C V I F O R U M

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In this Issue

Combinations, the key to global immunization

We've come a long way since English physician Edward Jenner 200 years ago used cowpox virus to protect people against smallpox and thereby discovered the first effective vaccine against a human disease. We now have vaccines against nearly 30 different diseases and work under way on new vaccines should double that figure within a decade or so. Admittedly, many of our current vaccines are far from ideal. But even so, the vaccines being used by WHO's Expanded Programme on Immunization (EPI) against just six common childhood diseases—diphtheria, whooping cough, neonatal tetanus, measles, and tuberculosis—are now reaching about 80% or 100 million of the world's children and are saving from death every year an estimated 3 million of them[1].

Of the nearly 13 million children that die every year over 2 million do so from diseases that could be prevented by existing vaccines.

There is still work to be done, though. Of the nearly 13 million children that die every year[1] over 2 million do so from diseases that could be prevented by existing vaccines[1]. Immunization coverage clearly has to be increased. Even sustaining the 80% level is proving difficult, particularly in Africa, where over the last two years coverage has dropped by 14% for the anti-tuberculosis BCG vaccine (now at 68%) and by 5% for the measles vaccine (now at 50%)[2].

Expense is certainly an issue: to deliver the protective vaccine molecules (antigens) to the world's annual cohort of 125 million "new" children[3] requires an estimated 500 million immunization contacts at an average cost of US$15 per fully immunized child. And funding for immunization programmes is becoming harder to find, because of, among other things, rising costs, so-called donor fatigue and conflicting demands on health and development resources.

The solution? A super-vaccine, of course, containing in a single dose all the antigens you need for lifelong protection against the most life-threatening and disabling diseases. Such was, in fact, the vision that attended the birth of the CVI in the autumn of 1990. And with the galloping advance of biotechnology, it may one day become reality. In the meantime, the move towards that ideal has begun with the development of combination vaccines.

UNICEF/Carolyn Watson

Combination vaccines should make immunization contacts, as in this session in Niger, more cost-effective.

Already in the 1940s and 1950s scientists began mixing into a single injectable product the antigenic substances used in vaccines against diphtheria and tetanus (which both use *toxoids* or inactivated bacterial toxins) plus whooping cough, or pertussis, (which uses killed whole bacteria). In 1949 the diphtheria-tetanus-pertussis (DTP) combination was licensed for use in children and started its long career as the backbone of most national and even international immunization programmes. In the mid-1950s, the first, injectable, polio vaccine was developed, using a combination of the three main types

Cover photo: Cam/Len Sirman

UNICEF/Jeremy Horner

Combination vaccines should make vaccination a less tearful event for many children.

(*serotypes*) of poliovirus found in nature; a decade later came an oral version of this vaccine, which could be used more easily in developing countries and which has become the basis for the current polio eradication initiative.

Work on combining antigens continued. In the mid-1960s, a French company brought out a formulation of DTP administered, through a special syringe, with inactivated poliovirus vaccine (IPV), a combination that became a true multi-antigen DTP/IPV product in 1985. Meanwhile, in the 1970s, the live (but weakened, or *attenuated*) viruses used in the vaccines against measles, mumps and rubella were combined into a single injectable product (MMR). And in the past year, a combination vaccine was licensed in the United States combining DTP with the antigen used to protect against *Haemophilus influenzae* type b (Hib), a microbe responsible for a number of diseases, the most serious being acute bacterial meningitis in infants.

So today, not counting the *trivalent* polio vaccine, which protects against three forms of the same pathogen, there are four main combination vaccines (DTP, DTP/IPV, DTP/Hib and MMR) that together protect against eight pathogenic organisms. And further combinations are in the pipeline (see diagram p. 5).

The advantages of combination vaccines are considerable. Since delivery of vaccines accounts for 90% of the cost of immunization, at least in developing countries, being able to deliver the equivalent of several vaccines in a single combination would make a considerable saving in costs, notably on labour, storage, needles, syringes and other logistical necessities. And if the combination is heat-resistant, it would eliminate the expense and complexity of a cold chain. EPI officials reckon a combination vaccine potent enough to cut the number of immunization contacts from five to one would almost halve the average US$15 cost of fully immunizing a child against the six EPI diseases (a cost which includes a significant proportion of fixed, non-reducible expenditures). Combination vaccines could, in other words, make immunization more affordable to national health services, while at the same time making it more acceptable to health care

A combination vaccine potent enough to cut the number of immunization contacts from five to one would almost halve the average US$15 cost of fully immunizing a child.

workers and their "clients." One result could be a fall in the current 25% drop-out rate among children scheduled to return for a subsequent dose of vaccine and an overall increase in immunization coverage rates.

There are still, however, technological limitations to stringing vaccine antigens together in single formulations. Lack of antigen purity is one. Clearly, the purer the antigens used in a combination, the more selective will be their action, the less likely the chances of interference or competition among the vaccine's different components, and the more easily reproduced for bulk manufacture and the less reactogenic the combination product will be.

The purity problem, however, concerns primarily DTP. To become the basis for future combinations, as many vaccine experts believe it should (see box), a purer DTP is needed. And indeed, in the past two or three years, a newer, purer DTP has emerged that uses, not the chemically inactivated, whole bacterial (*Bordetella pertussis*) cell that is the antigen in the standard DTP formulation, but rather one or more selectively identified antigenic structures or products (e.g. toxins) of *B. pertussis*. Several such *acellular* pertussis (aP) products have recently been licensed, and in the last year two have appeared combined with diphtheria and tetanus toxoids in a single vaccine product. Clinical trials of both these DTaP vaccines have shown them to be much less reactogenic than whole-cell vaccines containing the same D and T components[4]. And further trials are being conducted of a number of types of DTaP to determine

One result could be a fall in the current 25% drop-out rate among children scheduled to return for a subsequent dose.

Building on the diphtheria-tetanus-pertussis vaccine (DTP): a CVI strategy

The first multicomponent vaccine that brought the antigens protective against diphtheria, tetanus and pertussis into a single combination product (DTP) has a lot going for it. It has been around for over four decades and has been shown to have nearly 90% overall protective efficacy against the three diseases. And it is likely to be around for a long time: it is inconceivable, on present knowledge, that the three diseases, caused as they are by such widely prevalent organisms, will ever be eradicated. DTP, moreover, is safe: although adverse reactions do occur, they are almost invariably mild and certainly do not prevent the vaccine from being given to children at an early age (from two months). Finally, DTP's component antigens, particularly the diphtheria and tetanus toxoids, are chemically stable and unlikely to conflict with other antigens that might be added to the combination.

For all these reasons, plus the fact that 60 to 75% of DTP used in developing countries is manufactured locally in these countries and that the technology currently used to produce DTP is unlikely to be replaced in the foreseeable future, the CVI has decided to give high priority to the use of DTP as the core or platform of many future combinations.

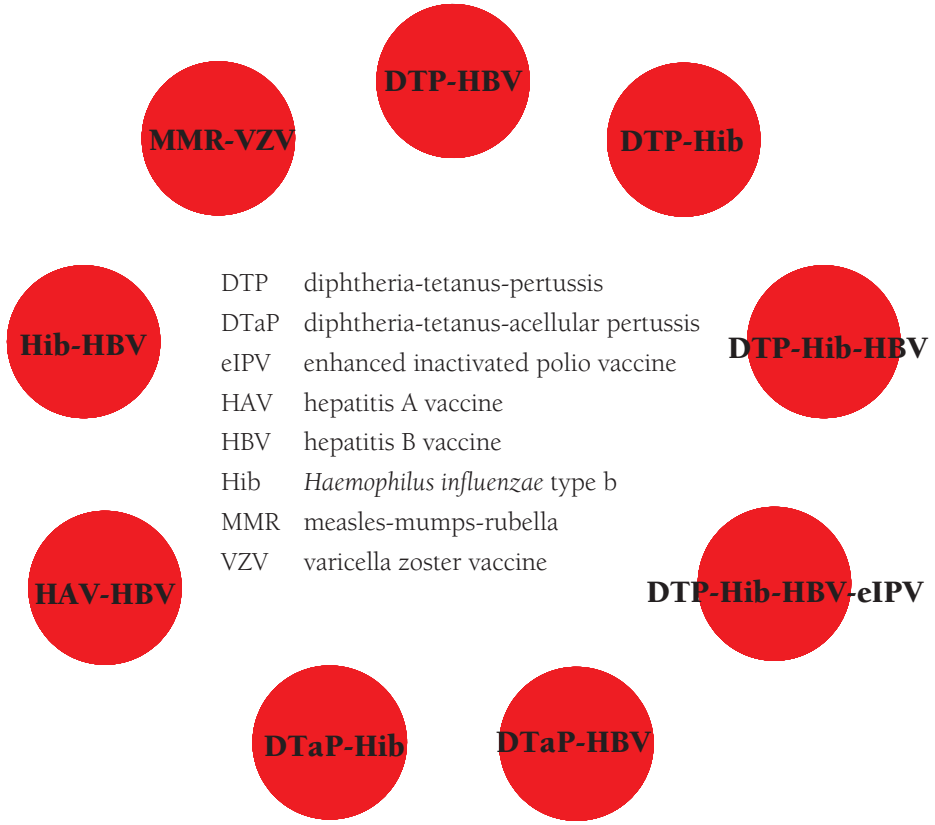
Indeed, a strategy paper presented at a CVI Consultation on DTP held in Geneva last June makes a plea for "a concerted effort to bring into worldwide use a DTP formulation which requires fewer doses, contains additional antigens, and can be manufactured and supplied at an affordable cost." Among the first antigens that could be tagged onto DTP, singly or together, the paper mentions *Haemophilus influenzae* type b (Hib) (a DTP/Hib combination has recently been licensed in the United States), hepatitis B virus (HBV), *Salmonella typhi* and *Streptococcus pneumoniae*.

One problem that could result from the accelerated development of DTP-based combinations, according to the paper, is a "technology gap" between, on the one hand, the industrial countries, where newer forms of DTP are likely to gain early acceptance, and, on the other, the developing countries, that are forced by lack of resources to hold onto their more traditional manufacturing methods. Encouraging developing countries to harmonize their manufacturing procedures and developed countries to participate in technology transfer and other arrangements with developing countries could attenuate the effects of this North-South disparity, the paper maintains.

Cost is another likely problem, as the newer combinations will probably be more expensive to develop. Here again, the CVI's global perspective should make it possible to offset increased costs and ensure adequate supply through collaborative arrangements with industry and careful prediction of demand.

Overall, the paper concludes, "the challenge [of bringing] the next generation of DTP combination vaccines into [global] use will require unprecedented coordination...[and] a major central management effort..."

Looking to the future: combination vaccines in the pipeline



Source: The Jordan Report 1993, *National Institute of Allergy and Infectious Diseases, USA*

whether the acellular product could replace whole-cell DTP for primary (i.e. initial) immunization.

Meanwhile, biotechnology and gene-juggling science are moving multi-antigen vaccine technology forward. Three examples:

•*Microencapsulation* involves coating vaccine antigens in protective *microspheres* small enough to be injected into the body. The microspheres consist of substances, usually combinations of polymers, that biodegrade inside the body into the body's natural substances and in doing so release the protective antigens. The rate of microsphere biodegradation, which depends on the size and composition of the microspheres, determines when and how quickly the antigens are released. Thus with a single injection, a vaccine consisting of a given number of microspheres of different size and chemical composition can deliver into the bloodstream, at preset times, a given number of different antigens providing protection against several diseases. It is still early days for microencapsulation technology, but preliminary findings in mice and monkeys are encouraging. Safety is a major concern, since once the microspheres have been injected, it will be impossible to switch off the preset antigen delivery schedule.

•*Vaccine vectors* are living or nonliving microorganisms or parts of microorganisms capable of conveying vaccine antigens into the bloodstream and at the same time of stimulating the recipient's immune system to react to the intrusion with strong protective, specific responses against the "passenger" antigens.

Examples of live virus vectors under study are vaccinia and other (mainly animal) poxviruses, hepatitis B virus, adenoviruses and herpes virus. Bacterial candidate vectors include BCG (*bacille*-Calmette-Guérin) and salmonella. The vector usually takes on board a vaccine antigen through some form of recombinant technology: the gene coding for the antigen is removed from its native pathogen (against which protection is required) and inserted into the genome of

Further trials are being conducted of a number of types of DTaP to determine whether the acellular product could replace whole-cell DTP for primary immunization.

the vector, which is thereby fooled into expressing the foreign antigen as one of its own molecules.

Among nonliving vectors of current interest is the core antigen of the hepatitis B virus, to which antigenic structures have been linked chemically or through recombinant technology. A movable genetic element or transposon ("jumping gene") of yeast is also being genetically tricked to code for a protein that forms virus-like particles (VLPs) capable of carrying vaccine antigens: these VLPs are being studied particularly for their potential as anti-HIV vaccine vectors.

Vector research has still many hurdles to overcome, including the difficulty of reconciling the biochemical differences among the various antigens being carried so as to produce a stable, effective vaccine product. Safety is also a concern when envisaging the administration in humans—particularly those with deficient immune systems—of a genetically modified microorganism or particle bearing its own immunological charge as well as that of its vaccine antigen load.

•*Multiple antigen peptides (MAPs)* are artificial constructs in which vaccine antigens are chemically strung on the symmetrical branches of tiny tree-like structures made of lysine, one of the body's growth-promoting amino acids. Research in mice has shown MAPs to be capable of giving protection against malaria. Work is under way at the Walter Reed Army Institute of Research in Washington, D.C., on the potential of these constructs to carry anti-HIV and other antigens.

Present-day technological prowess notwithstanding, the one-shot or even the more realistic 10- or 15-antigen vaccine is still something of a dream, given the formidable list of questions—scientific, technological, regulatory and economic—that have still to be answered. How, for example, will an infant's immature immune system respond to the simultaneous administration of a large number of antigens? How difficult will it be to design clinical trials on a combination vaccine that protects against several diseases? How difficult will it be for a combination vaccine developer to obtain rights to antigens and production processes currently owned by many parties? And how affordable will combinations vaccines be to developing countries? But as CVI Special Adviser Philip Russell, a vaccine expert currently with Johns Hopkins University in Baltimore, United States, says: "It's a dream well worth working towards, because in doing so we are breaking new ground in vaccine research and development, overcoming unforeseen obstacles, creating new partnerships, bringing more and more people into the vaccine arena. And we are also moving closer to achieving more immediate targets, like better vaccines against measles, tetanus and polio, and new four- or five-antigen combinations. We're gradually clearing paths through the jungle of unknowns in vaccine research and development. And that's what the CVI was brought into existence to do—to keep the world's eyes and imagination on the vision, but with its two feet solidly on the ground doing what has to be done first."

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Latin American countries converge on combo vaccines

Latin American countries have decided to join forces to improve the diphtheria-tetanus-pertussis vaccine (DTP) and develop DTP-based combination vaccines.

At a landmark CVI meeting held last September at the Washington, D.C. headquarters of the Pan American Health Organization (PAHO), representatives of vaccine manufacturers, public health officials and vaccine experts from all the countries of Latin America and the Caribbean met with their counterparts from industrialized countries and representatives of donor agencies to thrash out a regional DTP and combination vaccine strategy.

The meeting, which was organized in collaboration with PAHO's Regional Vaccine System (SIREVA), agreed to set up a "regional network of quality control laboratories" and establish a "programme for certifying vaccine producers" as a prerequisite to implementing the strategy.

Further information can be obtained from: Dr Akira Homma or Dr Ciro de Quadros, PAHO, 525 23rd Street N.W., Washington, D.C. 20037, USA.

References

[1] *The State of the World's Children 1993, p.5, UNICEF*

[2] *Expanded Programme on Immunization Information System, September 1993, WHO*

[3] *The Jordan Report, Accelerated Development of Vaccines 1993, NIAID, Bethesda, MD*

[4] *Anthony F. Bascom, US Food and Drug Administration, in an unpublished presentation to the International Workshop on* Combined Vaccines, *Bethesda, MD, 28-30 July, 1993*

Immunization in Mongolia: where are the people?

Mongolia—a "land of little more than 2 million people and 24 million sheep," as the British newspaper *The Economist* recently described it—is an immunization programme manager's nightmare. Health Minister Pagbajabyn Nymadawa agrees: "It's a big country—about three times the size of France, but with less than a hundredth of France's population. One inhabitant per square kilometre. The lowest population density in the world. And what's more, about half of our people are nomadic or semi-nomadic and live in rural areas. How do you find them? How do you reach the children, when many of them are on the move most of the year?"

At the best of times, carrying vaccines to the scattered mobile populations in Mongolia's vast steppes, desert plains, forests and mountains is no picnic. But it's even worse now. As the country shakes itself free of a central planning system, it is going through an economic crisis that, as Dr Nymadawa pointed out to last May's World Health Assembly, is placing the health service "in real danger of destruction." He blames this crisis for the steep rise in the maternal mortality rate over recent years: 273 per

Cam/Len Sirman

On the move in Mongolia, where about half of the population is nomadic

About half of our people are nomadic or semi-nomadic and live in rural areas. How do you find them? How do you reach the children?

IN A NUTSHELL	
Population (estd. 1992)	**2.3 million[1]**
No. of births a year:	**60,000[2]**
Infant mortality rate:	**60 per 1,000 live births[2]**
Under-5 mortality rate:	**84 per live births[3]**
% of national budget for health:	**10-12 [2]**
% of health budget on prevention:	**about 50**
% of 1-yr-olds immunized:	**87[3]**
human development ranking:	**100[3]**
main immunization thrusts:	**EPI infections and hepatitis B[2]**
priority vaccine needs unmet:	**combination vaccines for the EPI antigens; better vaccines for measles, tuberculosis and polio[2]**
major health concerns:	**high infant and maternal mortality[2]**
major ongoing health measures:	**dismantling the centrally planned health system, diversification of health care financing mechanisms, encouraging private sector development[2]**

Sources: 1. United Nations Population Division. 2. Government of Mongolia. 3. UNDP, Human Development Report 1993.

100,000 live births for the first six months of 1993, vs. 204 for 1992, 151 for 1991 and an average of 129 over the 1988-92 five-year period.

For Mongolia's immunization programme, one result of the crisis is a dire lack of logistic equipment. "We need 350 cars to equip all the country's *somons* (departments). That's only one car per *somon,* a territory of about a 100-km radius. But right now we only have about 200 usable cars for the whole country. And our maintenance facilities are minimal."

Given Mongolia's sparse population and difficult terrain, though, its greatest need with respect to immunization, Dr Nymadawa says, is for combination vaccines. "Imagine what a difference they would make! We would no longer have to make the same long, difficult journey, often ten times, to make sure everybody gets their full series of vaccinations."

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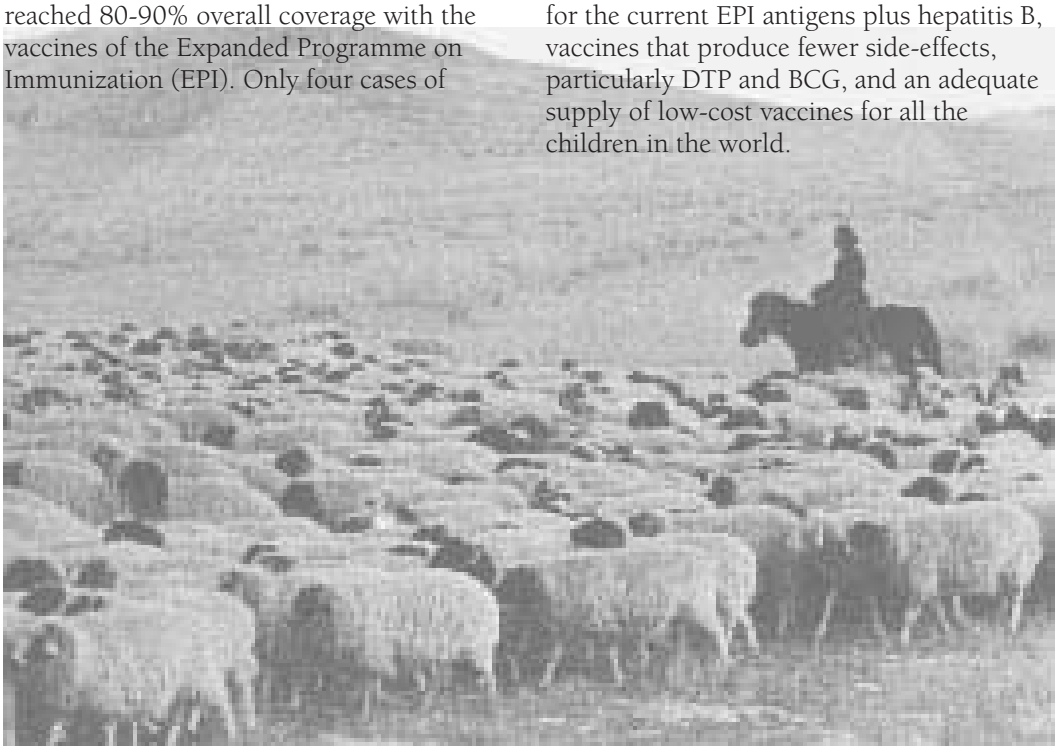
Also needed is an expansion of laboratory capabilities "to provide microbiological confirmation of atypical cases of infection and to conduct microbiological surveillance of wild poliovirus and serological surveillance of our population's immune status." At present, Mongolia has only its central laboratory in Ulaanbaatar.

Despite these difficulties, the country has reached 80-90% overall coverage with the vaccines of the Expanded Programme on Immunization (EPI). Only four cases of poliomyelitis, four cases of pertussis and two cases of tetanus have been reported since 1987. Between 1988 and 1992, numbers of diphtheria cases have dropped steadily from 24 to 0. And in July 1991 Mongolia began delivering to its population 200,000 doses of hepatitis B vaccine along with the six EPI vaccines—an undertaking that has doubled the country's annual vaccine expenditure to US$2 million but has almost halved the number of acute hepatitis cases.

With a magic wand, Dr Nymadawa says he would ask for a combined vaccine, at least for the current EPI antigens plus hepatitis B, vaccines that produce fewer side-effects, particularly DTP and BCG, and an adequate supply of low-cost vaccines for all the children in the world.

jm

Pagbajabyn Nymadawa



Cam/Len Sirman

Sheep, sheep everywhere and barely a human in sight. A Mongolian shepherd tends his flock.

Senegal links up with the past to protect the future

"An old woman from the village would take a group of us children down to the sea. There she'd wash us with sea water and make us drink a potion and get us to make sacrifices to ward off the curses of the bad spirits that had entered us."

The speaker is Lieutenant-Colonel Dr Lamine Cissé Sarr, Senegal's Director of Hygiene and Public Health. He is recalling a local custom that took place every winter in the Saloum Island village on Senegal's Atlantic coast, where he spent his childhood—a custom designed to protect children against disease.

"Our job now as public health officials," says Dr Sarr, "is to make the link between our intellectual messages about vaccination and the traditional customs of the people, like that old woman and her fellow community members in the Saloum village. We tell them that the curses of the bad spirits are called microbes and that the modern way of washing children with sea water is vaccination. Believe me, this way, we don't have much of a problem convincing people to accept vaccination."

Lamine Cissé Sarr

Indeed, Senegal's coverage rate for immunization against the six target diseases of the Expanded Programme on Immunization (EPI) was 82% for 1992. But beneath that overall average lurks a 25% high drop-out rate for vaccines against measles—and also yellow fever—two vaccines that have to be given after six months of age. And full coverage against neonatal tetanus in preg-

"The curses of the bad spirits are called microbes and ... the modern way of washing children with sea water is vaccination."

IN A NUTSHELL

Population (estd. 1992)	**7.7 million[1]**
No. of births a year:	**380,000[2]**
Infant mortality rate:	**84 per 1,000 live births[2]**
Under-5 mortality rate:	**182 per 1,000 live births[2]**
% of national budget for health:	**5[2]**
human development rank:	**150[3]**
main immunization thrusts:	**poliomyelitis, neonatal tetanus, hepatitis B, yellow fever[2]**
priority vaccine needs unmet:	**hepatitis B[2]**
major health concerns:	**malaria, overpopulation and its association with maternal mortality, diarrhoeal diseases and schistosomiasis[2]**
major ongoing health measures:	**closer integration of immunization programmes with the primary health care system, training of rural health workers in midwifery, introduction of health cost recovery systems[2]**

Sources: 1. United Nations Population Division. 2. Government of Senegal. 3. UNDP, Human Development Report 1993.

UNICEF/Steve Maines

Health for the people, by the people: villagers in Senegal meet to discuss the benefits of immunization.

So successful has Senegal's immunization programme been that it has become one of the country's health priorities.

nant women is a disappointing 35-40%, largely because expectant mothers fail to turn up for the booster dose which must be given two weeks before the expected delivery date. "Since this date is often as much a mystery for the woman herself as for us," Dr Sarr notes, "we often don't know when she should return for the booster."

The problem is compounded by the fact that the health workers who administer vaccines in rural areas are not qualified to perform antenatal examinations. "To remedy this," says Dr Sarr, "we've set up training programmes so that our rural health workers can carry out antental examinations and in that way increase coverage of tetanus immunization in pregnant women."

So successful has Senegal's immunization programme been—"we've reduced infantile mortality from 116 to 84 per 1,000 live births in the space of 5 years"—that it has become one of the country's health priorities, on which it spends over US$1 million a year. This is equivalent to 2.4% of the US$42 million annual health budget, itself 5% of the national budget. "We've even started integrating our immunization programme into the primary health care system. It is becoming completely decentralized, with the local population paying a nominal 15 US cents per vaccination act for each child and 30 US cents per adult. This helps pay for maintenance of vehicles, petrol, and even the cold chain." It also provides a hedge should UNICEF, "which gives us a lot of help in procuring vaccine," be forced one day to withdraw its assistance.

Given a magic wand, Dr Sarr says he would ask for better quality vaccines that resist heat, a guaranteed supply of drugs, including vaccines, and more resources for the training of health workers.

TO OUR READERS

As *CVI FORUM* goes to press, discussions are in progress on a restructuring of WHO's vaccine-related activities that may have implications for the organization and management of CVI's activities. We will report on this development in the next issue of *CVI FORUM* and have decided to suspend the *PROGRESS REPORT* section of the newsletter until the new structure is in place.

CVI WIRE

FROM the NIH

•***Combined Vaccines and Simultaneous Administration: Current Issues and Perspectives*** was the topic of a Food and Drug Administration (FDA) workshop held in Bethesda, MD, USA, on 28-30 July, 1993. Co-sponsored by the National Institute of Allergy and Infectious Diseases (NIAID) and other U.S. public health agencies, the workshop addressed the scientific complexities of combining vaccines. Participants also discussed the development of new methods of assessing vaccine safety, immunogenicity and protective efficacy, as well as the immunological correlates of protection.(See also article on pp. 2-6 of this issue of *CVI FORUM*.) The proceedings will be published in a forthcoming (yet to be decided) issue of *The Annals of the New York Academy of Sciences*.

Further information from: Dr Jim Williams, Office of Vaccines Research and Review, Center for Biologics Evaluation and Research, Food and Drug Administration, Rockville, MD 20857, USA [Tel:(1-301) 594-1098; Fax (1-301) 2958942].

•The NIAID has issued a Request for Applications (RFA) for funding for research on **innovative approaches to developing multivalent vaccines** that ensure safe, long-lasting immunity against multiple pathogenic agents, while providing a degree of immunogenicity equivalent to the single vaccine components. One of the most complex obstacles to developing such vaccines is the difficulty of incorporating fundamentally different products or antigens into a single matrix.

Further information from: Dr David Klein, Division of Microbiology and Infectious Diseases (DMID), NIAID, Solar Bldg, Room 3A-10, Bethesda, MD 20892, USA. [Tel:(1-301) 496-5305; Fax (1-301) 496-8030].

•The NIAID and the Agency for International Development (A.I.D.) have established a **Joint A.I.D./NIAID Malaria Vaccine Development Program**, which has issued an RFA for three-year research projects on the evaluation of various antigens as components of vaccines against *Plasmodium falciparum*.

Further information from: Dr B. Fenton Hall, Parasitology and Tropical Diseases Branch, NIAID, Solar Bldg, Room 3A-36, Bethesda, MD 20892, USA. [Tel: (1-301) 496-2544; Fax (1-301) 402-0804].

Children's Vaccine Initiative: Strategic Plan

A strategic plan has been drafted for the CVI by a panel of experts drawn from a broad range of vaccine-related disciplines. It outlines CVI's priorities in relation to the burden of the major diseases affecting children and to the world's vaccine needs, in the context of scientific feasibility and economic considerations. It proposes a plan for introducing a number of new vaccines into childhood immunization programmes over the next 15 years and recommends innovative mechanisms for reconciling the need for reasonable returns on investment in vaccine development and production with affordability of vaccines in the developing countries. And, finally, it addresses the importance of ensuring, through uniform standards of quality control and assurance, that all new and improved vaccines are of high quality, safety and efficacy. The plan will be updated in 1994.

For a copy of CVI's Strategic Plan (free of charge) write to: Dr Lindsay Martinez, Children's Vaccine Initiative, WHO/CDS, 1211 Geneva 27, Switzerland [fax: 41-22/788-2736].

MEETING CALENDAR

Readers organizing public meetings on topics related to vaccines are invited to submit announcements of such meetings giving the exact title, date and place of the meeting, as well as the name, address, telephone and fax numbers of a contact person, to The Editor, CVI FORUM *(see address and fax number on back page).*

21 January 1994
London, UK

Antimicrobial peptides

Sheila Pusinelli, Ciba Foundation, 41 Portland Place, London W1N 4BN, UK. Tel: (44-71) 636-9456; Fax: (44-71) 436-2840

4-6 February 1994
Newport Beach, CA, USA

5th international conference on lymphocyte activation and immune regulation

Nancy Domar, Conference Secretariat, Division of Basic and Clinical Immunology, Medical Sciences I, C-264, University of California, Irvine, CA 92717, USA. Tel: (1-714) 656-5818; Fax: (1-714) 856-4362

5-10 February 1994
Fort Lauderdale, FL, USA

Advances in gene technology: molecular biology and human disease

Miami Bio/Technology Winter Symposium, Room 314, Gautier Building, 1011 N.W. 15 Street, Miami, Fl 33136, USA

9-10 November 1994
Amsterdam, Netherlands

4th meeting of the CVI Consultative Group

Secretariat, Children's Vaccine Initiative, WHO/CDS, 1211 Geneva 27, Switzerland.

7-13 March 1994
Lake Tahoe, CA, USA

Antibody engineering: research and application of genes encoding immunoglobulins

Keystone Symposia, Drawer 1630, Silverthorne, CO 80498, USA. Tel: (1-303) 262-1230; Fax:(1-303) 262-1525

21-23 March 1994
Washington, DC, USA

Vaccines: new technology & applications

Conference Secretary, Cambridge Healthtech Institute, 1000 Winter Street, Suite 3700, Waltham , MA 02154, USA

10-17 April 1994
Keystone, CO, USA

Lymphocyte activation

Keystone Symposia, Drawer 1630, Silverthorne, CO 80498, USA. Tel: (1-303) 262-1230; Fax:(1-303) 262-1525

17-20 April 1944
London, UK

Vaccination and world health

Alice Dickens, Conference Secretary, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK

12-17 June 1994
Barcelona, Spain

12th European immunology meeting (EFIS)

Immunology Department, Hospital Clinic, Villaroel 170, 08036 Barcelona, Spain. Tel: (34-3) 454-4920; Fax: (34-3) 451-8038

4-6 July 1994
Brighton, UK

Biotechnology '94

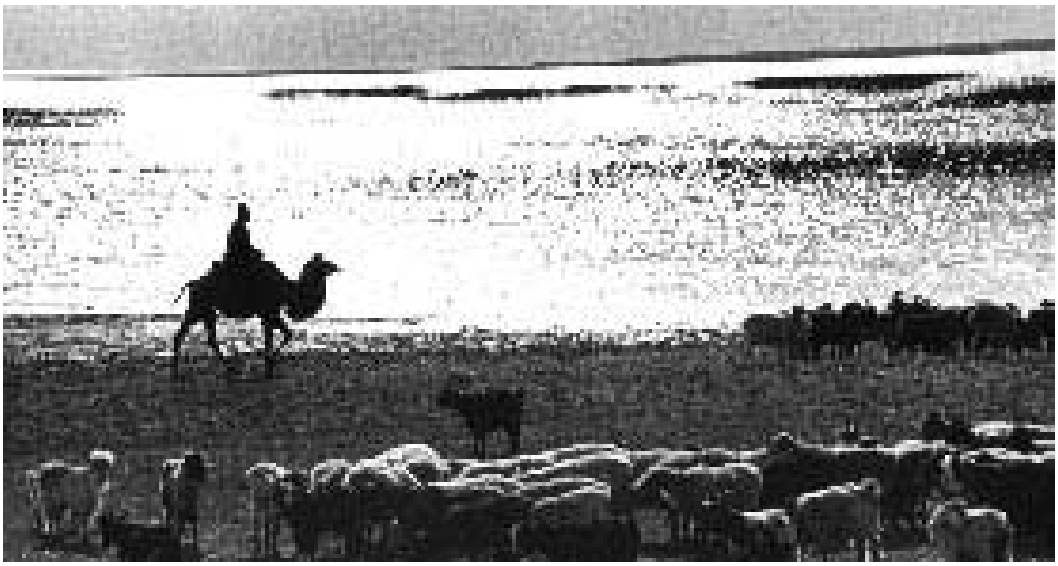
Conferences & Courses Dept, IChemE, 165-171 Railway Terrace, Rugby, Warwickshire CV21 3HQ, UK

17-20 November 1994
Monte Carlo, Monaco

Advances in gene technology: molecular biology and human disease

Christine Jones, The Miami Bio/Technology European Symposium at Monaco, 4 Little Essex Street, London WC2R 3LF, UK. Tel: (44-71) 836-6633 x2593; Fax: (44-71) 379-5417

PICTURE POSTSCRIPT



Cam Lee Sirman

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Editor: John Maurice

Design: Marilyn Langfeld

Editorial office:
CVI FORUM
Division of Communicable Diseases
World Health Organization
1211 Geneva 27, Switzerland

Telephone:
(41-22) 791-4144

Fax:
(41-22) 788-2736

Telex:
415416 OMS

Telegrams:
UNISANTE-GENEVE