient of this vaccine is human chorionic gonadotrophin (hCG)—a hormone produced by the fertilized egg and essential for the initiation of pregnancy. (It is hCG that is detected in pregnancy tests.) In the anti-fertility vaccine, the hCG component is linked to a “protein carrier” in order to stimulate the production of antibodies to hCG and thus prevent pregnancy. The protein carriers used in the clinical trials in India were diphtheria and tetanus toxoids.

In the Philippines, anti-abortion groups aware of the tests in India analysed tetanus toxoid and claimed to have detected the presence of hCG. However, when vaccines from seven different manufacturers were independently tested by the US Food and Drug Administration (FDA), the Netherlands Government, and by laboratories in several countries, the results were all negative. One laboratory demonstrated the unreliability of the test at low levels of detection by obtaining a “false positive” result when testing its sterile water supply.

WHO and UNICEF have made it clear that they strongly oppose the combination of any vaccines with anti-fertility vaccines. They also warn that the unsubstantiated claims by some anti-abortion groups could seriously undermine public confidence in tetanus toxoid and other vaccines in the countries involved, lower immunization coverage, and cost the lives of mothers and children.

Diphtheria

Diphtheria—a dreaded childhood illness in the pre-vaccine era—is re-emerging today in epidemics involving mainly adults and non-immunized children. As immunization levels have risen throughout the world and diphtheria has become rare—first in the industrialized world and later some developing countries as well—there has been a corresponding drop in the number of diphtheria organisms in circulation. As a result, there is less opportunity for boosting immunity through natural exposure to diphtheria organisms. Over time—even with consistently high levels of immunization coverage in children under one—vaccine-induced immunity wanes and groups of non-immune individuals build up, creating the ideal conditions to seed an epidemic.

In Algeria, for example, a diphtheria epidemic occurred in 1993-4 after a period of sustained high immunization coverage. There were 163 confirmed cases and 31 deaths—with adolescents and young adults mainly affected. And in Hubei Province in China, as diphtheria immunization coverage reached 82% in 1988, an outbreak occurred with 70% of those affected in the 20-plus age group.

Elsewhere, in the Newly Independent States of the former Soviet Union—where a dramatic fall in immunization coverage, massive population movements from rural to urban areas and serious economic problems helped spark off a major epidemic in 1990—the number of cases skyrocketed from under 2,000 in 1990 to over 47,000 by 1994. More than 2,500 people have died from diphtheria in this region over the past five years. In 1994, WHO and UNICEF declared the epidemic an international health emergency.

The potential flashpoints for epidemics are areas with two key groups of people vulnerable to the disease—adults who have lost their immunity and children who have not been immunized against diphtheria. This is exactly what sparked off the epidemic in Russia, Ukraine and in other Newly Independent States. By contrast, in neighbouring countries such as Finland and Poland where immunization coverage among children is consistently high (over 95%), only isolated cases of diphtheria have been reported over the past three years—despite increasing movement of people from the Newly Independent States.

Diphtheria is an infectious disease caused by a bacterium (*Corynebacterium diphtheriae*) and spread by coughing or sneezing or through contact with skin infections. It can affect the tonsils, upper respiratory tract and the heart. Although the disease can be treated with diphtheria antitoxin and antibiotics, even with appropriate treatment up to 10% of cases are fatal. The disease can involve serious complications, affecting the heart (myocarditis) and central nervous system, following the spread of diphtheria toxin to various organs.

WHO recommends that all countries should give priority to ensuring that at least 90% of children under one are immunized with three doses of DTP vaccine. The same high immunization coverage should be attained for booster doses of diphtheria toxoid in countries where these are included in immunization schedules. In developing countries where the reservoir of diphtheria organisms is large, the primary series of immunization may be enough to secure long-lasting immunity. However, in developing countries with sustained high levels of immunization coverage, a series of booster doses may also be needed—possibly one at the end of the second year of age (DTP) and/or another when the child begins school (a DT vaccine), or a dose at school-leaving (an adult Td combination with a reduced amount of diphtheria toxoid).

Tackling the problem of high-risk groups of adults, however, is more problematic. Possible strategies include 10-yearly immunization with Td vaccine, the use of Td vaccine instead of TT vaccine whenever tetanus toxoid is given (in a hospital casualty unit, for example), and the use of Td vaccine for high-risk groups such as military personnel, teachers, health care workers, travellers, alcoholics, and drug users.

Resurgence of diphtheria in Eastern Europe

In 1980, Europe accounted for less than 1% of the total number of diphtheria cases worldwide (about 600 out of almost 98,000 cases) and it was believed the disease would soon be eliminated. Today the tables have turned. By 1994, Europe alone accounted for almost 90% of all reported cases.

In 1993, 80% of reported cases were in the Russian Federation, 16% in Ukraine, and 3% in the other NIS. In 1994 the epidemic spread to Azerbaijan, Belarus, Georgia, Kazakhstan, Kyrgyzstan, Latvia, Moldova, and Uzbekistan. All other NIS of the former USSR reported diphtheria cases or localized outbreaks.

The epidemic is now reported to be spreading to other European countries including Bulgaria, Germany, Norway, and Poland. Other countries are also at risk of importation of the disease. Between 20% and 60% of adults over 25 in western Europe and North America are at high risk due to low levels of immunity.

Health economists estimate that the number of working days lost as a result of the epidemic was over a million in 1994 alone—a heavy toll in countries still in the throes of economic and social transition. In Moscow—one of the worst affected cities—outbreaks have been reported among the staff of hospitals and other medical services, railway stations and airports.

International aid agencies and governments are working together in an effort to get the epidemic under control. In February 1994, WHO established a European Task Force on Diphtheria Control and drew up a plan of action for the region, issuing technical manuals on the management and control of diphtheria and laboratory diagnosis of cases.

Meanwhile, a group of international development agencies and government representatives, led by the governments of the United States and Japan, established an Interagency Immunization Coordinating Committee (IICC) to help the NIS become self-sufficient in vaccine supplies. The committee—based at WHO's European Regional Office in Copenhagen—is giving priority to control of diphtheria and eradication of polio.

Donor-funded purchases of vaccines as well as supplies of anti-toxin and antibiotics have been sent to each of the NIS and a network of ten laboratories established to help improve surveillance and the exchange of information. In June 1995 an appeal was launched by WHO, UNICEF and the International Federation of the Red

In Eastern Europe over a million working days were lost in 1994 as a result of the diphtheria epidemic.



In China, high levels of diphtheria immunization coverage among children led to increasing incidence of the disease in adults.

Photo: UNICEF/Sean Sprague (2262/86)

Cross/Red Crescent Societies (IFRC) for a total of US\$ 42 million to help bring the diphtheria epidemic under control. But almost a year later only US\$ 9 million has been offered.

With hindsight, the resurgence of diphtheria in Eastern Europe could have been predicted. The first wave of the epidemic peaked in 1983, 1984, and 1985, with the number of cases exceeding 1,400 for each of these years. At this stage, there was a dramatic increase in the number of pre-school-aged children affected—an indication of low immunization coverage. By 1992 all age groups were increasingly affected—with peak incidence in children aged 5-10 and adults aged 30-50 years.

In Ukraine—one of the countries worst affected—coverage of infants with the primary series of three doses of DTP vaccine plummeted from 85% in 1981 to 46% in 1982. Five years later immunization coverage was still under 50%. In many urban areas in Russia—including Moscow and St Petersburg—coverage rates among infants ranged from 18% to 59%.

Economic problems in the Newly Independent States led to irregular supplies and shortages of vaccines. These problems were compounded by a misinformed campaign about vaccine safety and by a high number of “missed opportunities” for immunization—involving reliance by some doctors on an excessive list of contra-indications for DTP. There has also been a lack of information for parents about the importance of childhood immunization.

Meanwhile, although recent studies indicate that the potency of the diphtheria component of Russian DTP meets WHO requirements, there is evidence that in the early 1990s children in some areas were given adult strength Td vaccine with a reduced amount of diphtheria toxoid. As the number of non-immunized and inadequately immunized children increased, the pool of susceptibles lacking immunity was swelled by a growing number of adults with waning levels of immunity. The breakup of the former USSR occurred around the same time, creating the perfect catalyst for an epidemic—massive population movements that helped the spread of infection.

Today, each of the Newly Independent States has drawn up its own plan of action for preventing and controlling the epidemic, based on a WHO-UNICEF joint strategy. In addition to raising immunization levels through extensive mass immunization of all age groups, there is a need for prompt diagnosis and treatment of diphtheria cases together with rapid identification, tracing, and preventive treatment of close contacts in order to halt the spread of the disease. There is a reluctance by some doctors in the worst affected regions to use antibiotics to treat otherwise healthy contacts. But any delay in treating a suspected diphtheria carrier continues to place large numbers of people at risk of exposure to the disease.

Pertussis (whooping cough)

In 1994 there were an estimated 40 million cases of pertussis (whooping cough) worldwide and 360,000 deaths. Every year nearly 5 million children suffer from broncho-pneumonia as a result of pertussis infection, while 50,000 children develop long-term neurological complications—including permanent brain damage. In developing countries the death rate can exceed 15% but is usually not so high. In the industrialized countries it is much lower, with 4 deaths out of every 10,000 infected children.

The disease is under-reported, with only 1-2% of cases ever appearing in official statistics. One of the problems is the difficulty in differentiating the disease from other respiratory infections—especially when the case is mild or when there is no characteristic whooping sound. And even when the disease is suspected, laboratory confirmation is not always possible. Sometimes even the most sophisticated laboratories fail to isolate the bacterium (*Bordetella pertussis*).

Whole cell pertussis vaccine (one of the three components of DTP) has been on the market for almost half a century. In 1994, 80% of infants throughout the world received three doses of DTP before their first birthday and, as a result, 70 million cases of pertussis were prevented globally—and 610,000 deaths. While global coverage rates for DTP are high, in some countries less than a third of children are protected during their first year of life. In Afghanistan only 12% of children under one are immunized with DTP, in Chad 18%, in Zaire 29%, and 31% in Cameroon.



In Chad, less than 20% of children are immunized with DTP vaccine.

Photo: UNICEF/Giacomo Pirozzi (DO194-1182)

Young babies most vulnerable

A 1995 survey by WHO/GPV on immunization coverage for pertussis reveals that, as immunization has increased, the age distribution for pertussis has shifted from mainly 1 to 6 year old children to infants under one. Young babies are especially vulnerable because mothers pass on only minimal antibody protection during pregnancy. And whatever little protection they may have at birth rapidly disappears during the first few weeks of life—placing babies in the front line for pertussis infection if they are exposed to adults with the disease. The EPI schedule includes three doses of DTP vaccine within the first six months of life, but in developing countries immunizations are often delayed and there are high drop-out rates between the first and third doses of the vaccine.

In some industrialized countries—Germany, Italy, Russia, and the UK—an increase in the incidence of pertussis has been traced to a drop in immunization rates. In Italy, for example, where pertussis vaccine is “recommended” but not mandatory, only 50% of children under one were immunized against the disease in 1994. The underlying causes include complacency on the part of physicians and parents, litigation over alleged vaccine-related injuries, and propaganda spread by anti-immunization pressure groups.

In the UK, immunization coverage plummeted from 75% to 25% in the mid-70s following press coverage of suspected rare instances of permanent neurological damage after immunization with the pertussis component of DTP vaccine. While it later proved difficult to establish whether the link between the vaccine and neurological damage was causal or coincidental, public perception of the vaccine was badly dented. A major epidemic of pertussis followed between 1977 and 1979 and a second epidemic in 1981. The episode resulted in 100,000 additional cases of the disease and a rise in the number of deaths. When public confidence in the vaccine was later restored and immunization levels went up there was a corresponding drop in the incidence of the disease and the number of deaths.

Recent studies suggest that the number of adult cases of pertussis may be much higher than previously estimated and that adults may be a major source of transmission and reservoir for the disease. An outbreak in 1991, in a nursing home for the elderly in Wisconsin, in the United States, showed that adults could be infected by pertussis even in a community where no children were present. Elsewhere, adult-to-adult transmission has been reported in the Gambia. And a study in an outpatient clinic in Nashville, USA, found that out of 75 adults complaining of a persistent cough, 16 (almost a fifth) had pertussis. Meanwhile, the Centers for Disease Control and Prevention (CDC) in Atlanta report that the percentage of adolescent and adult cases in the United States almost doubled between 1979 and 1993 (up from 15% to 27% of the total number of reported cases).

In both developing and industrialized countries cases of pertussis are now increasingly reported among adults who were immunized and even among adults who had already contracted the disease before. It is now believed that vaccine-induced immunity wanes—disappearing altogether after 12 years. As a result, industrialized countries with a 40-year record of immunization against pertussis are likely to have a large pool of adults susceptible to the disease. By contrast, in developing countries—where immunization programmes have been established for only 10-15 years—young adults are still protected.

Whole cell vs acellular pertussis vaccines

Recent comparative trials of acellular and killed whole cell pertussis vaccines—in Sweden, Italy, Germany, and Senegal—could have major implications for the global production of DTP vaccine. The latest trials produced a 80-90% rate of efficacy for the new acellular pertussis vaccines—only a marginal reduction on the performance of some whole cell vaccines—but with a significant reduction in the mild side-effects associated with whole cell pertussis vaccine.

Acellular pertussis vaccine is already used in Japan and licensed for booster doses in the United States. The advantage of the new vaccine is that it is manufactured from purified or partially purified protein components of the bacterium (*Bordetella pertussis*) instead of whole killed bacteria. Although the vaccine is more expensive to manufacture, the process of testing it is cheaper, simpler and easier. During the purification process most of the non-protective toxic elements are removed. As a result, the vaccine does not provoke

the side-effects associated with whole cell pertussis vaccine, such as sore arms, and fever, which in some instances can lead to convulsions.

The discovery that acellular pertussis vaccine produces fewer side-effects is giving public health officials food for thought. For a start, acellular pertussis vaccine will be more expensive than its forerunner. It will increase the overall cost of immunization—without adding any new vaccines to the existing armoury of EPI vaccines. The danger is that industrialized countries will be able to afford it while most developing countries won't. The prospect of a two-tier system looms.

However, some immunization experts point out that a two-tier system already exists for whole cell vaccine—with not all children having access to high-quality whole cell vaccine.

Another factor is that most DTP—about 60%—is currently produced in developing countries. Although the new acellular pertussis vaccine can be combined with diphtheria and tetanus toxoids as readily as whole cell pertussis vaccine, it will be very expensive to produce and probably subject to intellectual property rights. Right now many developing country producers don't have access to the technology required to produce it. A few of the larger countries might possibly be able to switch over, but the rest would probably have to import the new vaccine and combine it with locally produced diphtheria and tetanus toxoids. Developing countries that currently import DTP will face the dilemma of whether to switch to the new vaccine. Most will probably be deterred by the increased cost.

The far-reaching implications of the successful trials of acellular pertussis vaccine will now have to be studied further. In the meantime, some remain sceptical about the added value of the new acellular pertussis vaccine. They point to the good track record of existing DTP vaccine—using technology developed 60 years ago—and question the usefulness of the newer, more expensive vaccine that will reduce the incidence of mild side-effects but will be marginally less effective than whole cell vaccines currently in use.

Tuberculosis

Tuberculosis (TB) kills more people than any other infectious disease—an estimated 3 million people a year, including almost 300,000 children under 15. At current rates of infection there are over 7,000 deaths and over 24,000 new cases every day. In April 1993, WHO declared the worsening tuberculosis epidemic a global health emergency.

An estimated two billion people—a third of the world's population—are already infected with *M. tuberculosis*. Over the next decade it is estimated that an additional 300 million people will become infected—in both industrialized and developing countries.

Only 10% of those infected go on to develop an active form of the disease. But the stakes are raised if those infected with *M. tuberculosis* are also infected with HIV. Together, the two diseases produce a deadly cocktail. Infection with HIV not only increases the chance of primary infection with TB, it also activates latent TB infection. A person infected with both HIV and TB is 30 times more likely to develop active TB than a person infected by TB alone. Conversely, infection with TB can also further suppress the immune system of an HIV-infected person and accelerate the onset of opportunistic infections.

By 1994, 5.6 million people were infected with both diseases—the majority (about 3.8 million) in Africa. By the year 2000, TB is expected to be the leading cause of death among HIV-positive people. Significantly, it is also the only AIDS-related infection that can be readily transmitted to people who are not HIV-positive. In Asia—where an estimated 1.1 billion people are already infected with TB and where the number of HIV cases is increasing rapidly—the number of co-infected people is likely to increase sevenfold between 1990 and the year 2000.

Tuberculosis spreads easily—transmitted by bacteria sprayed into the air by coughing or sneezing. Without treatment, a person with active TB can infect up to 15 people in a year. Although drug therapy is effective, treatment has to be rigorously followed for six months

An estimated 2 billion people are already infected and at risk of developing tuberculosis.

and drop-out rates are high. In many countries chemotherapy is now carried out under the daily supervision of health workers (at home, at work, or in outpatient clinics).

TB patients who stop taking antibiotics before they are cured continue to infect others and also risk developing and spreading multi-drug-resistant strains of the bacteria that are becoming increasingly difficult to treat. More than 50 million people are believed to have already been infected with drug-resistant strains. Today health workers and other contact groups are highly vulnerable to untreatable forms of the disease.

New vaccine development

The emergence of multi-drug-resistant TB has underscored the urgency of the need to develop a new vaccine to replace BCG (Bacille Calmette-Guérin), the vaccine currently used to immunize children. BCG—a live attenuated vaccine—was developed in 1921 and is still the most widely used vaccine in the EPI. In 1994, almost 90% of children under one throughout the world were immunized against TB.

However, the vaccine is only from 50% to 80% effective in protecting against the most severe childhood tuberculosis—TB meningitis (affecting the brain and spine) and miliary TB (which mainly affects the lungs but also spreads via the blood throughout the body). And it provides little or no protection against the adult form of the disease. BCG has a continuing role within child health programmes but is unlikely to have much impact on the worsening TB epidemic.

Research is currently under way to develop a new vaccine—not only more effective in preventing childhood TB but with extended protection into early adulthood (20-30), when most of the adult cases occur. Until recently there was little commercial interest in research into new tuberculosis vaccines. But the global epidemic of TB and HIV-related TB and the emergence of drug-resistant forms of the disease have sparked renewed interest in vaccine development. In February 1995 one of the main vaccine producers declared that production of a new vaccine against TB was its number one priority.



BCG is the most widely used EPI vaccine.

Photo: UNICEF/Howard Davies (D0195-0252)

A major scientific breakthrough in TB research is the deciphering of the genome sequence of *M. tuberculosis*—a mammoth task which is expected to be completed by the end of 1996. It is the result of a pioneering initiative by WHO, which involved the drawing up of a physical map of the genome as well as the first steps in its sequencing.

One of the starting points for vaccine development is the premise that because the existing vaccine is based on *Mycobacterium bovis*—a bacterium responsible for the bovine form of the disease—it may not contain all the antigens required to induce immunity against *M. tuberculosis* in humans. In addition, studies carried out in animals have shown that cured tuberculosis infection provides longer lasting immunity than immunization with BCG.

Of the four candidate vaccines developed so far, only one is based on the existing BCG vaccine. This has been produced by cloning genetic material from *M. tuberculosis* into BCG to make it immunologically closer to the bacterium that affects humans. Studies are also being carried out into the possibility of cloning immune stimulants (cytokines) into BCG to boost the immune response to the vaccine.

Another approach is described as a “bombing technique”. A section of the genome of *M. tuberculosis* is carefully targeted and literally blasted out—a process that leaves the protective antigens intact while disabling the pathogen’s ability to cause disease.

Meanwhile, the discovery that live vaccines provide better protection against tuberculosis than killed vaccines from the same strains has prompted a search for protective antigens among the proteins which are detected in live bacteria but absent from dead bacteria. Workers at the Statens Seruminstitut in Copenhagen have succeeded in cloning the gene of one of these proteins to produce a candidate vaccine. This has proved successful in animal tests and Phase I trials are now being planned.

A fourth candidate vaccine involves the injection of naked (pure) DNA instead of ready-made proteins. This DNA vaccine is also at an advanced stage and currently undergoing tests in animals.

DNA vaccines

A new kind of immunization technique under development—involving the injection of naked DNA—is to be tested for the first time on healthy human volunteers. The US Food and Drug Administration has given the go-ahead to trials at the National Institutes of Health in Bethesda of a DNA vaccine designed to protect against HIV infection. The vaccine has been developed jointly by a US biotechnology company and by researchers at the University of Pennsylvania. An earlier DNA vaccine—designed to delay or prevent the onset of AIDS in people already infected with HIV—is currently undergoing Phase 1 trials in the United States and Switzerland. Elsewhere, trials of a DNA vaccine against malaria are also on the drawing board. Meanwhile DNA vaccines are of particular interest in the development of vaccines against tuberculosis.

DNA vaccines are based on nucleic acid corresponding to one or more genes from a disease-causing virus or bacteria. The nucleic acid—selected because it codes for an antigen that can stimulate protective immunity—is grafted on to another piece of DNA, acting as a vector, and injected into muscle tissue. Once inside the cell, the gene prompts the cell to produce the antigen. The immune system in turn reacts to the foreign antigen—providing protection against the disease.

If successful, the new immunization technique would be a major breakthrough for vaccine development. DNA vaccines produce good cellular and antibody responses, they are more heat stable than existing vaccines, can be rapidly constructed, and should be less

expensive to produce than other new generation vaccines. A major advantage is that DNA vaccines contain no infectious organisms. The fragment of DNA used contains no more than the instructions for making a protective antigen. As a result, DNA vaccines should avoid the risk of unwanted side effects. In the longer term, the technique also holds out the prospect of developing a DNA vaccine that could protect children against a range of different diseases at the same time.

DNA vaccines can be administered in several ways. In addition to intramuscular injection, the DNA can be coated onto microscopic gold beads that are literally shot into skin cells using a DNA “gun”. Other delivery methods under consideration include the use of aerosols in the nose or throat.

Until recently, DNA vaccines had only been tested in animals. These tests produced varying degrees of protection against a range of diseases including influenza, leishmaniasis, malaria, and tuberculosis. Meanwhile, promising immune responses have been obtained in trials in monkeys of DNA vaccines against hepatitis B and Simian Immunodeficiency Virus (SIV), the monkey equivalent of HIV.

Fears that the foreign DNA could possibly be integrated into the host’s genetic make-up and subvert the genetic working of cells—activating genes with cancer-causing potential, for example—have so far proved unfounded. However, these and other related safety issues will require close and continuous monitoring over a long period.

Although very rapid progress is being made in vaccine development, efforts are still under way to determine exactly which immune responses correlate with protection against tuberculosis. Without this crucial information the efficacy of a candidate vaccine can only be measured by failure to develop the disease—a process that could take many years.

Hepatitis B

More than 2 billion people alive today have at some time in their lives been infected with the hepatitis B virus (HBV). Of these, about 350 million remain chronically infected carriers—a ticking time bomb that can transmit the disease for many years before going on to develop cirrhosis of the liver, or liver cancer. Every year there are over 4 million acute clinical cases of hepatitis B and about a million deaths. Primary liver cancer caused by hepatitis B is now one of the principal causes of cancer death in many parts of Africa, Asia, and the Pacific Basin.

Globally, child-to-child and mother-to-child transmission accounts for the majority of infections and carriers. Young children rarely develop acute clinical disease, but about 25% of children infected under the age of seven become carriers. In older children and adults, no more than 10% per cent become carriers. However, about 40% of infected older children and adults develop acute clinical hepatitis B with jaundice. The disease can also be transmitted through the use of unsterile needles or other medical equipment and through cultural practices which involve skin piercing.

In areas where there is low incidence of the disease (Western Europe, North America, much of Latin America, and Australia) mother-to-child and child-to-child transmission is less common and most infections occur in adults through sexual activity, needle sharing among intravenous drug users, and—less frequently—among medical workers exposed to blood products. In addition, many areas where the incidence of hepatitis B is generally low have large ethnic groups at higher risk of the disease.

Elsewhere, in parts of southern and Eastern Europe, the Middle East, western Asia, the Indian Subcontinent, and parts of Central and South America, both child-to-child and adult transmission oc-

cur. However, a high proportion of infections occur during adolescence and adulthood when acute clinical disease is more likely. As a result, acute viral hepatitis with jaundice is an important cause of morbidity in these areas.

The first vaccine against hepatitis B came on the market in late 1981 and an alternative recombinant vaccine has been commercially available since 1986. Both vaccines remain relatively expensive in comparison with the other EPI vaccines currently in use and this has proved a major stumbling block for governments ever since.

The use of HB vaccine in countries with a high incidence of the disease is closely linked to the socioeconomic level of the country involved. Of the countries where more than 8% of the population are HB carriers, immunization coverage is high, and the GNP per capita is over US\$ 500, most are using hepatitis B vaccine. But wherever the GNP is lower, HB vaccine is generally unavailable because these countries are mainly dependent on donors for their vaccines. And donors—with some exceptions—have so far been unwilling to purchase hepatitis B vaccines.

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WHO targets for the control of hepatitis B

In 1991 the EPI Global Advisory Group recommended that hepatitis B vaccine should be included in national immunization programmes in all countries with a hepatitis B carrier rate of 8% or over by 1995 and in every country by 1997. That recommendation was endorsed a year later by the World Health Assembly—a decade after the first hepatitis B vaccine became available. In 1994 the World Health Assembly added a disease reduction target for hepatitis B—an 80% reduction in the incidence of new HB carriers in children by the year 2001. When these targets are met, it is estimated that less than 1% of the children immunized each year will be HBV carriers.

So far, over 75 countries have introduced hepatitis B vaccine within their national immunization programmes. But less than half of these are countries with a HB carrier rate of 8% or over. They range from a carrier rate of 0.5% (Canada, France, the United States) to over 30% in the Pacific island State of Kiribati. In some of the countries hepatitis B vaccine is already universally available while in others the vaccine is being phased in over a longer time-frame.

In 1994 UNICEF developed a strategy to begin assisting countries with a high percentage of hepatitis B carriers obtain vaccine—provided they had over 70% immunization coverage overall, a low GNP per capita, and donor funding could be found. This mechanism has not been used so far but WHO and UNICEF are working closely together to ensure that it is. One of the reasons for donor reluctance to fund HB vaccine is that some of the poorest countries where the vaccine is needed have difficulty delivering the basic six EPI vaccines. In Africa, for example, despite a rise in overall immunization coverage during 1994, many countries still have immunization coverage of less than 50%. Another UNICEF strategy currently being developed in collaboration with WHO, the Vaccine Independence Initiative, is being used in the Pacific Island countries. If the regional trial of this scheme is successful it will ensure a sustainable supply of EPI vaccines including hepatitis B for this region through the WHO/UNICEF vaccine distribution system in Fiji. In the meantime, the Government of Australia has agreed to fund hepatitis B vaccine for many Pacific island countries over the next few years.

In the Americas, WHO's Regional Office for the Americas (AMRO) is considering the inclusion of hepatitis B vaccine in the list of vaccines available to countries through the Revolving Fund for vaccine procurement.

The Western Pacific Region of WHO—one of the worst affected regions—has succeeded in attracting donor support for purchase of hepatitis B vaccine. With the exception of six countries (Australia, Cambodia, Japan, Laos, Mongolia, and Vietnam) HB vaccine has been included in all national immunization programmes within the region. In China, however, which has the largest number of HB carriers in the world, parents have to pay for the vaccine, while other EPI antigens are supplied free of charge. As a result, coverage in large



Children in the Western Pacific Region are at high risk of hepatitis B infection.

Photo: UNICEF/John Isaac (93-BOU0627)

cities tends to be high (up to 90%) but the take-up in rural areas is much lower (from 15% to 20%). The Chinese Government is now planning to integrate HB vaccine into the EPI throughout China.

Elsewhere, in South-East Asia, Maldives, Thailand, and Indonesia use HB vaccine within the EPI. Bhutan is scheduled to start in 1996 (with assistance from the Danish Government) and Myanmar will do so once their own HB vaccine completes clinical trials.

In sub-Saharan Africa—where up to a sixth of the population are HBV carriers—only three countries (Botswana, the Gambia, and South Africa) use HB vaccine within the EPI. In this region primary liver cancer is today one of the main causes of cancer death in men—with most cases occurring around the age of 35, a period of high economic productivity and family responsibility.

In parts of Eastern Europe and the Asian Republics, between 5% and 15% of the population are HBV carriers and the incidence of acute hepatitis B and chronic liver disease is very high. While some countries have received donor funding for the purchase of HB vaccine (Albania, Bulgaria, Romania), the countries of the former USSR have not.

Meanwhile, in the Americas, the United States, Canada, St Kitts and Nevis, and Cuba have included HB vaccine in national immunization programmes. In Brazil, where HB immunization is provided in the Amazon region, the Government has decided to make this available countrywide.

The introduction of hepatitis B vaccine within the EPI has proved to be a sobering experience for both governments and public health experts. If donor support for purchase of HB vaccine cannot be mustered today for the countries in greatest need, will the next generation of vaccines—against Hib, meningitis, pneumococcal disease, or diarrhoeal diseases, for example—necessarily fare any better?

Hepatitis B vaccines

The first vaccine against hepatitis B, an inactivated vaccine derived from the plasma of HBV-positive donors, has an outstanding record of safety and effectiveness and has been used to immunize more than 200 million people. But the vaccine, the first vaccine against cancer, had two major disadvantages from the outset—both of which continue to dog its widespread acceptance and use. The introduction of the vaccine coincided with the onset of the AIDS epidemic in the early 1980s and initially there were fears that the new plasma-derived vaccine might be capable of transmitting the disease. By the time it was proved conclusively that the vaccine could not transmit HIV the damage had already been done. Even today many individuals and governments remain unconvinced and refuse to use this vaccine.

The second disadvantage has always been the cost—a concern that remains today despite a dramatic drop in price from US\$ 50 for three doses in 1982 to about US\$ 1.50 today. The problem is that—even at today's price—a course of hepatitis B vaccine still costs one and a half times as much as the total cost of the existing EPI vaccines combined (BCG, measles, 3 doses of DTP, and 4 doses of polio vaccine).

An alternative vaccine became available for use in 1986—a genetically engineered vaccine which was the first to be produced using this kind of technology. It is equally safe and effective as the plasma-derived alternative and can be produced in unlimited quantities through fermentation in yeast or mammalian cell culture. But this vaccine is even more expensive—at US\$ 3.30 or more for three doses in developing countries, over three times the total cost of the six EPI vaccines.

As the two major producers of hepatitis B vaccine in Europe and the United States switched to the new recombinant vaccine, manufacture of plasma-derived vaccines shifted to Asia. Competition from Asian manufacturers was a major reason for the dramatic fall in price of this vaccine—making it affordable for the first time in many developing countries. This shift was accelerated by the work of the International Task Force on Hepatitis B Immunization—a group of

The introduction of hepatitis B vaccine within the EPI has proved to be a sobering experience for both governments and public health experts.

experts from both industrialized and developing countries—which lobbied for the introduction of hepatitis B vaccine and helped create mass markets for it.

The Republic of Korea is the largest commercial producer of plasma-derived vaccines and China now produces 55 million doses of vaccine a year for its national immunization programme. Elsewhere, Viet Nam, Myanmar, India, and Mongolia have either started or are on line to produce their own plasma-derived vaccines.

DNA recombinant vaccines are currently produced in Belgium, Cuba, France, Israel, Japan, the Republic of Korea, and the USA.

Yellow fever

Yellow fever, an untreatable viral haemorrhagic disease with a high fatality rate, is a re-emerging disease with the potential for explosive epidemics. In the latest outbreak in Peru in 1995 there were 440 cases and 169 deaths over a six-month period. Today there are fears that the disease could surface among the poorest populations of the teeming megacities of Latin America or tropical Africa.

From the 1950s to the 1970s the disease—transmitted by mosquitoes—was kept at bay by mass vaccination and widespread vector control. Today yellow fever has come full circle. Urban poverty, overcrowding, and massive population movements coupled with poor immunization coverage and the abandonment or failure of vector control programmes have created the ideal conditions for explosive outbreaks in urban areas.

A safe and highly effective vaccine against yellow fever has been available since 1937. A single shot protects against the disease for at least 10 years, and probably for life. The problem is that many of the countries where yellow fever is endemic are among the poorest in the world. Of the 33 African countries at risk for yellow fever, more than two-thirds are classified by UNICEF as needing ongoing external support in obtaining vaccine. But as donors have shown scant interest in supporting the cost of yellow fever vaccine, these countries cannot afford to buy the vaccine—even at the UNICEF discounted price of US\$ 0.17 a dose. The cost of supplying the vaccine to the 21 million children born in these countries each year would be an estimated US\$ 4.6 million.

The Japanese International Cooperation Agency (JICA)—the strongest supporter of yellow fever immunization in Africa—has funded the purchase of yellow fever vaccine in several countries including Ghana, Nigeria, and Togo. JICA also sponsored inter-country training courses in Ghana in 1993, 1994, and 1995 on vaccine potency testing and the diagnosis of yellow fever. Meanwhile, the US Centers for Disease Control and Prevention, which is keen to promote improved surveillance for yellow fever as part of global efforts to monitor emerging infectious diseases, provided funding for a yellow fever laboratory training course in Kenya in 1995.

Immunization targets

Since 1988, WHO has recommended that in Africa yellow fever vaccine should be added to the existing list of EPI vaccines in high-risk countries—routinely immunizing all children at nine months, at the same time as measles immunization. The move was prompted by reports of the vulnerability of children in outbreaks of yellow fever in Africa as well as the high cost and disruption of mass immunization during epidemics. A 1993 cost-effectiveness study based on data from Nigeria showed that routine delivery of yellow fever vaccine in the EPI would be seven times as effective in reducing the number of cases and deaths as firefighting epidemics with emergency mass immunization.

In 1994 the Plan of Action for EPI in WHO's African Region set a new target for the control of yellow fever in children under five by the year 2000. To meet this, at-risk countries need to ensure immunization coverage every year of at least 80% of children under one. So far only one—Gambia, with 87% coverage in 1994—has come anywhere near meeting this target. Elsewhere, coverage ranges from 1% (Nigeria in 1993) to 51% (Burkina Faso in 1993).

Since 1990, a total of 16 countries have reported yellow fever vaccine coverage for one or more years. In a number of countries—notably Mali (down from 23% in 1992 to 0.2% in 1993) and Togo (down from 37% in 1992 to 14% in 1993) immunization coverage has slumped—in some cases due to the withdrawal of donor support. Vaccine coverage overall for the 33 countries at risk was only 11% in 1992 and down to 9% in 1994.

During the late 1980s WHO first began to receive reports of a sharp rise in the number of cases of yellow fever—most of them in Africa, with children increasingly affected and suffering the highest death rates. Between 1987 and 1991 there were more reports of yellow fever (18,735 cases and 4,522 deaths) than in any other five-year period since reporting began in 1948. But when under-reporting is taken into account, the true number of cases is estimated to be in excess of one million over this five-year period. After a drop in reported cases over the following two years (295 cases in 1992 and 393 cases in 1993) there was another steep rise in 1994 (1,313 cases).

In Gabon, the first ever reported outbreak of yellow fever occurred in 1994 in a remote mining camp in the forest. From there it spread to villages outside—a first step in the potential urbanization of the disease. A total of 30 cases were reported. In Ghana the same year there were 103 reports of yellow fever—44% of them in children under 15. In this outbreak, an emergency mass immunization campaign was launched to contain the spread of the disease. After an outbreak in Kenya, the Government announced plans to introduce yellow fever vaccine in the EPI of the districts involved. In Nigeria—one of the countries worst affected—there were 775 cases in an outbreak in Imo State in 1994. House-to-house surveillance in one community revealed that only 10% of cases were officially reported—with cases involving children least likely to be reported.

In the latest yellow fever outbreak in Liberia in 1995, WHO, governments, and international partners including Médecins sans Frontières launched an emergency immunization campaign aimed at immunizing over a million people. It was feared the disease could spread to neighbouring States including Côte d'Ivoire, Guinea, and Sierra Leone. Liberia has experienced large-scale population movements as a result of the civil war. Almost 150 cases of yellow fever were reported in the Liberia outbreak and six deaths (a lower death rate than usual).

In the Americas, yellow fever remains largely a forest disease affecting mostly forest workers. When the last urban epidemic occurred in Trinidad in 1954, the island was declared an emergency zone and international quarantine measures imposed—with disastrous consequences for the island economy.

Planning for epidemics

During recent routine inspections of global yellow fever vaccine production facilities, WHO has been assessing the overall production capacity for yellow fever vaccine in the event of the re-emergence of major urban epidemics—a possibility that is already exercising the minds of emergency health planners. Four manufacturers (Bio-Manguinhos in Brazil, the Pasteur Institute in Senegal, Pasteur-Mérieux in France, and Medeva-Evans in the UK) maintain a stockpile of vaccine and the total global production capacity is at least 270 million doses a year—enough to immunize 270 million people against the disease.

But what is worrying emergency health planners is whether the turnaround time for emergency vaccine delivery would be fast enough to curtail a major urban epidemic. Although manufacturers stockpile vaccine, most of it is stored in bulk and it would take some lead time to supply very large amounts. Even when the vaccine has been shipped, transported to distribution points, and administered, there will still be another ten-day delay before individuals produce sufficient antibodies to protect them against yellow fever. Throughout this time people remain at risk. Because of this, even a single case of yellow fever has to be taken very seriously as it could be the first sign of an explosive outbreak.



Children in developing countries often do not have access to vaccines that are widely available in the industrialized countries.

Photo: WHO-TDR/Lysiane Maurice

Vaccines available but not widely used in developing countries

Introduction

Some vaccines are widely available in the industrialized countries but less likely to be used in developing countries. One reason is the initial high cost of these vaccines. Another is the lack of data on the incidence and disease burden of vaccine-preventable diseases in developing countries. Without this, it is difficult to assess the cost-effectiveness of introducing new vaccines or to motivate policy-makers to introduce them.

A vaccine against Japanese encephalitis, for example, has been available for over 20 years and successfully used in Japan, but is still considered too expensive to be used in many of the worst affected countries. It is used on a limited scale in three countries but only in Thailand has it been added to the EPI schedule. Meanwhile, in the industrialized countries, where Hib conjugate vaccine has been available since 1990, it has led to a dramatic reduction in the incidence of Hib meningitis. But in the developing countries—where the bacterial infection accounts for an estimated 500,000 deaths from pneumonia and 50,000 from meningitis—the vaccine is not yet available because it is still considered too expensive.

Research is under way to try to lower the cost of Hib and Japanese encephalitis vaccines by modifying the vaccines or, in the case of Hib, by reducing the amount of antigen in the vaccine. Elsewhere, efforts to lower the cost of a new typhoid vaccine are being made through transferring the vaccine technology to a developing country manufacturer. Meanwhile China is now producing 20 million doses of another Japanese encephalitis vaccine at lower than world market cost for use within its own borders.

In developing countries there is a serious lack of data on the disease burden of some vaccine-preventable diseases.

In a number of developing countries, cost-effectiveness studies are under way to help determine whether new vaccines should be used universally or, in some cases, targeted to high-risk groups. They include studies on the use of vaccines against Hib, cholera, and typhoid. A survey is also being carried out to establish the incidence of rubella (German measles), the number of countries using this vaccine, and the impact of immunization on the incidence of congenital rubella. Although rubella vaccine has been on the market for 30 years, it has not been recommended in low income countries, especially where coverage for the EPI vaccines is low because low-level immunization in childhood could shift the incidence of the disease to older age groups—increasing the risk of congenital rubella syndrome in babies born to women infected during pregnancy.

Recent cost-effectiveness studies and other surveys have highlighted the serious lack of data on the disease burden of some vaccine-preventable diseases in developing countries. Without this information it is difficult to assess whether a vaccine would be cost-effective and almost impossible to convince cash-strapped governments or donors that they should provide funds to purchase new and more expensive vaccines.

At present, vaccine development is based on current market demand rather than epidemiological realities. Vaccines developed mainly for lucrative industrialized markets are allowed to filter down eventually to developing countries—provided the need is recognized and the price is right. But if the epidemiology of diseases was better charted in the developing countries, cost-effectiveness studies could be carried out before new vaccines are on the shelf. If a need was identified in developing countries from the outset—with the promise of a larger, though less profitable market—this would encourage manufacturers to adopt a multi-tiered pricing system tailored to a country's ability to pay. This would help avoid the lengthy delays that now take place before new vaccines reach those who need them in developing countries.

Anticipation—the missing element in the vaccine continuum

Roy Widdus, *Coordinator of the Children's Vaccine Initiative*, argues that the development and introduction of new vaccines could be speeded up and resources better targeted if a prior consensus was established on which are priority vaccines and how they would be used.

The development and introduction of new vaccines is a slow and expensive process. Everyone agrees that it should be faster and as responsive as possible to global public health needs. One of the problems is that decisions about research and development are being taken years, decades even, before a vaccine is expected to be in extensive use. Likewise, decisions on the sizing of a production plant often have to be taken years before manufacturers can expect to see any significant return on their investment. The whole system could be made more efficient and predictable with a little anticipation of which vaccines would be most useful for which diseases and how they would probably be used. However, the public health community has neglected its responsibilities in its partnership with industry.

An often-raised argument is that it is impossible to anticipate how a vaccine that does not yet exist would be used. While it is true that the final vaccine characteristics make a difference, the biggest determinants are the epidemiology of the disease and the potential convenience of the existing infrastructure. For pneumococcal pneumonia, for example, it is possible to state that, because of the age at which the disease most commonly occurs, the desired vaccine should be effective early in life (on the EPI schedule, for example) and would probably be used globally. This kind of guidance—which has never been provided by

the public health community—is needed across a wide range of vaccines, possibly 20-30 in late development.

It is also argued that anticipatory guidance would place a straitjacket on creative research and suppress innovation. However, if done intelligently, it should not. Anticipatory guidance must be regarded as a preliminary to vaccine development. There is a fine balance between providing something useful and vagueness, but in an era that calls for increasing accountability—even for research and development investments—it is only prudent to let those doing targeted research know what the target is.

The process of doing this anticipatory thinking would identify important gaps in the database — the measure of disease burden, for example. As a result, information gaps could be filled before the need for that information becomes critical—not in a reactive fashion that extends the decision-making and introduction processes.

Without anticipatory thinking and intelligent guidance on the likely use of future vaccines, resources will be wasted on projects that are not linked to real needs. With such guidance, priority vaccines could flow through the vaccine continuum from research and development to delivery, with minimal delays, and meet global needs earlier.

Haemophilus influenzae type b (Hib disease)

The disease

Haemophilus influenzae type b (Hib) is a leading cause of acute lower respiratory infection among young children—especially in developing countries. While it is difficult to assess the global burden of Hib disease, it is estimated that over 500,000 children a year die from Hib pneumonia.

Hib is also one of the leading causes of non-epidemic meningitis, which can lead to brain damage and acquired deafness. It is estimated that more than 50,000 children die from Hib meningitis every year. The disease affects mainly children under five (90% of all cases)—with peak incidence at 6-11 months. The overall case fatality rate ranges from under 5% in industrialized countries to 20%-50% in developing countries. Limited studies have shown the incidence of Hib meningitis to be highest in some developing countries—where it occurs at an earlier age—and among indigenous populations in the United States and Australia. The magnitude of the burden of disease in Asia and Eastern Europe is not known.

In England, Scandinavia, and the United States, the annual incidence rate of Hib meningitis among the under-fives prior to immunization with Hib vaccine was 20-40 cases in 100,000, and among Alaskan Inuit or Australian Aboriginal populations 150-450 in 100,000. Studies from The Gambia suggest that in Africa, Hib meningitis occurs in 300 out of 100,000 children under one, while the incidence of Hib pneumonia is much higher.

Hib disease is not reportable in developing countries, and surveys have been carried out in only a handful of developing countries so far. In addition, pneumonia and meningitis are frequently caused by other pathogens—*Streptococcus pneumoniae* and *Neisseria meningitidis*, for example. Correct diagnosis involves blood culture to confirm Hib pneumonia and a lumbar puncture followed by laboratory analysis to confirm Hib meningitis. But many hospitals in developing countries lack the facilities needed to carry out these analyses. Meanwhile, even in the best equipped hospitals and laboratories it is notoriously difficult to isolate the pathogen involved



A lumbar puncture and laboratory analysis is needed to confirm meningitis.

Photo: WHO/D. Henrioud

in cases of pneumonia. Only 10-15% of blood cultures from pneumonia patients prove positive. In addition, tests often prove negative due to earlier treatment with antibiotics. As a result, Hib disease is believed to be seriously under-reported.

Vaccine

In 1985, purified polysaccharide Hib vaccines first became available but they were not effective in the age group most at risk—children under 18 months. Since 1990, four new conjugate vaccines (linking a polysaccharide with a protein carrier) have been licensed for use in children from two months of age.

Today, three doses of Hib conjugate vaccine cost at least 15 times as much as the total cost of the original six EPI vaccines.

Hib vaccines are now available in most western industrialized countries. In Finland and Iceland, where the vaccine was introduced in 1992, the incidence of the disease fell dramatically and it has now almost been eliminated. Most other industrialized countries are now seeing equally dramatic reductions in disease incidence.

But will Hib vaccine work as well among children in developing countries? Will it be able to protect against Hib pneumonia, which is believed to be a more serious problem in developing countries? Studies have been carried out in western Gambia to determine to what extent the use of Hib vaccine can reduce the incidence of Hib pneumonia and meningitis among children. Initial results from trials carried out by the UK Medical Research Council (MRC), involving 42,000 children, indicate that the vaccine is effective in preventing Hib meningitis and pneumonia in a developing country.

If the Hib conjugate vaccine is found to be effective in developing countries, the next hurdle to be crossed will be the cost. The new vaccines are expensive to produce—and cost too much for routine use in developing countries. At today's prices in industrialized countries, three doses of Hib conjugate vaccine cost at least 15 times as much as the total cost—at UNICEF discounted prices—of the original six EPI vaccines. But that price could be expected to come down if there was a large market for Hib vaccine in developing countries. The combined DTP-Hib vaccine—which has the added advantage of not increasing the number of injections needed—comes with an even higher price tag. Production of the new vaccines in

developing countries could possibly help bring down costs but the technology transfer involved would be difficult and may be constrained by intellectual property rights.

Research is currently under way into the development of less expensive Hib vaccines or vaccine strategies. One approach—now being tested in animals—is a reduction in the amount of antigen in each of the three doses required, to see if the same level of efficacy can be achieved. A second approach—currently undergoing Phase 2 trials in Niger—involves the elimination of the first injection of Hib vaccine. The 200 children in the study are being given a Hib/tetanus toxoid conjugate vaccine in a two-dose schedule to coincide with the second and third injections of DTP vaccine. It is believed that the first dose of tetanus toxoid (in DTP) may have a priming effect equivalent to the first of three doses of Hib vaccine. The results of this study are expected in mid-1996. The third approach involves efforts to develop a synthetic polysaccharide which could then be linked with one of the currently used protein carriers. The polysaccharide is a chemically defined molecule located on the outer coating of the Hib bacterium. If an equally effective synthetic version could be developed it might help cut the cost of the vaccine.

Other possible options include maternal immunization during pregnancy to protect children during the first few months of life and a single dose of the vaccine for children at 12 months of age to help lower the Hib carrier rate, which appears to be higher in developing countries.

Meanwhile, hard data on the disease burden of Hib in developing countries and estimates of the cost-effectiveness of immunization strategies are needed. Without this information, cash-strapped governments and donors are unlikely to provide scarce resources to make Hib vaccines widely available to children in developing countries.

A wide-ranging study is now being carried out by the Children's Vaccine Initiative and WHO to determine whether Hib should be recommended for use in national immunization programmes in developing countries. It entails efforts to assess the disease burden of Hib in individual countries, as well as the effectiveness of existing

vaccines (both Hib conjugate and combined DTP-Hib vaccines) among children in developing countries. Also under scrutiny are the cost-effectiveness of adding Hib to EPI schedules, vaccine supply and quality issues, intellectual property rights, and joint manufacturing ventures, for example. The initial phase, due to be completed by mid-1997, is expected to set the stage for introducing Hib vaccine more widely, wherever appropriate.

Rubella (German measles)

The disease

Rubella (German measles) is a mild rash disease that affects mostly children. But if the disease is contracted by a woman during the three first months of pregnancy, the consequences for the developing foetus can be devastating. In up to 70% of cases the baby is born with permanent disabilities including blindness, deafness, brain damage, and heart defects. There is also a 50% increase in spontaneous abortions.

In developing countries it is estimated that every year about a quarter of a million babies are born with congenital rubella syndrome (CRS). In an epidemic year, there is likely to be a tenfold increase in the incidence of CRS in individual countries. Fatality rates are likely to be higher in developing countries, where health care systems cannot absorb the huge costs of treatment for conditions such as heart defects.

Rubella is not easy to diagnose because the symptoms are similar to those of other viral diseases. There is little data on the incidence of CRS in babies—especially in developing countries. However, in the absence of surveillance data, serological studies of levels of immunity among pregnant women give some idea of the level of risk. The highest rates of susceptibility to rubella have been found among island populations in Hawaii, Trinidad, and Jamaica where, prior to the introduction of vaccine, almost 50-60% of pregnant women had no immunity. Elsewhere in the Americas, the rates varied from 13% in Brazil to 40% in Panama; in Africa from 3% in South Africa and Nigeria to 25% in Kenya; in South-East Asia from 13% in India to 32% in Thailand; and in the Eastern Mediterranean region—the lowest figures—from 2-5% in Egypt and Kuwait to 15% in Morocco.



Women with no immunity to rubella are at risk when they reach childbearing age.

Photo: UNICEF/Giacomo Pirozzi (C-103)

Vaccine

A live attenuated rubella vaccine has been available since 1969. It is widely used in the industrialized world—although immunization schedules vary from one country to another. The vaccine is available as a single vaccine, in combination with measles vaccine (MR), or as a measles, mumps, and rubella combined vaccine (MMR).

In many industrialized countries, rubella vaccine is already included in routine infant immunization schedules (usually at fifteen months of age). In addition—or alternatively in a few countries—the vaccine is given to adolescent girls (as a booster or to catch adolescents who missed out on the vaccine in infancy and never contracted the disease) and to women of childbearing age with no immunity to the disease. This combined strategy—although expensive—is considered the speediest way to interrupt transmission of the disease while at the same time ensuring the protection of high-risk groups.

A number of developing countries have introduced monovalent (single antigen) rubella vaccine or rubella combination vaccines within their EPI, but the impact on the incidence of congenital rubella is not yet known as few countries can provide surveillance data.

In Oman, over 1,500 cases of rubella and 60 cases of congenital rubella syndrome occurred during an epidemic between 1992 and 1994—one of the largest outbreaks ever reported from a developing country. In response, the Ministry of Health launched a measles-rubella vaccine campaign in March 1994—targeting all children between 15 months and 17 years—and added MR vaccine to the routine immunization schedule. As well as providing protection against rubella, the MR vaccine provides a booster shot for measles vaccine—a follow-up to the initial dose at nine months of age.

In other developing countries, selective immunization strategies—targeting high-risk groups of females rather than infants of both sexes—are often adopted mainly on grounds of feasibility and cost. The problem is that unless high levels of immunization coverage can be guaranteed, the introduction of rubella vaccine in infancy may actually make matters worse. The danger is that low-level immunization in infancy without also targeting high-risk groups can cause a shift in the incidence of the disease to older age groups—heightening the risks for pregnant women.



In some countries, rubella vaccine is given to adolescent girls with no immunity to the disease.

Photo: UNICEF (C-79)

The Global Programme for Vaccines and Immunization is carrying out a review of rubella and the use of rubella vaccine in developing countries and looking into ways of assessing the disease burden of congenital rubella syndrome. Guidelines on the use of rubella vaccine and the importance of surveillance for congenital rubella are to be issued later this year. In the meantime developing countries are being advised to adopt rubella immunization strategies tailored to their ability to deliver the vaccine. Universal childhood immunization against rubella is recommended only if very high coverage—above 80%—can be assured and immunization of women of childbearing age is introduced at the same time. Otherwise, the preferred strategy is selective immunization of high-risk groups.

Chickenpox (varicella-zoster virus)

Chickenpox is a common childhood disease—affecting millions of children a year. Although the disease is usually mild in otherwise healthy children, it can be serious when contracted by older children or adults. In the United States a varicella vaccine has recently been added to childhood immunization schedules. Why?

The US Advisory Committee on Immunization Practices which made the recommendation based its 1995 decision largely on grounds of cost-effectiveness. Chickenpox is estimated to cost about US\$ 400 million a year in the United States—mainly in working days lost by parents with sick children. The new immunization programme is expected to cost less than a fifth of the money it will save.

A live attenuated varicella vaccine (Oka) developed in Japan in the early 70s is licensed for use in healthy children in Japan, and in several other countries for use in immunodeficient children, for whom the disease can be serious. The American vaccine (VARIVAX) was licensed in March 1995. It is given to children from 1 to 12 years old as a single injection. Adolescents and adults who have never contracted chickenpox—and are at risk of a more severe form of the disease—will be offered a series of two injections.

Japanese encephalitis

The disease

Japanese encephalitis—an untreatable viral disease transmitted by mosquitos—occurs in major epidemics in parts of Asia and the Pacific region. The disease occurs largely in rural agricultural areas—wherever mosquitos co-exist with pigs, wading birds or ducks that are carriers of the virus. But it can also occur on the outskirts of large cities. Rapid economic development in the Pacific Rim countries has greatly increased exposure to the virus. The number of cases can vary from 10,000 to 50,000 a year and the mortality rate is high—from 10% to 40%. In India, Nepal, and Sri Lanka there are an estimated 1,000 cases a year. Up to a third of survivors suffer severe neurological damage.

While efforts to control mosquitos by insecticide spraying have met with limited success, immunization of pigs was discovered to be an effective strategy in recent trials in Sri Lanka and Thailand.

Vaccine

An inactivated virus vaccine was developed in Japan over 20 years ago and has been successfully used there. The vaccine was licensed for use by travellers and military personnel in the United States in 1992 and is also used on a limited scale in India, Korea, and Taiwan. In only one country—Thailand, in 1995—has it been added to the EPI schedule. The vaccine is currently too expensive to be used extensively in many of the worst affected countries.

In China a live attenuated vaccine has now been developed. About 20 million doses a year are used to immunize children at the ages of one, two, and six. Although a case-control study has shown this vaccine to be highly effective, further studies are needed to evaluate its safety.

In the meantime, research is under way into the development of a safe and effective vaccine with longer-lasting immunity than the currently marketed inactivated vaccine. The aim is to produce an effective vaccine that is less expensive and can be more widely used. A recombinant candidate vaccine has been developed and found to be effective in mice. Efforts are now being made to increase the genetic stability of this vaccine by introducing further

Japanese encephalitis vaccine is still too expensive to be used in many of the worst affected countries.

mutations in the viral DNA. Meanwhile, progress has also been made in the development of a combined yellow fever/Japanese encephalitis vaccine.

Hepatitis A

The disease

Hepatitis A was once a universal infection of young children, but changes in sanitation and socioeconomic development have led to a profound change in the epidemiology of the disease over the past 50 years. Hepatitis A infection is asymptomatic in young children, and infection leads to lifelong immunity against clinical disease. However, over 80% of older children and adults who become infected develop classical symptoms of acute viral hepatitis, including jaundice, dark urine, extreme fatigue, loss of appetite, and abdominal tenderness. Although the disease is rarely fatal, it is very debilitating and leads to several weeks of work loss. However, there is no chronic carrier state, and no progression to chronic liver disease or liver cancer.

In the least developed countries most children are still infected during the first few years of life and hepatitis A is not yet a serious public health problem in those countries, except for travellers, military personnel, and other expatriates from industrialized countries. Middle and upper middle class children in rapidly developing countries often escape infection until older ages when they develop symptomatic infection. Outbreaks and sporadic cases of hepatitis A are now very common in rapidly developing countries in Asia, the Middle East, Latin America, and in transitional economies like Eastern and Central Europe and the CIS.

Children and young adults in industrialized countries now usually escape HAV infection, and remain susceptible to infection from travel to endemic areas or from exposure in foodborne or waterborne outbreaks. Hepatitis A also causes outbreaks in day care centres, institutions, among communities with lower levels of hygiene, including some ethnic sub-populations, and among drug users and homosexually active men.

Vaccine

Safe and effective vaccines against hepatitis A are now on the market. These are formalin-inactivated vaccines made in the same way as inactivated polio vaccine. Two or three doses are recommended, and protection is predicted to last for 10 to 20 years. Live attenuated vaccines are also available in China.

Hepatitis A vaccines are recommended and widely used by travelers from industrialized countries visiting developing countries, because hepatitis A is the most common vaccine-preventable disease in that group. There is much discussion on the use of this vaccine to control community-wide outbreaks of hepatitis A in industrialized countries, as well as its use in other high risk settings.

The least developed countries have less disease burden from hepatitis A, other health priorities involving greater morbidity and mortality, and severe financial constraints that would make routine use of HAV unlikely at this time. Countries with intermediate levels of sanitation have a great burden of disease from hepatitis A, and many have expressed interest in using the vaccine widely for children and adolescents. But the vaccine's high price tag—more than US \$20 per dose in Europe and North America—currently precludes its routine use in developing countries. Cost effectiveness analysis and work with manufacturers to determine an affordable price are essential before serious consideration can be given to mass public health use of the vaccine.

Cholera

The disease

Vibrio cholerae—one of the oldest scourges known to man—causes about 5.5 million cases of cholera every year and about 120,000 deaths. Over a fifth of those deaths occur among children under five and a quarter in children aged 5 to 14. Most cholera deaths occur in Africa and Asia. Without treatment (rehydration therapy and antibiotics) it is one of the most dangerous infectious diseases—with very rapid fluid loss leading to fatality rates as high as 40%. The disease is associated with poverty, poor sanitation, lack of hygiene and unsafe drinking water. It is spread by contaminated water or food and by person-to-person contact.



In 1994 there was an outbreak of cholera among refugees crowded into refugee camps in Zaire.

Photo: UNICEF/Betty Press (DO194-0288)

In 1991 there were more cases of cholera and more countries affected by the disease than in any other year on record. Both Latin America and Africa were hit by explosive epidemics. The first outbreak occurred in Peru and rapidly spread throughout South and Central America—sparing only seven countries. More than 4,000 people died. In the same year a major epidemic swept across Africa killing 14,000 people in over 20 countries.

Elsewhere, in India and Bangladesh the emergence of a new strain of *V. cholerae*—dubbed *V. cholerae* 0139 (Bengal)—was reported in late 1992 following an initial outbreak in Madras, India, followed by another among fishermen on remote islands in the Bay of Bengal. The new strain spread rapidly to China, Malaysia, Myanmar, Nepal, and Pakistan involving thousands of deaths—mainly among adults.

In 1994 there were large outbreaks of cholera in Guinea-Bissau, Somalia and among the large numbers of Rwandans crowded into refugee camps in Zaire. A year later an outbreak was reported in neighbouring Burundi. Elsewhere, cholera appeared in Italy and Eastern Europe with a 30-fold increase in cases between 1993 and 1994.

Although cholera is a reportable disease there is widespread reluctance by countries to report cases because of the possible impact on the economy. As a result, only about 10% of cholera cases are ever reported. Among the most reticent are countries with economies that are heavily dependant on tourism or food export markets. The 1991 outbreak of cholera in Peru, for example, had a major impact on the economy due to the collapse of the seafood industry.

In 1991, WHO established a Global Task Force on Cholera Control in an effort to strengthen the capacity of countries to prepare for and respond to increasing outbreaks of cholera. The Task Force is also monitoring reports of cholera strains resistant to the antibiotics recommended for the treatment of severely dehydrated cholera patients.

Vaccine

Until recently, the only available cholera vaccines were inactivated whole cell injectable vaccines which provided partial protection against cholera for only up to four months. The vaccines were used

by people travelling to areas where the disease is endemic but were never recommended by WHO for that purpose or for use in routine immunization programmes.

In Sweden, scientists have developed an oral vaccine that protects against the classical biotype *V. cholerae* 01 El Tor which emerged in the mid-60s. This vaccine—comprising killed bacteria and recombinant B subunit of cholera toxin—is already licensed in Sweden. The vaccine is freeze-dried and taken in water with the addition of buffer salts to counter the effect of stomach acids on the vaccine.

The vaccine was evaluated in large-scale Phase III trials in Bangladesh with a 3-year follow-up study completed in 1988. After 6 months, a 3-dose schedule of the vaccine provided 85% protection in all age groups (children aged two to adults). But from then onwards, the level of protection among children under five fell dramatically—dropping to zero within three years. By contrast, the overall protection rate in older age groups was 72% after three years.

Tests in Peru have shown that a two-dose schedule of the vaccine provided protection for six months against El Tor biotype in 85% of military recruits and among people with O blood group (associated in the earlier trials with low vaccine efficacy). The vaccine also proved to be effective after a modified two-dose schedule.

Meanwhile a bivalent killed whole cell vaccine has recently been developed—using the same method—which is designed to protect against both serogroup 01 and 0139 *V. cholerae* strains. This vaccine has been tested among volunteers in Sweden.

Another oral vaccine is now on the market in Switzerland which protects against the 01 strain of *V. cholerae*. This is a live single dose recombinant vaccine produced by the deletion of key genes encoding for toxin proteins. A field trial of this vaccine is under way in Indonesia. Meanwhile, efforts are continuing to develop a bivalent vaccine (against both 01 and 0139 strains) using the same recombinant methods. Trials of a candidate bivalent vaccine are under way among adult volunteers in the United States.

Vaccine or treatment?

The development of new vaccines against cholera raises immediate questions about their future use in developing countries. Would it be more cost-effective in high-risk countries to immunize the total population against cholera or to continue with the use of effective oral rehydration therapy and antibiotics to treat individual cases as they occur? Or should immunization be viewed as a complementary tool to fight the disease? Would immunization decrease efforts to improve sanitation—which could in turn lower the incidence of other diseases?

A new vaccine study now under way in Viet Nam will—it is hoped—provide some of the answers. The 4-year study will examine the cost-effectiveness of introducing a cholera vaccine in Viet Nam. The vaccine involved—a whole cell killed oral cholera vaccine comprising serogroups 01 and 0139 and based on Swedish technology—is being produced in Viet Nam for less than 10 cents a dose.

Meanwhile, the Global Programme for Vaccines and Immunization is working with the United Nations High Commissioner for Refugees (UNHCR) and NGOs to determine whether the oral killed vaccine should be used routinely in established refugee camps. Cholera is rife in refugee camps and emergency treatment can seriously disrupt routine health services. Studies in two established refugee camps will assess the potential value of using a cholera vaccine to prevent outbreaks among settled refugee populations. It will also look at the feasibility of administering a vaccine that requires a glassful of clean water to reconstitute each dose. Would it be as effective with less water? And could it be reconstituted in large amounts rather than in single doses? The answers to these and other questions should be available by early 1997.

Typhoid fever

The disease

Typhoid fever remains a serious problem in many developing countries. About 16 million cases occur throughout the world every year and 600,000 deaths. Most deaths occur in the 3-19 year age group. The disease is caused by *Salmonella typhi* and spread through contaminated food or water.

The misuse of antibiotics has led to increasing resistance to the drugs used to treat typhoid fever.

In developing countries the annual incidence of typhoid fever varies from 150 per 100,000 in South America to as high as 1,000 per 100,000 in some Asian countries. The disease can have a serious socioeconomic impact—keeping patients away from work for several weeks.

Although the disease can be treated with antibiotics, resistance to the recommended drugs is increasingly reported in many countries. In 1989, resistance to all three recommended “first line” drugs (Chloramphenicol, Ampicillin, and Co-Trimoxazole) was reported in Pakistan, India, China, and the Arabian Gulf. While alternative antibiotics (Quinolones and Cephalosporins) are now being used, there are reports from India and Pakistan of the need for increased dosages as well as early reports of resistance to Ciprofloxacin and Nalidixic acid.

Vaccine

Until recently the only available typhoid vaccine was inactivated whole cell vaccine given by injection—three injections one month apart followed by a booster dose 12 months later. Although this vaccine was very effective (80%) it was not often recommended for use in typhoid control programmes because it caused unwanted side-effects and required multiple doses. It was, however, used by people travelling to typhoid endemic areas.

Two new vaccines have now been developed and licensed. One is a live oral vaccine (Ty21a) developed in Switzerland and marketed there as Vivotif. It has been licensed in several countries. In a seven-year follow-up study of the vaccine in Chile it provided protection in 65% of school-age children. The vaccine is taken in two or three

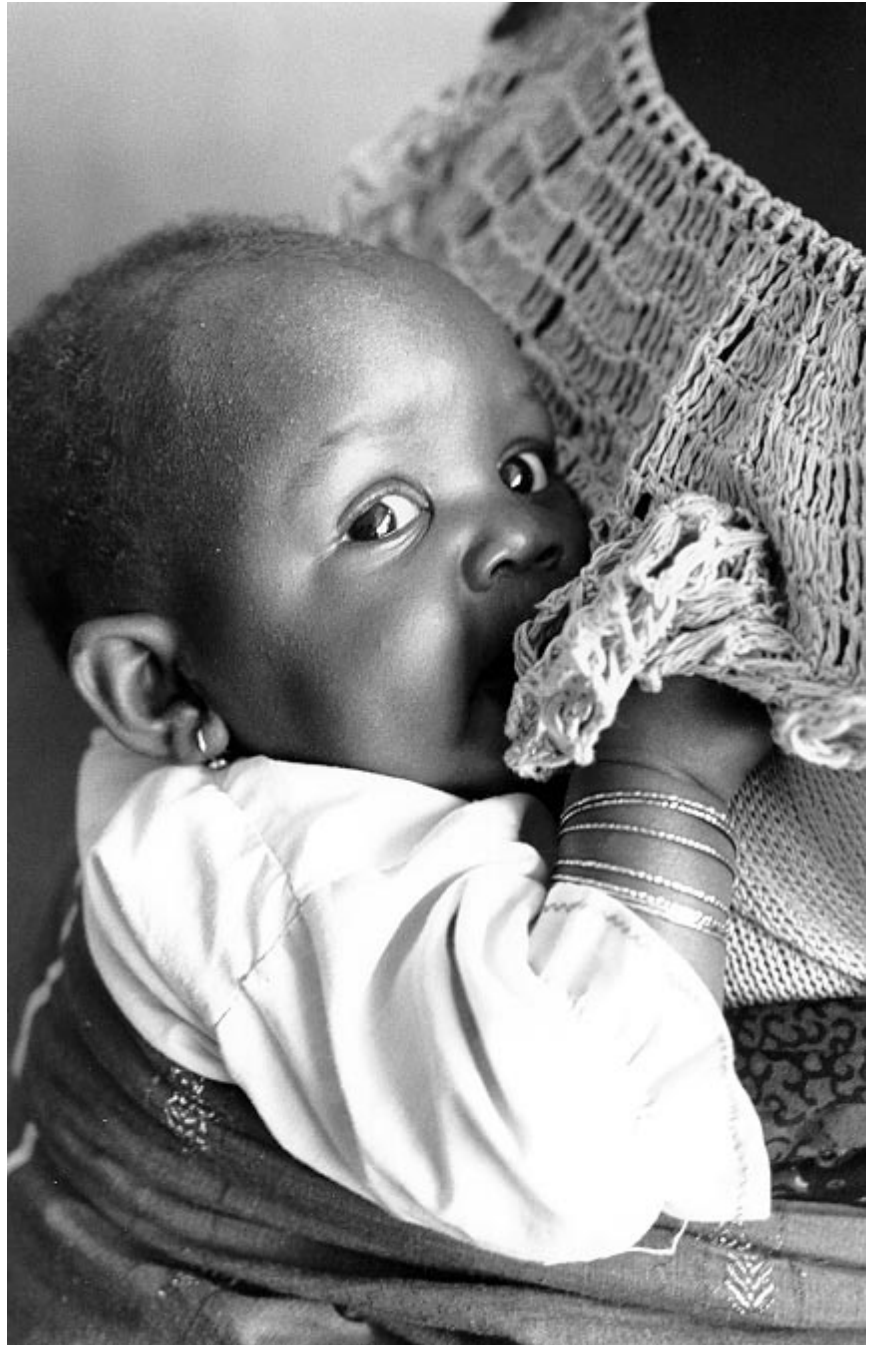
doses, each two days apart, and there is no evidence of interference when the vaccine is given at the same time as the oral live cholera vaccine.

An alternative injectable vaccine has also been developed, based on purified polysaccharide from *Salmonella typhi* freshly recovered from patients with typhoid fever. This single-dose vaccine has been tested in South Africa and in Nepal—providing up to 72% protection after two years and up to 55% protection after five years. It is now marketed in many European countries.

Like other pure polysaccharide vaccines it is not effective in children under two but this is not a high-risk group. When evaluated in children less than a year old it was found that the antibody response was low and lasted only two months. The vaccine—developed at the US National Institutes of Health (NIH)—is not patented and Viet Nam has now started to produce this vaccine for use within the country, following assistance from the NIH. A cost-effectiveness study is to be carried out on the introduction of this vaccine in Viet Nam and another study undertaken in Chile to determine whether the vaccine could be given with measles vaccine at 10-12 months of age.

Single-dose oral vaccines, produced by genetic engineering, are also under development. One candidate vaccine has been developed by scientists from the Baltimore-based Center for Vaccine Development in collaboration with vaccine manufacturers in the UK. This vaccine (CVD 908-Htra) produced promising results when tested in US volunteers.

Meanwhile, polysaccharide conjugate vaccines—aimed at obtaining a long-lasting immune response in infants—are also under development. These are based on a protein carrier linked to a polysaccharide.



Every four seconds a child dies from an acute respiratory infection, diarrhoeal disease, or malaria.

Photo: UNICEF/Maggie Murray-Lee (2975/88)

Key vaccines under development

Introduction

This section is a progress report on 10 new vaccines under development—a small proportion of the new vaccines against more than 60 different diseases listed in the latest Jordan Report, *Accelerated Development of New Vaccines 1995* (published by the US National Institutes of Health). They have been selected here because they include vaccines against some of the major killer diseases that affect children—acute respiratory infections, diarrhoeal diseases, and malaria. Together these diseases claim the lives of over 8 million children every year—one child death every four seconds.

In many cases the impetus for research has been a ready market in the industrialized countries—either because the disease exerts a heavy toll in these countries or, in the case of vaccines to prevent tropical diseases or diarrhoeal diseases, to exploit a lucrative market among travellers or military personnel. Ironically a vaccine against pneumococcal pneumonia and meningitis—which kill over a million children a year in developing countries—was developed largely to prevent the incidence of inner ear infections among children in the United States. In the case of HIV vaccine research, some manufacturers have now pulled out—deterred by the shrinking market in industrialized countries where the rate of infection appears to have slowed down, but also citing their fear of the political fallout from producing an expensive vaccine way beyond the means of developing countries where most infections now occur.

Meanwhile, vaccines are often licensed or allowed to reach a very advanced stage before they are tested extensively in developing countries. Hib vaccine, which has been on the market since 1990, has only recently been tested in developing countries to determine whether it is as effective as in the industrialized countries where it is

The initial cost of new vaccines is likely to be the biggest stumbling block to their immediate use in developing countries.

currently used. This results in the delayed introduction of vaccines, which is further compounded by the lack of data on the incidence and pattern of some diseases in developing countries. The epidemiology has often been extensively studied in the industrialized countries—but not extensively in developing countries.

Another common theme is the spiralling increase in resistance to the key drugs used to treat some diseases—pneumococcal pneumonia, shigella, and malaria, for example—underscoring the urgent need to develop new vaccines to prevent diseases that are in danger of becoming untreatable. Other diseases—although treatable—kill very rapidly once they reach a certain stage. Rotavirus, for example, can be inexpensively treated with oral rehydration therapy—but failure to treat the disease at the outset can lead to rapid death. A vaccine could prevent these deaths.

The initial cost of these newer vaccines is likely to be the biggest stumbling block to their immediate use in developing countries. In some cases—pneumococcal or meningococcal conjugate vaccines, for example—the technology used could not readily be transferred to developing-country manufacturers. The immediate priority is to develop a vaccine that works and then find ways of reducing the cost.

Pneumococcal disease

The disease

Every year in developing countries more than a million children under five die from pneumonia caused by *Streptococcus pneumoniae*. This form of bacterial pneumonia is the biggest killer among the acute respiratory infections—which together claim the lives of over four million children a year in the developing world. *S. pneumoniae* is also responsible for pneumococcal meningitis, which has a fatality rate about as high as other forms of meningitis and often leads to hearing loss or brain damage in children who survive.

It is notoriously difficult to determine the exact cause of pneumonia—especially in young children—even with the best laboratory facilities at hand. In most cases the pathogen involved is never identified. UNICEF and WHO have spearheaded an integrated approach to the treatment of children with the major life-threatening



It is notoriously difficult to determine the exact cause of pneumonia—even with the best laboratory facilities at hand.

Photo: WHO

In developing countries over 4 million children a year die from acute respiratory infections.

diseases—pneumonia, diarrhoea, malaria, measles, and malnutrition—which together account for 75% of all deaths in children under five.

While early treatment with antibiotics saves many lives, there is increasing evidence that the misuse of antibiotics has led to the appearance of drug-resistant strains of the bacteria in many countries. A four-year study in Pakistan, for example, revealed that over 95% of the pneumococci studied had reduced sensitivity to at least one antibiotic. While none were totally resistant to penicillin, 25% had reduced sensitivity to this antibiotic. More worryingly, almost 50% of the bacteria studied were found to be resistant to cotrimoxazole—the antibiotic of choice in Pakistan for treating acute respiratory infections. Elsewhere, in Saudi Arabia and Spain over 60% of *S. pneumoniae* were also found to be resistant to treatment with cotrimoxazole. These findings have intensified the search for new vaccines to prevent pneumococcal disease.

Vaccine

One of the major problems in developing a successful vaccine against *S. pneumoniae* is the large number of different serotypes involved. More than 83 serotypes of the bacterium are known to cause disease—although about 10 of these account for up to 70% of disease in young children. The frequency of the serotypes can vary from year to year, from one age group to another, and on a geographical basis as well.

Pneumococcal polysaccharide vaccines are available which protect against 23 of the known serotypes. But these are not effective in children under two—the age at which children are most vulnerable to the disease.

Much of the interest in pneumococcal vaccine development has been driven by the increasing incidence of *S. pneumoniae* inner ear infections (otitis media) among children in industrialized countries. However, new vaccines have been developed that incorporate *S. pneumoniae* serotypes responsible for pneumonia in developing countries. A number of candidate polysaccharide conjugate vaccines have now been developed and these are due to enter Phase II and III trials involving children in two industrialized countries. Trials of the vaccines in developing countries begin this year. The new

vaccines are designed to protect against about ten of the most frequent serotypes which account for up to 70% of cases in children. If successful, it is estimated these vaccines could reduce child deaths from pneumococcal pneumonia by up to 25%—saving over 250,000 lives a year.

But these conjugate vaccines are likely to prove expensive to produce as each of the antigens has to be conjugated separately—producing what amounts to a combined vaccine against up to 10 different antigens. To get round this problem, research is also under way to identify a common antigen that is shared by as many of the 83 serotypes as possible. Three proteins appear to be promising and these are being tested on mice. A common antigen—once isolated—could be produced in bulk through recombinant technology and would not need to be conjugated.

Another possible option is maternal immunization during pregnancy. Once the current tests with conjugate vaccines have revealed the level of antibodies needed to protect a child against pneumococcal pneumonia, it might be possible to develop a vaccine that could provide that level of protection via the placenta and breast milk.

This would be especially important in protecting infants during the first few months of life.

Meningococcal meningitis

The disease

Meningococcal meningitis is a severe bacterial disease that causes painful inflammation of the membranes covering the brain and spinal cord. It can lead to rapid death and permanent brain damage—especially in young children.

The disease—caused by the bacterium *Neisseria meningitidis*—can occur in explosive epidemics—especially in the so-called “meningitis belt” in sub-Saharan Africa, from Ethiopia in the east to Senegal in the west. However, the disease is now reported to be spreading further afield in Africa—affecting countries outside the meningitis belt—possibly as a result of climate change and increasing population movements. Today, an estimated 357 million people are at risk in Africa, where case fatality rates range from 8% to 20%. In the



Children and adolescents in sub-Saharan Africa are vulnerable to epidemics of meningococcal meningitis.

Photo: WHO/D. Henrioud

United States, the disease is now the second most common cause of bacterial meningitis—causing up to 4,000 cases a year, with a mortality rate of 5-15%.

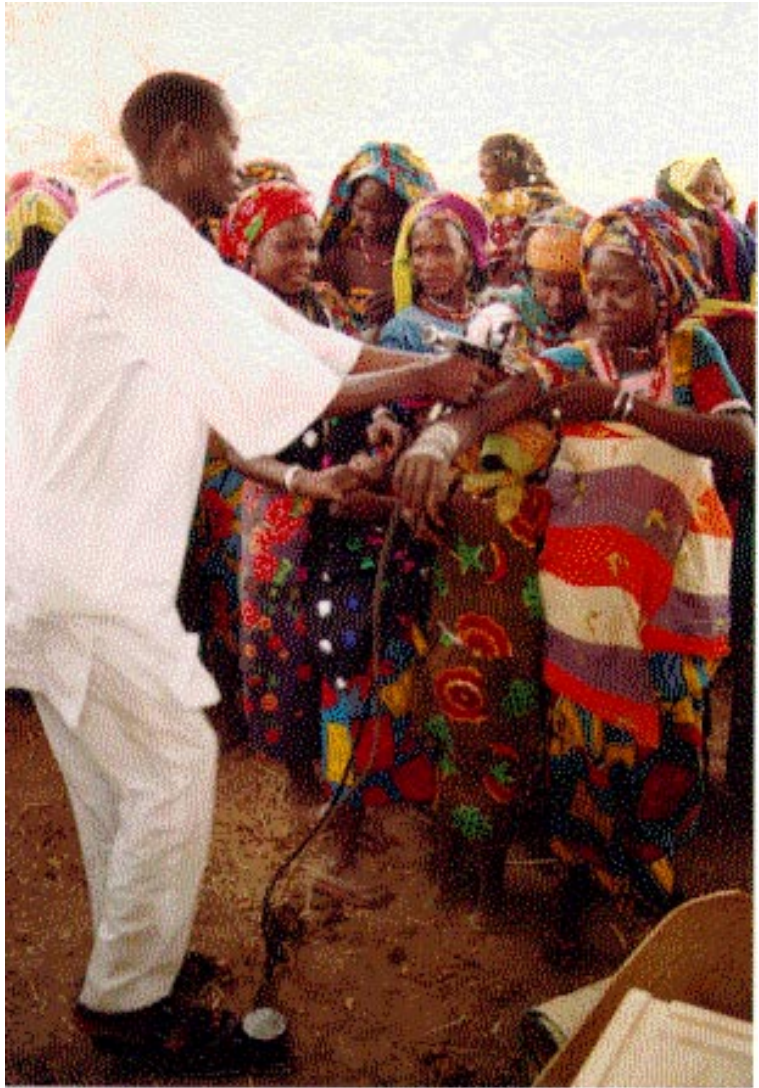
Meningococcal meningitis is endemic in countries throughout the world. Without taking epidemics into account, the disease accounts for about 300,000 cases of bacterial meningitis a year and over 30,000 deaths. It is more likely to occur in conditions of overcrowding and poor sanitation. In developing countries the disease is not always distinguished from other forms of bacterial meningitis (caused by *Haemophilus influenzae* or *Streptococcus pneumoniae*, for example) due to the lack of both laboratory facilities and the skills needed for analysis.

In a major epidemic in Ethiopia in 1989, there were over 41,000 cases of meningococcal meningitis. In Sudan a year earlier, over 32,000 cases were reported. During the 1980s a wave of epidemics also hit India, Nepal, Chile, and Cuba. In the most recent outbreaks in 1996, over 22,000 cases and almost 4,000 deaths have been reported in northern Nigeria, over 8,000 cases and over 700 deaths in Burkina Faso, almost 5,000 cases and over 500 deaths in Niger, according to recent estimates. Smaller outbreaks have also been reported in Benin, the Central African Republic, Chad, and Mali.

Vaccine

Meningococcal polysaccharide vaccines were developed in the 1960s in response to epidemics of meningitis among young military recruits in the United States. These vaccines are effective against *Neisseria meningitidis* groups A and C—the major cause of epidemics in sub-Saharan Africa—but, like the first generation Hib vaccines, they are not very effective among the age group most at risk, children under two. Because of this they have never been included in routine immunization programmes—even in the industrialized countries. However, the vaccines are useful in mass campaigns to help bring major epidemics under control. In April-May 1995, for example, the vaccine was used to immunize all children—including infants under two—during an outbreak of meningitis in Niger.

Meningococcal meningitis can occur in explosive epidemics.



In 1996, mass immunization campaigns were used to control a major epidemic of meningitis in northern Nigeria.

Photo: WHO/Maria Santamaria

In response to the urgent need for new vaccines to protect young children, three candidate polysaccharide conjugate vaccines have now been developed. These are to be tested in Phase II field trials in Niamey, Niger, and the results will be available in 1997.

Meanwhile the search goes on for a vaccine to protect against *Neisseria meningitidis* type B—the pathogen responsible for most cases of meningococcal meningitis outside Africa. Earlier efforts to develop a pure polysaccharide vaccine against this bacterium proved unsuccessful due to the low immunogenicity of the polysaccharide. Another drawback is its close resemblance to brain tissue—raising the spectre of the development of an auto-immune disease. In order to circumvent these problems, new vaccines are being developed. In these vaccines the polysaccharide is modified (to prevent it cross-reacting with brain tissue) before being conjugated with a protein carrier. Although these vaccines produced a satisfactory immune response in animals, there is still some concern about their use in humans.

An outer membrane type B vaccine has been developed and licensed for use in Cuba and is used in Brazil. This vaccine proved to be effective in 80% of medical students tested at the University of Cuba and protective in 72% of children aged four. However, the efficacy rate plummeted to below 50% at the age of two and was almost zero in younger children. Other candidate vaccines based on outer membrane protein have been developed in Norway and the United States—providing respectively 56% and 50% protective efficacy.

Respiratory syncytial virus (RSV)

The disease

Respiratory syncytial virus (RSV) is estimated to cause about 900,000 deaths a year—mainly in infants and young children. The virus is highly contagious and most children throughout the world are infected during the first two years of life. Previous infection does not protect against subsequent reinfection with the virus. In the industrialized countries respiratory syncytial virus is the largest single cause of lower respiratory tract infections in young infants. In the United States alone the disease is responsible for about 91,000 hospitalizations a year and 4,500 deaths—mainly in children under one.

The epidemiology of the disease has been little studied in developing countries and there is a lack of data on the incidence of the disease. A recent three-year study of hospitalized children in the Gambia found that there were epidemics of RSV in each consecutive year at the end of the wet season—with the most severe cases occurring in children under one. Other limited studies in developing countries have shown that RSV is often associated with bacterial infections such as *Streptococcus pneumoniae* and *Haemophilus influenzae* b (Hib).

In order to improve global surveillance of respiratory viruses, including RSV, WHO has developed a rapid diagnostic test. This technology has now been transferred to developing countries where it is used in 20 collaborating laboratories.

Vaccine

Vaccine development has been dogged by adverse reactions to the first candidate vaccine—a formalin-inactivated vaccine—tested in children during the late 1960s. For reasons not yet fully understood, when children injected with this vaccine were exposed to RSV several years later, they developed an abnormally severe form of the disease. Since then vaccine testing has been largely restricted to animal models and to a lesser extent to sero-positive adults and children.

A variety of vaccine approaches is currently being tested. A live attenuated vaccine based on a bovine strain of RSV has been developed at the US National Institutes of Health (NIH). This is currently undergoing Phase I and II tests in US volunteers and the results will be available this year.

Another approach is the culture at low temperatures (“cold passage”) of RSV. This process results in a shift in the genetic material of the virus and an inability to cause disease. The difficulty lies in ensuring that the attenuated virus provides the right level of protective antigens.

A third approach is the development of subunit vaccines consisting of purified viral protein. This vaccine was tested in more than 150 seropositive high-risk children in the United States and found to be



Immunization of women of childbearing age may be used to protect children during the first few months of life.

Photo: UNICEF/Roger Lemoyne (D0195-0881)

safe. However, the studies were too small to evaluate the efficacy of the vaccine. Studies are currently under way on the use of different adjuvants to boost the effectiveness of the vaccine.

Another possible strategy is the use of a subunit vaccine to immunize women of childbearing age and protect children during the first year of life when they are most vulnerable to RSV. The aim is to induce the passive transfer of maternal antibodies via the placenta and later in breast milk. Phase I studies involving US women who had just given birth were completed in 1993. They showed the vaccine to be highly immunogenic with only minimal side-effects.

The impetus for vaccine development has been largely the US market with its potential target of 4 million children born each year. The candidate vaccines will also be tested in developing countries to see if they are protective. In the meantime epidemiological studies are needed to assess the disease burden of RSV in developing countries. Without that data it will prove difficult, once a vaccine becomes available, to convince governments that it should be added to EPI schedules.

Rotavirus

The disease

Rotavirus is the leading cause of severe dehydrating diarrhoea in young children throughout the world—infecting nearly every child in the first few years of life. In developing countries it accounts for 870,000 deaths a year in children under five—about a quarter of all deaths from diarrhoeal diseases. In the United States, where there are up to 40 deaths from rotavirus every year, the disease is estimated to cost over US\$ 1 billion a year (including US\$ 500 million in medical costs).

Although rotavirus accounts for less than 10% of all cases of diarrhoea in young children in developing countries, it is particularly severe—resulting in a third of all hospital admissions for diarrhoea and a very high death toll. Since the disease affects children in both industrialized and developing countries, improvements in hygiene and sanitation have only a limited effect on the course of disease.

Rotavirus diarrhoea can be treated with rehydration therapy, but the best strategy would be to prevent the disease through immunization.

Vaccine

A variety of approaches is being used to develop a vaccine. The most advanced are live oral vaccines developed by scientists at the US National Institutes of Health and Wistar Institute, in collaboration with US vaccine manufacturers. These are “re-assortant” vaccines—so-called because they are based on an animal strain of rotavirus (from a monkey or cow) that has been modified by the substitution of gene segments from human strains of the virus. These genes encode protective antigens from the outer shell of the virus. The vaccines include genes from the four serotypes of rotavirus most commonly found—all of which occur in children. They are produced in tissue culture.

In two multi-centre trials in the United States, each involving over 1,000 children from 4 to 26 weeks old, the vaccine produced moderate protection (57%) against rotavirus diarrhoea but much higher protection (87%) against the more severe form of the disease. The vaccine is now being tested in children in Venezuela to see if it can dramatically reduce the number of hospital admissions and deaths in addition to reducing the overall incidence of rotavirus diarrhoea.

The first vaccine is expected to be licensed in the near future. But for use where? The involvement of US vaccine manufacturers in the research and development of this vaccine highlights the interest in the US and possibly European markets, where the vaccine is likely to be initially expensive.

One major advantage is that rotavirus vaccine could easily be included in the EPI schedule in developing countries without incurring any major additional delivery costs. The vaccine is given orally in a three-dose schedule (possibly more in some developing countries) and there is no evidence that it interferes with the effectiveness of other vaccines—such as OPV—when given at the same time.

In developing countries rotavirus diarrhoea kills 870,000 children under five every year.

However, since reassortant vaccines have never been 100% effective, the search for possible alternative vaccines is continuing. They include vaccines that protect against other human rotavirus strains, single-dose vaccines (involving microencapsulation of live or killed rotavirus), as well as other vaccine approaches such as baculovirus-expressed virus-like particles, and DNA vaccines. Elsewhere, researchers are studying the possibility of producing cheaper “edible” rotavirus vaccines through the development of transgenic plants.

Shigella (dysentery)

The disease

Of the estimated 3.5 million children who die from diarrhoeal diseases each year in developing countries almost 600,000 die from shigella (dysentery). The disease is endemic throughout the world and can occur in major epidemics in developing countries. Refugee populations and children suffering from malnutrition are among the most severely and most frequently affected.

For several months during 1994 shigella dysentery was the leading cause of death in the Rwandan refugee camps in Burundi, Tanzania, and Zaire. Elsewhere in Africa, 11 countries were hit by epidemics of the disease in 1994. Epidemic and endemic dysentery also occur in Asia. Meanwhile in the United States 32,000 cases of dysentery were reported in 1993—a 35% increase over the previous year.

There is widespread concern among public health experts at reports of the incidence of drug-resistant strains of shigella bacteria in developing countries—making it increasingly difficult to bring epidemics under control. In developing countries governments often cannot afford to import alternative, more expensive antibiotics when standard low-cost drugs become ineffective. In the Goma refugee camps in Zaire, the US Army stepped in to provide an alternative antibiotic—one of the new quinolones group of drugs—when standard treatment with nalidixic acid became ineffective. But these drugs are outside the price range of most developing countries. As treatment of dysentery becomes more difficult, efforts to develop vaccines to prevent the disease are increasingly important.

Vaccine

There are 4 clinically important species of shigellae but most cases of life-threatening disease are caused by just 2 species—*S. dysenteriae* and *S. flexneri*—and by 5 serotypes. *S. sonnei* is the leading cause of endemic disease in industrialized countries. In 1993 it was responsible for over 90% of cases of dysentery reported in the United States.

Several promising candidate shigella vaccines have been developed against individual or multiple species of shigellae. They include both injectable and oral vaccines. Injectable polysaccharide conjugate vaccines have been developed at the US National Institutes of Health (NIH) in collaboration with the Walter Reed Army Institute of Research (WRAIR). One candidate vaccine is polyvalent—comprising polysaccharides from *S. dysenteriae*, *S. flexneri*, and *S. sonnei* linked either to a recombinant protein or tetanus toxoid carrier. This vaccine has been evaluated for safety and immunogenicity in volunteers in Israel and will soon enter Phase III trials. Meanwhile a monovalent vaccine developed at WRAIR—comprising *S. sonnei* polysaccharide linked to a recombinant protein—protected over 40% of volunteers during an outbreak of *S. sonnei* in Israel. Another injectable ribosome-based *S. sonnei* candidate vaccine produced promising results when tested in mice.

Several live, oral vaccines are now being developed, using genetic engineering techniques, by scientists at the Pasteur Institute in France, the University of Maryland Center for Vaccine Development in the United States, and the Karolinska Institute in Sweden. The vaccines are based on the deletion of key genes to remove the pathogenic effects of the bacteria while leaving the genes encoding for protective antigens intact. These candidate vaccines, based on *S. flexneri* and *S. dysenteriae*, are now to be tested in Phase I trials. Elsewhere, scientists from WRAIR have developed a recombinant vaccine in which genes encoding for protective antigens from *S. flexneri* are inserted into a vector (*E. coli*). This oral candidate vaccine is now being evaluated in Phase II trials in Israel.

If oral vaccines against shigella are successful, it may be possible to eventually develop a combined oral vaccine that would protect against rotavirus, shigella, enterotoxigenic *Escherichia coli* (ETEC), cholera, and typhoid.

Refugees and malnourished children are most vulnerable to shigella dysentery.

ETEC (enterotoxigenic *Escherichia coli*)

The disease

In developing countries diarrhoeal disease caused by ETEC (enterotoxigenic *Escherichia coli*) is responsible for an estimated 300,000-700,000 deaths a year among children under five—almost 10-20% of the global total of deaths from diarrhoeal disease in this age group. The disease is poorly reported and detailed surveillance data are difficult to obtain.

ETEC is the most common cause of diarrhoea in developing countries—accounting for an estimated 400 million cases a year—although many episodes are relatively mild. The pathogen is also the leading cause of travellers' diarrhoea—accounting for at least 8 million cases among travellers from the United States every year. Like cholera, it can undermine fragile economies in countries that rely heavily on revenues from tourism.

In common with other diarrhoeal diseases, ETEC is associated with poor sanitation and lack of hygiene. It is spread by contaminated food and water as well as by person-to-person contact. Treatment involves oral rehydration therapy.

Vaccine

A promising candidate ETEC vaccine is now under development in Sweden. It is an oral recombinant vaccine based on antigens that prevent the bacteria from attaching to the intestines. Phase I trials of the vaccine in adult volunteers in Bangladesh have now been completed and Phase II trials are being carried out this year involving children in Egypt and Peru. The vaccine is lyophilized (freeze-dried) and taken in water in 2-3 doses. A successful ETEC vaccine might eventually be given with existing cholera vaccine in the same glass of water.

Elsewhere, a live attenuated ETEC vaccine developed at the University of Maryland American Center for Vaccine Development proved effective when tested in volunteers.

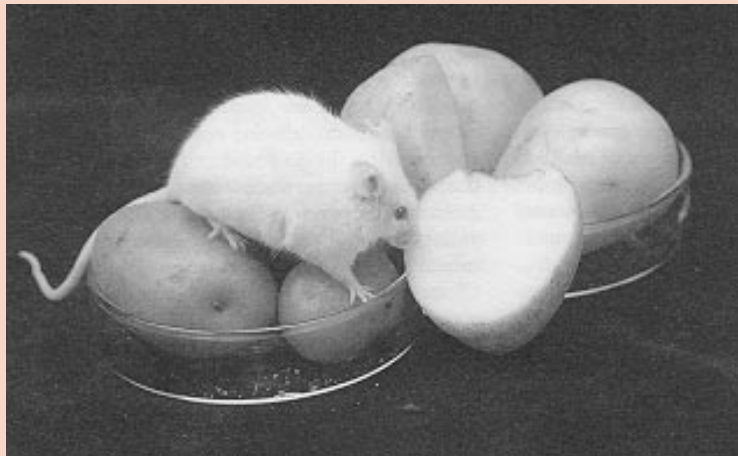
Edible vaccines

It sounds like science fiction but it isn't. Instead of a painful jab, some vaccines may one day be delivered through the food we eat. Researchers in the United States are growing potatoes genetically engineered to contain edible vaccines.

Instead of cultivating genetic material from viruses and bacteria in yeast or other cells the key genes are inserted into edible plants where they replicate—producing vaccines at a fraction of the cost.

And they appear to work—in animals at least. Mice have been successfully immunized against cholera/enterotoxigenic *E. coli* after they were fed raw potato containing a candidate vaccine. Meanwhile potatoes containing Hepatitis B vaccine produced what scientists describe as a “priming” effect in mice—resulting in a stronger immune response to low level immunization with commercial hepatitis B vaccine.

Now researchers at the Boyce Thompson Institute for Plant Research in New York are trying to develop a potato containing a candidate cholera vaccine and a vaccine against hepatitis B. Next they plan to genetically engineer a banana—a universal children's favourite—to provide unlimited quantities of low-cost hepatitis B or other vaccines for use in developing countries. Another possible target plant for vaccine delivery is soya—which could then be processed into a soya milk drink for children.



Mice have been successfully immunized by eating raw potato genetically engineered to produce vaccine.

Photo: Albert B. Alkek Institute

Within four years the research team hope to develop a prototype edible vaccine against hepatitis B that can be produced and delivered in developing countries for no more than ten cents a dose (a fifth of the current price of plasma-derived hepatitis B vaccine).

However, some scientists remain sceptical about the feasibility of developing an oral hepatitis B vaccine, since the hepatitis B virus surface antigen (HBsAg) is rapidly degraded in the digestive tract. Others are concerned about the problems involved in regulating the production of plants containing vaccines. Would they be regulated as food or biologicals? How could the dosage be controlled and consistency measured? Could people over-dose on vaccines? Would this approach lead to a two-tier system for developing and developed countries? And—the crunch question—would the public ever accept it? Public reservations about recent innovations such as irradiation of food, for example, suggest they may not.

HIV/AIDS

The disease

HIV infection continues to spread at an alarming rate. During 1994, 2.5 million people throughout the world were newly infected with HIV—about 5 new infections a minute. By the end of that year an estimated 24 million people had been infected with HIV since the start of the pandemic. Of those, 6 million had developed AIDS.

About 1.5 million babies have been infected with the virus so far—either before or during birth. Babies often go on to develop AIDS at a very early age and die within the first five years of life. By the year 2000 it is estimated that 30-40 million people will have been infected—including 5 million children—and 10 million will have developed AIDS.

In 1993, World Bank economists estimated that in developing countries—which account for 90% of all cases—the amount spent on health care for AIDS patients would triple to over US\$ 1 billion by the year 2000. AIDS-related disability and death affect mainly adults in their economically productive years and have a devastating social and economic impact in developing countries.

While the countries of central and eastern Africa are still the worst affected—with an estimated 11 million people infected so far—the two regions with the largest upsurge in cases in 1994 were south and south-east Asia where the number of HIV infections among adults leapt by 50% from 2 to 3 million. Together these two regions accounted for about 40% of all new infections during 1994. Elsewhere, the worst affected regions are Latin America and the Caribbean (2 million HIV infections so far) and North America (1 million HIV infections). Overall, more than 20 million adults are today living with HIV infection or AIDS. Almost two-thirds of them are men but the balance is expected to shift by the year 2000 as women are increasingly affected.

The ability of HIV to disable the human immune system has so far confounded efforts to develop an effective drug or vaccine. In the meantime, health education programmes throughout the world continue to help prevent the spread of HIV through promoting changes in sexual behaviour—especially the use of condoms—and safe injection practices. Preventive health education campaigns are believed



A young Malawian girl orphaned by AIDS.

Photo: UNICEF/Cindy Andrew (93-BOU0499)

to have been at least partly responsible for slowing down the rate of new infections among pregnant women in southern Zaire, in parts of Uganda, and among military recruits in northern Thailand. Elsewhere in the industrialized countries similar trends have been reported in Australia and in some groups in northern Europe, the United States, and Canada.

Meanwhile, a study carried out for WHO's Global Programme on Aids and the World Bank in the early 1990s estimated that comprehensive health education programmes to prevent AIDS and other sexually transmitted diseases would cost US\$ 1.5 billion to US\$ 2.9 billion a year for all developing countries—ten to fifteen times what they now spend—and would prevent about 9.5 million cases of HIV infection by the year 2000. The lowest projected cost equates with the US\$ 1.5 billion spent on global immunization through the EPI in 1995—preventing 3 million deaths a year.

Vaccine

HIV represents the most daunting challenge ever to vaccine development. The virus acts by disabling the human immune system—preventing it from mounting an immune response to infection. Could a live, attenuated vaccine do the same thing? This unknown risk factor has so far inhibited traditional vaccine approaches involving the development of killed or attenuated whole virus vaccines.

Another drawback—especially for a disease that can take a decade to develop following HIV infection—is that no one has yet established which immune responses, if any, are a measure of protection against HIV. Without this crucial information, clinical studies of candidate vaccines could take years.

Research has also been hampered by the lack of suitable animal models. Although chimpanzees have proved useful in testing candidate HIV vaccines, they usually remain healthy for a long period despite infection with HIV. And while some vaccines against HIV infection in chimpanzees have proved effective, most vaccines against a form of the disease found in monkeys—simian immunodeficiency virus (SIV)—have proved ineffective in macaque mon-

keys. These contradictory findings on the protective capacity of candidate vaccines in two animal models cast doubt on their relevance to protection in humans.

There are two genetically different but related types of virus—HIV-1 (which has now spread globally) and HIV-2 (restricted mainly to West Africa). Initial vaccine research—from the mid-1980s—was understandably directed towards prevention of the most widespread virus—HIV-1. However, in the early 1990s it was discovered that there are at least 10 different sub-types of HIV-1, unevenly distributed throughout the world. By then, vaccine development had focused mainly on just one of these—sub-type B—which occurs largely in the United States and Europe but not in most developing countries where the incidence of HIV is highest.

There is some laboratory evidence that cross-protection may be possible between the different sub-types but scientists are not yet sure. In the meantime WHO and the recently established Joint United Nations Programme on HIV/AIDS (UNAIDS) are trying to persuade vaccine manufacturers to develop vaccines that may protect against the virus strains that predominate in sub-Saharan Africa and other developing countries.

The issue was high on the agenda at a conference on AIDS in Africa held in the Ugandan capital, Kampala, in December 1995. As a result, at least one major vaccine manufacturer has now expressed interest in developing new candidate vaccines which may be more appropriate for sub-Saharan Africa.

Meanwhile, there is concern that candidate vaccines based on laboratory-adapted strains of HIV might not be able to protect against the naturally occurring (wild) virus. While laboratory strains of HIV can be neutralized by antibodies induced by experimental vaccines in animals or humans and by sera from infected individuals, wild viruses are poorly neutralized by sera from infected individuals and resistant to antibodies from immunized volunteers. However, chimpanzees have been found to be protected against wild viruses, even when the candidate vaccine used did not induce neutralizing antibodies against the challenge virus.

By the year 2000
about 30-40 million
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Just to complicate matters even further, the virus is known to replicate and mutate at an alarming rate. Can a vaccine be expected to protect against new emergent strains of the virus or will it soon become obsolete?

Despite these scientific obstacles, more than 20 candidate HIV-preventive vaccines have undergone Phase I clinical trials in volunteers in the industrialized countries to assess their safety and immunogenicity. Over 2,000 HIV-negative volunteers have participated in these trials since 1987. Additional Phase I and II trials are now under way among volunteers in Brazil, China, and Thailand to determine whether the vaccines are equally safe and immunogenic in developing countries.

The candidate vaccines include: recombinant subunit vaccines based on proteins from the outer covering of the virus (rgp120, rgp160); recombinant vaccines based on a live recombinant virus or bacteria (such as adenoviruses or BCG) expressing one or more HIV proteins; and chemically synthesized vaccines developed from a fragment of HIV protein. Other vaccine approaches under consideration include the use of DNA vaccines and the use of “pseudovirions”, which contain no genetic material. The possible development of live attenuated or killed whole cell vaccines has also not been ruled out. Meanwhile, researchers in Sweden and the United States are trying to develop vaccines against HIV-2. These are currently being tested in animals.

So far, no country has given the go-ahead to Phase III clinical trials to assess the efficacy of selected safe and immunogenic vaccines in protecting against HIV infection and disease. However, several industrialized and developing countries are now actively recruiting volunteers and drawing up plans. Despite the potential risks involved in large scale Phase III trials, many now believe that it would be unethical to delay the trials in the hope of a major breakthrough in understanding of the protective immune response. The two research efforts are now expected to run in tandem—each informing the other.



Health education campaigns are credited with helping slow down the rate of new HIV infection.

Photo: UNICEF/Howard Davies (DO195-0251)

The development of a safe, effective, and affordable HIV vaccine is expected to be a long and difficult process, involving multiple efficacy trials and case-control studies. However, with 7,500 new infections occurring every day, the researchers do not have time on their side. To make matters worse, vaccine manufacturers are no longer falling over each other in the rush to develop an HIV vaccine. Some of the smaller biotechnology companies have already fallen by the wayside—unable to sustain the long-term investment needed to tackle the scientific obstacles involved. And of the few major vaccine manufacturers that remain, most are struggling to maintain their research programmes. They complain they have very few incentives to develop a new vaccine—and several major disincentives. In addition to the scientific imponderables, manufacturers face uncertainties about the size of a future market in industrialized countries—their main profit base—as the rate of HIV infection in these countries appears to have slowed down. Even worse, they fear the political fallout from producing an expensive vaccine which—like the drug AZT—is likely to be beyond the price range of developing countries where 90% of cases occur.

The immediate priority is to develop an HIV vaccine—irrespective of the initial cost or difficulty in administering the vaccine. Once an effective vaccine has been developed, new technology—the use of naked DNA, for example—could be used to lower the cost and make the vaccine more widely available. In the meantime there appears to be a need to establish a better working relationship between the private and public sectors if urgently needed vaccines are to be developed at affordable prices.

Malaria

The disease

Malaria kills more than 1.5 million people a year in developing countries. Most of those deaths (90%) occur in Africa—mainly in children under five. It is estimated that a young child dies from malaria every 30 seconds.

There are between 300 and 500 million cases of malaria a year—exerting a heavy social and economic burden on developing countries. About 40% of the world's population—over 2 billion people—



Ninety per cent of malaria deaths occur in Africa.

Photo: WHO-TDR/Lindsay

are at risk in 90 countries. Only 10% of malaria cases occur outside Africa—over two-thirds of reported cases in just six countries: Brazil, Colombia, India, Solomon Islands, Sri Lanka, and Viet Nam.

In endemic areas malaria is often part of a cycle of deprivation and disease that leaves pregnant women and young children especially vulnerable. A combination of nutritional deficiencies and chronic malaria infection leaves many women suffering from anaemia. As a result, they give birth to underweight babies more likely to succumb to severe forms of malaria as well as a wide range of other life-threatening diseases such as pneumonia and diarrhoeal disease. Meanwhile, malaria during pregnancy increases the risk of miscarriage and maternal and neonatal deaths. Other high-risk groups are people on the move—refugees or internally displaced people, non-immune travellers, or migrant labourers—who enter areas where malaria is endemic.

Malaria is caused by a parasite and transmitted through a mosquito bite. The disease can also be transmitted by blood transfusions (of infected blood), and by contaminated needles or syringes. There are four different types of parasite but the majority of infections and deaths are caused by *Plasmodium falciparum*. The parasites act by invading the red blood cells and multiplying—causing the cells to rupture and self-destruct. Anaemia can then set in and—in the most severe cases—cerebral malaria involving convulsions, coma, and eventual death.

Malaria control strategy

A global malarial control strategy was adopted in 1992 by the Ministerial Conference on Malaria. The targets include implementation of malaria control programmes in at least 90% of malaria-endemic countries or territories by the year 1997 and a reduction of at least 20% in the number of malaria deaths in at least 75% of the countries affected by the year 2000. Research efforts to develop more effective tools for prevention and control of malaria are spearheaded by the World Bank/United Nations Development Programme (UNDP)/WHO Programme for Research and Training in Tropical Diseases (TDR).

The disease is being fought simultaneously on many fronts—with varying degrees of success and failure. While earlier attempts to control the vector were thwarted by the mosquito’s ability to develop resistance to once-effective DDT, carefully targeted vector control is still an important tool in areas where the approach is cost-effective and sustainable. Meanwhile, the use of bednets impregnated with insecticides may help slash the number of malaria deaths in children. A multi-centre study of their use in Africa showed they can cut deaths from all causes in children aged 1-4 by 25%. Other preventive strategies include efforts to improve sanitation and reduce the number of water sources available to the breeding mosquito. Efforts are also being made to monitor the impact on the incidence of malaria of environmental change caused by activities such as mining, road building, and new irrigation or agricultural projects, which can lead to the proliferation of new breeding sites for mosquitos.

The malaria control strategy emphasises the need for early diagnosis of the disease and prompt treatment with appropriate anti-malarial drugs. However, treatment is becoming increasingly difficult as the parasites acquire resistance to the key first-line drugs. Today new—and ever more expensive—anti-malarial drugs have to be used instead.

Vaccine

The limited success of preventive measures and the spiralling rate of resistance to anti-malarial drugs underline the need for an effective vaccine that can prevent the disease. But a vaccine—like DDT or anti-malarial drugs—is not foreseen as a “magic bullet” against malaria. The aim is to develop a vaccine that can be used alongside other malaria control activities such as early diagnosis and anti-malaria drug therapy, use of drugs to prevent malaria, and personal protection measures such as impregnated bednets.

No effective vaccine has yet been developed against a human parasite—and the challenges are formidable. As a result, most research is still being carried out within the public sector and not by vaccine manufacturers. Of the commercial enterprises involved, many are smaller start-up biotech companies rather than the major vaccine manufacturers.

A young child dies
from malaria every
30 seconds.

A vaccine against malaria is not foreseen as a silver bullet against the disease.

For a start, there is no ideal animal model for study of the disease or to test candidate vaccines. However, new models are being developed and tests are now being carried out in transgenic mice genetically engineered to contain human red blood cells. Meanwhile scientists are still trying to work out which immune responses are a measure of protection against malaria. Until this has been established, clinical trials of candidate vaccines will inevitably be lengthy and costly.

Another challenge is the complex life cycle of the malaria parasite—part of which occurs inside its human host, the rest inside the mosquito. There are three possible stages during the course of human infection when a vaccine might intervene. During the first stage the parasites are injected into the bloodstream and pass into the liver—a 20-minute journey—where they begin to multiply. Next comes the asexual blood stage when the parasites have passed through the liver and start to invade and destroy red blood cells. During the final phase, sexual stage parasites develop and are sucked up by a feeding mosquito. Once inside the insect, the parasites reproduce and the whole cycle starts all over again with the next mosquito bite. The ideal vaccine would be a “cocktail” that could act against all three stages—preventing both the disease and its transmission.

A candidate vaccine aimed at blocking development of the disease at the outset (the first stage) has been developed by researchers at New York University. This is a synthetic vaccine developed using several fragments of protein from the parasite. This so-called multiple antigenic peptide vaccine—MAP for short—is to be tested in Phase I trials during 1996.

Blood stage vaccines—which would not prevent the onset of infection but would help prevent serious illness and death—are also being tested. One developed by researchers in Australia—in a collaborative effort involving vaccine manufacturers and a public health institute—is a vaccine containing three recombinant proteins derived from the asexual blood stage parasite. Following the completion of Phase I tests in Australia this vaccine is now undergoing Phase II tests in Papua New Guinea in 1996. A second blood stage vaccine under development at the US National Institutes of Health



A vaccine would be used alongside other malaria control measures such as bednets impregnated with insecticide.

Photo: WHO-TDR/Mark Edwards

(NIH), and known as MSP-1 after the name of the blood stage surface protein used, will also be tested in 1996. Elsewhere, scientists in Sri Lanka have developed a synthetic candidate vaccine based on two peptides from the asexual blood stage of the parasite coupled to a diphtheria toxoid carrier. This vaccine is now being modified since the carrier produced some side-effects during Phase I tests in volunteers.

Meanwhile, the same NIH team have produced a vaccine to combat the sexual stage of the parasite and block transmission. This vaccine (known as Pfs-25 after the protein used) has been dubbed the “altruistic vaccine” because it offers no protection to the person immunized. Instead it acts by passively immunizing mosquitos—and preventing the development of the sexual-stage parasites that the insect ingests. The vaccine has been tested in animals and has now entered Phase I trials in the United States.

Two cocktail vaccines have also been developed. One is SPf66—a synthetic peptide vaccine developed in the mid-1980s by Dr Manuel Patarroyo with support from the Colombian Government. The vaccine incorporates fragments of proteins from both the first and second stage parasites and is designed to protect against disease but not against transmission. Phase II studies of the vaccine have been carried out in Africa—with mixed results. While a study in Tanzania in 1994 among children aged 1-5 showed the vaccine reduced the risk of developing malaria by about 30%, subsequent tests carried out in the Gambia in 1995 showed the vaccine had little or no effect on the incidence of seasonal malaria in children under one. Another study has been completed in Thailand and the results will be available during 1996. In May 1995, Dr Patarroyo gave WHO exclusive global rights to develop his vaccine for public sector use in developing countries.

The other, NYVAC 7—the most ambitious cocktail vaccine to date—has been developed at the Walter Reed Army Institute of Research (WRAIR) in the United States. This recombinant multi-component vaccine is based on attenuated vaccinia (cowpox) virus genetically altered by the insertion of seven different genes from all three stages of the parasite’s life cycle. It is designed to protect against both infection and disease transmission. Phase I/II tests have been completed in US volunteers and the results are due this year.



Forest workers are highly vulnerable to malaria infection.

Photo: WHO/Maxine Rude

Meanwhile, a cost-effectiveness study carried out by TDR—based on the projected cost of incorporating a vaccine into the EPI programme—estimated that immunization would cost US\$ 10-15 for every life saved. According to the economic study, a vaccine that could reduce the incidence of childhood mortality by 30% and provide immunity for at least three years would be as cost-effective as preventing the disease by the use of bednets impregnated with insecticide or preventive drugs. Further cost-effectiveness studies are now under way which will also take into account the social and economic costs of malaria.

Schistosomiasis (bilharzia)

The disease

After malaria, schistosomiasis is the second most prevalent tropical disease—imposing a high socio-economic burden on many developing countries. About 200 million adults and children in 74 countries are infected with the water-related parasites (schistosomes) and 20 million of them have a serious form of the disease or related disability. An estimated 200,000 people die from the disease every year.

Globally, about 600 million people are at risk. In areas with lakes, streams and large rivers the entire population may be infected. Most cases (over 80%) occur in Africa but schistosomiasis also poses a serious health threat in parts of the Americas and Asia. Rural areas in Egypt and central China are also badly affected.

Infection begins through contact with water contaminated with infected fresh-water snails—the intermediate host of the parasite. The parasites multiply inside the snail before being excreted into the water. Within seconds they can penetrate human skin—developing into worms inside their new host. The female worm is a prolific egg layer—with some species capable of producing up to 3,500 eggs a day over an average five-year lifespan. About half the eggs are excreted in faeces or urine—which may go on to re-contaminate water sources. The rest lodge in organs such as the liver and bladder, where they cause chronic and life-threatening diseases due to granulomas and fibrosis. Other long-term effects include anaemia



In severe cases of schistosomiasis the liver and spleen become enlarged.

Photo: WHO/E. Schwab

Schistosomiasis kills
about 200,000
people every year.

and chronic weakness. In some countries schistosomiasis is also associated with bladder cancer. In Egypt, schistosomiasis linked with cancer is the leading cause of death among men aged 20-44.

An increase in the number of dam schemes and irrigation projects has led to an explosion in the snail population in some areas—leaving agricultural workers—along with freshwater fishermen—especially vulnerable to the disease. Elsewhere, increasing population movements have contributed to the spread of the disease to urban areas and refugee settlements.

While efforts to prevent transmission of the disease by controlling the snail populations have met with only limited success, safe and effective drugs are now available to treat the disease. At the request of Kenya, Malawi, Nigeria, and Zambia, WHO has persuaded the manufacturers of praziquantel—the drug of choice—to reduce the price in order to make it more widely available to developing countries. The next step is to develop a vaccine that can prevent re-infection with the parasites.

Vaccine

Out of a range of candidate vaccines developed so far, six have been singled out as especially promising on the basis of tests in animals. They are based on protective antigens from the parasite *Schistosoma mansoni*—one of the five schistosome parasites that affect humans. They include two muscle proteins, two enzymes, and two surface molecules.

The World Bank/UNDP/WHO Programme for Research and Training in Tropical Diseases (TDR) is now working in collaboration with the National Institute of Allergy and Infectious Diseases (NIAID), and the Schistosomiasis Research Programme in Egypt, to select the most promising of the six vaccine candidates for further development. The decision will be made on the basis of the results of studies of immune responses to these antigens due to be carried out during 1996 and 1997. Meanwhile, TDR has also forged links with a commercial partner with the capacity for eventual large-scale production of a schistosomiasis vaccine.

Dengue

The disease

Every year 50 million people throughout the world are affected by dengue fever or the more serious dengue haemorrhagic fever which can lead to shock syndrome and death. More than half a million people are hospitalized each year and there are about 30,000 deaths a year. Children are especially vulnerable to the more serious—often fatal—form of the disease. If dengue haemorrhagic fever is diagnosed early enough—and treated with good supportive care—the mortality rate is under 5% but the symptoms often go unrecognized and up to a third of those infected may die.

Dengue is endemic in 100 countries—often occurring in explosive epidemics. Two and a half billion people are known to be at risk. The disease is rapidly spreading further afield as newly urbanized areas become infested with the major vector—the ubiquitous *Aedes aegypti* mosquito. While only nine countries reported outbreaks of dengue haemorrhagic fever between 1955 and 1970, a further 28 countries experienced outbreaks between 1970 and 1993.

In the latest outbreak in 1995 in Latin America and the Caribbean, more than 200,000 cases of dengue and more than 7,000 cases of dengue haemorrhagic fever were reported. In the first outbreak of dengue haemorrhagic fever in the Americas—in Cuba in 1981—more than 116,000 people were hospitalized over a three-month period and 158 people died—two-thirds of them children.

While efforts to control mosquito populations by the use of insecticide have proved unsuccessful, measures to improve sanitation can help reduce the number of mosquito breeding places. Meanwhile, efforts are continuing to develop a vaccine which can protect against both forms of the disease.

Vaccine

There are four different types of dengue viruses—the most widespread of the so-called arboviruses—and infection with one type of dengue virus offers no cross-protection against the others. Even worse, prior infection with dengue increases the risk of contracting

An estimated 2.5 billion people are at risk from dengue.

dengue haemorrhagic fever during a second episode of the disease. A vaccine should ideally protect against all four types of virus in order to minimize this risk.

A prototype tetravalent live attenuated vaccine has been developed (against all four strains)—using traditional cell culture methods—at Mahidol University in Bangkok. The vaccine has proved to be safe and immunogenic in Phase I and Phase II clinical trials. Phase III tests will start in Thailand this year in collaboration with the vaccine manufacturer Pasteur-Mérieux.

Elsewhere, several laboratories are working on the development of other candidate vaccines using infectious clone technology. Several bivalent candidate vaccines have been developed—using dengue 4 virus as the “backbone” for expressing viral antigen from dengue 1, 2, or 3 viruses. The vaccines produced a good immune response when tested in monkeys—protecting against the two virus types included in each vaccine.

A further six research groups are studying the possibility of using yellow fever virus—a closely-related arbovirus—as a vector, by adding genes encoding for the four types of dengue virus. A recombinant yellow fever/dengue vaccine—designed to protect against both diseases—is now being tested on small animals at the Oswaldo Cruz Foundation in Brazil.

Collaborative efforts are also under way to develop a simple diagnostic test which could help save lives by enabling rapid diagnosis of the disease.

Adding up the cost of new vaccines

Professor Ian Gust, *Director of Research and Development for the Australian vaccine manufacturer CSL Ltd, outlines some of the reasons why new vaccines are likely to cost more than the vaccines widely used today.*

Each of the major vaccine manufacturers is currently involved in the development of combination vaccines. The first dilemma we faced was: which ones? In the best of all worlds, the CVI would obtain a global consensus and provide vaccine manufacturers with a clear course of action. In reality, consensus is impossible, not only because of the contrariness of public health administrators, but because there are genuine differences in the epidemiology of diseases from country to country and major differences in local priorities. Because of the long lead times, manufacturers cannot afford to wait: decisions have already been made on the basis of the best advice available at the time. Several combinations based on DT or DTP plus IPV, hepatitis B, and Hib are in the clinic and others are under development.

We have tended to think that blending several licensed vaccines is a straightforward process, like an electrician following a wiring diagram. Nothing could be further from the truth. All manufacturers are finding that blending licensed vaccines is neither simple nor straightforward. Each combination has revealed unexpected problems—each requiring time, effort, and money to resolve.

Problems have been encountered with compatibility; some crude preparations appear to interfere with the immunogenicity of other components. Because of this, it may be necessary to adjust the concentrations of some components, or even to alter the formulation of the preparation of DTP to make it better able to support other antigens.

Another thing we have learnt is that the process is not cheap. In our case, we have spent more than two years reformulating the base vaccine, which—after validating the

production process, demonstrating batch-to-batch consistency, stability of the product, and evaluating it in some 800 children—has left little change from US\$ 10 million, all before the addition of any other antigens.

While traditional DTP is made by a process which has changed little over the past 50 years, two fundamental changes have occurred—both of which have implications for cost. Up to the 1940s, vaccine production was essentially a cottage industry. Most vaccines were produced in government-funded, government-directed public health institutes. Standards varied widely and there were minimal control mechanisms. Today vaccines are produced in purpose-built facilities, by highly trained staff, and by processes in which every step is documented and validated. Premises and products are subject to inspection, audit, and review.

Secondly, and perhaps most importantly, most of the vaccines under development are based on protected intellectual property. Combination vaccines which contain highly purified components covered by patents, or their successors based on alternative technologies, are likely to be more expensive than the commodity products they replace.

Meanwhile, the high costs of development, the complex regulatory environment, and the impact of government monopoly are having some dramatic effects on the industry. Some pharmaceutical companies are querying the value of their vaccine businesses; others are finding that the best way to recover development costs, avoid duplication of research, and take advantage of the economies of scale is through partnerships or mergers. This process is already under way and is likely to accelerate.



Over half the vaccine used in national immunization programmes each year is produced in developing countries.

Photo: WHO/S. Yabao

The nuts and bolts of immunization

Monitoring vaccine quality

Over 2 billion doses of vaccine are used in national immunization programmes each year. Over half this vaccine is produced in developing countries for local use—not all of it under conditions that ensure the vaccine is of high quality.

One of the key roles of WHO is the application of global standards for the quality control of vaccine production. These standards are laid down by a WHO committee of scientific experts—the Expert Committee on Biological Standardization.

The committee publishes production requirements for vaccines and other biologicals (there are currently almost 40 of these), establishes international standards for the testing of biological products, and draws up general requirements for biological regulation (sterility testing or Good Manufacturing Practice, for example).

In May 1992, the World Health Assembly issued a declaration urging all Member States “to use only vaccines that meet WHO requirements in their immunization programmes” and recommended that this policy should be clearly stated in national immunization plans.

Ultimate responsibility for vaccine quality rests with the vaccine manufacturer. Governments work in partnership with manufacturers through their National Control Authorities to ensure that vaccines are not only safe, potent, and effective at the time of licensing but that each consecutive batch is of equally high quality.

Although vaccine producers in both the private and public sectors are expected to conform to WHO standards, WHO has no supra-national authority to enforce them. Nor does it have the power to

inspect vaccine production if a producer does not agree. In theory, any country can produce sub-standard vaccine—provided it is for use exclusively within its own borders. However, if the country tries to export the vaccine, WHO can exert its influence—albeit indirectly—to discourage its purchase for use elsewhere. WHO does not maintain a blacklist but does publish an up-to-date list of the vaccine suppliers that it recommends for bulk purchase of individual vaccines. The list currently includes almost 20 manufacturers, of which four are from developing or newly industrialized countries. Manufacturers that wish to supply vaccines to UNICEF must first undergo a review of their manufacturing procedures and an inspection of their manufacturing facilities as well as an evaluation of the national regulatory authority. By and large, the system is working—successfully deterring governments from purchasing vaccines that do not meet WHO standards. However, a few countries continue to import or export vaccines that have not been adequately controlled and are of unknown quality.

In 1994, WHO made an inventory of vaccine quality control in 43 vaccine-producing countries—to ascertain to what extent global standards were being met. Six basic criteria were used to determine whether each national control authority was able to guarantee that vaccine produced was “of known good quality”. Were WHO standards a precondition for licensing a vaccine? Did the national control authority evaluate the clinical performance of the vaccine? Was a lot release system in place with each batch individually examined? Was there a system of laboratory testing and of inspection for Good Manufacturing Practice (GMP)? Was there a system of post-marketing surveillance—for example, to monitor for any adverse reactions?

Of the 43 countries surveyed, only 21—including both industrialized and developing countries—had all six control functions in place. Four vaccine-producing countries had none. The remaining 18 countries had some but not all functions in place.

A second inventory has been carried out to determine the quality of DTP production in 42 countries. The CVI is promoting research into combining DTP with other vaccines in order to simplify the process of administering vaccines. Two-thirds of DTP production

takes place in developing countries and there is a need to ensure that production processes are standardized and quality control stepped up before any new vaccines can be combined.

The DTP inventory involved 43 manufacturers in 42 countries. Half of them were in countries without fully functional national control systems and their vaccines could not be shown to meet WHO requirements. Although the production methods used for diphtheria and tetanus toxoid production were similar, about 10% of producers were failing to meet WHO minimum standards for the purity of the toxoids. The study also found that DTP production capacity exceeded global needs.

An earlier groundbreaking study in 1992-93 carried out by the CVI Task Force on Situation Analysis painted a similarly disturbing picture of inadequate standards in vaccine quality control in some countries. In one Asian country a simple error in the mathematical formulation of the tetanus toxoid vaccine resulted in the release and use of a vaccine which had only half the expected level of potency and did not meet WHO minimum potency levels. The error was uncovered after an alert physician noticed that immunized women were still getting the disease.

Elsewhere, in another vaccine-producing country, concern at the lack of independent analysis prompted the manufacturer to seek help from WHO in testing the potency of their tetanus toxoid vaccine. The vaccine was found to be sub-potent. Case-control studies showed the vaccine to be poorly effective and revealed a corresponding increase in the number of deaths from neonatal tetanus. The vaccine manufacturer shut down production until outside testing could be organized on a regular basis.

WHO has warned that compromising on vaccine standards can put lives needlessly at risk. Children immunized with low quality vaccines may die from the diseases which the vaccines were supposed to prevent. As a result, public confidence in immunization may be destroyed—putting even more lives at risk.

Children immunized with low-quality vaccines may die from the diseases the vaccines were supposed to prevent.

Manufacturers supplying vaccine to UNICEF (September, 1995)*

- BCG vaccine: Behringwerke (Germany), Connaught (Canada), Intervax (Bulgaria), Japan BCG, Medeva-Evans (UK), Pasteur-Mérieux (France), Statens Seruminstitut (Denmark).
- DTP vaccine: Behringwerke, Connaught, CSL (Australia), Pasteur-Mérieux, Serum Institute of India, Swiss Serum.
- DT vaccine: Behringwerke, Connaught, CSL, Human (Hungary), Pasteur-Mérieux, Biocine (Italy), Serum Institute of India, Swiss Serum.
- TT vaccine: Behringwerke, Connaught, CSL, Human, Pasteur-Mérieux, Biocine, Serum Institute of India, Swiss Serum.
- OPV vaccine: Behringwerke, Connaught, Pasteur-Mérieux, Biocine, SmithKline (Belgium).
- Measles vaccine: Connaught, Intervax (Croatia), Eisai (Japan), Medeva-Evans, Pasteur-Mérieux, Biocine, Serum Institute of India, SmithKline, Swiss Serum.
- Hepatitis B: Cheil Sugar (Republic of Korea), SmithKline.

* The absence of any US vaccine manufacturers from this list is explained by their access to a large and highly profitable market within the United States, which has an annual birth cohort of 4 million children, and by the adoption of standards which differ from those of WHO.

Vaccine supply¹

UNICEF, traditionally the main supplier of vaccine to developing countries, has launched an innovative global vaccine targeting system to ensure the sustainability of vaccine financing in individual countries. UNICEF's goal is to ensure that countries that can afford to pay for their own vaccines do so—freeing up funds that can be used to provide both new and existing vaccines for the world's poorest countries.

In order to determine which countries are—or could be—self-reliant and those that need continuing support to buy vaccine, UNICEF is using a grid system. The grid separates out countries that still

¹ This is an updated version of an article by John Maurice first published in *CVI Forum* (October 1995).

require external support to meet their vaccine needs from those that are or could be self-reliant. Plotted by wealth (per capita gross national product) and population size (which theoretically reflects the number of customers for a local vaccine production facility), countries fall into four bands, with the smallest, most indigent, clustered towards the bottom left-hand section of the grid (band A) and the more potentially or actually self-reliant in the successively higher bands. UNICEF's new support strategy will assure that Band A countries receive continuing support for current and new vaccines, but insist that they bear a small proportion of the cost, rising from 10% to 25% over the next three years. Band B countries are now being asked to support most of the cost of vaccines (from 80% to 100% over the next three years for current vaccines and 50% to 100% for new vaccines). For band C countries aid was phased out altogether by the end of 1995, with perhaps a one-time handout. Band D countries will be left to their own devices forthwith.

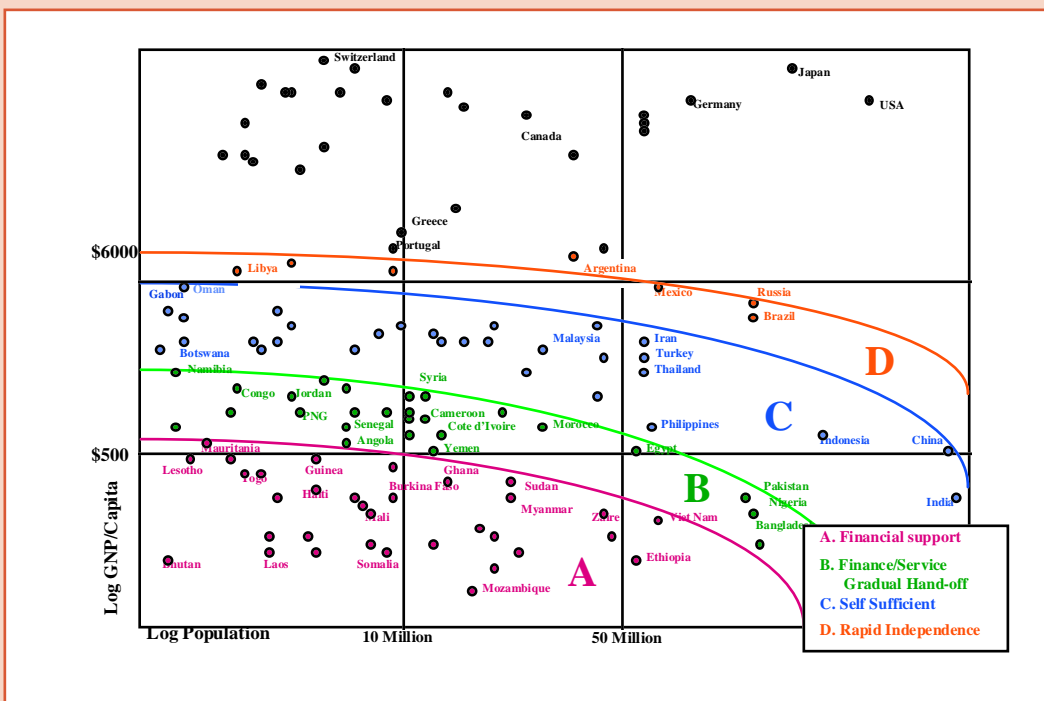
For those countries in transition to self-sufficiency—particularly Band B countries—UNICEF is offering other kinds of assistance, including training in vaccine procurement, and a financial mechanism—the Vaccine Independence Initiative. Under this scheme, a country works out its vaccine needs over a two- and five-year period and, with UNICEF acting as a procurement agent, the country pays for its vaccines through a revolving fund mechanism. So far, about a dozen countries have either joined or expressed interest in this initiative.

The global targeting plan appears to be working. By early 1996, about 25% of countries in Band A were already meeting their vaccine self-sufficiency targets (compared with only 2% in 1990). About 70% of countries in Band B were meeting or about to meet their target (compared with 40% in 1990), and 90% of countries in Band C were already on target (10% more than in 1990).

Donors are making use of UNICEF's new targeting strategy (for example, by selecting countries for bilateral funding in accordance with UNICEF's tiered or targeted approach). They can also ensure more efficient coordination of such funding by supporting a global vaccine fund. This idea is still at the drawing board stage, but could, according to UNICEF, buttress the new approach to vaccine supply.

UNICEF has established a new revolving fund mechanism to help countries pay for their vaccines.

Sustainable vaccine supply — Global targeting strategy



The UNICEF grid divides the world into four bands on the basis of wealth and population.

To each according to his need. UNICEF is using this grid to rank its vaccine supply support to countries. The grid separates out countries that still require external support to meet their vaccine needs from those that are, or could be, self-reliant. Plotted by wealth (per capita gross national product) and population size (which theoretically reflects the number of customers for a local vaccine production facility), countries fall into four bands: the smallest, most indigent, are clustered towards the bottom left-hand section of the grid (band A) and the more potentially or actually self-reliant in the successively higher bands. UNICEF's new support strategy

would assure band A countries of continuing support for current and new vaccines, but would insist that they bear a small proportion of the cost, rising from 10% to 25% over the next three years. Band B countries would be asked to support most of the cost of vaccines (from 80% to 100% over the next three years for current vaccines and 50% to 100% for new vaccines). For band C countries aid would be phased out altogether over the first year, with perhaps a one-time handout. Band D countries would be left to their own devices forthwith. The remaining countries are, of course, already self-reliant.

Face to face or hand in hand?

What developing countries need is to buy the new, generally more costly, vaccines for the poorest countries of the world—at prices that ensure they get the maximum vaccine for their money. The vaccine manufacturers want to make the maximum money from their vaccine. And never the twain shall meet—unless a common ground can be found. At last, it looks as if it has.

The common ground is a mutual understanding of two factors. Vaccine cost is driven by volume and by tiering prices to the ability of the customer to pay. Manufacturers need to recover the cost of research and development (R&D) but this cost can be recovered only from its rich customers. Once this cost has been recovered, selling vaccines at low-tiered prices to the large markets of developing countries becomes possible. However, the two markets must be kept separate. Vaccines at low-tiered prices must not become available to customers who can afford to cover the costs of R&D.

For example, a recent tender that UNICEF sent out to manufacturers in September 1995 was based on that understanding. It reminded manufacturers that UNICEF buys a lot of vaccine on behalf of developing countries—more than eight billion doses over the last ten years. It offered manufacturers access to a large but hitherto untapped market for their new vaccines in the poorest developing countries. It offered them the possibility of long-term agreements to purchase over a given number of years large volumes of one or more traditional vaccines for the Expanded Programme on Immunization (EPI). And it offered them the possibility of combining their offers for old and new vaccines in a single “bundle”. In return, UNICEF asked manufacturers to provide new vaccines at prices that developing countries can afford.

About a dozen manufacturers responded to the tender with proposals for imaginative vaccine supply arrangements covering a range of the less “traditional” vaccines, including hepatitis B, *Haemophilus influenzae* type b, a diphtheria-tetanus-pertussis (DTP)-hepatitis B combination, a measles-mumps-rubella combination, a DTP-injectable polio combination, and diphtheria antitoxin.

Across this new common ground, the two sides—public and private—have apparently started reaching out to each other. For the benefit, and survival, of millions of children.



Countries that can afford to pay for their own vaccines are now expected to do so.

Photo: WHO/H. Anenden

New vaccine production consortium

WHO is establishing a groundbreaking vaccine production consortium. Membership will comprise vaccine manufacturers who are committed to supporting public health priorities, in particular the goal of bringing onto the market affordable, easy-to-administer vaccines against all the major diseases affecting children.

The consortium will:

- provide a mechanism for international validation of high-quality local vaccine production in the developing world
- make it easier at national, regional and international level to pool research, administrative and legal resources, and also training activities, especially in the creation or improvement of good management and quality assurance and control systems
- give developing country manufacturers a forum for discussion of common problems—and possible solutions
- provide structured assistance—particularly the help of other manufacturers who have already reached a certain level of excellence—to manufacturers and governments willing to take the necessary steps towards quality vaccine production
- provide the international community with a convenient mechanism for channelling and prioritizing funding, and one that ensures management efficiency and accountability.

In the longer term, it is hoped the consortium will also allow easy access by developing country manufacturers to technological and research advances—enhancing capability for the production of new vaccines.

Criteria for membership will include good management, vaccine quality and technical excellence. The consortium will identify manufacturers whose vaccines are acceptable for purchase. It will help those who are spending money and effort trying to get into the picture, actually to achieve their goal. And it will help those who are never going to make it, to reconsider their options.

The first activity of the vaccine production consortium is a new vaccine training network that will offer training for vaccine producers and national control authorities and laboratories in developing countries. A network of training centres will provide training in key areas including: good manufacturing practice (GMP), good laboratory practice, quality control testing, and licensing criteria.

Disease surveillance

As global immunization coverage has increased dramatically over the past two decades and the incidence of disease has declined, immunization programme performance is today increasingly measured not by a head count of children immunized but—more importantly—by measuring the reduction in the incidence of disease.

Surveillance data are crucial in assessing whether disease reduction targets are being met and where resources should be targeted for maximum cost-effectiveness. These data are also needed to determine which vaccines are a priority and where vaccine research and development is needed. The lack of data on the incidence of Hib disease, rotavirus, RSV, and pneumococcal disease, for example, will delay the introduction of new vaccines because it is not known in which countries they are needed most. Surveillance is also essential to closely monitor programme safety—and ensure that any mistakes (unsafe injections or the use of sub-potent vaccine, for example) are pinpointed and rapidly corrected before there is a loss of public confidence. Meanwhile, any reports of unexplained side-effects associated with a vaccine also have to be carefully logged and investigated.

Recent assessments of disease surveillance systems carried out by WHO and the US Centers for Disease Control and Prevention (CDC) in 28 countries in WHO's African, East Mediterranean, and European regions have led to a number of key recommendations aimed at improving the monitoring, investigation, and reporting of disease.

First is the need for the reporting of data to be linked to specific public health actions—instead of merely providing data for archival records. An example is identifying areas at high risk for neonatal tetanus and ensuring that resources are targeted to these areas. Surveillance data can also be used to monitor trends in the incidence of measles and predict where epidemics may occur or to guide plans of action for diphtheria control in Eastern Europe.

The global effort to eradicate polio is also crucially dependent on disease surveillance—in this case the accurate reporting and investigation of every case of acute flaccid paralysis. National, regional, and global certification commissions will base their assessment of eradication on the absence of reported polio and on standard performance indicators that measure the effectiveness of surveillance. Unless countries can fulfil these criteria, they will be unable to prove they have eradicated the disease. WHO has placed epidemiologists in key countries to help improve surveillance by providing the technical back-up needed.

There is also a need to speed up reporting and ensure good feedback. In many countries reporting is delayed and information is often incomplete or unrepresentative. The innovative launch by WHO's Eastern Mediterranean Region of an information bulletin—the PolioFax—for example, led to major improvements in the speed and completeness of monthly reports of acute flaccid paralysis.

Another recommendation is the need to standardize and streamline disease surveillance so that accurate comparisons can be made, while—at the same time—remaining flexible enough to adapt to changing patterns of disease. Standard reporting procedures and a trimmed-down list of reportable diseases and form-filling would help in improving communication between surveillance partners. Meanwhile there is a widespread need for improved staffing, better training and motivation, and a much clearer definition of who does what. In some of the countries assessed, simply clarifying who was responsible for what activity resulted in dramatic improvements in surveillance.

Last is the need for good communications systems. Some countries have overcome problems by introducing a messenger system or by using public or animal transport or radio communication to transfer data. Elsewhere, modems, E-mail and satellite telephones are already being used. In most of the countries involved in the survey, computer hardware was available at the central level but in some cases there was a lack of appropriate software. The Global Programme for Vaccines and Immunization in collaboration with the US Centers for Disease Control has now developed a software programme designed to help standardize and improve the analysis of surveillance data.

Epidemiologists have been placed in key countries to provide technical backup for disease surveillance.

Assessments reveal severe shortcomings in disease surveillance

Assessments carried out by WHO and the US Centers for Disease Control and Prevention (CDC) in 28 countries have uncovered wide-ranging problems in disease surveillance systems. In many countries data were being gathered on far too many diseases—more than 50 in some cases—but the information was rarely if ever used.

Health workers were found to be spending excessive time and energy filling in forms—without ever using the data themselves. All too often the information was never analysed or used at any level—largely because most of the data were irrelevant but also because of a lack of time, motivation or the necessary skills.

The outcome in many countries is an unwieldy, inefficient surveillance system of limited use in guiding public health activities. In the absence of clear definition or prioritization of information needs, disease surveillance can lapse into a state of archival disease recording only.

In some countries, smallpox was still on the list of reportable diseases in 1993—16 years after the disease was eradicated. Even worse, one country reported several cases of smallpox and 860 cases of polio during 1993—but no one had investigated. The assessment team later discovered that most of the polio cases and all the smallpox cases were due to a clerical error.

Elsewhere, incorrect interpretation of surveillance data to determine the magnitude of hepatitis B as a public health problem led to gross underestimates of the disease burden in some endemic countries. The slip-up—involving the use of data on the incidence of the disease instead of HB carrier rates—led to the adoption of inappropriate immunization strategies.

Also highlighted was an inability to deliver information on time and a failure to share information among surveillance partners (national immunization programme managers, laboratory personnel, doctors, and epidemiologists). There was also a failure to provide feedback to those who needed to know. In some countries specimens were sent to laboratories without the relevant epidemiological data and unnecessary delays ensued. Elsewhere, laboratory specimens suffered damaging heat exposure because they were sent to laboratories at weekends or outside working hours. Conflicts between academics and officials from the Ministry of Health were commonplace, and there was a general lack of good teamwork.

In developing countries with poor telecommunications WHO is testing a new short-wave radio communications system which could help speed up the exchange and analysis of computerized surveillance data. The system—originally designed for use by sheep farmers in remote areas of Australia—involves the transfer of data through a short-wave radio system. Once the data has been transferred to a short-wave radio it can be “polled” at any time—even in the middle of the night—by an automatic short-wave radio link, analysed, updated, and “paged” (returned) by the same route. If successful, the system could prove invaluable in tracking down the last pockets of polio transmission.

Surveillance for adverse reactions to immunization

When something goes wrong and a child becomes sick after being given a vaccine, public confidence in immunization can evaporate overnight. During the time it takes to rebuild that confidence, many more children are likely to become sick because parents refused to have them immunized.

While rare cases of serious vaccine-related illness can have tragic consequences for the children involved, studies have consistently shown that the risks of vaccine-related side-effects are infinitesimal when set against the risk of complications arising from natural disease in an unprotected child. A 1984 study by WHO’s Expanded Programme on Immunization found that the risk of permanent brain damage following whooping cough, for example, was 3,000 times greater than the risk associated with the use of the vaccine itself. Meanwhile, the risk of measles-related encephalitis was estimated to be up to 4,000 times greater than the risk associated with measles vaccine.

More recently, a 1991 study in the United States by the Institute of Medicine found there was a causal relationship between DTP vaccine and anaphylaxis (extreme hypersensitivity to a component of the vaccine)—an estimated 2 cases for every 100,000 injections of the vaccine. The report also found a direct link between the pertussis component of DTP vaccine and extended periods of inconsolable crying (from 0.1% to 6% of children given an injection of DTP) and between rubella vaccine and acute arthritis in adult women (13% to 15% of women immunized). It also confirmed—despite weaker evidence for this—the findings of a 1981 study in the UK



The global effort to eradicate polio is crucially dependent on disease surveillance.

Photo: WHO-PAHO/C. Gaggero

(The National Childhood Encephalopathy Study) which estimated that the risk of acute encephalopathy following a DTP injection was from 0 to 10.5 for every million injections given.

One of the major problems in assessing risk is the difficulty in establishing whether the “vaccine-related” illness would have occurred anyway. It may have been coincidental or triggered off in advance by the vaccine. Some conditions—especially fever and neurological syndromes—also occur spontaneously among non-immunized children. Convulsions have been reported following DTP or measles immunization, but the background rate is high. At the age of 3-15 months, the monthly incidence rate of convulsions ranges from 8 to 14 in every 10,000 children.

In 1991, a WHO study of adverse events following immunization highlighted the fact that EPI vaccines are given to children at an early age when acute viral and bacterial infections are common. These adverse events are often incorrectly linked to recent immunization, especially if a similar non-specific syndrome has been reported in the medical literature. The study found that most genuinely vaccine-related events were mild, relatively common, and temporary, and concluded that more severe vaccine-induced adverse events were a fraction of the complications resulting from the natural disease itself.

However, as immunization coverage increases and diseases become rare, the relative risks of vaccine-related illness increase. The use of live attenuated oral polio vaccine (OPV), for example, carries a very small risk of polio paralysis both for the person immunized and for close contacts—an estimated two cases for every 5 million doses of OPV. But in the United States, where polio has been eradicated, the only source of polio is now the vaccine itself. Because of this the United States is to switch to a combined schedule of two doses of inactivated polio vaccine (IPV)—which carries no risk of paralysis—followed by two doses of OPV.

A few industrialized countries have established compensation schemes which provide payouts for specific serious reactions that occur after immunization—even where the link is impossible to prove. The aim is to avoid protracted court cases and help maintain

the effectiveness of immunization programmes. In the United States a compensation system was established by the Government after vaccine manufacturers placed large surcharges on DTP vaccine to cover the cost of defending vaccine-related law suits. The Government was forced to act when the price of DTP shot through the roof—from 35 cents to US\$ 15 a dose. The National Childhood Vaccine Injury Act (NCVIA) passed in 1986 by the US Congress lists a series of vaccine-related reactions for which parents can be compensated. In exchange, parents must waive all rights to sue for compensation through the courts.

In developing countries the most common cause of vaccine-related side-effects is human error—either in the storage, reconstitution, or administration of vaccines. In a number of well-documented cases children have suffered vaccine-related illnesses because they were given unsafe vaccines or injections. In some cases vaccine caused unwanted side-effects in children because it was stored at the wrong temperature (placed in a freezer, for example, because the fridge was too full), used beyond its expiry date when it was no longer potent, or reconstituted with the wrong diluent. Elsewhere, contaminated needles were used because of shortages or poor sterilization techniques and drugs mistakenly administered instead of vaccines. In all these cases children's lives—and in the event of needlestick injuries, those of health workers—were needlessly placed at risk.

The launch of a safe injections initiative following the Yamoussoukro Declaration on the Safety of Injections in 1994, the introduction in January 1996 of vaccine vial monitors, and continuing research efforts aimed at simplifying the administration of vaccines should all help in eliminating these kinds of errors.

In the meantime good surveillance is critical in pinpointing programme errors and correcting them before public confidence in immunization is undermined. In Zimbabwe, an outbreak of lymphadenitis (involving abscesses and inflammation of the lymph nodes) in 1982, three months after immunization with BCG vaccine, was traced to a switch to a different strain of vaccine that was cheaper but caused more side-effects. The ensuing investigation also succeeded in high-

lighting a number of errors—vaccines that were not properly re-constituted and injections not always given intradermally—which, once corrected, helped strengthen the immunization programme.

Elsewhere, five children suffered severe reactions after immunization with measles vaccine—vomiting, fever, headache, and prostration—and two of them died from toxic shock syndrome, despite hospital treatment. An investigation at the health centre involved revealed that vials of reconstituted measles vaccine were being saved and re-used instead of being discarded at the end of each session. As a result, children had been given vaccine from a vial that was contaminated with bacteria.

In response to a request from national immunization programme managers, WHO has produced a field guide to help improve surveillance of adverse events following immunization. This outlines procedures for investigation, reporting, and action following reports of possible vaccine-related illness. It is anticipated that as reporting, investigation and analysis of these incidents improve, immunization programme performance will be strengthened.

Cold chain

The cold chain—a network of fridges, freezers, and cold boxes, organized by teams of people throughout the world—is the backbone of the Expanded Programme on Immunization. It ensures that vaccine is kept at the correct temperature from the moment it leaves the vaccine manufacturer, right through its shipping and storage to the moment it is given to a child.

Transport can be a major problem—especially in remote areas. Motor bikes developed for use by farmers in the Australian bush have been adapted to meet the specifications needed for vaccine delivery. Elsewhere, health workers make use of horses and even dug-out canoes to ensure that vaccine gets through to children in the remotest health centre. If a weak link appears anywhere along the chain and the system fails, children's lives may be put at risk.

The system has to be tailored to meet every condition: regions with intermittent or no electricity supplies; where war or crippling debt have led to the collapse of national distribution networks; and where

In developing countries the most common cause of vaccine-related side-effects is human error.

The cold-life performance of CFC-free fridges and freezers has been slashed by an alarming 20–40%.

the temperature—even inside a building—falls below zero in winter—freezing vaccines that need safe storage at a higher temperature.

Today the biggest challenge facing cold chain and logistics experts has come from an unexpected quarter—the phasing out of ozone-depleting CFCs (chlorofluorocarbons). WHO and UNICEF were prompt in recommending a gradual and systematic switchover to CFC-free refrigerants in line with the Montreal Protocol which calls for the phaseout of CFCs in developed countries by 1 January 1996 and in developing countries 10 years later. (The EU countries have set an earlier deadline of 1 January 1995.)

But what no one knew at the time was that CFC-free equipment would turn out to be a lot less efficient than the standardized equipment it replaced. The so-called cold-life performance of the new equipment was slashed by an alarming 20–40%—a margin that could compromise the safety of vaccines in certain conditions. The smallest fridge used for vaccine storage—standard equipment in many health centres—can no longer be used because it can't make ice. The performance of cold boxes and vaccine carriers has fallen by at least 20% and recent tests on CFC-free solar refrigerators have revealed that temperature control, energy consumption, and icepack freezing capacity are all compromised by the use of CFC-free refrigerants and insulation foams. The performance of domestic refrigerators—which some countries use for vaccine storage against the advice of WHO and UNICEF—has slumped even further following the development of CFC-free models. Tests have shown that these fail to stay within the safe temperature range. China uses over 50,000 domestic refrigerators, Pakistan 5,000, and the Philippines 3000—but these countries have yet to switch over to CFC-free production.

Other logistical problems have also arisen. One is the need for the safe disposal of equipment containing CFC gases. This has to be removed to a central point where the gas can be removed and safely stored in gas-tight cylinders. Another problem is the need to ensure that maintenance and repair of CFC and CFC-free fridges is not confused. The danger is that—unless equipment is clearly marked—fridges may be contaminated with the wrong kind of gas, causing



The cold chain is a network of fridges, freezers, and cold boxes organized by teams of people throughout the world.

Photo: WHO/UNICEF (21850C-1537)

tubes to become blocked. WHO and UNICEF are working with governments to ensure that cold chain repair and maintenance technicians are properly equipped and trained to handle both CFC and CFC-free systems. And they are also working together with manufacturers—against the clock—to find ways of ensuring that CFC-free equipment meets the specifications required for safe vaccine storage. In the meantime the gradual introduction of innovative vaccine vial monitors—time and temperature indicators—will prove an invaluable asset in controlling the shelf-life of vaccines and monitoring any failures in the cold chain.

Vaccine crisis in Eastern Europe

The fragmentation of the former Soviet Union has had a devastating impact on immunization services in the Newly Independent States (NIS). For a start, the cost of importing vaccine from Russia has risen by a staggering amount. Vaccine prices increased by 570% in 1992 and by as much as 6,250% the following year. Meanwhile a lack of management and decision-making expertise within fledgling health services crippled the public health sector. Ailing cold chain and distribution systems collapsed, and mounting debt and high inflation destabilized national economies—bringing immunization and other public services to a standstill.

While many Eastern European countries share the same problems, they also have to contend with chronic shortages of injection and sterilization equipment. A new problem for both the NIS and Eastern European countries is the impact of fuel shortages and economy measures on the cold storage of vaccine. As the temperature inside once-heated buildings plunges below zero in winter, the temperature inside fridges also drops—freezing and damaging some of the vaccines.

One solution—used in Mongolia—is to dig a hole two metres deep and store vaccine below the permafrost level where temperatures remain constant. One manufacturer has recently developed a new fridge that can maintain a temperature above zero and WHO and UNICEF have asked manufacturers to publish data on the performance of their cold boxes in sub-zero temperatures. In the meantime, further research is needed to develop ways of modifying existing cold storage and refrigerated equipment in areas with sub-zero temperatures.

Safe injections initiative

Almost a billion injections are given to women and children each year through national immunization programmes in developing countries. In 1994, WHO reported that surveys carried out in four of its six regions indicated that up to a third of immunization injections were unsterile—and therefore unsafe.

But immunization injections account for less than 10% of injections administered within the health sector. And medical injections have an even worse safety record. More than half of all non-immunization injections in developing countries are believed to be unsafe.

Surveys carried out for WHO and UNICEF have revealed a disturbing pattern of unsafe injection practices that can put the lives of both children and health workers at risk. Contaminated needles and syringes are sometimes reused—putting children at risk of cross infection with blood-borne diseases such as hepatitis B and HIV. In one health centre in Romania health workers were found to be packaging used disposable syringes for resale—using a hot iron to reseal the packaging. Elsewhere, reusable plastic syringes are inadequately sterilized and injections are sometimes wrongly administered—resulting in injection-site abscesses. Improper disposal of contaminated needles and syringes is another problem—placing the wider community at risk. Meanwhile, the incidence of accidental needlestick injury to health workers is alarmingly high—an estimated 5 needlestick accidents for every 100 injections.

A survey carried out for UNICEF in Eastern Europe in 1992-93 revealed that almost 50% of health centres were giving unsafe injections and/or using vaccine of doubtful potency. In 13% of health centres there were no disposable syringes and no sterilizing equipment either. The study also revealed that children—especially orphans—were being subjected to an excessive number of injections in addition to immunization—an average of 115 injections in all during their first year. One orphan had been given over 500 injections.

In 1994, a conference in Côte d'Ivoire involving more than 50 African countries endorsed the so-called Yamoussoukro Declaration on the safety of injections. Under this declaration, immunization

Up to a third of immunization injections are believed to be unsafe.

programme managers and workers pledge to ensure that every injection is sterile and the public pledge to demand the right of access to injections that are safe. The Declaration also sets a target of 95% safe injections by the year 1997.

UNICEF, which supplies injection equipment to many developing countries, now recommends the use of auto-destruct syringes instead of disposable, single-use syringes in order to avoid the hazards of unsafe injection practices. The advantage of these syringes is that they cannot be reused or recycled for sale. But they are more expensive than either disposable or reusable (sterilizable) syringes and once contaminated they still require safe disposal. Over the past 3-4 years, annual sales of auto-destruct syringes have increased more than tenfold—from 5 million to 60 million today.

But by the year 2000 a new device—the low workload jet injector—is expected to revolutionize the business of giving injections. Adapted from a more powerful model first developed for the mass immunization of military personnel during the Second World War and from a smaller device used by diabetics for the daily injection of insulin, this device can project high-speed—100 metres a second—intramuscular injections, penetrating the skin without the use of needles.

High workload jet injectors are already used in some countries—mainly when large numbers of people are immunized during outbreaks or in refugee camps. Low workload jet injectors could be marketed for about US\$ 300, and used for about 20,000 injections without needing maintenance—providing two years' service in the average health centre. The device will be cheap, convenient, avoid the risks of needlestick injuries, and leave nothing behind for disposal. It also holds out the prospect of use with vaccines in powder form—measles vaccine, for example—which are currently at the research stage. It may also be used at a future date to deliver several vaccines at the same time—by mounting multiple vaccine vials on the injector.

However, tests have shown that the existing models already in use are not risk-free. Although no needle is used, some children have been found to bleed—raising the spectre of cross-infection unless

the metal cap is sterilized or changed before any subsequent immunizations. When tested on animal models the metal cap was found to be contaminated after 1 in 7 injections.

Tests are now being carried out by WHO in collaboration with the US Centers for Disease Control and the UK Public Health Laboratory Service on both high workload and prototype low workload jet injectors in an effort to eliminate the risk of contamination. Two possible adaptations are the development of a disposable plastic head or a disposal sheath to ensure that the device remains sterile. Meanwhile, Phase I laboratory tests are already under way and limited field trials are scheduled to take place during 1996 and 1997 in Brazil and the Philippines.