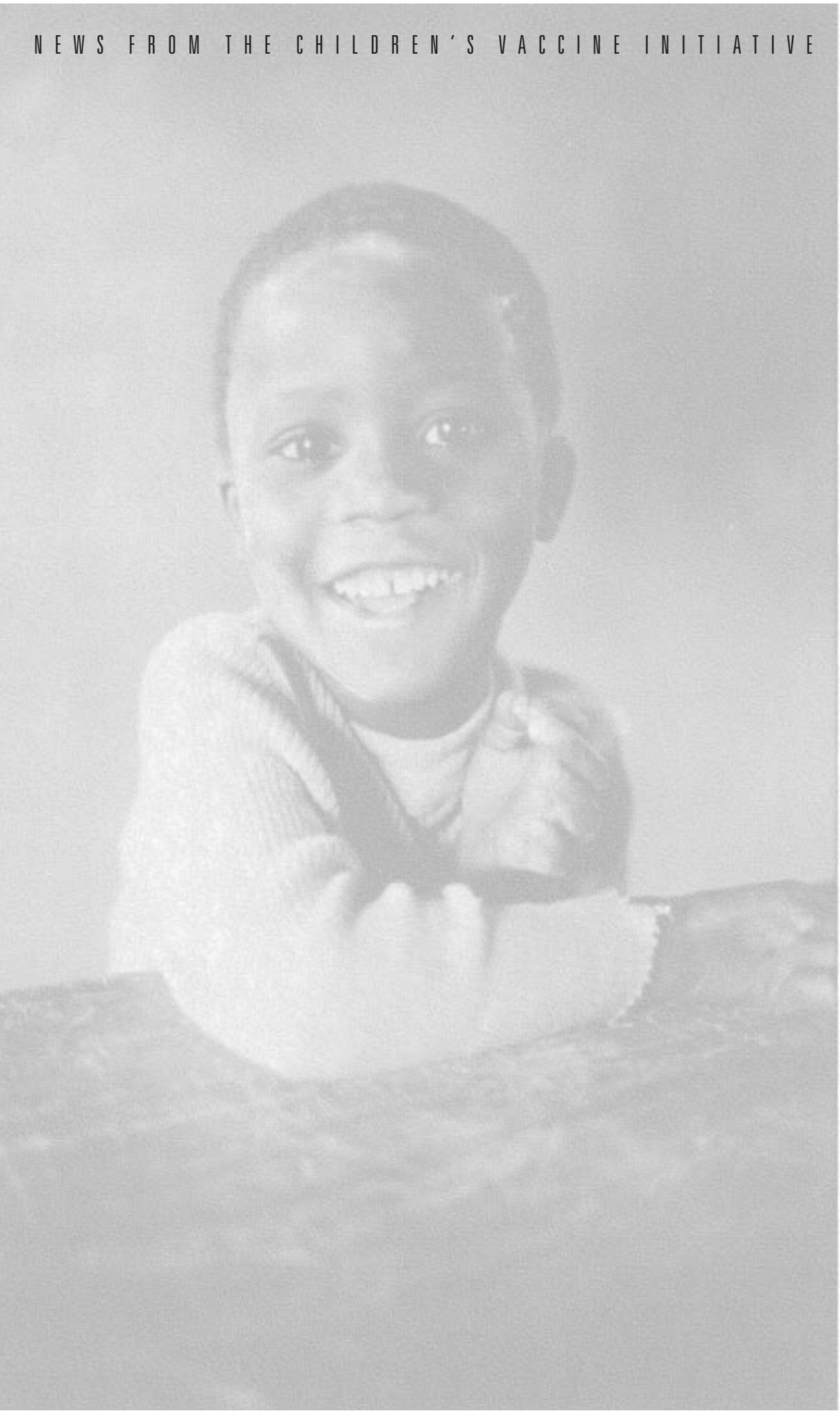
C V I F O R U M

NEWS FROM THE CHILDREN'S VACCINE INITIATIVE



Number 2
October 1992

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 will provide lasting protection against a wide range of childhood diseases, and be simple to administer and affordable.

In this Issue

UNICEF redefines roles, but remains "firmly committed" to immunization

UNICEF will continue to be an "operational" organization devoted primarily to the "downstream" or "end-user" side of the vaccine spectrum, Terrel Hill, Senior Health Advisor of UNICEF's Child Survival Unit, told CVI FORUM. At its meeting last June, he said, UNICEF's Executive Board insisted that "we leave research and the upstream side to the other partners of the CVI coalition".

Dr Hill, echoing the Board's resolutions, sees UNICEF's main roles in relation to immunization and the CVI as: increasing, through operational research, the efficiency and effectiveness of the EPI, in which UNICEF has invested more than $500 million since 1985; supporting countries in their efforts to strengthen their epidemiology and disease surveillance capacity so as to ensure maximum impact of UNICEF's investment; help assure the current supply of vaccines; and help the entry of new vaccines into the EPI.

One misconception Dr Hill wants to dispel is that UNICEF's commitment to the global immunization effort is waning. "It is true," he said, "that we have cut the proportion of our resources allocated to immunization from 28 to 20 percent, because other priorities, like education, reducing infantile mortality from diarrhoeal diseases and acute respiratory infections, also have claims on these resources."

Acronyms and initialisms in this issue

ACIP	Immunization Practices Advisory Committee (of the CDC)
CDC	Centers for Disease Control
CVI	Children's Vaccine Initiative
DPT	diphtheria, pertussis and tetanus vaccine
EPI	(WHO) Expanded Programme on Immunization
GNP	Gross National Product
PVD	WHO/UNDP Programme for Vaccine Development
UNDP	United Nations Development Programme
UNICEF	United Nations Children's Fund

Note: $=US$ unless otherwise stated

Nevertheless, Dr Hill stressed, "we are still firmly committed to the immunization effort and to the goal of a sustained 90 percent coverage. We still believe immunization is an ideal mechanism for strengthening countries' health services and that it has made primary health care come alive."

Over the past decade, noted Dr Hill, UNICEF has become the major international procurer of vaccines through its donation of billions of doses of vaccines to developing countries. "Over the past three or four years the demand for vaccines has grown and we are finding ourselves under increasing pressure to continue to act as a last resort for countries unable to pay for their vaccines."

Terrel Hill

The CVI could, he believes, take some of this pressure off UNICEF. The current crisis in vaccine supply, with price increases, problems of quality control and production difficulties in certain countries, as well as soaring demand, "has led us to use CVI mechanisms to develop some exciting ways whereby the EPI can be assured of a sustained supply of high-quality vaccines for the six diseases on its current agenda."

These mechanisms are the CVI's Task Forces on Situation Analysis (see page 12) and Quality Control (see page 11). They should, Dr Hill said, enable developing countries to become true partners in the international vaccine market. And together with the CVI's Task Force on Priority Setting and Strategic Plans (see page 10), in which UNICEF plays an active role, "the CVI will ensure that this international market will meet the special needs of developing countries to a greater extent than it has in the past".

In this respect, a guiding principle, in Dr Hill's view, could be the concern voiced by Mira Seth, India's Secretary for Human

Resource Development, who chaired the UNICEF Board meeting, namely, that "vaccines must be considered a development, not a commercial, commodity".

Dr Hill said he is "excited and encouraged" by the way the CVI is demonstrating its ability to tackle the current vaccine crisis. "I must admit I was sceptical about the original goal of a magic single-dose vaccine against all childhood maladies: I don't really believe it is technically feasible within the next few decades. But what I'm seeing now is that, as the CVI is learning to solve the problems of current vaccines, it is at the same time preparing the ground for the introduction of newer and better vaccines. That's a development we didn't anticipate a year ago. So, if in 40 years from now we still have to give two or three separate vaccines that protect against 10 or 15 diseases, that to me is worth a magic vaccine. That to me would be a success story."

A word of caution: If the CVI becomes too "protective", if it builds too many fences to protect its name against unethical or otherwise unacceptable activities, if it refuses its imprimatur to all but a selected few, it could end up as "a small club of privileged members, with limited resources and limited scope for action". All groups working in some way towards the CVI goals—organizations, individual countries with their institutions and programmes, commercial firms, research groups—should feel "ownership and excitement" at being part of the CVI, in Dr Hill's view.

"Everyone should be brought into what is essentially a mechanism for getting things done."

UNICEF/Carolyn Watson

Infants being vaccinated at the Brikama Health Centre, Gambia

"Vaccines must be considered a development, not a commercial, commodity."

Some concerns of a vaccine "end-user"

Robert Kim-Farley is Director of WHO's Expanded Programme on Immunization (EPI). In the interview below he explains how he believes the CVI could best advance the goals of his programme and solve some of the problems that have beset vaccine development in the past.

Q ***How necessary is the CVI, from your perspective?***

A The greatest value of the CVI, in my opinion, is its ability both to draw the world's attention to the fact that new or improved vaccines are available or will soon be available and to find ways of making sure these vaccines are used to protect children in the countries of greatest need. In other words, the CVI is filling the need for visibility and political awareness about vaccines and the need for practical plans to bring these vaccines from "bench to bush", to use a development cliché.

Q ***Has the world being doing so badly without a CVI?***

A Most, if not all, of the vaccines we have, were developed with the industrialized world in mind and with the hope that there would be a trickle-down

"Some of the vaccines were initially developed without taking into account the immunization schedules of developing countries."

effect to the developing world. That hasn't happened to the extent we would have liked. Moreover, some of the vaccines were initially developed without taking into account the immunization schedules of developing countries. With the CVI, I for one am looking for what I call the "seamless integration" of product development from conception to delivery that should avoid such problems.

Q *Problems, such as...*

A Take the hepatitis B vaccine. It has been available for the past ten years. It is safe and effective. And since 1987 EPI's Global Advisory Group has recommended its inclusion in our routine operations. Yet, despite the fact that its price has plummeted from around $50 to below $3 for a full immunization course, many developing countries still can't afford it. The story could be much the same for other vaccines that will come out in the future—an AIDS vaccine, a malaria vaccine, and so on. The CVI must explore mechanisms for reducing the costs of producing a vaccine and find the best ways—say, by transfer of technology, straight financing, or supportive mechanisms like the Vaccine Independence Initiative—of ensuring its delivery to those who need it. That's a unique, complex role for the CVI but it should put an end to the kind of tragedy we've been witnessing with the hepatitis B vaccine, the tragedy of a vaccine capable of saving one-to-two million lives a year but not yet in widespread public health use.

Q *More specifically, how do you believe your programme can get the most out of the CVI?*

A The first payoff for the EPI, especially for new vaccines, will be to have a body, like the CVI, that is concerned with the broad issues—not just the initial research and development, but also beyond that into production, transfer of technology and introduction into immunization programmes in developing countries. The EPI can then work out the best strategies for using a vaccine, monitoring immunization activities, evaluating impact, and so on. With its Task Force on Situation Analysis (see page 12), the CVI is also helping us sort out the extent to which a country can buy or produce vaccines or take a share in production. And its Task Force on Quality Control (see page 11) is helping us to ensure that a vaccine produced in a given country is safe and effective.

Q *So you see the CVI's and the EPI's activities as complementary ?*

A Yes, research and development is a good example. Our R & D activities concern questions like: What is the best measles immunization schedule? How wide an area must be covered by vaccination to control a polio outbreak? What is the best way to identify high-risk areas for neonatal tetanus? How can diagnostic tests be improved? These are more specifically EPI activities, and of course they need continued funding.

Robert Kim-Farley

Q *Do you have any concerns about directions that the CVI is taking—or not taking?*

A I have a general concern about the balance between practical problems facing us now and long-term goals. As the CVI evolves, I'm sure it will achieve the right mix and ease the creative tension between these two poles: on the one hand, you have programmes like the EPI wanting to see an immediate, usable result; on the other, you have the visionary expectations of those prepared to wait 30 years to see the birth of a

UNICEF/Sean Sprague

Immunization session in Guizhou Province, China

single children's vaccine. Right now, there does seem to be a good balance, but I wouldn't want the CVI to take off and put most of its efforts into the upstream end of the spectrum to the detriment of the here-and-now practicalities.

***Q** Sticking to practicalities, then, are there considerations that you would not want to see the CVI neglect in its push for new vaccines?*

A In supporting the development of a new vaccine, the CVI must take into account things like the magnitude of the health problem; the expected impact of the vaccine; the duration of immunity it confers; the number and severity of adverse reactions we can "live with" in relation to the health problem; its cost; its impact on existing vaccine logistics, such as temperature tolerance, storage characteristics and packaging volume; and its "fit" within the current schedule of immunization contacts at 6, 10, 14 weeks and nine months of age. A vaccine brought into existence without due attention to these details may have difficulty entering national immunization programmes.

***Q** What about the rising cost of vaccines and the increasing demand for vaccines to meet the needs of the Polio Eradication Initiative? Isn't that a major concern for EPI?*

A Yes, this again is an area where we are expecting a lot of help from CVI's Task Force on Situation Analysis. On the other hand, I am often dismayed when a ministry of health decides to spend its finite resources on the purchase of a new scanner for the country's central hospital rather than on meeting its vaccine needs. We have to be sure that our health dollar is buying the most cost-beneficial intervention we can make and we should remember that there's no better intervention than immunization: a vaccine is by far the most cost-effective weapon we have against disease and it should be given highest priority when finite resources are being allocated.

"A vaccine is by far the most cost-effective weapon we have against disease and it should be given highest priority."

Plotting a solution to the world's vaccine supply problems

It has come to be known familiarly as "the Batson-Evans grid", after the two EPI technical officers—Amie Batson and Peter Evans—who thought it up. Some even see it as a vaccine supply "mandala"—meditate long enough on it and you will be struck by new insights. Whatever you call it, it is causing something of a stir in the vaccine "community".

"What it is," says Mr Evans, "is simply a framework for working out for a given country whether aid money is really needed to support its vaccine supply and if so, whether the support should go more to production or to procurement, so that the country will need less and less aid as it becomes more and more 'vaccine-independent'".

"All countries should be encouraged to finance their own vaccine supply to the extent that they are able to do so."

Use of the grid, Ms Batson adds, could make for "more efficient use of donor resources to ensure the availability of vaccines for current and future needs throughout the world".

The grid (see opposite) is constructed by plotting the position of countries of interest by wealth (y-axis) and population size (x-axis). The position of a country on the grid gives an indication of the extent to which, in relation to its wealth, it needs support, if at all, the type of support it needs (services or financing) and the extent to which, in relation to its population size, it can cater for its own vaccine supply needs through procurement of vaccines or a mix of procurement and production sharing or production alone. Interpretation of the grid is based on a logical assumption: the help a country needs in obtaining vaccines is inversely proportional to its wealth; the ability of a country to produce its own vaccines (i.e. support a vaccine producing industry) is directly proportional to the size of its population.

"Generally speaking," Mr Evans says, "all countries should be encouraged to finance their own vaccine supply to the extent that they are able to do so. This grid makes it easier to judge that extent."

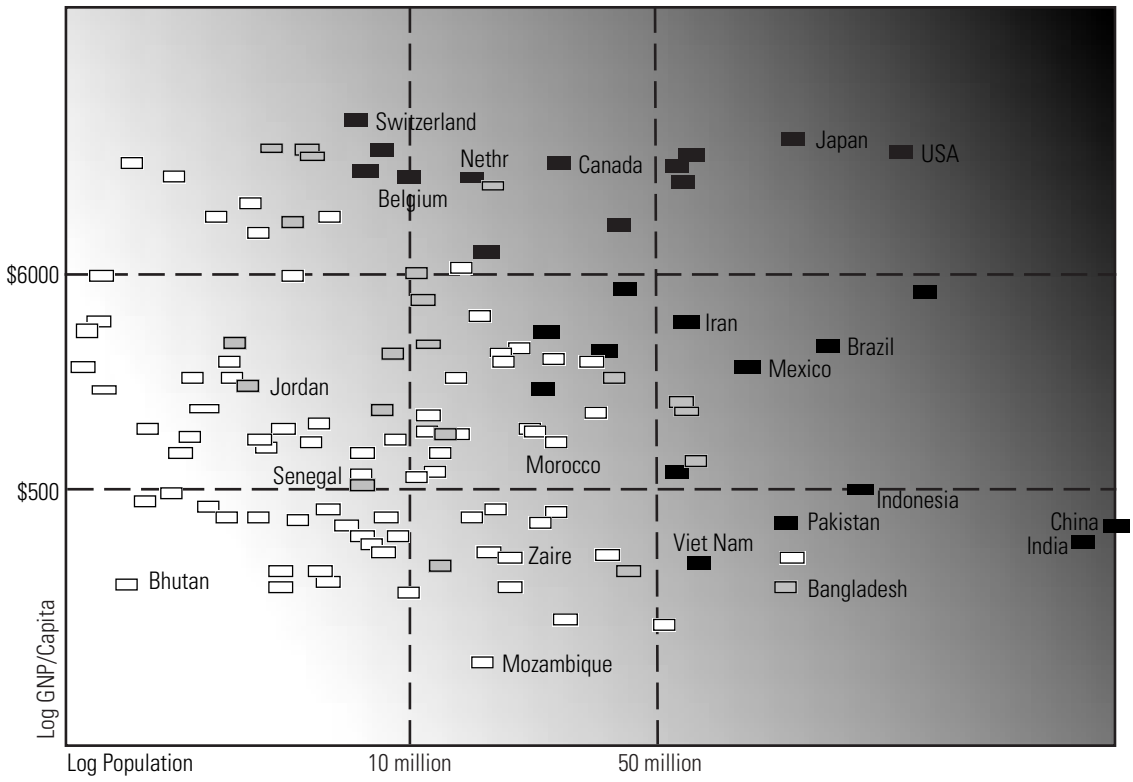
Clearly, the richer countries at the top of the grid should be encouraged to fill their vaccine needs with their own resources, without donor aid, using these resources more for procurement if they have small populations (towards the left-hand side of the grid) and more for production if they have large populations (towards the right-hand side of the grid). Conversely, the poorer countries at the bottom end of the grid need most support, which should be spent on helping the smaller of these countries to procure vaccines (left side of the grid), the larger countries to produce their own vaccines (right side) and mid-sized countries to buy and/or produce depending on their relative wealth and size and the availability of vaccine production facilities.

Since its conception at the beginning of this year, the grid has met with a generally enthusiastic response. For CVI's Management Advisory Committee, which was given a special showing of the grid in May, it is "a valuable framework and perspective on which to base strategy".

Says Mr Evans:"It's at least stimulating people to try and gather reliable country data on vaccine production and procurement, and the preliminary information we're getting gives food for thought." He cited these findings:

- 80 percent of the world's children are born in countries producing one or more of the vaccines used by the EPI;
- nearly 60 percent of vaccine being used in the world is produced within the countries using it;
- some relatively rich countries, able to pay for vaccines, have been receiving them free of charge;
- some countries attempting to start up production of vaccines that are difficult to produce, such as hepatitis B or polio vaccine, appear to be too small and too poor to justify investment in such production facilities.

Vaccine Supply "Mandala"



Guide to Donor Aid

Independent	Independent	Independent
Procurement Services Provide supportive services in: – Procurement – Management – Financing	**Procurement/ Production-Sharing Services** – Evaluate feasibility of production sharing – Provide supportive procurement service	**Production Services** – Strengthen/expand production as necessary – Strengthen quality assurance
Financing – Continue support – Encourage vaccine allocation in national budget	**Financing for Procurement/ Production Sharing** – Continue support – Encourage vaccine allocation in national budget	**Financing for Production** – Continue support – Evaluate feasibility of production/ production sharing – Strengthen/expand production as necessary – Strengthen quality assurance

The above example of the so-called "Batson-Evans grid" shows the positions of 130 countries (of which only a few are named) differing in wealth (per capita GNP according to the UNICEF's State of the World's Children 1991, with cut-off points based on the World Bank's GNP per capita income groups for 1991) and population size (with cut-off points based on, among other things, past experience of the market size needed to support a local vaccine industry). Countries that produce vaccines locally are shaded, either in black for those that produce the viral vaccines, like polio and measles vaccines, or hatched, for those that produce the bacterial vaccines, like tetanus toxoid and DPT. Those that have no vaccine manufacturing capability are blank.

Eighty percent of the world's children are born in countries producing one or more of the vaccines used by the EPI.

The perilous path to a better measles vaccine

by
Philip D. Minor

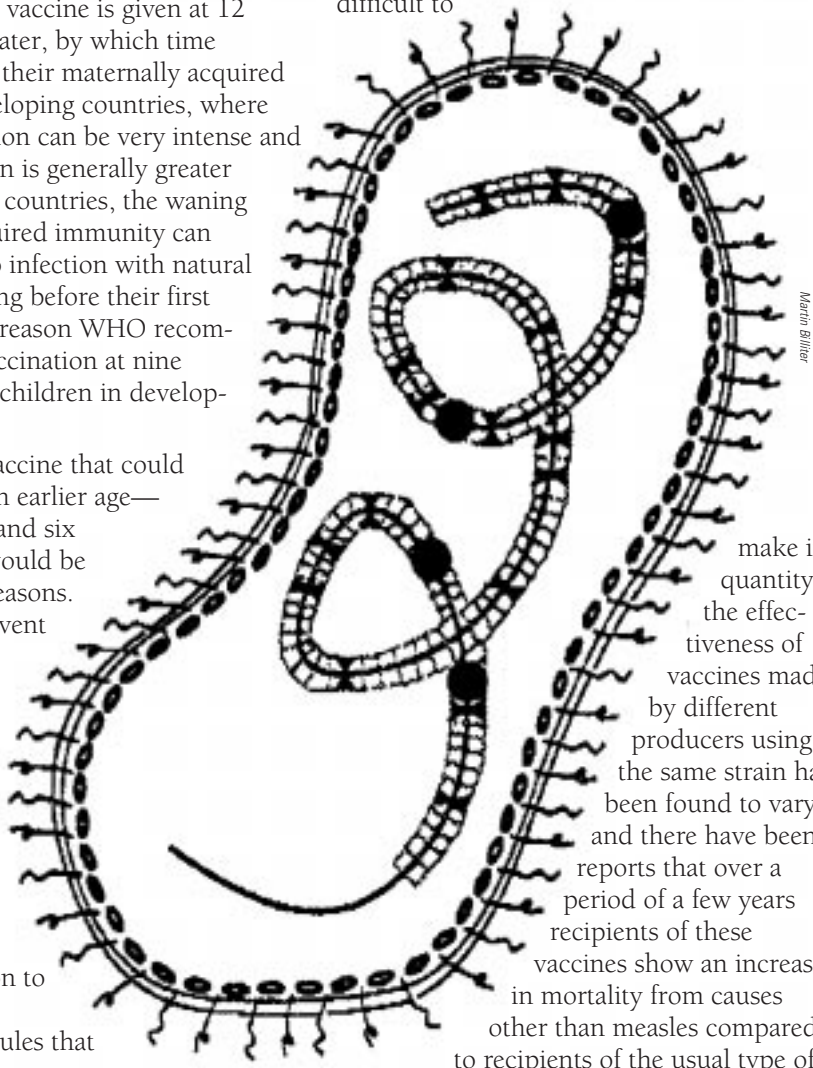
In developing countries, the waning of maternally acquired immunity can expose children to infection with natural measles viruses long before their first birthday.

Currently, measles vaccines in use throughout the world are live attenuated viruses which infect recipients without causing disease and which, when properly used, prevent disease due to natural measles viruses. One constraint on their use, however, is the fact that the natural immunity to measles that a child acquires from its mother at birth can prevent infection by these vaccines. This is why, in developed countries, measles vaccine is given at 12 months of age or later, by which time children have lost their maternally acquired immunity. In developing countries, where measles transmission can be very intense and the risk of infection is generally greater than in developed countries, the waning of maternally acquired immunity can expose children to infection with natural measles viruses long before their first birthday. For this reason WHO recommends measles vaccination at nine months of age for children in developing countries.

Yet, a measles vaccine that could be given at an even earlier age—say, between two and six months of age—would be valuable for two reasons. First, it would prevent measles in very young children, who suffer a very high mortality rate from the disease in developing countries. Second, and just as important, it would enable measles vaccination to fit neatly into the existing EPI schedules that concentrate on this age-group, thereby limiting the number of contacts needed with health workers and the loss of children to measles immunization programmes.

One approach to the obstacle of maternally acquired immunity and to achieving measles vaccination at a very young age is to use live vaccines of high enough virus concentration to elicit protective immunity despite the presence of maternal antibodies but not so high as to be dangerous.

Several clinical trials of such high-titre measles vaccines have been conducted in children at six months of age and the results have been promising. Indeed, one strain used in these trials has proved just as effective in immunizing these young children as the current low-titre vaccines are in older children. There have been difficulties though, with the high-titre vaccines: their commercial availability on a large scale could be a problem since they are technically difficult to make in quantity; the effectiveness of vaccines made by different producers using the same strain has been found to vary; and there have been reports that over a period of a few years recipients of these vaccines show an increase in mortality from causes other than measles compared to recipients of the usual type of vaccine. Largely for these reasons, WHO now recommends that high-titre measles vaccines be dropped from routine immunization programmes.



Martin Bilitter

NIBS

Philip Minor

All in all, it is likely that immunization of very young children against measles is going to require the use of nonliving or inactivated vaccine strains, but several concerns must be considered before new vaccines of this type are accepted:

•Some of the measles vaccines used in the early 1960s were inactivated (and thus noninfectious) viral preparations—either partially purified proteins or killed viruses. Recipients of these preparations sometimes developed a serious, atypical form of the disease when exposed to natural virus, presumably because they had developed an incomplete or inappropriate immune response. New vaccines must be shown to be free of this risk before they can be used. But it is possible that all inactivated vaccines carry such a risk.

•Measles infection—both natural infection and to a lesser extent infection with vaccine strains—is known to suppress the immune response. This immunosuppression is probably a consequence of the infectious process but conceivably could be due to exposure to a measles antigen alone. If so, immunization of very young children against measles could be hazardous with any kind of vaccines.

•Viruses of the same family (Paramyxoviridae) as the measles virus—especially those responsible for respiratory disease in humans and canine distemper in dogs—have been found, when used in inactivated form in vaccines, to give poor protection against disease even when they produce a detectable immune response. By analogy, the efficacy of inactivated measles vaccines may also be poor.

•Inactivated vaccines are thought to produce less long-lived immune responses than do live vaccines: they may therefore postpone the development of measles to a later age, when it might occur in an unusual, possibly unpleasant, form.

In addition to considerations of the safety and efficacy of a measles vaccine in relation to measles itself, there are also concerns about the types of materials which may be used in an improved measles vaccine. Three are of particular interest: novel immunity-boosting adjuvants (such as the so-called ISCOMs or immunostimulating complexes) administered with measles virus antigens ; formulations (such as microspheres) providing slow-release of measles virus antigens; and other viruses, such as poxviruses or adenoviruses, genetically manipulated to express suitable measles virus antigens.

These novel materials will be have to be shown to be acceptable for human use, especially in the very young; the sterility and potency of slow-release formulations are difficult to assess; and genetically manipulated viruses raise questions about their virulence and environmental innocuousness.

A recent WHO review of "Measles control in the 1990s" (prepared for the CVI by Robert M. Scott and John Clements of the EPI and by Paul-Henri Lambert and Yuri Pervikov of the PVD) describes the attributes

It is likely that immunization of very young children against measles is going to require the use of nonliving or inactivated vaccine strains.

of an ideal measles vaccine: it should be safe, be able to induce life-long protective immunity in almost 100 percent of recipients with a single dose administered by a noninvasive route shortly after birth, be compatible with other antigens dispensed at the same time, be able to provoke mucosal immunity, interrupt wild measles virus transmission and retain potency at 45°C for seven days, and be not much more expensive than current vaccines. "An ideal measles vaccine," the review points out, however, "is not yet to hand."

While the list of obstacles to the development of such a vaccine seems long and daunting and while the consequences of "getting it wrong" could be disastrous, most of the difficulties can in principle be overcome. Certainly, the stakes are high. To succeed would mean bringing to heel the biggest child-killing infection in the world—currently, 29 million cases a year and over one million deaths, and this despite a global immunization coverage of over 80 percent.

Developments in our understanding of viruses and host responses since the first measles vaccines were introduced three decades ago make the challenge both attractive and exciting.

Dr Minor is head of the Division of Virology at the National Institute for Biological Standards and Control at Potters Bar, in the United Kingdom. He has recently been appointed chairman of the Product Development Group on an Improved Measles Vaccine that the CVI is in the process of establishing (see page 14).

To succeed would mean bringing to heel the biggest child-killing infection in the world.

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, 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

Work is well under way on the background papers relating to the 12 vaccines identified at the Task Force meeting last February as requiring urgent development or improvement. The papers will consider each vaccine from several standpoints—epidemiology and disease burden, science and technology, scale-up and production, "special issues" (such as regionally important diseases, early vaccine testing in developing countries, potential impact of an AIDS vaccine, regional disease eradication efforts and the impact of political, economic and social change) and quantitative analysis.

Full papers on seven vaccines (polio, tetanus, measles, pneumococcal pneumonia, *Haemophilus influenzae* b + DPT, hepatitis B + DPT, and pertussis) will be available for the Consultative Group meeting in November. Shorter papers for the remaining five vaccines (dengue, *Escherichia coli*, meningococcal meningitis, rotavirus and typhoid) will also be available and will be expanded further next year. A special paper will be prepared on DPT because this vaccine is produced in many developing countries and a DPT formulation requiring fewer doses could simplify EPI operations considerably.

At its meeting in Meech Lake, Canada, last May, the CVI's Management Advisory Committee requested that the Task Force mandate include advice on resource allocation and on the relative priorities of basic, applied and development research. The Committee also called for the Task Force to give special attention to the transfer of technology.

The next meeting of the Task Force will be held towards the end of October near Washington, D.C.

Comment

by Richard Mahoney, Task Force Secretary

In preparing its recommendations for the Consultative Group meeting in November the Task Force will balance, on the one hand, the need to make these recommendations specific enough to provide a basis for concrete decisions by the CVI with, on the other, an appreciation of the wide range of possible options. Developing recommendations on priorities is a difficult and complex undertaking. The Task Force recognizes that this job can be done successfully only by calling on the wisdom of a large number of individuals from all corners of the vaccine development and delivery world. Thus, in addition to recruiting outstanding members to its own ranks, the Task Force has made—and is continuing to make— vigorous efforts to acquire the input of numerous other leading vaccine professionals.

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

A subgroup of the Task Force met in Geneva, Switzerland, in June to work on the drafting of guidelines for CVI relations with development collaborators. The subgroup will meet again at the end of September to finalize the guidelines, which will be presented to the November meetings of CVI's Consultative Group and Management Advisory Committee.

Completion of its work on these guidelines will fulfil the mandate of the Task Force, which was originally set up as a short-term expedient with a specific time-limited task. However, at its June meeting, the Management Advisory Committee felt that the CVI needs to have a permanent resource for ongoing relations between its various working groups (Task Forces and Product Development Groups) and collaborators from industry. It recommended therefore that this Task Force be reconvened under different terms of reference and, to the extent necessary, with a renewed membership.

Comment

by Richard Mahoney, Task Force Secretary

We hope the guidelines will provide an innovative approach to relations between the CVI and industry and stimulate collaboration between the two.

More generally, the work of the Task Force is already providing a forum for a dialogue between industry and the public sector on a number of critical questions, among them: How best can the CVI stimulate production of prototype quantities of new vaccines? How can it harness the expertise of private industry in order to facilitate the transfer of technology to developing countries?

Although profit and patents are often alluded to as the central concerns of industry, this dialogue is showing that industry also wishes to understand the needs of the public sector and to contribute to the development of new vaccines that will protect all children, of developed and developing countries alike.

Finally, there is not a single "industry" involved in vaccine development: there are large multinational companies; smaller, private and public sector companies; biotechnology firms; and companies contracted to prepare test lots of vaccines. The CVI has to be prepared to work with all these types of firms and its relations with each type will be different. Successful management of these relations could well be a key to the CVI's success.

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

Because of the impending crisis in vaccine supply and the expected shortage of polio vaccine to meet the needs of the Polio Eradication Initiative, it was decided that the first countries to be put on the priority list for assessment by the Task Force's teams of advisers would be those already producing oral polio vaccine and that the first assessments would relate to quality control and regulatory standards for this vaccine.

This summer, Task Force teams visited China and Viet Nam to review these countries' licensing and quality assurance procedures for locally produced oral polio vaccine. The first meeting of the Task Force, expected to be held in mid-November, will review these teams' reports.

In the near future, the Task Force will probably increase the priority list of countries to be assessed to include India and Iran (in addition to Brazil, Egypt, Indonesia and Mexico, which have still to be visited).

Comment

by David Magrath, Task Force Secretary

The visits to China and Viet Nam made this summer by the Task Force's teams of advisers proved a valuable introduction to the complexities of the evaluation procedure. Despite some difficulties, the teams identified ways in which these countries could better assure vaccine quality. They noted an adequate level of scientific expertise available for vaccine production and quality control in the two countries. On the other hand, in some areas, they found room for improvement in manufacturing and licensing practices. At its first meeting the Task Force will consider proposals to remedy deficiencies in these areas.

"Industry also wishes to understand the needs of the public sector and to contribute to the development of new vaccines."

In general, two main factors are impeding faster progress in achieving the Task Force's objectives. One is the natural caution of countries, which would rather wait until the Task Force and its ability to provide assistance have been firmly established before submitting to its evaluation process. Another, more serious impediment, is the lack of independent experts with the necessary experience in pharmaceutical inspection procedures combined with the more specific experience of production, quality control and licensing of vaccines, and who are prepared to undertake country visits on behalf of the Task Force.

Task Force on Situation Analysis

Terms of reference

To assess the global demand, supply and funding of children's vaccines.

Update of activities

At the May meeting of the CVI's Management Advisory Committee in Meech Lake, Canada, the Task Force presented a framework for rapidly identifying a country's relative vaccine production capacity and its relative need of assistance for vaccine production or procurement (see page 6, "Plotting a solution to the world's vaccine supply problems"). Using this framework, the Task Force identified countries that require priority assistance in strengthening their vaccine production capacity and/or in procurement of vaccines (see below).

Eradication campaigns will require significantly more vaccine than is being produced and will call for new investment.

The creation of the framework—by Amie Batson and Peter Evans, both with the EPI—is adding impetus to the gathering of accurate vaccine production and procurement data for as many countries as possible. The Task Force intends to verify all the vaccine data being gathered on individual countries and make them publicly available. Already, use of the framework to analyse the data collected up to now suggests that the current global vaccine supply exceeds the current global demand, at least for routine vaccine use, but eradication campaigns (for measles and polio, for example) will require significantly more vaccine (twofold, in the case of polio vaccine) than is being produced and will call for new investment to expand production facilities.

The Management Advisory Committee strongly endorsed the framework and recommended that the Task Force, in collaboration with the "Quality Control" Task Force, include the quality of vaccine production facilities in its data analyses.

About a dozen countries a year are expected to seek assistance in accordance with the strategy being developed by the Task Force. Already in August, Morocco joined the Vaccine Independence Initiative, the joint UNICEF/WHO scheme, which will be a cornerstone of the strategy, and which uses several mechanisms to provide supportive services to countries that wish to become more independent in procuring vaccines.

At its meeting in Copenhagen on 21-22 September, the Task Force agreed on activities to be conducted in five main areas: demand for vaccines, supply through procurement, supply through local production or production sharing, relations with donors, and global strategies for existing and new vaccines:

- *Demand for vaccines:* the Task Force will (1) evaluate responses to a questionnaire sent by UNICEF to all its field offices requesting, for each country, detailed information on forecasted vaccine needs over a ten-year period, intended vaccine supply strategies and sources of funding; (2) create and distribute simple tools to help countries to predict their vaccine needs; (3) conduct studies on the impact of different strategies on vaccine demand.
- *Procurement:* the Task Force will assist UNICEF in implementing the Vaccine Independence Initiative, so that countries can take increasing responsibility for the funding of their vaccine supply.
- *Production:* the meeting drew up a list of eight countries whose production capacities would be assessed by joint teams from the "Quality Control" and "Situation Analysis" Task Forces. In each country the teams would examine the vaccine market; the economics and financing of vaccine production; the regulatory, quality control and assurance procedures; management issues; and technology needs.
- *Relations with donors:* the Task Force will, from the earliest stages, involve donors in the planning and implementation of national and global supply strategies. It will also seek help from donors in identifying countries for which Task Force action is needed.
- *Global vaccine strategies:* the Task Force will further explore the current total vaccine market and such issues as market segmentation and the mix of public and private markets within countries, with a view to identifying strategies for ensuring the quantity, quality, appropriate prices and rapid availability of new vaccines.

Comment

by Peter Evans, Task Force Secretary

There has been a shift of focus in the Task Force's mandate. Originally set up to pave the way for the introduction of new vaccines into EPI operations, this Task Force has been forced by current problems of vaccine funding to turn its attention to the supply of existing EPI vaccines. An understanding of these

problems, which have delayed EPI's adoption of the new hepatitis B vaccine, should help the Task Force fulfil in the future its original task of speeding up the introduction of new vaccines into operational use.

Task Force on the Strengthening of National Epidemiological Capacities

Terms of reference

To help countries to 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 final stages of organization. Potential members have been contacted and a first meeting will probably be held before the November 1992 meeting of the CVI's Consultative Group.

Dr Claire Broome, Assistant Director for Science at the CDC in Atlanta, Georgia, in the United States, has been appointed chairman of the Task Force. An experienced epidemiologist specializing in vaccine-preventable diseases, Dr Broome is currently Executive Secretary of the CDC's Immunization Practices Advisory Committee (ACIP).

Comment

by Ron Waldman, Task Force Co-secretary, with Henrick B. Zoffman

At its forthcoming first meeting the Task Force will finalize its terms of reference, which we hope to circulate among participants of the Consultative Group meeting in November with a view to discussing how best to implement these terms.

In general, our Task Force will attempt to satisfy countries' epidemiological needs across the entire spectrum of activities encompassed by the CVI, from research to the provision of health care. More specifically, it will represent the needs of end-users—mainly national immunization programmes—of new and better vaccines.

Among its other functions, the Task Force will help countries to identify sites for trials of new vaccines and to design and implement these trials and analyse their results. It may also evaluate new and/or improved methods of determining the epidemiological impact of vaccines.

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

The Group has signed agreements with five research teams and is negotiating agreements with one other. Significant progress has been made in work on thermostability, according to the interim reports of three of the teams. The two approaches being followed—use of compounds that bind to the hydrophobic pocket of the poliovirion and use of special drying techniques—are showing promise. Both approaches offer the advantage of not requiring a major capital investment and of being readily transferable to vaccine manufacturers, even in developing countries.

Several compounds have been found that reversibly stabilize the antigenic structure of the poliovirion for at least seven days at 42°C. For at least one of these compounds toxicology data are available and a national licensing authority has granted Investigational New Drug status.

As for the second approach, processes have been found that render the polio vaccine in dried form while retaining some degree of its potency.

In both cases, the next step—probably to be taken early in 1993— will be for the Group to invite all potential product developers to submit proposals for limited clinical testing of a pilot lot of improved oral polio vaccine.

Comment

by Julie Milstien, Group Secretary

The progress on thermostability is particularly encouraging, especially as it is based on work with commercial vaccine bulk and thus should be transposable to a "real life" context. In general, the progress being made, despite unavoidable delays, suggests it will be possible to meet the target date of 1995 for the development of a thermostable oral polio vaccine that can be used in global immunization programmes.

The progress being made suggests it will be possible to meet the target date of 1995 for the development of a thermostable oral polio vaccine.

Product Development Group on Single-Dose 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

At a meeting of the PVD's Steering Committee on Transdisease Vaccinology held on 8 April 1992 the four research teams collaborating on a controlled-release tetanus toxoid vaccine reported that in mice their pilot products (tetanus toxoid encapsulated in microspheres) prime the immune response and induce antibody production that lasts for several months. The antibodies react in an ELISA and neutralize toxin. Immunological boosting, however, has not yet been achieved. Although there is still no formulation that mimics the conventional alum-adsorbed tetanus toxoid vaccine given in a three-dose schedule, antibody levels seem to be high and sustained enough to raise the Group's expectations that the goal of a single-dose tetanus vaccine will one day be attained. Overall, however, the response is still less satisfactory than that achieved with conventional tetanus toxoid vaccine, and considerable work is still needed.

"A momentum seems to have been created that could lead to commitment within the vaccine industry."

Meanwhile, the PVD Task Force on Controlled-Release Vaccines, whose membership overlaps with that of this Group, are addressing such issues as the quality of tetanus toxoid to be used in the controlled-release vaccine, its stability, determination of microsphere tetanus toxoid loading and protocols for vaccine tests, including potency tests. The PVD is also exploring possible oral formulations and alternative delivery systems, such as the use of *Salmonella* as a vector.

Other efforts being made by the Group include those to :

- assess the risk of adverse reactions to microsphere tetanus toxoid vaccines and develop experimental tests to detect such reactions (recirculation of small microsphere particles, for example, could possibly cause reactions at a distance from the inoculation site);
- assess intellectual property rights for microencapsulated vaccines;
- identify a volunteer population "naive" to tetanus toxoid that would be suitable for the first human trials of a tetanus toxoid vaccine;
- determine possible problems involved in the transfer of microencapsulation technology to developing countries;
- evaluate the potential for integrating a microsphere tetanus toxoid vaccine in the EPI.

The Group has advertised in several journals for collaboration from vaccine manufacturers and vaccine-related biotechnology companies with expertise in microencapsulation. Initial responses have been promising and agreements with some collaborators will probably be made in the near future.

The next meeting of the Group will take place in October, 1992.

Comment

by Paul-Henri Lambert and Teresa Aguado, Group Secretaries

There is clearly a long way to go before the Group achieves the goal of a usable controlled-release single-dose tetanus toxoid vaccine, but initial results are promising and a momentum seems to have been created that could lead to commitment within the vaccine industry to collaborate.

Product Development Group on an Improved Measles Vaccine

Terms of Reference

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

Update of Activities

A planning meeting was held in September in Bethesda, Maryland, USA, to discuss the composition of the Group and the approaches it should adopt to achieve its objectives. The meeting was chaired by Philip Minor, head of the Division of Virology at the National Institute for Biological Standards and Control at Potters Bar, in the United Kingdom. Dr Minor has accepted chairmanship of the Group.

The meeting stressed the urgent need for a new measles vaccine which could be given within the EPI framework at or near the time of birth and used for the control and eventual eradication of measles. Among the obstacles to be overcome, the meeting expressed particular concern about the risk of atypical measles, which had led to the withdrawal of a killed measles vaccine in the past.

Meeting participants reviewed current vaccine candidates being developed: they include vectored

vaccines, such as the canary pox vectored vaccines now in Phase I trials in France, and killed vaccines used with different adjuvants (ISCOMs, virosomes, etc.).

It was decided that the different research teams known to be working on new measles vaccine formulations should be approached by the Group to determine whether the CVI should offer to participate in the further development of these products.

The Group would also, through advertisements in the scientific literature, seek the interest of as yet unidentified teams conducting research related to the development of a measles vaccine.

Comment

by Robert Scott, Group Secretary

A key factor in pursuing the Group's planned activities will be its ability to develop a satisfactory working relationship with the institutions—in both the public and the private sector— working on a measles vaccine. Another critical factor will be to define how the activities of the Group will dovetail with those of other vaccine-related programmes, such as the PVD and the EPI. Both factors must obviously be taken into account in defining the final composition and work plan of the Group.

NOTICE BOARD

From the Meech Lake meeting of the "MAC"

M. Young

Margaret Catley-Carlson (left), Canada's Deputy Minister of Health and Welfare, addressing the CVI's Management Advisory Committee (MAC) at its meeting last May in Meech Lake, Canada. Beside her is Suryanarayan Ramachandran, Chairman of the Committee, and Lindsay Martinez, Executive Secretary of the CVI. The Committee stressed, among other points, how important it will be for public health authorities in developing countries to commit themselves to the CVI's objectives and for the public sector and industry to form partnerships under the CVI "umbrella".

For a full report of this meeting, write to: Dr Lindsay Martinez, CVI Executive Secretary, WHO/CDS, 1211 Geneva 27, Switzerland.

CVI's Consultative Group to meet in November

The second annual meeting of the CVI's Consultative Group will be held at the Geneva headquarters of the WHO on 16-17 November 1992. The Consultative Group brings together once a year all the partners of the CVI coalition— international development agencies, donor agencies and countries, nongovernmental organizations, vaccine users, vaccine producers, researchers, and other groups and individuals interested in vaccines (for a summary review of last year's meeting, see CVI FORUM issue No.2, April 1992).

This year's meeting will be chaired by Margaret Catley-Carlson, Canada's Deputy Minister of Health and Welfare. A keynote address will be given by Alain Mérieux, Chairman of Pasteur Mérieux Sérums et Vaccins.

Meeting participants will also hear status reports from the CVI's different operating units (task forces and product development groups). Delegates from industry, funding organizations and immunization programmes will air their views in special round-table panel discussions.

For further information on this meeting or a full report of the previous meeting, write to: Dr Lindsay Martinez, CVI Executive Secretary, WHO/CDS, 1211 Geneva 27, Switzerland.

LETTERS TO THE EDITOR

To Our Readers

As part of the CVI's objective of stimulating communication and an exchange of views on issues related to vaccines, particularly vaccines for children, we invite readers to contribute to a *Letters to the Editor* section, which could begin in the next (January 1993) issue of CVI FORUM. Letters can be submitted 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.

Send letters, preferably typed, to: The Editor, CVI FORUM, WHO/CDS, Avenue Appia, 1211 Genève 27, Switzerland.

PICTURE POSTSCRIPT

Lysiane Maurice

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