C V I F O R U M

NEWS FROM THE CHILDREN'S VACCINE INITIATIVE

Number 1
April 1992

The Children's Vaccine Initiative (CVI)
is an informal association
of public and private groups dedicated to helping
the world community focus, accelerate and apply
advances in science to the development,
manufacture and efficient delivery of new and better
vaccines for the world's children.
It was launched in response to the Declaration of
New York, made shortly before the World Summit
for Children in 1990, which called for
a global commitment to the production and delivery of
"ideal children's vaccines"
that provide lasting protection against
a wide range of diseases, are simple to administer
and are affordable.The CVI was established 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),
and has its secretariat in WHO.

Inside

The CVI: a new programme, but how different?

Suryanarayan Ramachandran is Chairman of two of the CVI's key operational structures, its Management Advisory Committee and its Task Force on Priority Setting and Strategic Planning (see page 8). In the interview below he answers questions about the CVI and its objectives.

Q ***How does the CVI stand out in the already crowded galaxy of development programmes?***

A The CVI is unique, I believe, in the manner of its conception and birth, the boldness of its objectives, the breadth of its mandate and the synergy of its relations with existing programmes.

First, the CVI was conceived at a unique occasion: the World Summit for Children in 1990, where government leaders from over 150 countries expressed the need for new and better vaccines as a prerequisite to a better future for every child. And its birth over the past year was attended by no less than five major development agencies — UNICEF, UNDP, The Rockefeller Foundation, The World Bank and WHO.

Second, these founding agencies were bold enough to commit themselves to what many believed to be an impossibly utopian goal: namely, the development of a vaccine that, in a single dose given at birth, would protect the world's 140 million or so infants against all the major diseases of childhood.

Third, I know of no other programme in the area of child survival that covers such a broad spectrum of activities related to vaccine development, from research and development to post-marketing surveillance and reporting and between them, the intermediate steps of testing, scale-up, manufacture, and so on.

And fourth, in order to acquire maximum cost-effectiveness, the CVI is designed to mesh with, and build upon, the strengths of existing programmes, like WHO's Expanded Programme on Immunization (EPI) and the UNDP/WHO Programme for Vaccine Development (PVD).

Q ***What can the developing world expect to gain from the CVI?***

A Access to the most effective, safest vaccines that can be produced through the most advanced technology available. At present, despite attempts at transferring technology from developed to developing countries, many public sector programmes in the Third World just can't afford some of the best vaccines being made for developed countries.

The CVI will also help developing countries to strengthen their capacity to gather the epidemiological data needed to evaluate their vaccine needs. It will also, in the long term anyway, assist them in building up the manufacturing capability needed to make their own vaccines.

Dr S. Ramachandran

My country, India, is a good example of a country that should benefit from the CVI, particularly in basic vaccine research. But it also stands to gain in vaccine manufacture, quality control systems and vaccine delivery. And because the CVI is not restricted to a given set of diseases as the EPI is, it can help India acquire vaccines that will protect against locally prevalent diseases, like tuberculosis, malaria, leprosy, lymphatic filariasis, and so on.

Q ***Will the CVI use EPI's vaccine delivery system or develop its own logistic infrastructure for reaching the children with its own vaccines?***

A Where a good infrastructure exists, for whatever part of the vaccine development process, the CVI will make use of it when possible. For example, it makes sense for us to piggy-back CVI products on the EPI vaccines via the EPI delivery system. In the

"Where a good infrastructure exists, for whatever part of the vaccine development process, the CVI will make use of it."

same way, we already take advantage of the PVD, moving the products of its basic research right on through the whole vaccine development spectrum. And yes, there may be some duplication, but I see it more as combining efforts to reach common goals more quickly rather than wasteful overlap.

Q ***How will the CVI reconcile its goal of bolstering Third World vaccine manufacturing resources and the risk of its high-tech vaccines being beyond the manufacturing capacity of developing countries? And once these new vaccines are produced, won't they put developing country manufacturers out of business?***

A The new vaccines won't appear on the market overnight. It's going to take several years. Developing country manufacturers have time to learn how to absorb the new technologies and modernize their production facilities.

Q ***Does the CVI mandate stop when a CVI vaccine is in the field use?***

A CVI's mandate goes beyond that stage. It includes an evaluation of the impact of a vaccine on the burden of diseases in an area. It even goes as far as advising governments about immunization strategies needed to ensure long-term control of these diseases.

Q ***The pharmaceutical industry has for a long time been apathetic, perhaps understandably so, about vaccine development for the Third World. How will the CVI revive industry interest?***

A By involving manufacturers right from the start in the planning and execution of CVI activities. By ensuring that they derive a suitable return on their investment and recover their costs. And, generally, by motivating them to contribute their expertise in basic research and development, production, quality control, regulatory procedures and delivery systems to the CVI process, in which they have a rightful role to play and of which they are an integral part.

Q ***Who will pay for the vaccines that emerge from the CVI process?***

A There is a clear need to devise new funding arrangements to ensure that the CVI vaccines will be used where they are most needed in developing and developed countries. This is one of the most important issues that the CVI will have to deal with. The CVI, inasmuch as it represents such a broad range of interests, is in a good position to serve as a forum where new formulas and solutions can be worked out that are acceptable to all parties concerned, in particular manufacturers, multilateral and bilateral donors, and developing country governments.

Exploiting scientific advances

Philip Russell, Special Advisor to the CVI, believes the goals of this new programme are attainable. In the interview below, he discusses the scientific grounds for his optimism.

"If it does what it was created to do," says Dr Russell, "the CVI will speed up the vaccine development process, make it more efficient, and orchestrate the emergence of better vaccines and new vaccines that will prevent most, if not all, of today's preventable child-killing diseases."

This is not wishful thinking, he insists. "The technology is there. It has just not been exploited. Many exciting options for development of new vaccines remain in the laboratory and do not progress to the product development stage."

Dr P.K. Russell

The reason? "Up to now there has been no mechanism for overseeing the whole process, from conception of a vaccine at the laboratory bench to its development by industry

"Up to now there has been no mechanism for overseeing the whole process, from conception of a vaccine at the laboratory bench to its development by industry and its incorporation into vaccine programmes."

and its incorporation into vaccine programmes. The CVI has been set up to do just that and to link all of the components of an equation that up to now has defied attempts to solve it."

Two recently developed technologies could hasten the attainment of the CVI goals, in Dr Russell's view. One is the microencapsulation process, whereby vaccines can be enclosed in an injectable microsphere or microcapsule from which they are released at pre-set times and rates (see page 6). The other is the use of live viral or attenuated bacterial vectors, genetically engineered to express the desired vaccine antigen structures and thereby induce immunity to specific infectious agents.

Live vectors, Dr Russell believes, may be a much less costly option than using inactive protein antigens or inactivated whole bacterial or viral particles. A single vaccine dose needs something like 10,000 million particles of an inactive virus, whereas with a live vector the immunizing dose may be orders of magnitude lower. Moreover, inactive purified protein products may require costly fermentation and purification procedures. "Generally, we have learned a lot about live vectors," he says, "especially from their veterinary use, such as with the vaccinia-vectored rinderpest and rabies vaccines." On the negative side, attempts to use salmonella to vector *Shigella* genes have not been entirely successful. And further back along the research pipeline, the potential of BCG as a vaccine carrier is still being explored.

Microencapsulation of inactive protein products, on the other hand, could provide a short-cut to a multicomponent vaccine against several diseases. "There are certainly technical and manufacturing problems in delivering several vaccine antigens in a single product," notes Dr Russell. Putting the antigens into several different microspheres and the microspheres into a single microcapsule could get around such problems, although there is some concern about the fact that once the microspheres are in the body there is no way of removing them.

Is there a limit to the number of antigens a "super-vaccine" could carry?

"Some scientists are talking of 15 or 20 antigens," Dr Russell says. "We just don't know the limit right now and cannot be dogmatic about it." Research is needed, though, to find out whether the immature immune system of the newborn can fully respond to immunogens administered simultaneously. "If it can't, we're going to have to administer our antigens separately."

Moreover, some antigens, he notes, are more suited to live vectors and others to inactive vaccine products and putting the two groups within a single vaccine product may not be possible. Viral vectors, like vaccinia, seem most effective in expressing the antigens of other viruses, like rabies, measles and possibly respiratory syncytial virus. One of their drawbacks, however, is that they cannot effectively express some viral protein antigens, such as those of poliovirus, nor the polysaccharide antigens of the *Haemophilus* and meningococcus conjugated vaccines, which are more suited to the microencapsulation technique. "As things stand, I don't see the two approaches — live vectors and inactive products — coming together in one vaccine within the next two decades," Dr Russell says.

Given their undeniable operational advantages, why is the CVI not going all out for oral vaccines rather than still working on injectable products?

"Clearly, an oral vaccine offers many advantages. But right now we don't know enough to produce a truly effective oral multicomponent vaccine. We just don't know how to get antigens efficiently through the intestinal epithelium into the lymphatics. To date, this is still an inefficient route of administration."

The scientific obstacles the CVI will face are not insurmountable, Dr Russell believes. "They're just challenges. There are only two really critical factors that will make or break the CVI: having enough public sector resources to see the programme through to its achievements and ensuring the collaboration of private industry."

Funding in the order of US$200-300 million is going to be required over the next decade to achieve the short-term CVI goals, Dr Russell estimates. This, however, includes investment already being made in vaccine research by private industry and by national agencies. The National Institutes of Health in the United States alone spends around US$150 million a year (of which half on AIDS vaccine research). Dr Russell is optimistic that the necessary funds will be made available.

He is also confident that the CVI will enjoy the participation of private industry. "We've

"Research is needed, though, to find out whether the immature immune system of the newborn can fully respond to immunogens administered simultaneously."

opened a new channel of communication with industry and the signs are that they are eager to participate. We must make sure this channel remains open and functioning."

What are the first results we can expect from CVI activities?

Dr Russell foresees a heat-stable oral polio vaccine coming off the production line "in a year or two", followed three or four years later by a single-dose tetanus toxoid vaccine.

As for longer-term goals, "my crystal ball doesn't see that far ahead".

Dr R.H. Henderson (left), WHO Assistant Director-General, who opened the CVI's first Consultative Group meeting, and Prof O. Ransome-Kuti, Nigeria's Health Minister, in the Chair.

"Every year an estimated two million deaths and five million cases of disability occur from diseases preventable by vaccines."

CVI's partners come together for first major scene-setting meeting

Vaccines offer the best chance of improving the health of the developing world, according to Olekoye Ransome-Kuti, Minister of Health for Nigeria and Chairman of the first meeting of CVI's Consultative Group, which was held at WHO in Geneva, Switzerland, in December 1991.

Professor Ransome-Kuti sketched the public health backdrop against which the CVI was created. Every year, he said, an estimated two million deaths and five million cases of disability occur from diseases preventable by vaccines. He noted that acute diarrhoea of viral or bacterial origin causes three to five million deaths and accounts for at least a third of deaths in children under five; acute respiratory infections kill more than two million people, mostly children; malaria affects 150 million people and kills an estimated one million children. And there are no satisfactory vaccines available for these diseases.

To achieve the goals set by the 1990 World Summit for Children for the year 2000 — poliomyelitis eradicated, measles deaths slashed by 95%, neonatal tetanus eliminated and maintenance of a 90% immunization rate for the six EPI diseases — better vaccines are needed, Prof Ransome-Kuti said. They should require few visits and no refrigeration, protect against more than one disease and cost less. More efficient vaccines could also be used in developed countries, where, he warned, immunization coverage against measles, diphtheria and pertussis has fallen to dangerous levels in some areas.

Lindsay Martinez, CVI Executive Secretary, believes that the CVI will translate "the promise of science into valuable products for the benefit of children worldwide". That promise is based on a recognition that, backed by "an exceptional, coordinated international effort", modern science *can* produce a new generation of children's vaccines. Given that industry has a limited incentive to develop new vaccines and that existing funding mechanisms cannot provide

the resources needed, "innovative collaborative partnerships and funding arrangements must be devised," said Dr Martinez.

Johannes ("Jan") P. Pronk, Netherlands Minister of Development Cooperation, reminded the meeting that new vaccines could save five or six million lives annually up to the year 2000. He believes an "anti-poverty strategy" is needed for the 1990s, especially as the gap between rich and poor is widening. The poorest social groups should also be brought into decisions about health priorities, he said, including priorities about the development and deployment of new vaccines.

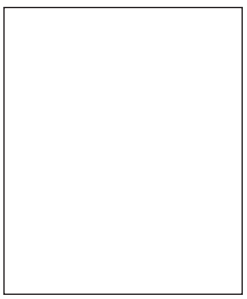
The poorest social groups should also be brought into decisions about health priorities, including priorities about the development and deployment of new vaccines.

Mr J. Pronk (left), Netherland's Minister for Development Cooperation, and Dr A.R. Measham of The World Bank.

Mr Pronk cited figures illustrating the present focus of the research community: Of the US$30 000 million currently spent on health research worldwide, only US$1600 million or 5% is allocated to the health problems of the developing world, and of this US$1600 million, just under a half comes from the developing countries themselves. Moreover, the drug industry spends only 3% of its total research budget on developing country health problems — a situation that results in "injustice or gross inefficiency in the utilization of available resources".

Because such research is conducted almost totally in industrialized countries, Mr Pronk said, its results are not readily accessible to developing country populations; vaccines developed against diseases that claim many victims remain on Western shelves because the potential consumers [in developing countries] cannot afford them.

Advances in vaccine research and development



Dr P.L. Ogra

◆ Pearay L. Ogra, John Sealy Chairman and Professor of Pediatrics at the University of Texas in Galveston, Texas, USA, heads a research group studying how "the plethora of immune competence in the mucosal immune system" can be exploited to protect individuals and populations against the 80-90% of infectious diseases acquired through viral or bacterial invasion of the mucosal tissues of the gastrointestinal, respiratory and genital tracts.

Dr Ogra listed some of the viruses that use mucosal portals of entry: respiratory syncytial virus (RSV), poliovirus, influenza virus, adenoviruses, measles virus, rotavirus, rubella virus and human immunodeficiency virus (HIV). Bacteria using this route include mycobacteria, possibly streptococci, *Bordetella-pertussis*, *Shigella* organisms, *Vibrio cholera*, *Escherichia coli*, *Salmonellae* and many other respiratory and enteric pathogens.

Recent animal and human studies, he said, have shown oral immunization with a number of viral and bacterial immunogens to be highly effective in inducing a strong protective immune response against respiratory, intestinal or genital infections.

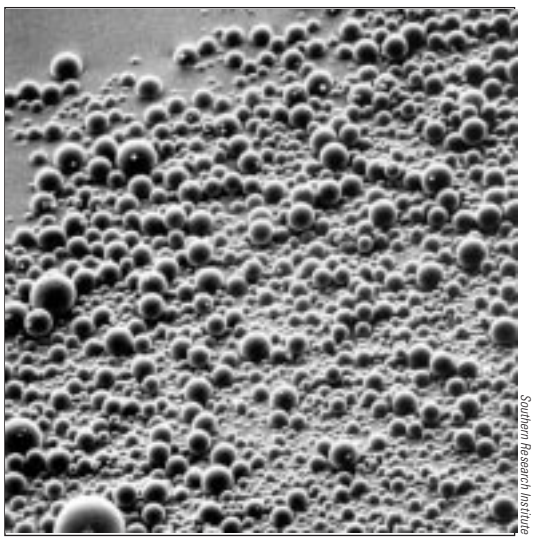
Much research is still needed, though, to identify the factors that determine the degree of protection obtained, the best delivery systems for oral vaccines and precise determinants of virulence in the pathogenic agents against which vaccines could be directed to obtain maximum protection.

Dr J. Eldridge

◆ John H. Eldridge of the University of Alabama Department of Microbiology in Birmingham, Alabama, USA, described the microencapsulation process, whereby a drug or vaccine is coated in a protective sphere or microsphere small enough to be administered by injection. The microspheres release the active product at a rate determined by their size

and chemical composition (usually a mix of the copolymers used to make surgical sutures and controlled-release implants). After injection, the microspheres induce only a minimal inflammatory response and biodegrade into normal body constituents.

- A single injection of microspheres of different chemical composition and/or size can provide a vaccine delivery system ensuring pulsed antigen release: tissue and blood levels of the microencapsulated antigens will peak at pre-set times over a two-year period, mimicking an immunization schedule of primary and booster dose administrations.
- The different microspheres do not interact with each other, making it possible to administer several different vaccines in a single injection, each vaccine microencapsulated in such a way as to ensure its own specific pulsed schedule independently of the other vaccines.
- The microspheres hold the product in a dry state, obviating the need for heat stabilizers or a cold chain.
- Microspheres less than 10μ in diameter are engulfed at the injection site by macrophages, which deliver them to nearby lymph nodes and from there to the main components (notably, T-cells) of the immune system: they are therefore unaffected by the presence of any specific (e.g., maternal) antibodies that contraindicate the perinatal use of many current vaccines.



Southern Research Institute

Microspheres containing a staphylococcal enterotoxin B toxoid vaccine.

- Microencapsulated vaccines are protected from the acidic and enzymatic environment of the gastrointestinal tract that limits use of oral immunization: in animal studies, orally administered staphylococcal enterotoxin B vaccine encapsulated in microspheres induced IgG anti-toxin antibodies in blood and IgA secretory anti-toxin antibodies in saliva, gut fluids and bronchio-alveolar lavage fluids, whereas without microencapsulation oral administration of the vaccine had no effect.

Dr E. Paoletti

◆ Enzo Paoletti of Virogenetics Corporation in Troy, New York, USA, described work on the use of pox viruses as vectors for recombinant vaccines. He and his colleagues genetically altered a vaccinia virus to attenuate its virulence and replicating capacity, and to render it harmless in mammals. "NYVAC", as they dubbed this vaccine vector, retained its "excellent immunizing potential" when expressing foreign genes, Dr Paoletti told the meeting.

A canary poxvirus was chosen by the Virogenetics team for a second vector, called "ALVAC", which is capable of replicating only in avian species and therefore offers a high degree of safety for use in mammals. ALVAC, genetically manipulated to express foreign antigens, induced "significant" protective immunity when inoculated into laboratory animals. Equipped with a recombinant rabies glycoprotein antigen, the vector induced a strong specific antibody response in chimpanzees. Very low doses in human volunteers elicited neutralizing antibodies to rabies virus, said Dr Paoletti, and were "well tolerated".

Fitted with the two major glycoproteins of measles virus (the fusion and haemagglutinin glycoproteins), ALVAC also provoked protective antibody responses in numerous species of laboratory animals. The ALVAC-measles recombinant vaccine will soon be tested in human subjects.

Microspheres less than 10μ in diameter are engulfed at the injection site by macrophages, which deliver them to nearby lymph nodes and from there to the main components of the immune system.

Dr F.E. André

◆ Francis E. André, Vice-President and Director of Medical and Scientific Services at SmithKline Beecham Biologicals, Rixensart, Belgium, believes a combination vaccine containing 10 antigens is "technically feasible". This vaccine could protect against eight diseases — diphtheria, tetanus, pertussis, measles, poliomyelitis, hepatitis B, *Haemophilus influenzae* b pneumonia, lower respiratory disease due to respiratory syncytial virus and hepatitis A. Developing such a product, however, is "fraught with difficulties", he warned. These include:

- incompatibilities between preservatives, antigens, adjuvant and vehicle (excipient), making it difficult to achieve a stable, effective formulation;
- a higher risk of adverse reactions than with simpler vaccines;
- painstaking (and therefore time-consuming and costly) laboratory and clinical testing simply to determine feasibility;
- the likelihood that a "commercially viable" price enabling recovery of development costs would be "quite high".

Novel approaches to the development of combination vaccines might circumvent many of these obstacles, Dr André said. They include the use of more potent adjuvants, microencapsulated antigens and orally administered live attenuated vectors genetically engineered to express the protective antigens of many pathogenic organisms.

Panelists from different segments of the CVI "umbrella" gave their views on the CVI and its objectives. A sampling:

For the panel representing vaccine users, there is a crucial need for users in developing countries to be consulted early on in the CVI process about their local epidemiological situation and their vaccine needs (see page 11, "Task Force on the Strengthening of National Epidemiological Capacities"). The panelists representing vaccine producers drew attention to some of the problems facing industry in relation to vaccine development: poor patent protection, stringent price regulation, a growing market in product mimics of sometimes doubtful quality and falling profits (see page 9, "Task Force on Relations with Development Collaborators"). Finally, the panelists representing collaborating organizations and programmes called for a long-term commitment to basic research, for careful monitoring of quality, quantity and distribution of vaccines, and for consideration of local vaccine production as an important source of vaccines worldwide (see page 10, "Task Force on Needs Assessment and National Control Authorities of Developing Countries" and "Task Force on Situation Analysis of Global Vaccine Supply").

There is a crucial need for users in developing countries to be consulted early on in the CVI process about their local epidemiological situation and their vaccine needs.

The full report of this Consultative Group meeting can be obtained on request from: Dr Lindsay Martinez, CVI Executive Secretary, WHO/CDS, 1211 Geneva 27, Switzerland.

PROGRESS REPORT

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 and on regular updating of the CVI's Strategic plan, and to monitor progress being made by other task forces and by product development groups.

Update of activities

The Task Force held its first meeting on 20-21 February 1992 in New York. Participants conducted a detailed assessment of vaccine requirements for diseases within and outside WHO's Expanded Programme on Immunization (EPI), as well as diseases of major regional importance, and drew up a tentative list of infections/vaccines requiring priority action, namely: dengue, *Escherichia coli*, *Haemophilus influenzae b* (within a multicomponent vaccine), hepatitis B (within a multicomponent vaccine), measles (a vaccine for administration shortly after birth), meningococcal meningitis, pertussis (an acellular

vaccine), polio (a heat-stable oral vaccine), rotavirus, pneumococcal pneumonia, tetanus (a single-dose vaccine for maternal immunization) and typhoid.

The Task Force also identified five priority areas of technology: oral administration, single-dose preparation, heat stability, adjuvants and multivalent vaccines.

Studies are being commissioned on each of the priority vaccines/infections and the findings will be reviewed by a Task Force subgroup. At its meeting in October 1992, the Task Force will compile these reports into a master document for presentation to the Consultative Group meeting to be held in mid-November 1992.

Comment

by Dr Suryanarayan Ramachandran, Task Force Chairman

At this first meeting, we tried to define the scope of the Task Force's mandate. Identifying the priorities for vaccine development called for an assessment of such issues as disease burdens, vaccine science and technology, macroeconomics of vaccine production and utilization, national and regional vaccine requirements, and availability of vaccine-related infrastructures. We also felt that, in order to ensure the initial interest of industry, the priority vaccines chosen should stand a reasonable chance of completing the development process at least before the end of the century.

Task Force on Relations with Development Collaborators

Terms of reference

To provide the CVI's Product Development Groups and the CVI Secretariat with guidelines for negotiating product development agreements with interested public and private sector parties.

Update of activities

The Task Force held its first meeting in Geneva on 17-18 February 1992. Issues discussed included:

- Procurement policies

The Task Force noted that manufacturers have found it necessary to raise prices of EPI vaccines, that total procurement costs are likely to rise as the number of available vaccines grows and that costs of vaccines using new technologies may be high as a result of high research and development costs. In addition, companies potentially interested in developing vaccines require some assurance that a market exists for these products.

- Intellectual property rights

The Task Force expressed concern that the issue of intellectual property rights could prove a costly and complex hurdle for the CVI, particularly for multivalent vaccines, since many parties may hold rights to different vaccine components.

- Contract research

Contracts for specific development projects that are only part of the entire vaccine development process are likely to be of interest only to groups doing research at universities or working with non-profit organizations and smaller biotechnology firms. Large companies would consider collaboration only on projects that carry a product through to the marketing stage, i.e., that cover scale-up, manufacture, sales and regulatory procedures. Moreover, these larger companies would require evidence of potential market demand and prior clarification regarding ownership of intellectual property rights.

- Limited use vaccines

Industry could contribute production facilities and expertise for vaccines that would be used only in developing countries, provided costs were recoverable.

- Regulatory issues

Regulatory standards need to be re-assessed to ensure that they do not hinder the development of vaccines for use only in developing countries. The CVI, because of the expertise available to it, should be in a position to help companies obtain regulatory approval and rationalize regulatory requirements.

- Classification of vaccines for purposes of CVI/industry relations

Task Force members from private industry presented to the meeting a table listing a sampling of vaccines for which different types of CVI-industry interaction is required (with some overlap for certain vaccines): (1) existing EPI vaccines in their current forms (measles, diphtheria, polio, pertussis, tuberculosis and tetanus), for which CVI has no industry-related role but which require increased funding for continued procurement; (2) existing non-EPI vaccines (hepatitis A and B, *H. influenzae* b, yellow fever, typhoid) for which major procurement programmes must be launched; (3) improved vaccines, both EPI and non-EPI (pertussis, measles, mumps, neonatal tetanus, polio), for which industrial collaboration will have to be negotiated on a case-by-case basis; (4) new vaccines with potentially important markets (cholera, hepatitis A, herpes, AIDS), which will call for CVI assistance on regulatory issues and the setting up of clinical trials; and (5) vaccines for almost exclusive use in developing countries (dengue, Japanese encephalitis and parasitic diseases, such as schistosomiasis, malaria, etc.), for which industry requires logistic and possibly financial support.

The Task Force appointed a subgroup to finalize recommendations on CVI/industry "co-development" agreements and on negotiating policies for the CVI. These recommendations will be presented to the May meeting of the CVI's Management Advisory Committee.

The issue of intellectual property rights could prove a costly and complex hurdle for the CVI, particularly for multivalent vaccines.

Comment

by Dr Richard Arnold, Task Force Chairman

This first meeting underlined the difficulty of matching economic realities with expectations, but it was a significant step in the right direction. I believe the CVI will work if we can find a way of bridging the needs of industry — the only realistic source of the vaccines — with public sector needs. Reconciling the two is going to involve the efforts of donors, recipient countries and other interested parties, and, of course, industry itself.

Task Force on Needs Assessment and National Control Authorities of Developing Countries

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

The Task Force is in the process of being formed and is expected to hold its first meeting some time in the autumn of 1992.

Meanwhile, a "priority" list has been drawn up of five countries to be offered a review of their licensing procedures, using oral polio vaccine as a model: Brazil, China, Indonesia, Mexico and Viet Nam. Before the end of 1992 the Task Force will assign three independent inspectors to visit these countries and verify their vaccine licensing procedures. It will assess the inspectors' reports and, if need be, arrange for the strengthening of national licensing capabilities.

Comment

by Dr David Magrath, Task Force Secretary

The Task Force will act as an international inspection group working outside the UN system. It will provide credibility to vaccine production in developing countries, while ensuring that the world's children are being given safe and effective vaccines. It is essential, therefore, that its members — especially its inspectors — be chosen for their independence, authoritative stature and sound judgment. Moreover, the inspections must be conducted in accordance with a uniform set of guidelines, in order to ensure impartiality.

Local vaccine production, which accounts for 40-60 percent of world supply, may be significantly affected by the introduction of new technologies.

Task Force on Situation Analysis of Global Vaccine Supply

Terms of reference

To assess worldwide capacity for development, production and delivery of children's vaccines and achieve the best use of available buying power to foster vaccine development and assure supply.

Update of activities

The Task Force held its first meeting on 12-13 March 1992 in Boston, Massachusetts, USA.

The meeting participants agreed that an immediate priority of the Task Force is to determine the capacity of world vaccine production to meet short-term EPI needs. The meeting concluded that, on the strength of EPI surveys, production capacity, at least on the basis of current immunization strategies, is adequate.

A second, less immediate priority noted by the meeting participants is to assess the world's long-term vaccine production capacity in relation to future introduction of new vaccines, particularly multivalent vaccines.

The Task Force also noted that local vaccine production, which accounts for 40-60 percent of world supply, may be significantly affected by the introduction of new technologies, and stressed the need to take this possibility into account before introducing new vaccines.

Future tasks to be completed by Task Force members:

- an inventory of manufacturers of the EPI vaccines, with estimates of 1991 production levels;
- a study of the different factors — including the role of EPI — that influence the worldwide demand for vaccines;
- a survey of current public vaccine funding, in order to devise a funding strategy for vaccine procurement and to enlist in the CVI process as many sources of public funding as possible;
- a report on the consequences of CVI's product development activities on local vaccine production;
- information from potential manufacturers of vaccines that could be incorporated into the EPI programme about plans they may have to develop: (a) vaccines for *H. influenzae* b, hepatitis B and pertussis (in combination); (b) vaccines already under development through the CVI's existing or proposed Product Development Groups (heat-stable polio vaccine, controlled-release tetanus toxoid vaccine and better measles vaccine); (c) vaccines for use in developing countries generally.

The next meeting of the Task Force is tentatively planned for 21-22 September 1992 in Copenhagen.

Comment

by Dr Anthony Robbins, Task Force Secretary

This Task Force was set up in response to UNICEF's need for comprehensive information on worldwide vaccine production capacity with a view to better assurance of global vaccine supply. Among the difficult issues the Task Force is grappling with: (1) how new vaccines will be incorporated into the UNICEF/EPI system; (2) the assessment of future trends in vaccine manufacturing capacity and vaccine demand— a crucial prerequisite for long-term planning both of manufacture and procurement of vaccines.

Task Force on the Strengthening of National Epidemiological Capacities

Terms of reference

To help countries strengthen their capability to collect, analyse and use sound epidemiological data that are essential for the efficient incorporation of new and better vaccines into their national immunization programmes; also to provide epidemiological services and identify important epidemiological issues for other CVI Task Forces and Product Development Groups.

Update of activities

The Task Force is in the process of being constituted and is expected to hold its first meeting by mid-1992.

Comment

by Dr Ron Waldman, Task Force Co-secretary

In many countries the quality or level of use of epidemiological data for the formulation of health policy and managerial decision-making is inadequate. There is a clear need to improve the community-based collection and analysis of disease surveillance data to guide prompt local intervention. Moreover, with the high levels of vaccine coverage now being reached in most countries, reliable data are also required to measure the impact of vaccine use on the health status of populations.

Product Development Group for 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

This, the first of the CVI's Product Development Groups, was created shortly after a joint meeting of the EPI and the WHO/UNDP Programme for Vaccine Development (PVD) in June 1991, at which it was decided to request proposals for research on (1) compounds capable of stabilizing the poliovirus by binding to the so-called "hydrophobic pocket" of its capsid protein and (2) methods of drying the polio vaccine without causing an unacceptable loss of potency.

At its first meeting, held in Geneva on 25 November 1991, the Group examined the 11 research proposals received in response to the request. Six were chosen for funding (for a total of US$320,000). By June 1992, the findings from these research projects should make it possible to assess the feasibility of both approaches. Thereafter, one or other or a combination of the two approaches could be used to develop a thermostable oral polio vaccine suitable for human use.

The Group will meet again in Geneva in November 1992.

Comment

by Dr Julie Milstien, Group Secretary

Wide use of the Sabin trivalent attenuated poliovirus vaccine over the past two decades has virtually rid the developed world of poliomyelitis as a public health problem and is well on the way to doing so in many parts of the developing world. There are, however, problems with this vaccine: seroconversion rates following the three doses, although nearly 100 percent in developed countries, are only 70-73 percent in developing countries. This relatively low "take rate" may be related to the suboptimal antibody responses (especially to types 1 and 3 polioviruses) that the Sabin vaccine produces in some cases. It may also be due to some extent to the vaccine's heat sensitivity (it can generally be kept for only two-to-three days at 37°C without losing potency). The problem should not be a barrier to polio eradication, however, if the vaccine is used according to the strategies recommended by WHO.

Nevertheless, as we enter the final stages of the polio eradication effort, thermostability does assume greater importance. A thermostable vaccine could be used by health workers engaged, beyond the cold chain, in house-to-house "mopping-up" vaccination campaigns.

The Group estimates that it could cost around $5 million to develop a thermostable oral polio vaccine over the next three years. However, such a vaccine would greatly accelerate the eradication of the disease, particularly in countries lacking an infrastructure for effective delivery of the current heat-sensitive

With the high levels of vaccine coverage now being reached in most countries, reliable data are also required to measure the impact of vaccine use on the health status of populations.

vaccine. Apart from the saving of lives, eradication would bring an enormous saving in money even in the Western Hemisphere, where vaccination must continue as long as wild poliovirus exists anywhere in the world (the United States alone currently spends more than US$100 million a year on polio vaccination).

Product Development Group on Controlled-Release Tetanus Toxoid Vaccines

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 Group held its first meeting in Geneva on 27 January 1992. Prior to the meeting, the PVD had received 24 vaccine development projects from research groups working on controlled-release systems in the public and private sectors. The Group retained four projects that seemed likely to fulfil its basic requirements for further development, namely that the vaccine could be administered in a single injection providing a dose-release schedule mimicking the standard regimen, with an initial strong protective immune response followed by boosting of immunity at around 2 and 12 months. All four projects involve the use of biodegradable microspheres.

Tests in monkeys of one product began at the end of February 1992 in Kenya and preliminary results could be available within about a year. Tests of the other products (also in monkeys) will begin in April 1992. If these studies validate the controlled-release concept for a tetanus toxoid vaccine and demonstrate the safety and lack of toxicity of the pilot products, the Group will negotiate joint venture agreements between microsphere developers and industrial vaccine producers, begin a study of intellectual property rights, establish regulatory guidelines for industrial collaborators and prepare for phase I trials in human volunteers.

The Group will meet again in Geneva on 9 April 1992.

Comment

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

The currently used tetanus toxoid vaccine provides 100 percent protection but requires three to five injections over one to three years. This regimen has a drop-out rate of up to 60 percent in some countries. If a vaccine with the same efficacy could be given in a single dose, it should greatly increase immunization coverage, especially among the 200 million or so women of child-bearing age living in high-risk areas.

Possible hurdles that could delay the development of the single-dose, controlled-release tetanus toxoid vaccine include the meticulous regulatory process required for the novel microsphere-vaccine combination, the complex issue of property rights and the unusually long period of safety testing for a product that has been programmed to produce an immune reaction over an extended period but cannot be removed from the body.

There is also a likelihood that many manufacturers of the current vaccine — there are about 50, most of them in developing countries — would be forced to stop production because the new tetanus toxoid vaccine would require technology beyond their reach. On the other hand, replacement of the current vaccine by a new microencapsulated product is not likely to occur before the end of the century; nearly 50 percent of UNICEF's tetanus toxoid needs are met by only two companies; and some developing countries could acquire microencapsulation capability, as India has done.

The new vaccine will probably be more expensive, dose for dose, than the current vaccine, but its higher cost should be offset by greater operational efficiency.

As for development of an oral — and therefore even more "user-friendly" — tetanus toxoid vaccine, this is still a very distant possibility.

Product Development Group on an Improved Measles Vaccine

Terms of Reference

To promote and manage the industrial development of an improved measles vaccine that can be given to infants before six months of age.

Update of Activities

A strategy for developing a better measles vaccine is currently under review. It is planned to form this Group some time in 1992.

CVI FORUM is published three times a year by the Children's Vaccine Initiative (CVI). All material submitted to CVI FORUM undergoes editorial review. Articles and illustrations published in CVI FORUM which are not copyrighted may be reproduced, provided credit is given to CVI FORUM and provided such reproduction is not used for commercial purposes. Signed articles do not necessarily reflect the views of the founding agencies (UNICEF, UNDP, The Rockefeller Foundation, The World Bank, WHO).

Editor: John Maurice

Design: Marilyn Langfeld

Photographs not otherwise credited: J. Maurice

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

Telephone:
(41-22) 791-4144

CVI Fax:
(41-22) 788-2736

Telex:
415416 OMS

Telegrams:
UNISANTE-GENEVE