# C V I F O R U M

NEWS FROM THE CHILDREN'S VACCINE INITIATIVE

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The Children's Vaccine Initiative (CVI) was established in 1991 by the United Nations Children's Fund (UNICEF), the United Nations Development Programme (UNDP), The Rockefeller Foundation, The World Bank and the World Health Organization (WHO) to create a global commitment to the development of a new generation of children's vaccines that could provide lasting protection against a wide range of childhood diseases and be simple to administer and affordable.

## In this Issue



# *The CVI "on the crest of a new wave", but watch out for the pitfalls*

*Issue No. 2 of* CVI FORUM *(October 1992, pages 2-5) carried views from representatives of UNICEF and the EPI, both focused more on the "downstream" or delivery side of the vaccine spectrum. In the interview below, Gustav Nossal, Chairman of the PVD's Scientific Advisory Group of Experts and Director of the Walter and Eliza Hall Institute of Medical Research in Melbourne, Australia, expresses his views from a more "upstream" or basic research perspective.*

An opportunity. A door. An opening. A visiting card.

With a smile as broad and bright as the land he comes from, Prof Sir Gustav Nossal looks for the image that best conveys his perception of the CVI.

A flagship of the vaccinology community.

"That's it. Or rather that's what the CVI could become."

The CVI's advent, Prof Nossal believes, coincides with a worldwide revival of interest in vaccines. "Twenty years ago, the glamour began to abandon vaccinology for the more academic fields of tumour and transplantation immunology. But in the last ten years the academic community has been galvanized into thinking anew about the scientific and human importance of vaccines. The CVI comes on the crest of a new wave of fervour in the vaccine community. In that sense it has an opportunity to become that community's flagship or visiting card."

The CVI itself also offers new opportunities, the Australian immunologist believes. Few people today, he says, would deny that vaccines are history's most cost-effective public health tool. "Yet, the budgets of health officials the world over are so strained and constrained by health care delivery, it's hard to get them interested in prevention." Most developed countries, Prof Nossal notes, spend less than 1 percent of their global health budget on prevention. "With the CVI now we have a massive chance to put the priorities where they belong, and they belong with prevention."

There are, however, pitfalls, he warns.

One pitfall is to make overoptimistic promises. A "one-shot for everything" vaccine, for example is unrealistic, at least as a target for the next decade. "I'm a genuine believer in the technological fix. I see no reason why, in the fullness of time, the one-shot shouldn't come. But let's be realistic about the time-frame. Not ten but rather 20 or 30 years." The fault, he adds, is not with the CVI alone. "Decision-makers in funding agencies and governments are notoriously reluctant to accept realistic time-frames for research and development. Eleven years, for example, is what it takes on average to bring a drug from an idea into the clinic."

But take heart, he tells these decision-makers. "Remember the historic dimension of the vaccines you are helping to bring into existence. Once you have a vaccine that can rid the world of measles or polio, it's there for ever. You can't 'undiscover' or 'undevelop' it. Let that be a counterweight to the funds and the time needed to bring these things into the world."

A critical pitfall, in Prof Nossal's view, would be mismanagement of the "grey areas and necessary tensions" created by the frontiers between the different programmes working on vaccines.

### *Abbreviations, acronyms and initialisms used in this issue:*

| | |
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| CTL | cytotoxic lymphocyte |
| CVI | Children's Vaccine Initiative |
| DTP | diphtheria, tetanus and (whole cell) pertussis (vaccine) |
| EPI | (WHO) Expanded Programme on Immunization |
| FIA | Freund's incomplete adjuvant |
| HIV | human immunodeficiency virus |
| ISCOM | immune-stimulating complex |
| LPS | lipopolysaccharide |
| MHC | major histocompatibility complex |
| MPL | monophosphoryl lipid A |
| NIH | (United States) National Institutes of Health |
| PAHO | Pan American Health Organization |
| PVD | WHO/UNDP Programme for Vaccine Development |
| UNDP | United Nations Development Programme |
| UNICEF | United Nations Children's Fund |
| WHO | World Health Organization |

*Note: $=US$ unless otherwise stated*

*Gustav Nossal*

Relations with the PVD, for which, as Chairman of its expert committee, Prof Nossal has a special interest, are "particularly sensitive". The PVD, he says, has become "an important world coordinating force in medium-to-long-term research in vaccinology" and has recently widened its mandate to include all major bacterial and viral diseases, with the exception of AIDS. But, he cautions, the PVD is not just a basic research programme. "It owes part of its credibility to its ability to move products from basic research into early clinical trials." The CVI should not try and take over that 'donor-friendly' side to PVD activities. On the other hand, the PVD is not "built" to organize phase III trials or to develop relations with industry. "That's what the CVI is best geared to deal with."

On the delivery side, the EPI "has its ear to the ground". The CVI, Prof Nossal feels, should "do a lot of listening to the EPI to remain in touch with the needs and priorities of the countries". Through the EPI the CVI can shape its own priorities.

All in all, he says, the CVI should become "a global coordinating agency, with the PVD a basic research arm and the EPI a delivery arm". And with the "moral force" of its founding agencies—UNICEF, UNDP, The Rockefeller Foundation, The World Bank and WHO—and of the circumstances of its creation—the 1990 World Summit for Children where over 150 heads of state gave their endorsement to its objectives—the CVI has the leverage to pressure countries with large medical research and health care delivery facilities to "open up their books and join the CVI family".

The Nossal smile becomes rueful: "No, we don't live in an ideal world. The CVI is a door, but it's still a small door and some of the big guys out there in the western world will no doubt find it hard to stoop to pass through it."

Nudged into a prophetic mode, Prof Nossal offers a few pet predictions about progress over the next decade:

- Polio and measles—"there's no good scientific reason why we shouldn't repeat the smallpox success several times; it's more a question of delivery than further research".
- Diarrhoeal diseases—"the diarrhoeal disease vaccines that we developed 50 years ago have been broadly disappointing"; but with the "disciplined research" now under way we should have better vaccines; already, the efficacy of cholera vaccine is moving up from 50 percent protection for six months to 70 percent for 12 months.
- Parasitic diseases—"the complex parasites of malaria and the other major tropical diseases will crack: that's a dream, but I'm really convinced it will become reality over the next ten years".

Most developed countries spend less than 1 percent of their global health budget on prevention.

*2nd Consultative Group meeting*

## *CVI partners harvest early practical results but still find room for dreams*

Immunization holds perhaps the greatest promise of sustainability among health interventions and can serve as a beachhead for a broad range of essential health services.

The mood, the tempo and the "action" were very different from those of the 1991 meeting of the CVI's Consultative Group (see *CVI FORUM* No. 1, pages 5-8), when representatives of the CVI's partners— international health, development and donor agencies, vaccine manufacturers and nongovernmental organizations—set the stage for future action against a backdrop of dreams, hopes and speculations.The Group's second meeting, held last November in Geneva, was treated to an early harvest of preliminary results—results of research on a thermostable oral polio vaccine and a single-dose tetanus toxoid vaccine; results of analyses of the world's vaccine supply, and of the cost-effectiveness of different vaccines; and results of attempts to seek new forms of collaborative arrangements, especially between vaccine manufacturers and researchers.

Towards the end of the meeting's second day, when the "hard reality" of reports and results was clearly beginning to weary many of the 200 participants, the mood suddenly shifted as Stephen Simon of the Canadian International Development Agency (CIDA) injected into the meeting something of the spirit in which the CVI was originally conceived.

The CVI, Dr Simon said, is "a bold and visionary attempt to harness the most life-affirming expressions of science and technology to the strivings of the highest human instincts" and, as such, "offers us a blueprint to help shape a more positive future".

CIDA's support of the CVI—its donation of C$2 million announced at the 1991 Consultative Group meeting made the agency the CVI's first major bilateral donor—reflects the value it accords immunization in general, Dr Simon noted.

Immunization, he said, holds perhaps the greatest promise of sustainability among health interventions and can serve as a beachhead for a broad range of essential health services. Its "primary beneficiaries" are women and children, "the most marginalized of the impoverished". It is also one of the most effective ways of "ensuring that children survive long enough to be exposed to and acted on by a host of other factors—family love and support, education, nutrition, recreation, individual rights and freedoms, etc.—which together make for healthy and whole human beings". In other words, it offers children a "*laissez passer* whereby, through the vulnerability of their early years, they can at least gain entry to a continuum culminating in complete physical, mental and social wellbeing".

T.Farkas/WHO

***Stephen Simon***

Dr Simon expressed these views during a round-table discussion among representatives of funding organizations. (Other views are outlined below.)

In a keynote address, Alain Mérieux, Chairman of Pasteur Mérieux Sérums et Vaccins, challenged the CVI to reconcile the apparently contradictory terms of a new paradox: How to respond to the world's vaccine needs without threatening the survival of industry.

Manufacturers of biological products, he warned, are having to function in a "new and tougher environment...that could jeopardize their response to global needs". This environment, he said, with its "pervasive regulation, the omnipresence of industrial property and a heavy burden of civil liability", could slow down, even paralyse, technological innovation in production and increase the costs of research, development and clinical trials.

T.Farkas/WHO

***Alain Mérieux***

At the same time the vaccine industry is facing an explosion in demand from the developing countries, whose needs have increased tenfold over the past decade and now account for nearly 80 percent of the world vaccine market. Since the transfer of technology to these countries has "not yet been sufficiently successful", only the industrialized countries, Mr Mérieux noted, will be capable "of assuring prompt supplies of large quantities [of vaccine] that meet international standards of quality, and at competitive prices". With "all the new constraints on industry", he added, fewer and fewer manufacturers have the will and resources to do so.

Yet, he urged, "we must not forget that thousands of children are dying every day throughout the world for lack of immunization. We have neither the time, nor the resources nor, above all, the right to continue to go about our business in the old way". Only "new rules of the game" and a global partnership can overcome these new challenges facing the vaccine industry. "Are WHO and the partners to the CVI prepared to recognize the decisive role of industry? Is industry prepared to accept the new rules?"

The new approach, he explained, rests on "new forms of partnership that bring together public and private, political, scientific and economic interests". The success of this partnership, Mr Mérieux concluded, "will depend on a renewed sense of purpose in the biological industry, which will then be recognized for its crucial contribution to vaccinology".

Three round-table discussions gave panelists a chance to air views from their respective segments of the CVI "umbrella"—industry, vaccine users and funding organizations.

"... thousands of children are dying every day throughout the world for lack of immunization. We have neither the time, nor the resources nor, above all, the right to continue to go about our business in the old way."


T.Farkas/WHO

***Chairperson Margaret Catley-Carson, President-Elect of the Population Council (New York), addresses the CVI's 2nd Consultative Group meeting, watched by WHO Assistant Director-General Ralph Henderson.***

Some jottings:

•*From industry*: new vaccines have been undervalued for many years; they will cost more but will need to be "sold" as a cost-effective intervention; regulatory standards will have to be uniform throughout the world, so that vaccines can be sold anywhere, whatever their place of production; there is no shortage of bulk oral polio, measles or hepatitis B vaccine, and processing of bulk in developing countries may be the most economical solution to local production in these countries; transfer of technology should include the technology of finishing, exchange of information and quality control.

•*From vaccine users*: the cost of vaccines is becoming critical since the quantities needed are now so large; in 1992, the average cost of vaccines to UNICEF and PAHO increased by 23 percent; in the same year, the Moroccan government, which recently joined the Vaccine Independence Initiative, took over the country's financing of vaccines from international agencies; shortage of polio vaccine is critical in China, which requires an estimated 460 million doses a year; Nigeria recorded a worrying drop in immunization coverage in 1991, down to 60 percent vs. the 1990 level of 80 percent; in an outbreak of measles in 1990, 30 percent of infected children had been vaccinated, suggesting the need for better quality control; wastage rates of up to 60 percent have been reported in Nigeria.

•*From funding organizations*: in CVI policy and decision-making insufficient attention is being paid to the interests of the children of the world and to the participation of developing countries; CVI programmes should be determined by the priorities of developing countries; new vaccines must be developed even if there is no market for them in industrialized countries.

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SCIENCE AND TECHNOLOGY

## *Adjuvants for new or improved vaccines: some current research options*

***by***
***Jerald C. Sadoff***

As our knowledge of the antigens capable of inducing protective immunity expands, along with our ability to produce these antigens as vaccines, so has our appreciation of the need for adjuvants to stimulate the immune response. Progress in recombinant technology, for example, makes it possible to develop vaccines based on smaller, better characterized antigens: these vaccines will not only be easier to produce; thanks to adjuvants they will also possess greater potency.

This point is illustrated by early work on an experimental vaccine against the potentially lethal *Plasmodium falciparum* species of the malaria parasite. Despite the fact that this vaccine consisted of a recombinant protein genetically designed to produce an effective immune response, it only induced consistently high levels of antibodies in human subjects when a suitable adjuvant delivery system was added to it.

***Jerald C. Sadoff***

Adjuvants were first used to stimulate the immune system in 1877, when Louis Pasteur discovered that mixing certain substances with an antigen can enhance the immune response to that antigen. However, it was the French veterinarian Gaston Ramon, father of the first diphtheria and tetanus vaccines, who 50 years later pioneered the concept of

## *ISCOMs: antigen delivery with a bang*

*by*
*Albert D.M.E. Osterhaus*

The ISCOM or "immune-stimulating complex" is a novel antigen delivery system that possesses a surprising range of immunological assets:

- First, unlike other nonliving vaccine vehicles or presentation systems, ISCOMs can rouse to action all three arms of the immune system: the helper (CD4-positive) T cells, that recognize antigenic determinants (the immunologically critical parts of antigens) in association with molecules of the so-called class II major histocompatibility complex (MHC) and that are involved in immune responses to antigens not synthesized within the host cell (such as most bacterial antigens); the cytotoxic or killer (CD8-positive) T cells that recognize antigenic determinants in association with class I MHC molecules and that are involved in immune responses to antigens synthesized within the host cell (such as viral antigens); and the B cells that produce antibodies which directly recognize foreign antigens.
- Second, the ISCOM is not only a vaccine antigen vehicle; it also has a built-in adjuvant that potentiates immune stimulation and may be responsible for the strong, long-lived immune response the ISCOM elicits.

ISCOMs were first described in 1984 by the Swedish virologist Bror Morein. His group, in collaboration with us, had been experimenting with Quil A, a glucoside (plant sugar) derived from the bark of a South American tree and commonly used as an adjuvant in veterinary vaccines, and had found that a purified form of Quil A spontaneously forms a matrix that traps—by a hydrophobic (or water-repellent) polar interaction—the proteins on the surfaces of viruses or on the membranes of bacteria and parasites. The result is an ISCOM, a tiny (40 nm in diameter) man-made particle, which is basically a subunit vaccine enmeshed in an adjuvant. One ISCOM can hold about 10-12 protein molecules.

Since Dr Morein's original description, ISCOMs have been extensively studied as an adjuvant system for vaccines against many viral, bacterial and parasitic infections. They have been shown to be potent enhancers of long-lasting specific antibody responses, even in the presence of passively transferred antibodies: results of recent animal experiments in our laboratory, in fact, suggest that an ISCOM delivering measles virus proteins may overcome the obstacle of maternally acquired antibodies to measles virus, an obstacle which precludes administration of a measles vaccine to infants under six months of age.

It has also been shown that ISCOMs can be successfully administered through mucosal

E.H. Rozendal/RIVM

***Albert D.M.E. Osterhaus***

surfaces, a route which also avoids the obstacle of maternal circulating antibodies in young infants. Mucosal administration raises the possibility that ISCOMs might be used for vaccines against respiratory infections and even for oral delivery of some vaccines currently administered by injection.

Largely because of their efficiency in producing "complete" immune responses, ISCOMs have induced protective immunity in virtually all the systems in which they have been studied, even where other adjuvant or presentation systems have failed. Our studies on their potential for inducing protection against retroviruses, notably the simian immunodeficiency virus (SIV) and feline leukaemia virus (FeLV), suggest that they could play a key role in the development of an AIDS vaccine. To this end, we are currently investigating the potential of an ISCOM-HIV (human immunodeficiency virus) candidate vaccine.

***Prof Osterhaus is head of the Laboratory of Immunobiology at the National Institute of Public Health and Environmental Protection (RIVM) in Bilthoven, Netherlands.***



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immunostimulation: he showed that the injection of certain killed bacilli or bacillary extracts could augment the antibody responses of animals or human subjects. Ramon's work inspired Jules Freund and Katherine MacDermot in the United States to develop in the early 1940s the widely used Freund's adjuvant, a mixture of mineral oil, heat-killed *Mycobacterium tuberculosis* and an emulsifying agent (lanolin or Arlacel A).

Adjuvants work through a variety of mechanisms. They can, for example, prolong the delivery of the vaccine antigen; expose those parts (epitopes) of the antigen capable of stimulating a specific immune response; enhance and direct the mechanisms whereby antigenic structures are processed and presented to the immune system; and induce the release of the cellular mediators (cytokines) that modulate the immune response.

More than 30 different adjuvants or adjuvant systems are currently being investigated for their ability to enhance humoral (antibody) or cellular responses, systemic or local. A few examples follow.

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### *Stimulation of humoral immunity*

•Alum is an aluminium salt used to enhance humoral immunity to DTP vaccine, *Haemophilus influenzae* vaccines and a variety of experimental vaccines. Although quite safe—it is the only adjuvant so far licensed and used for human vaccines—alum has not been very effective in human subjects when used with experimental recombinant vaccines against malaria or human immunodeficiency virus (HIV) infection, with synthetic peptide antimalaria vaccines or with the outer membrane protein vaccine against group B meningococcal disease.

•Freund's incomplete adjuvant (FIA), which contains a nonbiodegradable mineral oil and a stabilizing substance, Arlacel A (but not the mycobacterium contained in Freund's complete adjuvant), enhances antibody responses and has been used widely in human trials. Local tissue necrosis due to release of free fatty acids from the Arlacel A has raised concerns about the possibility of adverse reactions and limited the use of FIA. Recent promising data from animal studies, however, suggest that it might be used with recombinant HIV vaccines.

• Monophosphoryl lipid A (MPL), a partially detoxified fatty substance extracted from a bacterial endotoxin (the toxic cell wall component of certain bacteria) also possesses potent but apparently quite safe antibody boosting activity and is one of the most promising adjuvants yet to reach human trials. Liposomes (tiny artificial pouches consisting of artificial membranes and an inner aqueous compartment) that contain a recombinant peptide from a malaria parasite protein (its so-called circumsporozoite protein) together with MPL have been found capable of safely and reliably inducing high levels of specific antibody in human subjects. It is the liposomes, in fact, that make it possible to safely deliver otherwise toxic concentrations of MPL. There is some evidence that MPL exerts its adjuvant action partly by suppressing so-called suppressor T cells. Dosage requirements and economic considerations have still to be defined.

• Virosomes, which are liposomes containing small quantities of viral lipid membrane, offer a very promising approach to immune stimulation: virosomes containing inactivated hepatitis A virus particles together with influenza virus haemagglutinin have induced high levels of anti-hepatitis A antibody in preliminary human trials.

• Other adjuvant systems, such as the various peptidic forms of muramyl (an important component of the mycobacterial cell wall), immune-stimulating complexes (ISCOMs) (see box), so-called nonionic block polymer and Syntex Adjuvant Formulation (SAF), and interleukin-2 (the cell growth factor produced by T cells), have all shown promise in enhancing antibody responses in animals. Clinical trials are required to confirm that promise.

### *Stimulation of cellular immunity*

A strong cellular response to many disease antigens requires the activation of cytotoxic or killer (CD8-positive) T-lymphocytes (CTLs) that recognize cells invaded by viruses and other intracellular parasites, i.e.

that are "restricted" to so-called class I major histocompatibility complex (MHC) "self" molecules. For nonliving vaccines to induce such a response (a so-called $TH_1$ response) special antigen-presenting systems will have to be activated and probably adjuvants will be required to achieve this.

Induction of class I-restricted CTLs, for example, normally involves a process that takes place within the invaded cell: it breaks down the foreign antigen into small fragments or peptides, 9 to 11 amino acids long; binds each peptide to a class I molecule; and presents the MHC-peptide complexes on the surface of the cell where they can be recognized by CTLs. This complex process is most easily accomplished by viruses and other parasites that produce antigens within the cell cytoplasm.

Adjuvant systems that hold promise of enabling nonliving vaccines to induce protective immunity against diseases involving intracellular invasion, such as leishmaniasis, AIDS and malaria, include:

- liposomes containing MPL (see above) and recombinant antigens, which have induced CD8-positive class I-restricted CTLs in mice, presumably by delivering antigen to the MHC class I molecules within the cell cytoplasm;
- ISCOMs, which have also induced class I-restricted CTLs against HIV antigens;
- QS21, an adjuvant derived from the Quil A used to make ISCOMs, which, added to proteins combined with alum, also induces class I-restricted CD8-positive CTLs in animals.

### *Stimulation of immunity in the gut mucosa*

Induction of local immunity in the gut with nonliving, noninvasive antigens in order to provide protection against diarrhoeal diseases may also require adjuvants. For example, without an adjuvant, purified lipopolysaccharide (LPS) (a compound produced by gram-negative bacteria) from two bacteria *Shigella* and *Campylobacter* and purified pili (the hair-like strands extending from bacteria) of *E. coli* do not readily produce an immune response when given orally to animals. On the other hand, inactivated cholera whole cells containing an inactive recombinant fragment (B subunit) of cholera toxin *are* immunogenic when given orally to human subjects and *can* protect against cholera without adjuvants.

Among the adjuvant approaches being explored are the following:

- Active cholera toxin or its counterpart, *E. coli* heat labile enterotoxin, when given orally to animals, enhances the immunogenicity of antigens such as *Campylobacter* LPS, the potent immunogenic protein haemocyanin extracted from the keyhole limpet and influenza virus haemagglutinin. This approach, however, will only be useful if the adjuvant activity of the toxins exceeds their toxicity to a degree compatible with human safety.
- *Shigella* LPS incorporated into complexes containing meningococcal outer membrane protein forms so-called "proteosomes". Given orally to mice and guinea-pigs, proteosomes induce local antibody and stimulate cells to secrete antigen-specific antibody, thus providing protection from challenge with *Shigella*. In addition to their "adjuvanticity", proteosomes also appear capable of targeting antigen to the gut's immunologically involved "M cells".

Adjuvants will certainly be required for many of the new and improved vaccines currently on the CVI agenda. In some cases, they may simply induce enough of a response to obviate the need for timed-release systems (using microencapsulation techniques, for example) and booster doses of vaccine.

In the last analysis, the usefulness of adjuvants will be determined by the specificity of their activity, their safety and their cost.

***Dr Sadoff, a colonel of the United States Army Medical Corps, is Director of the Division of Communicable Diseases and Immunology at the Walter Reed Army Institute of Research and Walter Reed Medical Center in Washington, D.C., and Chairman of the PVD's Steering Committee on Diarrhoeal Disease Vaccines.***

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*from the CVI's Task Forces and Product Development Groups*

## *Task Force on Priority Setting and Strategic Plans*



### *Terms of reference*

To advise the CVI on priorities for action on new products, on the possible creation of new task forces or product development groups, on regular updating of the CVI's Strategic plan and on resource allocation, and to monitor progress being made by other task forces and product development groups.

### *Update of activities*

Last November, Task Force Chairman Suryanarayan Ramachandran presented recommendations to the CVI's Consultative Group (see page 4) based on a wide-ranging analysis conducted by the Task Force's ten members working in collaboration with nearly 50 experts from around the world. In summary, the five Task Force recommendations called for:

- additional resources for research, especially for the PVD and national vaccine research programmes, with particular emphasis on infective organisms, mechanisms of immunity, potential immunogens and animal models;
- additional resources to improve systems for introducing new vaccines into immunization programmes and for assessing the impact of vaccines;
- resources to ensure a sustained supply of current and future vaccines, with special attention to the production and quality assurance/control capabilities of developing countries;
- continuing support for work on a heat-stable polio vaccine, a single-dose tetanus vaccine and a measles vaccine to be administered shortly after birth;
- a global CVI effort to develop multicomponent vaccines using DTP as a "platform".

The Task Force also made specific recommendations based on an analysis of the 12 vaccines it had identified as requiring urgent evaluation (see *CVI FORUM* No. 1, April 1992, page 8). Three additional vaccines—against malaria, *Shigella* infection and tuberculosis—will be analysed by the Task Force in 1993. A Task Force calculation put the estimated resources required to implement its recommendations at $150 to $270 million over the next five years (in addition to current investments), equivalent to between $5 and $9 million per product developed.

### *Comment*

*by Richard Mahoney, Task Force Secretary*

Of its five recommendations, the Task Force considers the fifth, concerning the development of multicomponent vaccines with DTP as a platform, to have the highest priority and to be the most effective strategy for introducing new vaccines into the EPI delivery system. It was supported, among other things, by the findings of a cost-effectiveness analysis of the 12 "priority" vaccines that pointed to the substantial benefits of adding hepatitis B and *Haemophilus influenzae* b vaccines to DTP.

The other four recommendations seek to strengthen what the Task Force identified as the five "pillars" on which the CVI rests: (1) vaccine research, (2) vaccine delivery and operational research, (3) vaccine supply, (4) vaccine production and (5) individual countries.

The Task Force's recommendations will be submitted as a formal proposal to the CVI's Management Advisory Committee.

In 1993 the Task Force will continue its cost-effectiveness analysis in conjunction with the preparation by the The World Bank of its 1993 World Development Report, which will focus on health. The Task Force will also gather more information about the priorities of developing countries and continue to explore innovative ways of collaborating with industry.

... the five "pillars" on which the CVI rests: vaccine research, vaccine delivery and operational research, vaccine supply, vaccine production and individual countries.

## Task Force on Quality Control and Regulatory Procedures

### Terms of reference

To evaluate and, if necessary, strengthen national licensing procedures to assure the quality of vaccines used in immunization programmes.

### Update of activities

At its meeting in Geneva on 12-13 November 1992 the Task Force reviewed reports from the teams of experts who had visited China and Vietnam in the summer. It recommended, among other things, that the health ministries of these countries should give higher priority to regulatory control of vaccines. They should also bolster and if need be increase the authority of their National Control Authority staff.

To enhance the efficiency and effectiveness of future country evaluations the Task Force recommended that, where appropriate, they should be conducted by teams consisting jointly of members of the Task Forces on Quality Control and Situation Analysis. In addition, the Task Force confirmed that the evaluation team members should be chosen for their expertise in: (a) regulatory and industrial aspects of vaccine production and control; (b) forecasting demand for vaccines over a ten-year period; (c) requirements and specifications for production equipment; (d) plant management and administration; and (e) the economics and financing of procurement vs. production strategies

The Task Force also recommended that final reports based on country visits should be provided to country authorities, who should advise the Task Force within two months whether or not they intend to implement its recommendations. As soon as the national government expresses support to implementation of these recommendations, the Task Force will assist in the drawing up of plans and in the mobilizing of the necessary resources.

### Comment

*by David Magrath, Task Force Secretary*

In its review of current activities the Task Force recognized a conflict or dilemma between, on the one hand, the need to present its findings openly and unequivocally and, on the other, the need to preserve confidentiality in relation to the national authorities of countries being evaluated. The first term of this conflict—openness—is a prerequisite to effective collaboration of the Task Force with all its CVI partners and also to effective coordination by the CVI of activities related to quality control and domestic vaccine production. The second—confidentiality—is a prerequisite to continuing acceptance of the Task Force's evaluations by country authorities, who may, justifiably, object to their quality control shortcomings being publicized before they have had a chance to take remedial action or otherwise respond to criticism. Resolving or learning to live with this dilemma will likely be a major concern of the Task Force over the coming year.

## Task Force on Situation Analysis

### Terms of reference

To assess the global demand, supply and funding of children's vaccines, and to facilitate and monitor the efforts of countries to increase their self-sufficiency in vaccine production and/or procurement.

### Update of activities

In November and December 1992 two joint teams from the Task Forces on Situation Analysis and Quality Control visited Bangladesh and Egypt to develop, together with the national authorities and donors participating in the countries' immunization programmes, a vaccine supply strategy covering the next ten years.

In Bangladesh, the team focused on tetanus toxoid vaccine production, since local production of this vaccine ceased in 1990. The team found that producing tetanus toxoid would be cost-effective for Bangladesh and recommended a number of inexpensive ways in which the country's production facility could be upgraded and an independent quality assurance system set up.

In Egypt, vaccine production facilities seem to be more than adequate to meet oral polio vaccine requirements, provided bulk vaccine can be provided. They are also adequate for the country's needs of tetanus toxoid and eventually DTP, if current attempts to upgrade its pertussis production capability are successful. The team made recommendations for the implementation of Good Manufacturing Practices and for the setting up of an independent National Control Authority.

... a conflict or dilemma between, on the one hand, the need to present its findings openly and unequivocally and, on the other, the need to preserve confidentiality.

## Product Development Group for Development of a Thermostable Oral Poliomyelitis Vaccine

### Terms of reference

To promote and manage the industrial development of a heat-stable oral polio vaccine capable of withstanding at least seven days at a temperature of 45°C without losing more than 0.5 $\log_{10}$ potency for each of the three vaccine virus serotypes.

### Update of activities

At its second meeting on 14 December 1992, the Group heard promising reports from collaborating research teams. Progress is being made towards achieving the Group's objective.

One approach being explored—the use of compounds that bind to the hydrophobic pocket of the poliovirion—has led to the identification of several candidates. Pirodavir, the most promising, has been approved for human use and has been found to stabilize the antigenicity of oral polio vaccine for one week at temperatures of up to 42°C (only 3°C lower than the target). Pirodavir also stabilizes infectivity of the virus over this period but not to a degree significantly greater than that achieved with current stabilizers. Research on the disparity between stabilization of antigenicity and that of infectivity is now a priority.

The second approach uses an innovative drying strategy involving trehalose (*alpha*-D-glucopyranosyl-*alpha*-D-glucopyranoside), a naturally occurring disaccharide with an impressive ability to stabilize many biologically active macromolecules. Using this approach, the investigators have produced a dried oral polio vaccine that is completely stable at 45°C for one week and thus meets the target for stability. The drying process, however, causes a 1.5-2.0 $\log_{10}$ loss of potency.

At the December meeting, participants agreed that a promising approach to solving these technical problems—a less than complete stabilization of infectivity and a loss of virus potency—may well be the combined use of the pocket-binding and the drying techniques. This combination will be explored over the coming months.

### Comment

*by Julie Milstien, Group Secretary*

In its first year the Group established a network of development collaborators. It is now approaching a pivotal point: the work it has already supported has produced an oral polio vaccine of significantly improved thermostability; it remains to be seen if one of the two approaches being followed—or a combination of both—will be successful in increasing thermostability without undue loss of potency.

A hydrophobic pocket-binding compound is not likely to involve excessive production costs, since only very small amounts would be needed. Moreover, the technology could be shared fairly easily with firms currently producing and/or bottling oral polio vaccine.

A dried product, on the other hand, would probably be more costly, although the Group is encouraging the development of novel packaging that would reduce drying costs and vaccine wastage. The drying technology being explored should, moreover, be accessible to most vaccine producing laboratories.

It is becoming increasingly evident that a thermostable oral polio vaccine would not only be a major asset to the Polio Eradication Initiative but would also have the potential to switch the current emphasis on a "cold chain", with its necessary complement of refrigerators and freezers, to a "time chain", based on an efficient distribution system.

It is also possible that the drying approach being explored by the Group may be useful for the improvement of other EPI vaccines, such as the measles vaccine.

... it remains to be seen if one of the two approaches being followed—or a combination of both—will be successful in increasing thermostability without undue loss of potency.

## Product Development Group on a Single-Dose Tetanus Toxoid Vaccine

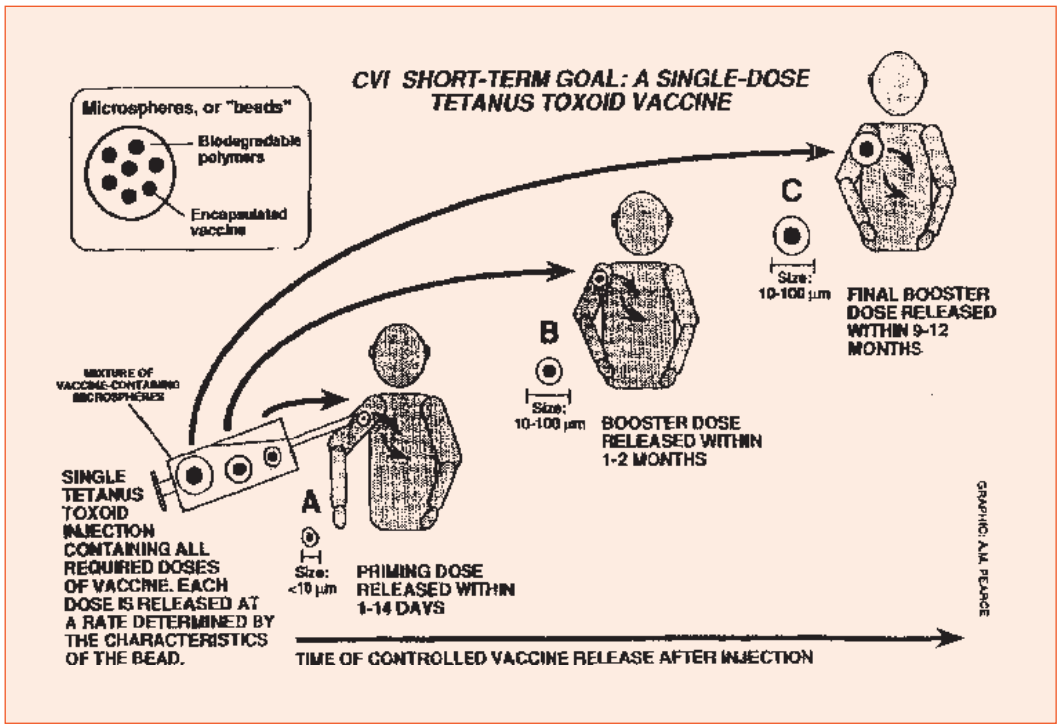
### Terms of reference

To promote and manage the industrial development of a single-dose, controlled-release tetanus toxoid vaccine to be used for maternal immunization against neonatal tetanus.

### Update of activities

The second meeting of the Group, held on 14 October 1992 in Geneva, agreed that a number of considerations have to be taken into account before microencapsulated tetanus toxoid vaccines could enter Phase I trials. These considerations include (a) potency criteria for candidate vaccines in mice, guinea-pigs and monkeys, (b) safety criteria, including local toxicity of antigen-containing polymers in rabbits and life-threatening reactions from the antigen itself, (c) the availability of pure toxoid and (d) terminal sterilization vs. aseptic processing.

Reports from three research teams collaborating with the Group pointed to progress in the formulation of the three types of microspheres being developed (type 1 for priming, types 2 and 3 for early and late boosting). None of the products has shown boosting in mice, but most of them raise antibodies able to




A.M.Pearce

neutralize or inhibit toxin binding and provide a certain degree of protection in mice, and some formulations are able to induce long-lasting immunity in this animal model. One of the three groups that had found it difficult to produce a stable microencapsulated tetanus toxoid vaccine at 37°C seems to be solving the problem by using pure polymers and a stabilizer.

A fourth collaborating team has recently joined the project, much to the satisfaction of the Group, since this team has reported priming and boosting of immunity with suitable proportions of the polymers of lactic acid (PLA) and glycolic acid (PGA) used for delivery of a staphylococcal enterotoxin B antigen.

### *Comment*

*by Teresa Aguado and Paul-Henri Lambert, Group Secretaries*

Over the past year the CVI and the PVD have jointly funded the Group's project and this satisfactory arrangement will continue in 1993. In the coming year it is hoped that vaccine manufacturers will begin to participate with the collaborating teams to carry forward the industrial development of their products. Several firms have responded encouragingly to the Group's advertisements seeking collaboration.

... the lack of sufficient funds to purchase oral polio vaccine has become the greatest obstacle to polio eradication.

## C V I W I R E

### *FROM the EPI*

•In October 1992 the EPI's Global Advisory Group warned that the **lack of sufficient funds to purchase oral polio vaccine** has become the greatest obstacle to polio eradication. This problem is likely to be prominent in discussions at the World Health Assembly in May 1993. The Global Advisory Group recommended that all countries draw up a plan to ensure adequate long-term supply of oral polio vaccine, as well as other EPI vaccines.

•**Vaccine vial indicators** are now available that indicate when the vaccine has been kept for too long at too high a temperature and should be thrown away. These indicators will greatly simplify the monitoring of vaccine storage, handling and transport, particularly of polio vaccine, the most heat-sensitive of the EPI vaccines. They will

reduce the risk of vaccine that has lost its original potency being administered to children. And, for some vaccines, they will also reduce the wastage (believed to be in the order of several million dollars) that results from opened—but not yet empty— vials being discarded after an immunization session. The challenge now is for the CVI partners, especially manufacturers, to ensure that this technology is applied as soon as possible.

*Information from: Dr Robert Kim-Farley, Director, Expanded Programme on Immunization (EPI), WHO, 1211 Geneva 27 [tel: (41-22) 791-4798; fax: (41-22) 788-0591].*

Measles has recently re-emerged as a public health problem in the United States and continues to be a deadly disease in the developing world.

## *FROM the NIH*

•Measles has recently re-emerged as a public health problem in the United States and continues to be a deadly disease in the developing world. The United States National Institute of Allergy and Infectious Diseases (NIAID) has launched a **new measles vaccine initiative** for the development of safe new measles vaccines that are highly effective when administered in early infancy and will aid in the control and eventual eradication of measles. The NIAID requests investigator-initiated research grant applications focused on the study of measles virus and the host's response to infection as it relates to the safe induction of protective immunity. This announcement is intended to stimulate innovative approaches across medical research disciplines, with an emphasis on safely overcoming the maternal antibody barrier and inducing long-lasting protective immunity. Six to eight grants of four years' duration are anticipated for the $1.5 million per year available for this initiative. [See *NIH Guide for Grants and Contracts*, Vol. 21(43), December 1992].

*Inquiries to: Dr James M. Meegan, Virology Branch, DMID, NIAID, NIH, Solar Bldg, Room 3A15, Bethesda, MD 20892, USA. Tel:(1-301) 496-7453; Fax (1-301) 496-8030.*

## *FROM the PVD*

•Several PVD-sponsored projects are showing progress, notably on:

(1) a **group A/C meningococcal vaccine** designed for integration into the EPI: one conjugate is under clinical trial in Africa and one or two more will soon be available; (2) a **group B meningococcal vaccine**: two candidates are undergoing an immunogenicity trial in Iceland; (3) a **measles vaccine to be administered shortly after birth**: a recently formed PVD working group is setting up an international research network to speed up development of subunit vaccines using new delivery systems (such as ISCOMs, see page 7), to coordinate preclinical assessment of new vaccines using live viral and bacterial vectors (such as canary pox, BCG) and to develop new genetic tools for the attenuation of wild measles virus; the PVD has established a central facility in the Dutch National Institute of Public Health and Environmental Protection (RIVM), where new candidate vaccines can be tested in a standardized primate model under PVD supervision; and (4) a **tuberculosis vaccine**—two approaches are being explored: one attempts to genetically manipulate BCG to express antigens best able to induce protective immunity; the other—the more promising approach—seeks to produce a new strain of *Mycobacterium tuberculosis* genetically attenuated to induce protective immunity without producing disease.

•Current **PVD research priorities** are: 1) improving vaccine efficacy and vaccine delivery systems (including live vaccine vectors, mucosal immunization and controlled-release systems); 2) developing new vaccines against the major viral and bacterial diseases (including measles, bacterial and viral diarrhoea, meningococcal meningitis and pneumococcal pneumonia, tuberculosis, dengue and Japanese encephalitis).

*Information from: Dr Paul-Henri Lambert, Microbiology and Immunology Support Services, WHO, 1211 Geneva 27 [tel: (41-22) 791-3282; fax: (41-22) 788-2937].*

# 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).* CVI FORUM *cannot accept responsibility for errors in items published in this calendar. However, information is welcomed from readers who notice such errors.*

*1-2 February 1993 Palo Alto, USA*

**Epitope selection technologies for pharmaceutical design**

James W. Larrick, Palo Alto Institute for Molecular Medicine, 2462 Wyandotte Street, Mountain View, CA 94043, USA

*1-8 February 1993 Taos, USA*

**Molecular aspects of B lymphocyte differentiation**

Keystone Symposia, Drawer 1630, Silverthorne, CO 80498, USA

*8-14 February 1993 Taos, USA*

**Emerging principles for vaccine development: antigen processing and presentation**

A. Peterson, Keystone Symposia, Drawer 1630, Silverthorne, CO 80498, USA

*12-19 March 1993 Lake Tahoe, USA*

**Molecular biology of human pathogenic viruses**

Peter M. Palese, Keystone Symposia, Drawer 1630, Silverthorne, CO 80498, USA

*17-24 March 1993 Taos, USA*

**Molecular immunology of virus infections**

Carol S. Rees, Keystone Symposia, Drawer 1630, Silverthorne, CO 80498, USA

*6-8 April 1993 Health Sciences Centre, Kuwait*

**International conference on T-cell subsets and cytokines: interplay in infectious diseases**

Secretary of TCSC Conference, Faculty of Medicine, Room No. 51, Kuwait University, P.O. Box 24923, Safat, 13110 Kuwait. Tel: (965) 631-9602; Fax: (965) 533-0472/531-8454

*23-26 May 1993 Albany, NY, USA*

**Recombinant vectors in vaccine development**

Kathleen Cavanagh, Symposium Coordinator, Nucleic Acid Technologies Foundation, Wadsworth Center for Laboratories and Research, P.O. Box 509, Albany, NY 12201, USA. Tel:(1-518) 474-7760; Fax: (1-518) 474-3439

*23-26 May 1993 Aarhus, Denmark*

**6th annual meeting of the Scandinavian Society for Immunology**

Jens Chr. Jensenius, Institute of Medical Microbiology, The Bartholin Building, University of Aarhus, DK-8000, Aarhus C, Denmark

*24-25 May 1993 Princeton, USA*

**5th Princeton liposome conference: the basics and the breakthroughs**

E. Templeton, Conference Coordinator, c/o The Liposome Company, Inc., One Research Way, Princeton, NJ 08540, USA. Tel: (1-609) 452-7060

*24 June-5 July 1993 Cape Sounion Beach, Greece*

**Targeting of drugs: advances in system constructs**

Prof Gregory Gregoriadis, Centre for Drug Delivery Research, The School of Pharmacy, 29-39 Brunswick Square, London WC1N 1AX, UK. Tel: (44-71) 753-5822/5820; Fax: (44-71) 278-0622

*8-13 August 1993 Glasgow, UK*

**9th international congress of virology**

D.H. Watson, Chairman, National Organizing Committee, University of Leeds, Leeds LS2 9JT, UK

*6-10 September 1993 Paris, France*

**Immunopotentiators in modern vaccines**

Mr John Herriot, Meetings Management, Straight Mile House, Tilford Road, Rushmoor, Farnham, Surrey GU10 2EP, UK

*12-15 September 1993 London, UK*

**7th international congress on rapid methods and automation in microbiology and immunology**

Ms Pauline Dudgeon, RAMI-93 Secretariat, Sleights Limited, 14 Dalling Road, London W6 OJB, UK

*12-17 June 1994 Barcelona, Spain*

**12th European immunology meeting (EFIS)**

Immunology Department, Hospital Clinic, Villaroel 170, 08036 Barcelona,

# LETTERS TO THE EDITOR

## *Vaccines for—and by—the Third World*

The development of new vaccines is largely based on knowledge derived from laboratory and clinical research in developed countries. Developing countries are usually involved at a late stage, when candidate vaccines are tested on human volunteers. In that way, we may quite often end up with vaccines that are not ideal for use in developing countries and that do not respect the highly variable pattern of responses of people of differing racial backgrounds, health and nutritional status, and do not take note of prevailing local conditions.

For example, at the time when virus strains were being selected for the polio vaccine, if heat stability had been taken into account,

more robust organisms might have been chosen. Had more work been done on the clinical immunology of measles in developing countries, some of the problems encountered in the use of the vaccine might have been anticipated.

May I suggest that the CVI ensure that both basic research and the clinical immunology needed to develop vaccines are carried out with the close collaboration of clinicians and immunologists working locally in developing countries? Only in this way do we stand a reasonable chance of producing vaccines that meet the needs—physiological and geographical—of all end-users.

*Adetokunbo O. Lucas*
*Professor of International Health*
*Harvard School of Public Health*
*Boston, Massachusetts, USA*

## *Acellular pertussis vaccines*

I wish to comment on the possibility of manufacture of acellular pertussis vaccines in developing countries. At least three factors must be taken into account before any such attempt be made.

First, acellular vaccines must be shown to be as effective as whole cell vaccines in protection against large challenges of organisms in countries where pertussis is endemic. Fortunately, an acellular pertussis vaccine trial is currently in progress in Senegal.

Second, the cost of acellular vaccines should not be significantly higher than that of whole cell vaccines. Today, the opposite is the case.

Third, developing countries would need a high level of technology for production of purified antigens. Few production facilities outside of developed countries can meet those standards.

*Stanley A. Plotkin, M.D.*
*Medical and Scientific Director*
*Pasteur Mérieux Connaught*
*Emeritus Professor University of Pennsylvania (USA)*
*Marnes-La-Coquette, France*

***Letters submitted for publication in* CVI FORUM *can be in English, French or Spanish. They will be considered for publication on the basis of their potential interest to the broad readership of* CVI FORUM. *Those selected for publication may be edited for space and clarity, and will be translated into the two languages other than that chosen by the writer (*CVI FORUM *is published in English, French and Spanish). Send letters, preferably typed, to: The Editor,* CVI FORUM, *WHO/CDS, Avenue Appia, 1211 Genève 27, Switzerland.***

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## PICTURE POSTSCRIPT

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