A Children's Vaccine
Can one shot do it all?

by

Scott B. Halstead
Bruce G. Gellin
The Rockefeller Foundation

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The year is 2010. The place, the village of Manpura-Upazila one of thousands on the deltaic branches of the Ganges and Brahmaputra Rivers. The annual floods and the fierce cyclones which roar off the Bay of Bengal, only 50 miles distant, make life here precarious. The villagers of Manpura farm the most densely populated land on earth. Despite efforts over the years, sanitary conditions are primitive and the organisms which cause contagious respiratory and diarrheal infection are ubiquitous. A young Bangladesh mother, age 23, is giving birth to her first born, a boy. The nurse-midwife after assisting with an uncomplicated, but long and tiring delivery, feeds the new born baby a few drops of a white liquid using a small eye dropper. The baby swallows the liquid. Over the next 3 months the infant will develop strong and lasting immunity to the twenty major childhood killer infections of the 20th century. Six months earlier, the mother-to-be had done her part by swallowing a vaccine capsule designed to stimulate high levels of antibodies which would be carried through her placenta into the unborn baby's blood. Other antibodies from the same vaccine would be secreted in her breast milk. These secretory antibodies would play a special role in protecting her infant by creating a barrier to the intestinal and respiratory infections carried in water and food.

Is this an impossible dream? Not if a global effort, born in 1990, succeeds. It plans to bring into existence a

"children's vaccine," an inexpensive, orally administered, universal, multi-antigen (disease) vaccine that will maintain its potency without refrigeration, which will be delivered at birth and designed for children everywhere. When required, special vaccines will be added to combat the local or regional diseases which afflict Third World children.

BACKGROUND:

VACCINES: HOW DO THEY WORK AND HOW ARE THEY MADE?

Immunization is one of the safest and most cost-effective ways of preventing disease, disability and death. As a practical, preventive tool, vaccines are about 200 years-old. The first vaccine discovered was that by William Jenner, who in 1796 took the fluid from the pustule of a cow-pox lesion on the hand of milkmaid, Sarah Phipps, and inoculated it into the skin of another human being. Appropriately enough this weakened form of smallpox was called "vaccine" after "vacca" the Latin word for cow; hence, vaccination. It required nearly another 100 years for the second useful vaccine to appear, the famous treatment of rabid animal bites developed by Louis Pasteur. In 1993, the total number of available vaccines is surprisingly small; they have appeared in a steady, slow procession during the last century (see figure 1)

There are three kinds of vaccines: 1) genetically altered living organisms which grow in the body but don't produce disease, 2) inactivated whole or pieces of organisms, or 3) inactivated toxic products of microorganisms.

Genetically altered living organisms include vaccines against smallpox, yellow fever, oral poliomyelitis, measles, mumps and rubella viruses and bacterial vaccines, including Bacillus Calmette-Guerin (BCG), a form of bovine tuberculosis, and a newly licensed oral typhoid fever vaccine. In general, viral vaccines produce very long lasting immunity, often for a lifetime.

Vaccines made from inactivated organisms include whooping cough (pertussis), cholera, meningococcus, pneumococcus, Hemophilus influenza b, killed poliomyelitis, and hepatitis types A and B

Finally, inactivated toxins (toxoid vaccines) are available which protect against tetanus (lockjaw) and diphtheria. Newer cholera vaccines use this principle.

Viral vaccines work by eliciting the production of antibodies which seek out and destroy viruses once they enter the body. Antibodies are specific protein molecules produced by a type of white blood cell called a B lymphocyte. After

inoculation of vaccines under the skin or into muscle, antigens are taken up by another white blood cell, the macrophage, which digests vaccine proteins into small molecular bits which are then presented to B lymphocytes to stimulate antibody production. For some diseases, particularly bacterial infections, antigen-containing macrophages induce specific T lymphocytes which can attack and kill infected cells. This kind of immunity is called cellular immunity.

Until very recently, vaccines were manufactured using relatively crude methods. For most of history, smallpox vaccine was made by inoculating cowpox virus into the skin of young cattle, scraping off and then bottling the pustular material. Bacterial vaccines were made in huge vats and inactivated with chemicals. Most viral vaccines are produced by inoculating living viruses in cultures of cells which are grown on the inside surface of glass bottles. The virus released into the nutrient fluid is collected, purified and bottled as vaccine.

Modern vaccines which are produced in industrialized countries are carefully regulated from the development to the manufacturing stage, assuring the best possible product from the standpoint of effectiveness and safety. Vaccines are manufactured in facilities which comply with laws which prescribe Good Manufacturing Practices (GMP). Generally, vaccines are produced in rooms supplied with air which is filtered to remove

any contaminating organisms and using equipment which is carefully calibrated to maintain exacting standards and produce vaccines of high uniformity. Most vaccines are produced using the so-called fermentation process in which cell or bacterial cultures are grown in large stainless steel vats, into which all needed reagents are fed according to measured metabolic need.

Vaccine research has taken a quantum leap forward due to the biotechnology revolution. The full genetic code is now known for most pathogenic microorganisms and purposefully selected genes can be translated into short or long chains of amino acids (peptides or proteins) which can be manufactured accurately in very large volumes. It is also possible to insert selected genes into complete viruses such as a vaccinia virus. When inoculated into the skin, the vaccinia virus produces its own genetic products plus the products from the inserted genes. In this way, for example, a single vaccinia virus might induce immunity to rabies, human immunodeficiency virus, herpes viruses or other viruses.

WHY VACCINES ARE NEEDED: THE CHILD SURVIVAL MOVEMENT

In the 1960s and 1970s, improved medical care and investments in economic development were beginning to bring some infectious diseases under control, reducing childhood death rates. Continuing high fertility rates led to rapid population growth. This placed insupportable burdens on the poor and

threatened to again raise infant mortality rates. As illustrated (Fig. 2) infants are at high risk of dying when born to mothers who are too young or too old or, when they are born in rapid succession or born late in the birth order. Clearly, reduced fertility rates are necessary to child survival.

Increasingly, an important feedback loop was understood: high death rates in infants and children led parents to target their family size at levels which would compensate for expected losses. For example (Fig. 3), those countries which had the highest infant mortality rates in 1960 subsequently had the smallest rates of decline in crude birth rates by 1988. For example, if infant and child mortality rates were in the vicinity of 50%, parents who wished to have three children surviving to adulthood might choose to have six children.

In 1974, when it was clear that the global campaign to eradicate smallpox was going to succeed (see medical and Health Survival, 1978, Donald A. Henderson. Smallpox: Eradication of a Killer), the World Health Organization (WHO) took a bold step. It decided to apply the lessons of the smallpox campaign more broadly, creating the Expanded Program of Immunization (EPI). The goal - to immunize the world's children by 1990 against six diseases: diphtheria, pertussis (whooping cough), tetanus (lockjaw), tuberculosis, measles and poliomyelitis. Operationally, the accepted target was that 80% of children would

be fully immunized. To achieve full immunization requires that each child receive five separate injections and four swallows of oral polio vaccine, all in the first nine months of life (see Fig. 4).

When the EPI began its work, less than 5% of the world's children had been fully immunized. Ten years later, in 1984, this number had risen to only 25%. Something had to be done if the 1990 goal was to be realized.

In the 1983, the United Nations Children's Fund (UNICEF) declared "a children's revolution," emphasizing four cost-effective means to reduce childhood mortality: growth monitoring, oral rehydration for diarrhea, breast feeding and immunization. That year, at the urging of Jonas Salk, discoverer of the polio vaccine, and Robert McNamara, former President of the World Bank, UNICEF and WHO decided to accelerate the global immunization campaign. This was initiated at a March 1984 meeting held at the Rockefeller Foundation's Bellagio Conference Center, Lake Como, Italy. At that conference WHO, UNICEF, the United Nations Development Program (UNDP), the World Bank and the Rockefeller Foundation (UNDP), created the Task Force for Child Survival. To lead the Task Force, Dr. William Foege was chosen. Dr. Foege was a veteran of the smallpox campaign and former Director of the Centers for Disease Control in Atlanta, Georgia.

The accelerated campaign which followed fully justified the hopes of its sponsors. On October 8, 1991, at the United Nations Headquarters in New York, Dr. Hiroshi Nakajima, Director General of WHO and Mr. James Grant, Executive Director of UNICEF were able to announce that the 1990 goals of fully immunizing 80% of the world's children had been achieved (Fig. 5) Immunization was saving 3.5 million lives each year. Emboldened, WHO announced plans to eliminate neonatal tetanus, eradicate poliomyelitis and reduce measles deaths by 95%, all by the year 2000!

IMMUNIZATION: SUCCESS AND FAILURES

INDUSTRIALIZED COUNTRIES

SUCCESSES

The discovery and successful use of polio vaccines in 1956 began what may be called the age of vaccines. It is true that from early in the 20th century children were immunized against diphtheria, pertussis and tetanus (DPT) and in some countries BCG. After the appearance of polio in 1956, quickly followed vaccines against measles, rubella, mumps, hepatitis B, pneumococcus, the meningococcus and Hemophilus influenza. Beginning in the 1970's in the United States, through the leadership of the Centers of Disease control, polio, measles and rubella vaccines were given in mass campaigns, and their use enforced by school entry laws. Poliomyelitis was successfully eradicated from the United States by 1975; for a time measles

also seemed destined to disappear. Similar successes were recorded in virtually all industrialized countries.

FAILURES

However, vaccine success bred failure. To be fully immunized, the modern child requires seventeen different inoculations and six visits to a physician's office over the first 15 months of life. Without the imminent threat of epidemics, many parents simply "forgot" to have their children immunized. Tragically, in the United States many health insurance programs do not cover immunizations. Small wonder that only 60% of American children under 2 years of age are fully immunized. Among U.S. inner city populations, childhood immunization rates are well below those in many developing countries, including some of the world's poorest. Since nearly all American children are born in hospitals, if a comprehensive and long-lasting immunization series could be administered at birth, such a "childrens' vaccine" might reduce parents' reluctance to have their children immunized and, the cost and effort involved in the present system of multiple physician visits.

DEVELOPING COUNTRIES: THE EPI-UNICEF VACCINE DELIVERY SYSTEM

With the attainment of the 1990 immunization goals there was good news and bad news. The good news was that EPI had helped most of the world's 160 developing countries build a vaccine

delivery system that works, one that could easily carry more vaccines to children. The bad news is that 20% of the world's children had not been fully immunized. They are particularly poor, vulnerable and often inaccessible. Without major new interventions in the decade of the 1990s, over 100 million children will die from infectious diseases.

SUCCESSES

The EPI required developing countries to exercise their health systems as never before. The task was formidable. In 1991 it is estimated that 238 million doses of BCG, 523 million doses of DPT, 305 million doses of measles and 689 million doses of polio vaccines moved from central stores to the periphery. To accomplish this, a vast system for detailed planning and, above all, for the training of a critical mass of national immunization program managers had to be created. Essential equipment was purchased and installed. To preserve vaccines at the appropriate temperature, new items such as solar refrigerators, had to be designed, manufactured and distributed. Equipment catalogues were published and repair capacity strengthened up and down the line. Temperature indicators were invented (Fig. 6). These inform program managers at a glance whether vaccines have always been kept at the required temperatures. All this was necessary to establish a vital cold chain from seaports and airports to the most remote clinics. EPI also developed "auto destruct", single-

injection syringes or other devices which would permit immunization without the reuse of needles or syringes, a practice which, if not prevented, could spread blood-borne diseases such as AIDS or hepatitis B.

FAILURES

The magnitude of EPI and the promise of universal child immunization have brought to light important obstacles to be overcome: improving the shelf-life of vaccines, reaching the "missing 20%" of unimmunized infants, overcoming the maternal antibody barrier to early immunization, improving national vaccine manufacturing capability and getting new antigens in the vaccine development pipeline.

SHELF-LIFE AND WASTAGE

Three of the six the EPI vaccines are made from living organisms: tuberculosis (BCG), measles and poliovirus vaccines. The others are complex proteins. Each has special storage and temperature requirements for optimum stability. BCG and DPT will remain potent for up to one year at refrigerator temperatures. Measles and polio vaccines require freezing temperatures (-15°C to -25°C) for long term storage. But DPT vaccines lose potency if frozen. Most measles vaccine is freeze-dried and bottled. The shelf-life of this product is many years at refrigerator or freezer temperatures. To be administered, dried measles vaccine is dissolved in sterile water. This suspension must be used within 24 hours. It is far cheaper to package measles vaccine in

multidose than single dose vials. Since many vaccine clinics are not open daily, reconstituted vaccines from multi-dose vials are often wasted. Indeed, it is estimated that 50% of UNICEF supplied measles vaccine is wasted. Polio vaccine cannot be freeze-dried but must be stored frozen. It is stable for weeks at refrigerator temperatures but only a matter of hours at room temperature. The need to maintain both refrigerator and freezer temperatures in the cold chain is expensive; it can and does result in storage of vaccines at the wrong temperature causing loss of potency and requiring their destruction.

THE MISSING 20%

To achieve optimal protective effect, all vaccines except BCG require booster doses following the primary series. It comes as no surprise that the proportion of children who receive the third dose of polio and DPT vaccines is lowest in Africa (Fig. 7), the region with the least developed health infrastructure. But, in reality because of population size, the largest numbers of unimmunized or partially immunized infants are found in China, India, Indonesia, and Nigeria; 20% in India alone. Many children who receive a first dose of vaccine fail to return for subsequent doses ("dropouts") (Fig. 8). In addition, many potential opportunities for immunization are being missed. A particular problem is the failure to immunize eligible children who are brought to health facilities because of sickness. A major step toward achieving the target of 80% immunization coverage could be

reached if all children who are brought to clinics - for whatever purpose - were screened and given needed immunizations. In surveys of health facilities, 69% of children needing immunization were not vaccinated before leaving the clinic. Of those eligible who had not been immunized the most common reason was that the clinic did not provide immunization as a part of acute care. This is often because it is difficult to keep vaccines available at all times due to their limited shelf-life.

A child's access to vaccines is further limited by the necessity of injection. This requires that vaccines be given by a person with training in vaccine administration and needle handling. These constraints require that children be brought to clinics or vaccination centers rather than have vaccines administered at home.

Another important immunization challenge is neo-natal tetanus which causes some 740,000 deaths per year, second only to measles among vaccine-preventable diseases. Neonatal tetanus results from the contamination of the umbilical stump shortly after birth by use of unsterile methods of cutting the cord or by application to the cut stump of matter such as cow dung or mud to stop the bleeding. Once infected with tetanus, the infected newborn will first be unable to suck and then be unable to swallow or breathe. Some 85% of cases die in the first weeks of life. With the persistence of unhygienic living conditions and

traditional birth practices, the key approach to eliminating neonatal tetanus is to immunize prospective mothers with a primary series of tetanus toxoid vaccination. While five doses are optimal (Fig. 9), at least two doses are recommended. Yet, two-dose coverage in 1990 to women of child-bearing age was a mere 25%. Full use of every contact with the health services to provide tetanus toxoid to perspective mothers would help to improve coverage.

MATERNAL ANTIBODY

Circulating antibodies conveyed from the mother to the unborn child are an important defense against infectious diseases. But, maternal antibodies can also prevent an immune response to a vaccine. The most serious problem is with live-attenuated measles vaccine. Maternal antibody can completely inactivate the vaccine virus and prevent a "take." Measles vaccine coverage is lower than other EPI vaccines. This is due in part to the difficulty of reaching infants at age nine months as compared with the relatively higher participation of mothers whose infants are six weeks of age. The earlier an infant loses maternal antibody and becomes susceptible to measles, the more severe the disease. This is particularly true when infants are poorly nourished.Measles continues to kill 1.4 million children each year (fig. 10). A majority of these deaths are in Africa where maternally transmitted antibody has a particularly short life.

IMPROVING NATIONAL VACCINE PRODUCTION

Although there is substantial variation, locally produced tetanus toxoid, measles vaccine and DPT is given to 71%, 61% and 60% of children in EPI programs. It is important to note that vaccine coverage rates correspond to availability of locally made vaccines, 92% vs 70% when the same vaccine is imported. Also, there is less wastage of locally produced vaccines than imported and donated vaccines. Therefore, local production is one of the keys to national program efficiency as well as to self-sufficiency. While this degree of independence is useful, it raises concerns about the efficacy and safety of these vaccines which can only be assured by strong national quality control systems.

NEW VACCINES: THE CHILDREN'S VACCINE INITIATIVE

There are still some 14 million children who die each year; about 10 million of infectious diseases. Many can be prevented with existing vaccines or are diseases for which vaccine prevention is a theoretical possibility (Fig. 10, 11).

The EPI delivery system has created a base from which significant new gains can be achieved to "Protect the World's Children." Vaccines which are available or which might come into

existence in the next decade could be incorporated into the EPI strategy.

If vaccines could be developed which solved the failures of the current EPI program, virtually universal coverage might be attainable. The major contributions to failures in the current program are listed in figure 12 and shown in the adjacent column is the technical solution. As shown, the two most important technical innovations needed are vaccines which are stable for many days at room temperature, or alternatively, a single dose (or reduced dose) multi-antigen vaccine which could be given at or near birth when contacts with the health system are maximal. Wastage, drop-outs, and missed opportunities would all be improved by either or both innovations. The rate of immunizing mothers against tetanus could be markedly improved if a single-shot tetanus vaccine could be developed.

With new vaccines and a reduced dosage schedule, particularly if these vaccines were stable at tropical temperatures and, if possible, given orally, <u>then</u> the poorest and most remote children might be reached with maximal efficiency and protected against a whole range of infectious diseases. A multi-component, heat-stable oral vaccine could be given to village health workers for house to house delivery to reach the 20% of unvaccinated children. Or vaccine could be dispensed dose by dose from multi-dose vials containing stable vaccines which would be perfectly preserved for many weeks in clinic refrigerators.

By-passing maternal antibody may require novel approaches. Delayed-release of vaccines (described below) may be just such an approach. Finally, cost. UNICEF studies also show important cost savings with the CVI. Assuming that the required number of vaccinations could be reduced from 5 to 3. If an 80% coverage rate could be maintained over a 20 year period there would be an average of savings in costs for delivering the present 6 vaccines of 15%, or a cumulated savings of $5.1 to $6.4 billion. Costs of vaccine delivery can be reduced by requiring fewer immunizations but, in the final analysis, only competition and technical innovation will be effective in containing costs. The number of technically competent national or regional vaccine manufacturers is an important part of the equation.

HOW MIGHT A CHILDREN'S VACCINE BE BROUGHT INTO EXISTENCE?

Needed is an applied research program designed to move vaccines for Third World children from the "bench to the bush." Fortunately, the practice of combining vaccines is well established. DPT has long been given as a combined vaccine; the three polio viruses were given together, as was the measles, mumps and rubella live-attenuated vaccines. But, a major effort is required to eliminate the requirement for multiple doses and to make it possible to give all required vaccines in one or two doses. A reduced-dosage children's vaccine would require new ways to combine antigens, such as, microspheres or microcapsules

or the ability to engineer multiple genes into large microorganisms. Examples include the pox viruses, BCG or the live-attenuated typhoid bacterial vaccine. Because of the small economies of developing countries, market forces will not bring new vaccines into existence. A mechanism which does not exist was needed to select between technical options, to focus research and development efforts, to raise capital and engage vaccine manufacturers.

A mechanism was suggested at a WHO meeting, Innovative Approaches for the Development of Third-World Vaccines, held in Geneva in June 1990. The concept of a reduced dose, multi-antigen vaccine quickly won support from the national and international scientific communities. In a remarkably short time, on September 10, 1990 members of these communities issued the Declaration of New York which called for a Children's Vaccine Initiative (CVI). In February 1991, 15 organizations, foundations, multilateral and bilateral development assistance agencies met at the Seven Springs Conference Center, Mt. Kisco, New York to create a Children's Vaccine Initiative Consultative Group (CVI/CG).

THE GLOBAL CVI

In 1993, the CVI/CG has the following components: A Chairman who provides overall strategy, management and policy guidance, a Special Advisor who gives technical leadership to product

development; a Secretariat, which extends administrative support and is located at the WHO Headquarters in Geneva; Product Development Groups (PDG) which oversee technical development, and Task Forces (TFs) which select new vaccines and propose policy; a Standing Committee formed of five funding agencies, WHO, UNICEF, UNDP, the World Bank and the Rockefeller Foundation; an 18 member Management Advisory Committee composed of representatives of developing country health ministries and vaccine manufacturers, development assistance agencies, the biologics standards community and the pharmaceutical manufacturers; and a Consultative Group (CG). Participants at the first two CG meeting in Geneva in 1991 and 1992 included representatives of more than 100 entities - foundations, research agencies, multilateral and bilateral development assistance agencies, pharmaceutical companies, health ministries and private voluntary organizations.

HOW DOES THE CVI/CG WORK?

Foremost, the CVI/CG is a planning, consensus-building, communications, decision-making and R&D management organization. Outside the U.S. Department of Defense and private industry no comparable organization for the creation of health products has ever been created. As its first activity, the CVI/CG appointed five Task Forces:

1. Priority Setting and Strategic Planning

2. Preparation of Guidelines for Relations with Vaccine Development Collaborators.
3. Situation Analysis of Global Vaccine Supply
4. Assessment of Vaccine Regulatory Capabilities and Needs
5. Strengthening National Epidemiological Capacity for Supporting Vaccine Programs

Next, three Product Development Groups were formed: a Single-Dose Tetanus Toxoid, Heat-Stable Oral Polio Vaccine and Improved Measles Vaccine. In the future, products recommended for development by the Priority Setting and Strategic Planning Task Force will be assigned to an appropriate PDG. The PDG will then steer the product through the final stages of development, identify potential manufacturers, competitively award production contracts, oversee vaccine production, and carry out Phase I through Phase III testing in human volunteers.

The Single-Dose Tetanus Toxoid PDG seeks to bring into existence a delayed release vaccine using a new polymer technology. Spherical, sustained-release polymer particles can be either monolithic, with the antigen to be released interspersed throughout the particle (microspheres) or consist of a core reservoir of antigen surrounded by an outer polymer shell (microcapusles). Antigen trapped in microspheres is released in a sustained fashion which depends upon the rate of degradation of the polymer. In contrast, microcapsules release antigen in a

pulse when the wall is breached. While both microspheres and microcapsules may be used in delayed-release vaccines only microcapsules will be considered here.

Microencapsulation involves the coating of an antigen by a protective wall made up of the polymers of DL-lactide and glycolide (Poly(DL-lactide-co-glycolide): DL-PLG (Fig. 13). The microencapsulated material is a free-flowing powder of spherical particles which can be produced in a size range from <1μm to as large as 3mm in diameter. DL-PLG is in a class of biodegradable and biocompatible co-polymers from which resorbable sutures, resorbable surgical clips and controlled-release drug implants are produced. The polymers themselves have been approved for human use and have a long record of safety in human beings. To produce a vaccine, dried antigen would be coated with DL-PLG. This should result in a vaccine which has an extended shelf-life without the need for stabilizers or a cold chain.

The rate at which DL-PLG biodegrades is a function of the ratio of lactide to glycolide. Administration of a vaccine which contains one-half of the microcapsules formulated with equimolar lactide and glycolide (50:50 DL-PLG) and one-half being a 100:0 formulation results in sustained antibody response with a plateau level achieved on day 230. A delayed-release vaccine can be made in which an unencapsulated antigen is available to stimulate a primary antibody response. This is combined with any number of

encapsulated "pulsed" booster vaccines which are released over a two-year period. Furthermore, microcapsules containing several different antigens, each being released at an optimal immunizing schedule, can be mixed together to produce a multi-antigen, one-shot vaccine. After introduction into the body, DL-PLG induces a minimal inflammatory response and biodegrades through hydrolysis of its ester linkages to yield lactic and glycolic acids, normal body metabolic products. Antigens encapsulated in spheres 10μm in diameter or less are ingested by macrophages and serve to increase the immune response. Further, such antigen is unavailable to pre-existing antibody, such as that acquired by maternal-fetal transport.

A further possible application of microcapsulation is an oral vaccine. Microencapsulation in DL-PLG effectively protects protein antigens from the acidity and proteolytic enzymes in the stomach and small intestine. Microcapsules of less than 10μm in diameter are taken up by intestinal macrophages which then migrate to regional lymph nodes stimulating systemic antibody. This route of antigen presentation also results in the production of secretory antibodies which appear in the saliva, respiratory tract secretions, tears and breast milk. Secretory antibodies help to protect against enteric and respiratory tract infections. Breast milk can be an important source of passively transferred secretory antibodies which are effective in protecting suckling infants against disease.

By early 1993 the Single-Dose Tetanus Toxoid PDG plans to award contracts to prepare a microencapsulated vaccine. This will require partnering of vaccine and microencapsulation manufacturers. Several different microencapsulation processes will be evaluated as will different formulations of DL-PLG. These will be tested in animals to determine which produces the best antibody response. Cost and ease of production may be factors in selecting a manufacturing process since it is desirable to keep the price of these vaccines low and to enable present third world manufacturers of TT to adopt the process.

Once an optimal formulation is obtained, careful safety tests will be performed in a number of animal species. The concern here will be the degree of local inflammation produced by these long-acting vaccines. Of greater concern, but of unknown risk until human testing is started, is the occurrence and frequency of allergic reactions. In genetically susceptible persons or in individuals previously sensitized, injection of foreign proteins produces any of a number of unwanted immunologic reactions, such as hives or delayed-type hypersensitivity. Safety is the principal reason for performing Phase I (limited, close observation) and Phase II (larger, less closely monitored) trials of biologicals and drugs in human subjects. If all goes well, Phase I trials of a one-shot tetanus toxoid vaccine could take place in 1993 or 1994.

MULTIPLE ANTIGENS: 1993 AND BEYOND

Many of the infectious diseases which cause deaths of children (Fig. 10 & 11) can be prevented by existing vaccines. Today we can visualize how vaccines made from inactivated antigens might be added to a Single-Dose Children's Vaccine. For example, the following vaccine is theoretically possible:

Diphtheria
Pertussis
Tetanus
S. pneumoniae
H. influenza
Influenza A
Hepatitis A
Hepatitis B
Japanese encephalitis
Meningococcus types A, C

Live-attenuated vaccines exist for tuberculosis, measles, polio, yellow fever, typhoid fever, rubella, mumps, varicella (chicken pox) and dengue types 1-4. In theory, many of these might be combined. Because of circulating antibody, administration of some of these vaccines would have to be postponed until at least nine months of age. There is a way around this problem. Currently, it is possible to incorporate

genes from these agents into pox viruses, BCG or attenuated typhoid. Such a construct would provide a multi-antigen vaccine and a technique of introducing a living organism (e.g. the pox virus) which will not be attacked and destroyed by maternal antibody. Once safely in a permissive cell, the replication process will secrete antigens from cells or express antigens on cell surfaces stimulating antibody production.

From the vantage of 1993, a Children's Vaccine is beginning to take shape. Such a vaccine could be given by mouth as a mixture of inactivated antigens in microcapsules together with an injected vaccine composed of antigens genetically engineered into a living microorganism. To be fully effective in saving lives new vaccines must be developed against major causes of diarrhea, respiratory syncytial virus and such killers as malaria, HIV and tuberculosis.

Even using existing vaccines, many strategies must be explored to choose the one which permits the creation of the best combination vaccines. It is likely that the jury of scientific experts which will find the technical solutions and carry these into production, will be one selected by CVI.

Fig 1

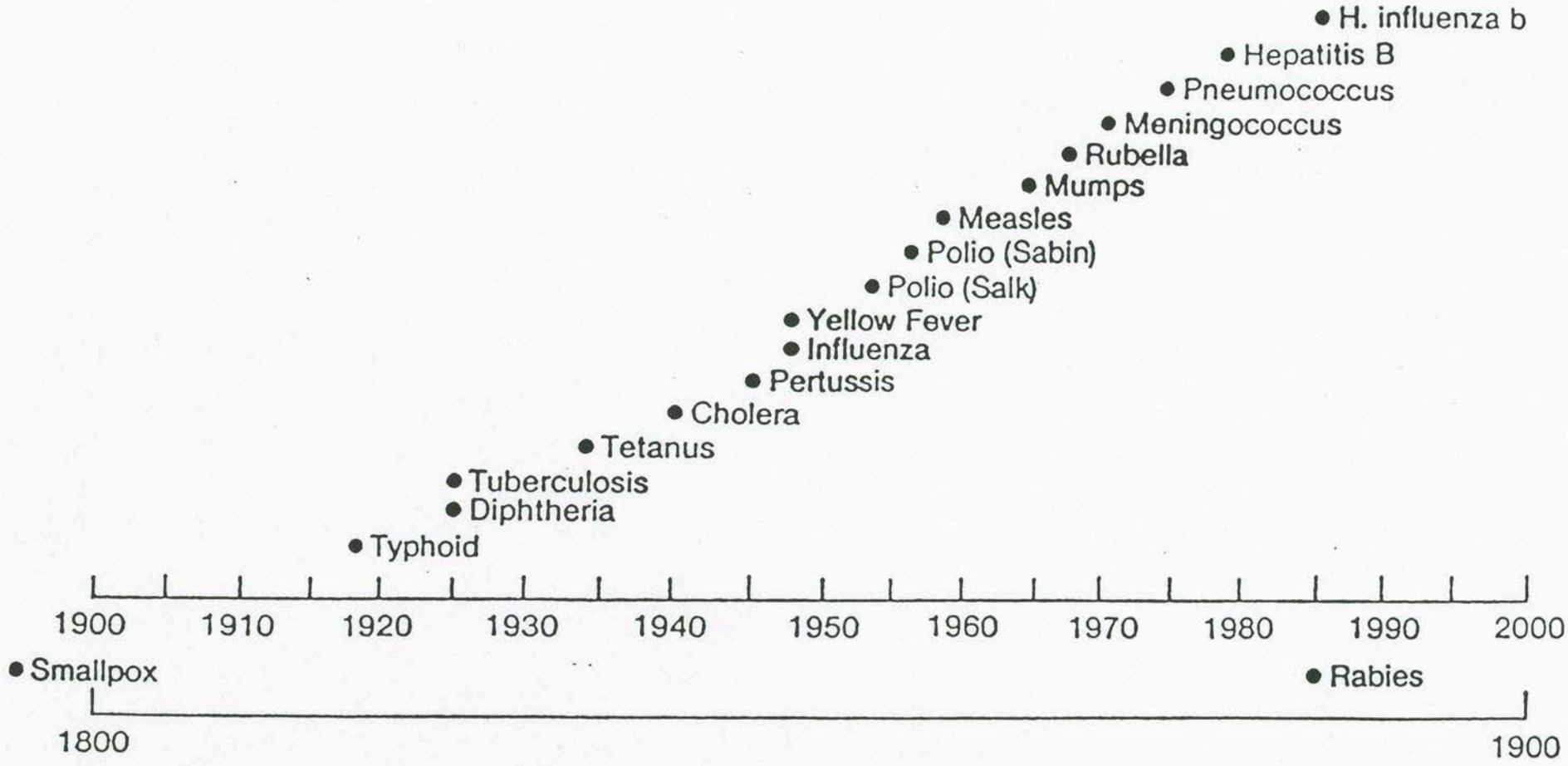

H. influenza b
Hepatitis B
Pneumococcus
Meningococcus
Rubella
Mumps
Measles
Polio (Sabin)
Polio (Salk)
Yellow Fever
Influenza
Pertussis
Cholera
Tetanus
Tuberculosis
Diphtheria
Typhoid
1900
1910
1920
1930
1940
1950
1960
1970
1980
1990
2000
Smallpox
Rabies
1800
1900

FIGURE 2

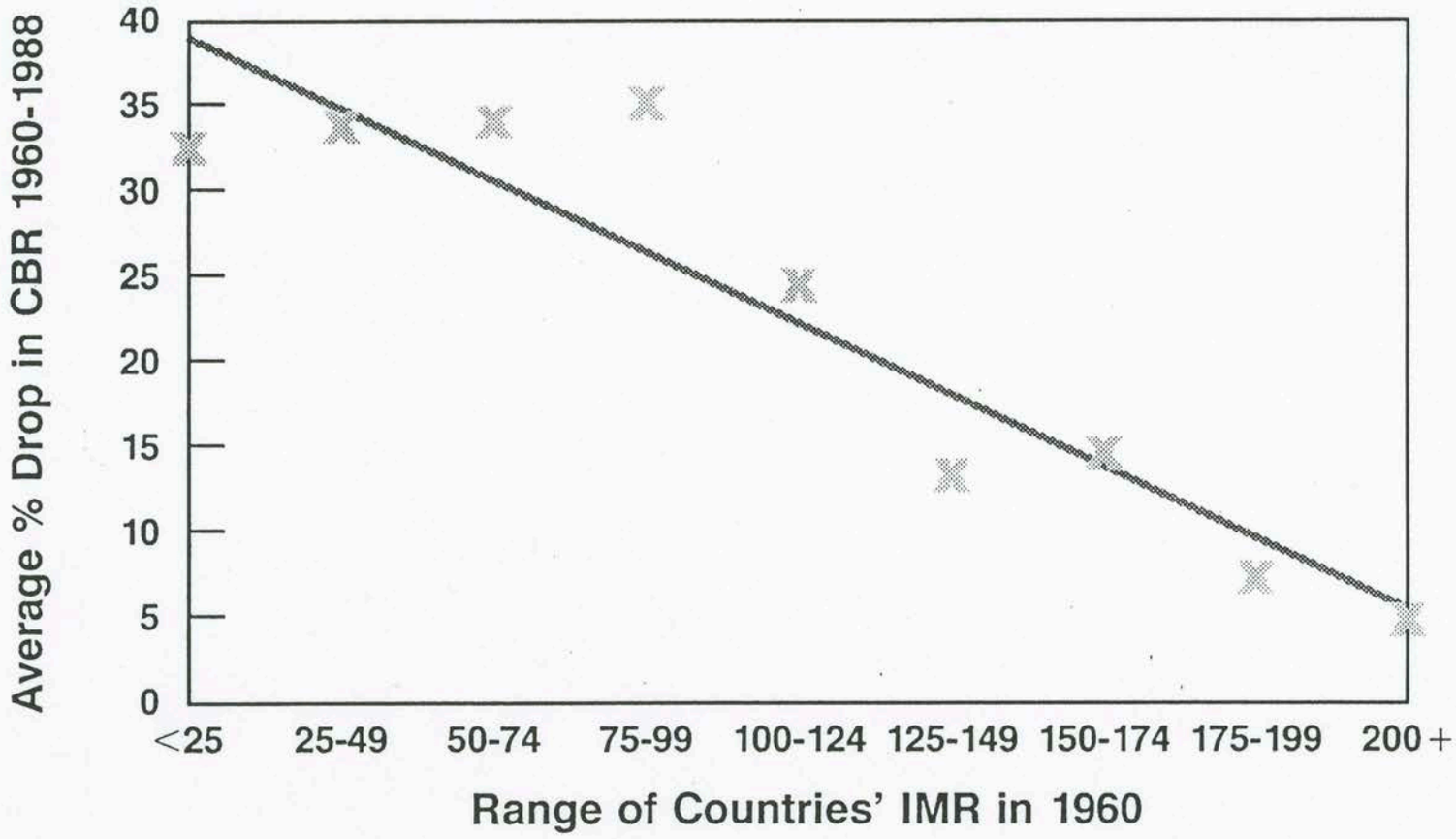
IMMUNIZING BABIES IN THE EPI

VACCINE	AGE
BCG	Birth
Polio-1	Birth
DPT-1	6 weeks
Polio-2	
DPT-2	10 weeks
Polio-3	
DPT-3	14 weeks
Polio-4	
Measles	9 months

FIGURE 3.

Global Changes in Crude Birth Rates

1960 to 1988, by Initial IMR Range



$r^2 = .86$

Fig 4 B

as a third, but the quality of child care, of health, nutrition, and education, would inevitably rise as parents were able to invest more of their time, energy and money in a smaller number of children.

Fourth, population growth would be slowed. Evidence from the *World Fertility Survey* suggests that if women who do not want to become pregnant were empowered to exercise that choice then the rate of population growth in the developing world would fall by approximately 30% (fig. 9). Meeting the existing demand for knowledge about birth planning would therefore also contribute to an improvement in per capita incomes and a reduction in environmental pressures.

With so many substantial advantages to be had from the meeting of an existing demand at an affordable cost, the promotion of the knowledge and the means of timing births also lays claim to consideration as one of the first priorities of the 1990s.

6. The attack on malnutrition

The last item on this agenda of specific actions for the children of the 1990s concerns the progress that could now be made in improving child nutrition.

The roots of malnutrition are so deeply embedded in the soil of poverty, it is often argued, that only economic development can loosen their grip. But such a response amounts to little more than opting out of the problem.

First, it is simply unacceptable that over 150 million children under five should suffer from malnutrition in a world which has the capacity to prevent it (fig. 10).

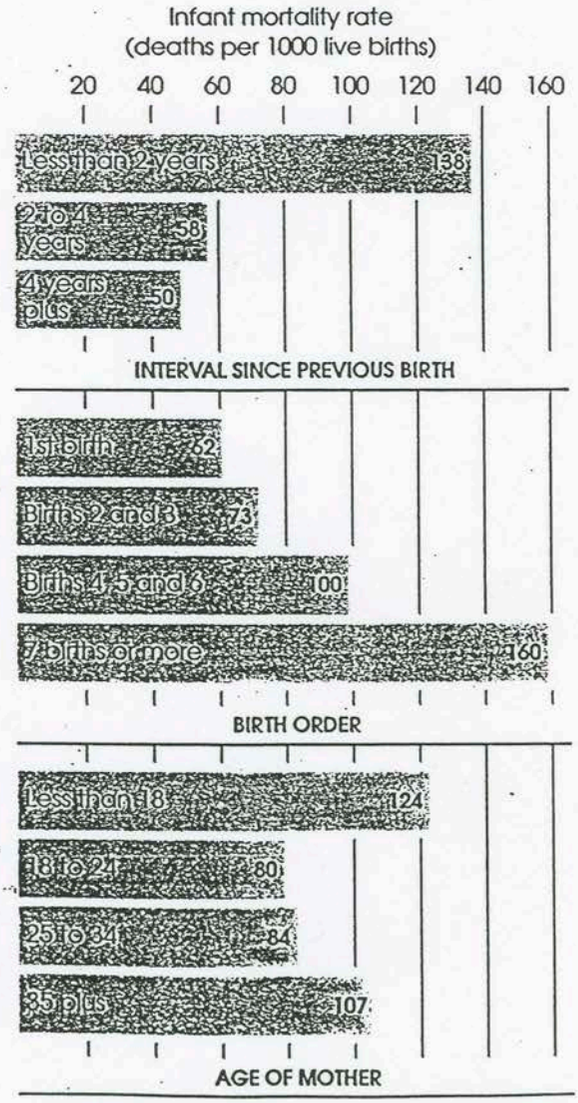
Second, malnutrition impairs the physical and mental development of children and the working and earning capacity of adults; it is therefore a cause as well as a consequence of poverty.

Third, several countries have managed to reduce malnutrition drastically, even though per capita incomes remain low.

Fig. 8 Timing births and saving lives

Birth spacing is one of the most vital of all factors in the health of both mothers and children. Both infant and maternal deaths are heavily concentrated among those births which are 'too many or too close' or to mothers who are 'too young or too old'.

Infant mortality by age of mother, birth order, and interval between births, Brazil, 1976–86



Source: Institute for Resource Development, Demographic and Health Surveys, Columbia, Maryland.

Fig 5 (or photo of Audrey Hepburn at UN? Jimmy Carter

The quiet catastrophe

Two principal facts dominated the World Summit for Children.

The first was the fact of the quiet catastrophe - the 40,000 child deaths each day from ordinary malnutrition and disease, the 150 million children who live on with ill health and poor growth, the 100 million 6 to 11-year-olds who are not in school.

The second was the fact that the means of ending this quiet catastrophe are now both available and affordable. Large-scale trials and studies in many nations in recent years have vastly increased both the world's understanding of the problems and its capacity to solve them.

The question at the centre of the World Summit was therefore whether morality would keep step with capacity, whether what *could* now be done *would* now be done.

It was a question given an extra dimension by the fact that the Summit for Children came less than two months after the United Nations had been called upon to act in response to the crisis in the Persian Gulf. The juxtaposition of these two major events at the United Nations could not have been more poignant; for it posed the question of whether the international community was prepared to act on the important as well as on the immediate, and in the interests of the powerless as well as those of the powerful.

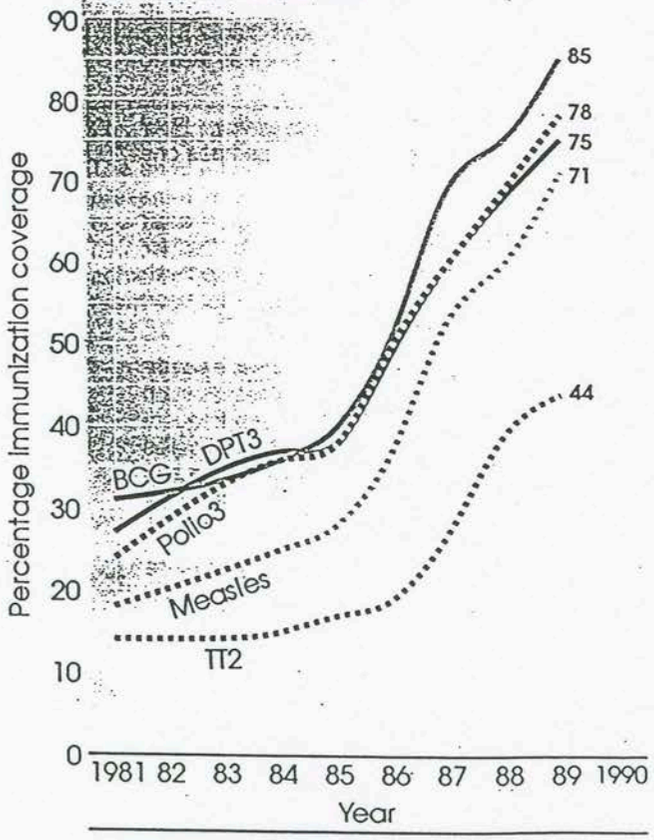
None of these questions could be answered in full at the Summit itself. For they are questions which will be answered not by the declarations of a day but by the deeds of a decade.

But what did emerge from that Sunday in September was an entirely new commitment to the children of the quiet catastrophe.

On that Sunday, for the first time, the centre of the stage was occupied not by the victims of any sudden disaster, any earthquake, famine, or flood, but by the children who are the victims of the much greater daily disaster of malnutrition and disease. For the first time, their case was put before the assembled political leaders of the world. For the first time, their voice went out around the world. For the first time, their claim was acknowledged by headlines in virtually every country. And if the world keeps faith with the commitments made that day, then of these children it might at last be said that their time has come.

Fig.1 Increase in immunization coverage for infants in developing countries, 1981-89

The graph shows the developing world's progress towards the target of 80% immunization by the end of 1990. Figures for 1990 will be available in early 1991. China is not included in the data until 1986.



TT2 = two anti-tetanus injections, during pregnancy, to protect against tetanus of the new-born.

Source: WHO and UNICEF.

You Should Immunize Every Eligible Woman Who Brings a Child to Your Clinic

Check STOP!watch monitors and expiry dates to help ensure that your TT is potent.
Screen *every* woman of child-bearing age when she brings a child to your immunization session. Immunize every woman who is eligible for a dose of TT.
Give the woman a life-time immunization record if she does not already have one. Ask her to bring the record every time she comes to an immunization session.
Advise every woman to complete a 5 dose TT schedule in order to protect her future newborns. Make a return appointment if she needs another immunization.

BECAUSE

Expired or frozen vaccine may not be potent. If the vaccine has ever been frozen or is past its expiry date it should be discarded.

The TT status of many women who accompany a child to an immunization session may not be up-to-date. Take this opportunity to protect the mother and her future children against tetanus before she delivers again.

Every TT injection should be recorded on a life time immunization record. A listing of injection dates helps to ensure that future immunizations will be given at the correct time.

Women who understand the importance of TT and have a follow-up appointment are more likely to return for their next immunization. This results in lower drop-out rates and higher TT coverage for your clinic.

You Should Guarantee that No Woman Attending Your Antenatal Clinic Will Have Dying of NT

Administer TT at the first anter
Record all doses on the woman's
munization record.
Advise every woman who will del
where to get a clean delivery kit
use it. If kits are not available i
advise her to:
(1) tell birth attendants to wash
carefully with soap and water
nail pick to clean under finge
the delivery.
(2) put a clean cloth or plastic
surface where the baby will be
(3) tie the cord with clean strips o
(4) cut the cord with a new, clean
(5) put only clean cloths on the co
Make an appointment to see the
or two weeks after delivery.

Content of a Clean Delive

- Soap
- New razor
- Nail pick
- Four clear
- Plastic sheet
- Three clea

Instructions for non-literate

BECAUSE

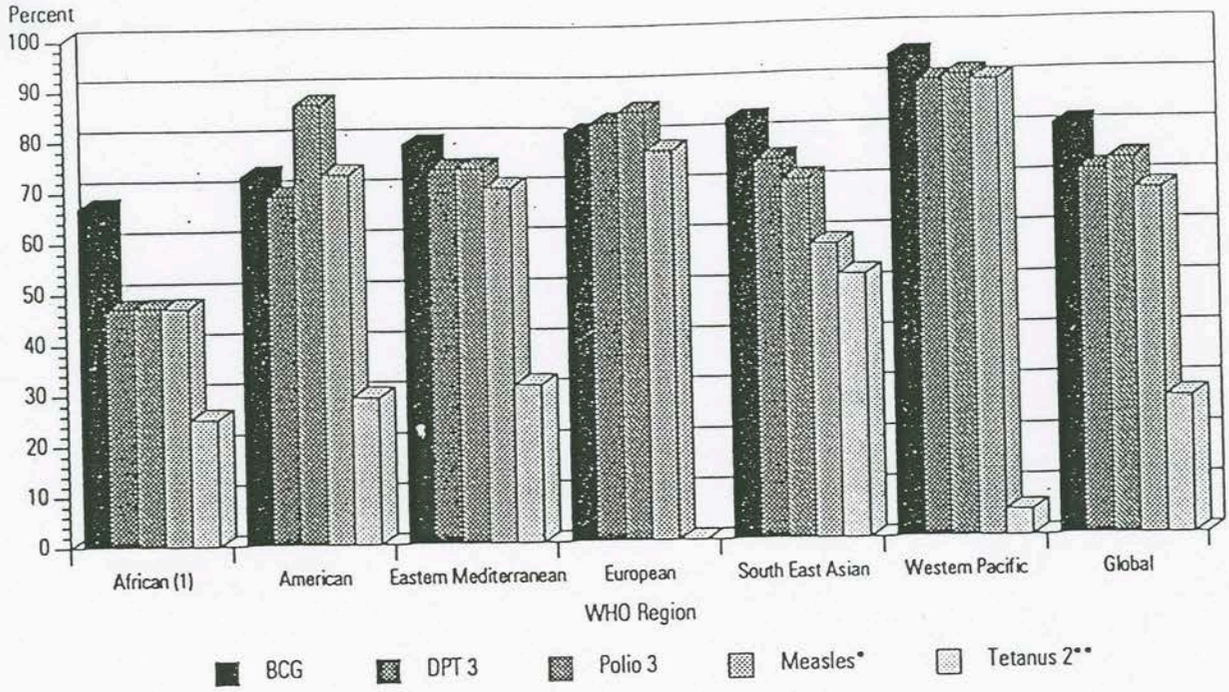
TT is safe for both the woman and baby any time during pregnancy given at the first antenatal contac enough time before delivery to g dose if needed.

Clean delivery and cord care mother and baby from tetanus related infections.

You need to see the mother and within one or two weeks after deli sure they are both healthy, up munizations and advise on breas fant immunization and family pla

Figure 7

Estimated percentage of children immunized in the first year of life and percentage of pregnant women immunized against tetanus by WHO Region, based on information available, June 1990.



* Coverage data for children up to 60 months are included for countries recommending immunization at, or later than, 12 months.
** Boosters included.
(1) Excluding South Africa

and subscribed to the approach of moving toward that goal through a series of sequential vaccine improvements which emphasize the development of vaccines which:

- require one or two rather than multiple doses;
- can be given earlier in life;
- can be combined in novel ways to reduce the number of injections or visits required;
- are more heat stable; and
- are affordable.

Report on the World Summit for Children

The World Summit for Children was held in New York on 29 - 30 September 1990. Seventy-one heads of state and representatives from 69 other countries met to review problems related to providing adequate conditions for the growth and survival of the world's children. This meeting was important for many reasons. First, it initiated or accelerated programmes which related to the plight of children. Second, it focused world attention on the predica-

Fig 8

IMMUNIZATION COVERAGE WITH DPT 1&3 and TT 1&2 VACCINES and RELEVANT DROP-OUT RATES IN SEVERAL COUNTRIES - 1987 to 1990

Immunization coverage with DPT 1 and 3 and TT 1 and 2 vaccines and relevant drop-out rates in several countries, 1987 - 1989

FIGURE 7

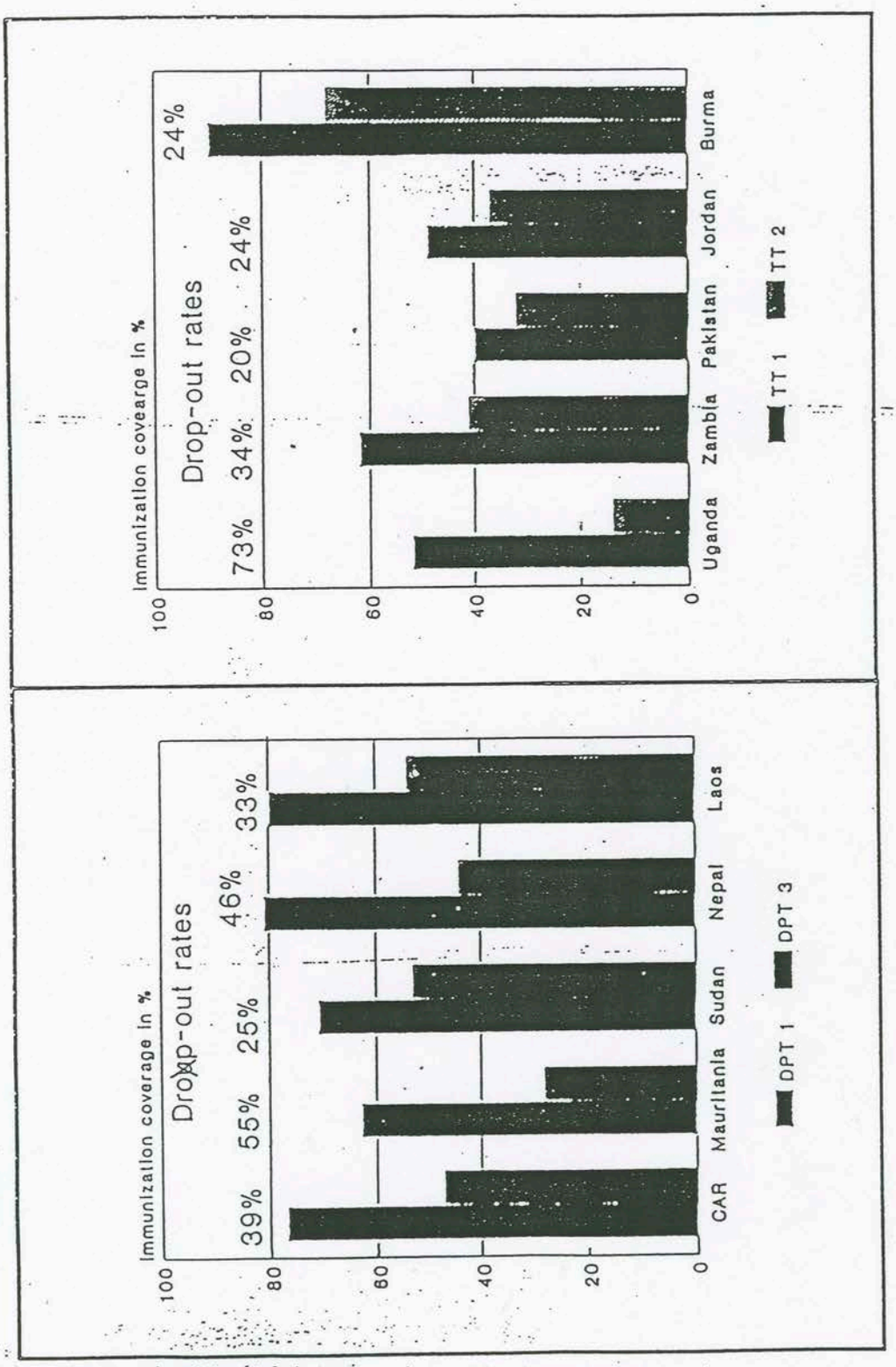


FIGURE ~~8~~ 9

IMMUNIZING MOTHERS AGAINST TETANUS
THE 5-DOSE SCHEDULE OF TETANUS TOXOID (TT)

DOSE	TIME
TT-1	First contact
TT-2	4 weeks later
TT-3	6 months after TT-2
TT-4	1 year after TT-3
TT-5	2 years after TT-4

FIGURE 10

DEATHS OF INFANTS AND CHILDREN DUE TO INFECTIOUS DISEASES

DISEASE	DEATHS/YEAR (MILLIONS)	VACCINE STATUS
Measles	1.4	Exists
Neonatal tetanus	.75	Exists
Diphtheria	.005	Exists
Pertussis	.49	Exists
Tuberculosis	.003	Needs improvement
(Poliomyelitis)	(.19 paralysis)	Exists
Respiratory infections	2.2	See separate list
Diarrheal diseases	4.0	See separate list
Hepatitis B&A	.1	Exists
Meningitis	.1	Exists
Malaria	1.0	Research phase
	10.05	

SOURCE: World Health Organization, Expanded Programme on Immunization. Annual Report, December, 1990

FIGURE 11

Primary pathogens causing deaths from respiratory diseases

ORGANISM	PROPORTION OF DEATHS (%)	STATUS OF VACCINES
S. pneumoniae	22.5	Exists
H. influenza	11.5	Exists
Influenza virus	10.0	Exists
Respiratory syncytial virus	7.0	Research phase
Parainfluenza virus	5.5	Research phase
Staphylococcus aureus	4.0	Research phase
Others	39.1	
	100.0	

Primary pathogens causing deaths from diarrheal diseases

ORGANISM	PROPORTION OF DEATHS (%)	STATUS OF VACCINES
Rotavirus	20	Research phase
Enterotoxigenic E. coli	18	Research phase
Shigella	15	Research phase
Cholera	3	Needs improvement
Salmonella	1	S. Typhus Exists
Others	43	
	100	

Source: Walsh, J.A. Establishing Health Priorities in the Developing World. UNDP, 1988.

Figure 12

Failures in the current EPI vaccine delivery system and possible remedies

FAILURES	REMEDIES
Shelf-life	Heat-stability
Wastage	Heat-stability
Missing 20%	
Drop-outs	Heat-stability/one-dose
Missed opportunities	Heat-stability/one-dose
Immunization of mothers	One-dose
Maternal antibody	One-dose/new vaccine
Improving national production cost	Technology transfer
Deaths due to other diseases	New vaccines/one-dose

Fig 13

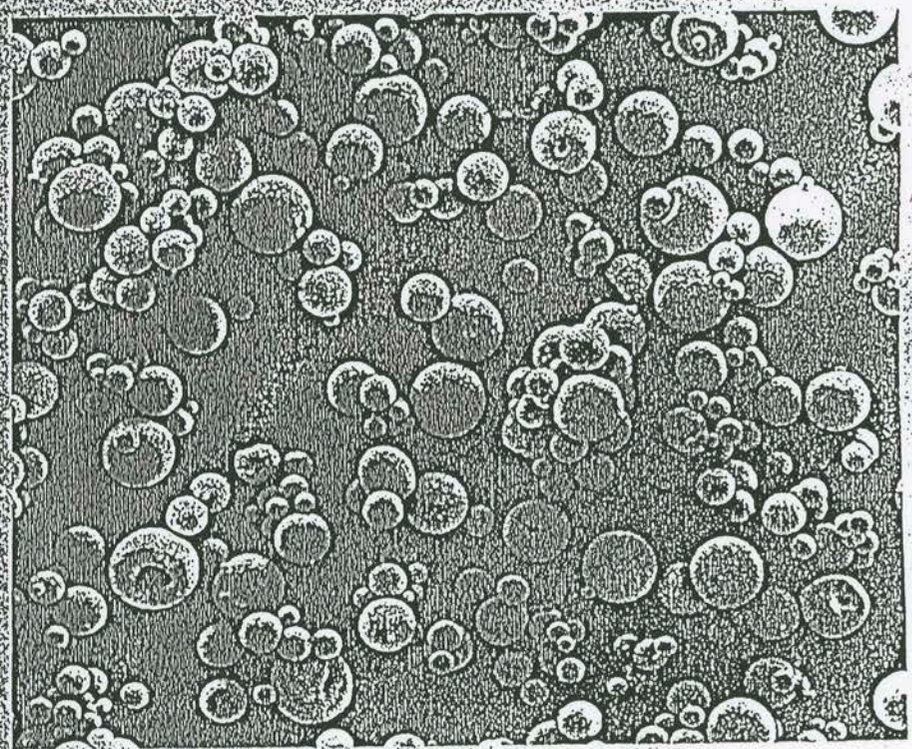
mic repeated injections. The PVD-funded studies have ogressed quickly, and several projects have produced erent candidate microencapsulated, one-shot tetanus ccines. The first comparative animal tests will start early 1991. Eventually, the same technology will be plied to other vaccines which now require multiple shots.

The **live-vaccine carrier approach** is the second path research towards a one-shot vaccine. Unrelated live viral bacterial vaccines will be employed as carriers to deliver a cond vaccine more efficiently. Genes which code for the otective components of a vaccine are inserted into the nome of a currently available viral (e.g. smallpox vaccine) bacterial (e.g. BCG) vaccine. The PVD has funded a mber of early studies focusing on improving general erall aspects of this technique. Other components of PVD using specific aspects of this approach to produce new improved vaccines.

ogress towards oral vaccines. Work in this area is at an rly stage of development. The first goal is to convert ccines that need repeated oral administrations into one- se oral vaccines. The second goal is to convert vaccines at now need to be inoculated into orally administered ccines. The methods to be employed are the orementioned microencapsulation and the live-vaccine rrier approaches.

ogress towards multiple vaccines delivered in one- se or one-shot. It is hoped that work in this area will lead the children's vaccine. The technological tools scribed above to make a one-shot vaccine with one ntigen will also be used to make a one-shot vaccine with ultiple antigens.

AN ENCAPSULATED ONE-SHOT TETANUS VACCINE PREPARED UNDER THE PROGRAMME FOR VACCINE DEVELOPMENT



Further information on the Programme for Vaccine Development may be obtained from:

Microbiology and Immunology (MIM)
World Health Organization
CH-1211 Geneva 27
Switzerland

Facsimile: (022) 788 29 67 (MIM)
(022) 791 07 46 (WHO general)
Telex: 415416 OMS
Telephone: (022) 791 26 04

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Gilbert Uzan, Agence GAMMA, Paris
Stolle Research and Development Corporation, Cincinnati, Ohio, USA

Stolle - source of photo for Fig 11