C V I F O R U M

Special Progress Report Issue

Progress since the 1990 World Summit for Children

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In this issue

CHILDREN'S VACCINE INITIATIVE

EDITORIAL

Reconciling opposites – the vision and the work

This issue of *CVI FORUM* coincides with the fifth annual meeting of the CVI's consultative group, which meets in São Paulo, Brazil, to review progress since the World Summit for Children in 1990. The articles in this special "progress report" issue describe advances – as well as some strategic retreats – in the different sectors of the CVI spectrum.

From my standpoint, though, as CVI Executive Secretary, the most important advances are not technical – although as the boxes on pages 4 and 5 show, there has been progress towards new and better vaccines – but rather conceptual. In the past five years there has been a shift in the conceptual framework, or paradigm, if you like, within which people in all walks of the disease prevention community work and think. The CVI's birth coincided with that conceptual shift.

Already in the 1980s, enthusiasm over antibiotics as tools for preventing disease had started to wane in the face of growing microbial resistance and health experts were turning to vaccines as an obvious alternative. Obvious, among other things, because WHO's Expanded Programme on Immunization (EPI) was in full swing and delivering vaccines to over 70% of the world's children and vaccines were saving approximately two to three million children per year from preventable diseases. So the mood was upbeat and much hope was being pinned on the expanding power of science to continue, even accelerate, the movement. New vaccines, in particular, could, it was estimated, save another five to six million lives annually.

That aim was translated into a visionary "supervaccine" and the CVI was given the task of turning the vision into reality. Now whatever one feels about visions – and sceptics have pooh-poohed the supervaccine vision as pie-in-the-sky – this one did capture the feeling of the time. It truly, to my mind, enshrined a desire that had come of age – a desire to use the new-found power of science and technology to stop children dying needlessly. What was missing and what fuelled the scepticism, was the lack of a down-to-earth plan showing how the vision could be achieved. We now have that plan, and the steps – and there will be many – are beginning to take shape.

So, where are we now, five years later?

The CVI has matured, thanks to its broader governing base, which includes the five original sponsoring agencies but also representatives from eight countries. It also, for the first time, has a full-time Coordinator, who works with me in managing the secretariat, the task forces and other operational groups. It has also acquired a much more clearly defined mandate in relation to the global vaccine community in general and to the WHO's Global Programme for Vaccines and Immunization (GPV) in particular. And it has witnessed progress on two major fronts of its mandate: fostering consensus and stimulating support for work on vaccines and immunization.

The CVI has witnessed progress on two major fronts of its mandate: fostering consensus and stimulating support for work on vaccines and immunization.

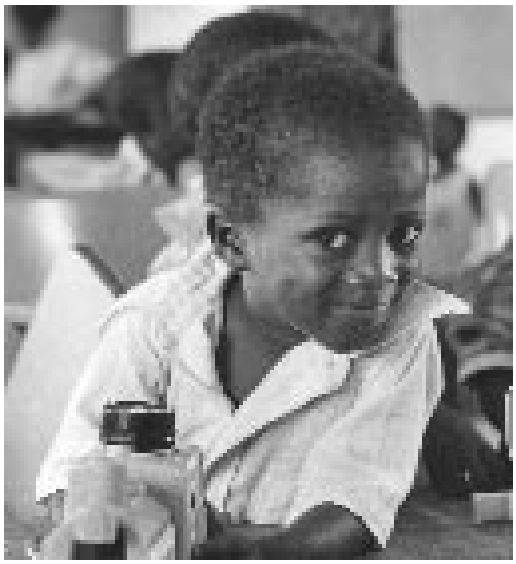
To start with consensus building, we now have in the CVI and thanks to the CVI a true coalition, a true consensus, around vaccines and immunization.

Today, the founding fathers – the World Bank, the Rockefeller Foundation, the WHO, UNICEF and the UNDP – are committed and working with the countries and other partners that meet as "interested parties" to keep the CVI secretariat on course.

As for the "hands-on" sector of the community, the CVI has brought researchers and other experts together from diverse and often distant points on the vaccine development spectrum to work on specific objectives, such as the single-dose tetanus toxoid vaccine.

Within the WHO, too, the CVI is linking brains and energies. An example is the task force the CVI is forming between three

COVER PHOTO:
The Viking ship Gaia sails from Europe to Latin America carrying on its sail the slogan proclaimed in the Declaration of New York, which launched the CVI five years ago.
Cocer photo: UNICEF/R. Mera



UNICEF/J. Hartley

DID YOU SAY SUPER VACCINE? Yes, and it's the CVI's job to keep reminding the world of that visionary goal.

WHO divisions or programmes to speed up work on developing and introducing new vaccines. The WHO's approach to vaccines generally has been greatly influenced by the CVI. In pre-CVI days, for example, the Organization never dreamed it would be taking on vaccine development from basic research of candidate molecules right up to the almost finished product stage. Moreover, it was giving far too little attention to the need for planning to introduce new vaccines that were ready for field use.

And surely, without the CVI, a dialogue of the deaf would still be dogging relations between the public and the private sectors generally and more specifically the WHO and industry. There is no doubt that the WHO is coming to understand better the concerns of industry over, for example, levels of pricing to cover R&D costs, market predictability and product liability, and is taking steps to address these concerns.

Industry too is clearly thinking more about the vaccine needs of developing countries – a good example is the willingness of some manufacturers to formulate pneumococcal vaccine candidates with strains prevalent in developing countries – and will be participating as a full partner in many future CVI committees and task forces. Moreover, in its striving to ensure that the world's children receive consistently high quality vaccines, the CVI is encouraging closer collaboration – through regional and other groupings – between public and private sector manufacturers, on the one hand, and between manufacturers from developing and developed countries, on the other. The CVI's support for SIREVA, a Latin American grouping, and for a global consortium of vaccine manufacturers, are two examples of progress in bringing producers together to improve vaccine quality in developing countries.

There are also clear signs of increased support for vaccine research and immunization. Among the donor agencies, the World Bank, which up to now had not put a financial stamp on its moral commitment, has just pledged a US$2.5 million contribution to the CVI secretariat for three years starting in 1995. And the UNDP, from the start the major financial contributor to the CVI secretariat, has invested US$800,000 in designing the new International Vaccine Institute (IVI), created in Seoul with Korean support (including a Korean investment of US$790,000 to date).

Countries too are showing a greater commitment to the CVI.

Two of the world's economic giants, for example, the United States and Japan, have included the CVI's goals in their "Common Agenda," with the United States focussing on the Americas and Japan on the Western Pacific and the Association of South East Asian Nations (ASEAN).

In the United States, annual spending on vaccine research by the National Institutes of Health (NIH) has more than doubled from the 1990 total of US$145 million to an estimated US$303 million for 1995 (this last total includes an estimated US$121 million for research on AIDS vaccines). In addition, the Agency for International Development (USAID) has increased its funding for vaccines and immunization by 45% from US$51 million in 1991 to an estimated US$74 million for 1995. And in Atlanta, Georgia, the Centers for Disease Control and Prevention (CDC) are receiving for 1995 an extra US$11.2 million from the US Congress to support immunization activities under the global polio eradication effort.

As for Japan, it has steadily raised its financial backing of the CVI secretariat from its initial contribution of US$500,000 for

Without the CVI, a dialogue of the deaf would still be dogging relations between the public and the private sectors.

The advent of the CVI has made it easier for vaccine researchers to find support.

Progress in developing new vaccines – a sampling

Respiratory infections

- *Streptococcus pneumoniae* (pneumococcus) – Newer vaccines are being developed that use the conjugation technique to make them, unlike the current vaccines, effective in children of all ages. Some candidate vaccines against strains prevalent in developing countries are in efficacy trials.
- *Haemophilus influenzae* type b (Hib) – Four new conjugate vaccines have been licensed, one in a combination with diphtheria-tetanus-pertussis (DTP). A conjugate vaccine gave 86% efficacy against Hib related meningitis in a trial in Chile. Another, still being studied in the Gambia, appears to be effective against the Hib carrier state.

AIDS

- More than 20 vaccine candidates have shown promise in animal studies and several are moving towards Phase III trials in developing countries. Most of these are subunit vaccines, consisting of proteins derived from a large protein, gp160 or gp120, on the HIV envelope.

Dengue and Japanese encephalitis

- Dengue – Several monovalent vaccine candidates (against one strain) are in Phase I trials and one tetravalent vaccine (against all four strains) is about to enter Phase III trials.
- Japanese encephalitis – One live, attenuated vaccine has shown 98.5% protective efficacy in extensive trials in China but is so far unavailable elsewhere. Another, an inactivated virus vaccine, was licensed in the US in 1992, but is still expensive.

Diarrhoeal diseases

- Rotavirus – Two live oral vaccine candidates have undergone field trials in the US, which showed them to have 70-80% efficacy against severe disease. Licensing procedures should begin next year.
- ETEC (enterotoxigenic *Escherichia coli*) – An oral, three-dose subunit vaccine is currently in Phase I trials in Sweden and should enter Phase II and Phase III trials next Spring in a developing country.
- *Shigella* – An injectable vaccine showed 70% protective efficacy in a Phase II trial in Israel and an oral vaccine is showing promise in US volunteers. The technology used to produce these two candidates may be applicable to strains that cause the disease in developing countries.
- Cholera – Two new oral vaccines were recently licensed in Sweden and Switzerland.

Hepatitis

- Five years ago only 20 countries had introduced the hepatitis B vaccine into their routine immunization programmes vs. 75 countries so far in 1995. Research is under way on vaccines against the recently isolated hepatitis C and E viruses.

Malaria

- Six candidate vaccines against falciparum malaria are in or about to enter clinical trials. Only one, Spf66, the Colombian vaccine, has been extensively studied in field trials, with mixed results.

Measles

- See article on pages 22-24.

Meningitis

- caused by Hib (see under respiratory infections)
- caused by *Neisseria meningitidis* – Phase I and II trials are under way on existing vaccines against serogroups A and C, chemically modified and conjugated to a carrier protein to enhance their immunogenicity. Work is also under way on the notoriously difficult task of developing a serogroup B vaccine

Polio

- See article on pages 19-20.

Schistosomiasis

- Six *Schistosoma mansoni* antigens have shown protective efficacy in animals and are about to be tested for their ability to elicit cellular and antibody immune responses in tissue and serum samples collected in endemic areas.

Tetanus

- See article on pages 17-18.

Tuberculosis

- Three new candidate vaccines are in animal tests and research is in progress on the immunological basis of protection.

Typhoid fever

- A live, attenuated three-dose oral vaccine gives 67% protection in endemic areas and a single-dose injectable polysaccharide vaccine gives about 72% protection after two years and 51% after five years (booster doses needed every two or three years). Several second-generation live recombinant vaccines are now in development.

Whooping cough

- See article on pages 14-16.

Progress in improving vaccines – a sampling

Better quality

• An inventory has been made of vaccine producers and many needing to improve vaccine quality have been identified. 14 countries have been chosen for in-depth assessment and help in strengthening quality vaccine production (see pages 9-13). Together they account for about half of the world demand for the diphtheria-tetanus-pertussis (DTP) combination and virtually all that is produced in the Third World.

More easily administered

• Oral vectors are in an advanced stage of development for a number of vaccines and a number have completed large-scale efficacy trials.

Fewer doses

• Purer formulations have been made of some vaccines, such as the acellular pertussis vaccines, which appear to be more effective and to require fewer doses than the less pure versions (see pages.....). A whole slew of new adjuvants and methods of presenting antigens are being tested for their ability to enhance the immune response to vaccines.

Effective earlier in life

• Linking (conjugating) vaccines with antigens from polysaccharide encapsulated bacteria can lower the age of effective use of the vaccines to under two years for vaccines against *Haemophilus influenzae* type b (Hib), pneumococcus and meningococcus.

Fewer side-effects

• Recent trials of acellular pertussis vaccines showed them to produce fewer immediate side-effects than the whole-cell pertussis vaccines (see pages 14-16).

More stable

• Deuterium oxide has been identified as a good stabilizer for certain viral vaccines. Research is also continuing on lyophilization techniques and the use of certain vectors with good stability characteristics.

Protect against more diseases

• At least six new vaccines have been licensed since 1990 (Hib, DTP-Hib, Japanese encephalitis, hepatitis A, cholera and varicella) and at least ten are in clinical trials (pneumococcus, rotavirus, leishmaniasis, malaria, respiratory syncytial virus, herpes, enterotoxigenic *Escherichia coli, Shigella* and HIV). The vaccine industry is making efforts to remove chemical and immunological obstacles to combining as many of these new vaccines as possible. At least six different combination approaches are under active development, including chemical combination and vector technologies using vaccinia, polio, *Salmonella*, BCG and nucleic acid immunization.

1992 to US$750,000 for 1994. It has also become a strong supporter of immunization and, among other things, is backing a national immunization campaign in Bangladesh and polio eradication activities in India.

The European Union, too, is investing more heavily than before in vaccine research. The annual budget of "Biotech," for example, its major research programme concerned with vaccine development, has risen from about US$500,000 in the late 1980s to more than US$2.5 million over the past three years.

Generally speaking, I believe the advent of the CVI has made it easier for vaccine researchers to justify their work and obtain support for it.

Getting people to work together and getting institutions to cough up increasingly large sums of money are no mean feats, I'd say. Two main factors underlie this success: One is the power of the original CVI vision to galvanize the world into sustained action, to *pull* people towards a distant goal. The other is the growing appreciation of the "added value" of a CVI that, rather than becoming a supervaccine development programme, remains above the competitive fray, free to *push*, assemble and support the many collaborators doing the funding and the nitty-gritty research and development work.

To keep up and even accelerate the momentum over the next five years, let me call on all members of the global vaccine community to work with the CVI as it fulfils its two-way mission, pulling us forward towards the vaccines of tomorrow and giving us the sense of urgency and the support for what has to be done today.

Jong-Wook Lee

Executive Secretary,
The Children's Vaccine Initiative

The CVI remains above the competitive fray, free to push, assemble and support the many collaborators.

MANAGEMENT & FINANCE

A new role for the CVI – making music to save the world's children

With the CVI, the musicians play as an orchestra, each knowing his or her part at each moment of the symphony.

Without the CVI the world's efforts at preventing infectious diseases would be like the attempts of a bunch of musicians to play fine music without a conductor or score. The result: cacophony and wasted talent. With the CVI, the musicians play as an orchestra, each knowing his or her part at each moment of the symphony. The result: harmony and the attainment of a goal through a concerted, directed effort. And the difference is that one is a system, the other a "non-system." No prizes for guessing which is which.

This is how Dr Roy Widdus, the CVI's new Coordinator, sees the role of the CVI. "The orchestra, if you like, is the broad CVI coalition, made up of all the players involved in vaccine development, supply, quality assurance and vaccine delivery. The CVI secretariat is in many ways like the conductor, who cajoles and encourages the musicians. He makes sure they respect the timing set by the score and acts as catalyst for the music and as broker between the composer, the players and the audience. But the conductor never dictates to the players and can never replace them, since they have the resources and the expertise, each in his or her specific area."

The CVI, Dr Widdus believes, will provide the world with its first rational vaccine development system. "What we've had up to now is a non-system, or rather a multiplicity of systems, many driven predominantly by commercial concerns – which is a good incentive for innovation – but none, as systems, really responsive to the public health needs of the world."

Part of the CVI's catalytic role is building consensus on priorities, says Dr Widdus. Among the partners who will benefit from this role will be the public sector development agencies and national health authorities. The CVI secretariat will only coordinate funding and R&D activities targeted to fill very specific gaps. Private industry, too, will benefit, he believes, "since the CVI will provide commercial vaccine producers with an evaluation of Third World markets for their vaccines and thereby enhance the predictability of their R&D investments in products destined mainly for such markets."

To accomplish this role of identifying priorities and needs and gaps, the CVI will use several "tools" or opportunities: they include the Consultative Group, an annual forum where the views of all sectors of the vaccine world are voiced; the CVI's Scientific Advisory Group of Experts (aptly, if a tad pompously, acronymed "the SAGE"), which keeps the CVI's secretariat and partners on the right technical and scientific keel; and the CVI's Meeting of Interested Parties (saddled with the decidedly unpretentious acronym, "the MIP"), a sort of

UNICEF/C. Edinger

WHAT'S IN IT FOR ME? The CVI "system" will respond to the needs of all populations, however poor.

multinational, multidisciplinary steering committee that oversees the year-to-year running of the CVI secretariat.

Then there's the CVI's strategic plan, which spells out the CVI's objectives over different time spans. A blueprint for some, a bible for others, the strategic plan is a flexible document that will constantly be updated, thanks, among other things, to input from all the above CVI management and advisory groups. A task force on strategic planning is being formed to work with the secretariat on keeping the strategic plan up to date with changing needs and priorities. Another, broad-based task force – the task force on new vaccines – will look in depth at the benefits, costs and true value of introducing new vaccines and at strategies for using them.

But building consensus on priorities is only one of the CVI's catalytic functions. Dr Widdus sees three others:

• *Reminding the world that it should invest heavily in vaccines* – because they are the most cost-effective things ever invented to keep people healthy, because current global investment in vaccines is not commensurate with their public health value and because a lot of work and money are needed to invent new and improve existing vaccines if everyone in the world, particularly every child, is to benefit from them (advocacy, in short).

Here, the CVI will use whatever communications strategies – media seminars, publications, public awareness campaigns, face-to-face briefings, and so on – are best suited to the needs of the time, place and objectives. Important CVI meetings, both technical (on, say, obstacles to the production of acellular pertussis vaccines in developing countries) and administrative (like the annual Consultative Group meeting mentioned above), can offer opportunities for this kind of "awareness raising."

• *Getting people to agree about what needs to be done* (planning) *and getting them to work together to do it* (coordination) *for specific high-priority tasks*. Planning product development and other targeted activities will call for the formation of broad-based groups – product development groups or task forces – made up of individuals selected for their specific expertise.

Moreover, the CVI can take advantage of its special relationships with many "doers" – among them the GPV – each with its specialized know-how. The CVI is also supporting the creation of a global consortium of vaccine manufacturers (see Box on page 12) that will link different (even sometimes opposing) vaccine production poles – public and private, developing and developed – to improve vaccine quality worldwide.

• *Doing what has to be done, if nobody else will do it*. When the CVI first went into business, some people envisaged it as a kind of parallel programme to the WHO and saw its role as covering the development end of the R&D spectrum. The need for such a programme, says Dr Widdus, may well have changed with the creation of the GPV and with the expectation that the CVI will leave the doing to others. "Except," notes Dr Widdus, "where the doing isn't being done." Hence, the continuing work of the CVI's product development groups on better measles vaccines (see pages 22-24), a single-dose tetanus toxoid vaccine (pages 19-20) and a heat-stable oral polio vaccine (which may not be continuing, see page...) and of its ad hoc working group on DTP and DTP-based combinations (pages 14-16). New groups, moreover, could form in response to other unmet needs and would be managed for the CVI by those best equipped to do so.

Such is the vocation for the "new and better defined CVI" that is taking shape. But how much will the world have to pay for its work?

"There are two levels of financing," says Dr Widdus, "and they should not be confused." On one level is the amount of money the world is spending on vaccines and immunization, which is estimated currently to be in the order of US$6 billion a year. On the other, is the amount of money going to and through the CVI secretariat, and that has never exceeded US$5 million since the CVI came into existence. "Part of the confusion between the two arose," Dr Widdus believes, "because of the early image

Current global investment in vaccines is not commensurate with their public health value.

The CVI secretariat will indicate to decision- and policy-makers just how the pie should be used to give the world what it needs in new and better vaccines.

of the CVI not only as a coordinating, so-called umbrella organization, which it has retained, but also as a vaccine developer itself, which it has now largely discarded."

The global US$6 billion includes national immunization programmes, the total vaccine market in developing and industrial countries, vaccine research by national agencies and vaccine R&D by industry – not only the mammoth firms that dominate the market but also the welter of small biotechnology companies that have sprouted up to take advantage of the new molecular genetics. "It's not as much as the US$200 billion pharmaceutical market," says Dr Widdus, "but it's still a huge pie." And although the CVI secretariat sees only a tiny slice of it, "how it is being spent and whether it is being spent in a world-wise way is what the CVI is now all about."

In other words, the CVI secretariat will indicate to decision- and policy-makers just how the pie should be used to give the world what it needs in new and better vaccines. That's its priority-setting and consensus-building function, which the secretariat performs through the work of its task force on strategic planning. (This task force may soon be helped by the already mentioned new vaccine task force, which will bring together experts from many WHO divisions or programmes.) It is also the CVI's job to ensure that the pie is used more efficiently, more cost-effectively. That's the coordinating function. In addition, the CVI will work to increase the size of the pie. That's its advocacy and resource-mobilizing function.

Only US$5-6 million should be required by the secretariat to fulfil these functions, Dr Widdus estimates, with about a third going to each function. "Only, that is, in comparison with the amount being spent globally on vaccines," he adds. "Only, too, with regard to the impact that the CVI could make. That's because globally we're starting from virtually nothing. We don't have a rational system for directing resources to where they could give the best value. We're almost at point zero. So anything the CVI does will be added value and an enormous step forward."

Trouble is, funds available to the secretariat for 1995 amount so far to about only US$3.5 million. "If we don't meet our budget estimates of US$5.2 million for 1996," says Dr Widdus, "we will have to cut back on several activities." Candidates for the axe include activities on evaluating the cost-effectiveness of new vaccines and planning ways of funding their introduction into immunization programmes, the strengthening of quality assurance among local producers and some advocacy operations.

The world without the CVI

Without the CVI, too many children – currently eight million a year – will continue to die from infectious diseases preventable by current or future vaccines, because:

- there will be no agreement among the different sectors of the vaccine development and delivery community about what is needed globally to protect more children against more infectious diseases;
- individual groups driven by individual interests will work in relative isolation, leaving large gaps in the overall effort needed to bring new and better vaccines into the world;
- the potential of the commercial vaccine industry to contribute to filling the world's vaccine needs, as determined by public health considerations, will remain underutilized.

TO OUR READERS

An important topic not dealt with in depth in this issue will be featured in a forthcoming issue of *CVI FORUM*: Obstacles and incentives to private industry's contribution to the CVI goals.

CVI GOAL – QUALITY VACCINES FOR ALL CHILDREN

Casting off vaccine supply charity – the pace quickens

Self-sufficiency, self-reliance, independence, autonomy. Call it what you will. But the idea – encouraging countries to take on the burden of fulfilling their vaccine needs and thereby gaining more control over vaccine supply management – makes sense. And it has been floating around since the CVI began four years ago. The good news, according to UNICEF and WHO analysts, is that over half of developing countries buy some or all of their vaccines. "And the trend," says Mr Peter Evans, Chief of Vaccine Supply and Quality (VSQ) at WHO's Global Programme for Vaccines and Immunization (GPV), "is irrefutable. The proportion of countries paying for their own vaccines is growing."

The bad news, though, is that, as VSQ officer Ms Amie Batson notes, "it's growing too slowly: all countries are capable of paying something for their vaccines but there are still over 50 countries that rely entirely on outside help." What has been holding things up, she believes, is a combination of three factors: the rigidity – at least until very recently – of WHO's and UNICEF's vaccine supply strategy, a lack of political will on the part of the countries concerned and the absence of a system whereby donor support can be coordinated and geared to the differing needs and capabilities of the different countries.

But all that is changing, Ms Batson says. "There's a real revolution taking place and it is pulling the international development community out of its traditional approaches to vaccine supply into a more flexible system capable of dealing with the more heterogeneous reality out there."

The "revolution" has several components to it. A more targeted vaccine supply strategy is one. Traditionally, the aim has been to get the six vaccine antigens of the EPI (Expanded Programme on Immunization) to as many children in as many countries as possible in a kind of blanket approach. With about 80% of children now vaccinated against polio, tuberculosis, diphtheria, pertussis, tetanus and measles before the age of 12 months, that effort has been extremely successful. "Now," says Ms Batson, "we're at the stage where, to make this success sustainable and to prepare the way for the introduction of new and possibly more expensive vaccines into national immunization programmes, we have to tailor-make a strategy for each country. And that means putting some or all of the onus for vaccine supply on the countries, each according to its capability."

UNICEF/E. Tolmie

NOT YET INDEPENDENT...but more and more countries are meeting their own vaccine needs without outside help.

UNICEF is traditionally the main purveyor of vaccine to developing countries – to the tune of US$60 million a year. But with new, more costly vaccines appearing on the horizon, prices of current vaccines rising and donor funding slumping, the agency is particularly keen to see countries standing more on their own feet. To this end, it has begun implementing a new "global targeting plan" designed to shift some of the burden onto countries big enough or wealthy enough to carry it and to target its services more to countries patently still unable to go it alone.

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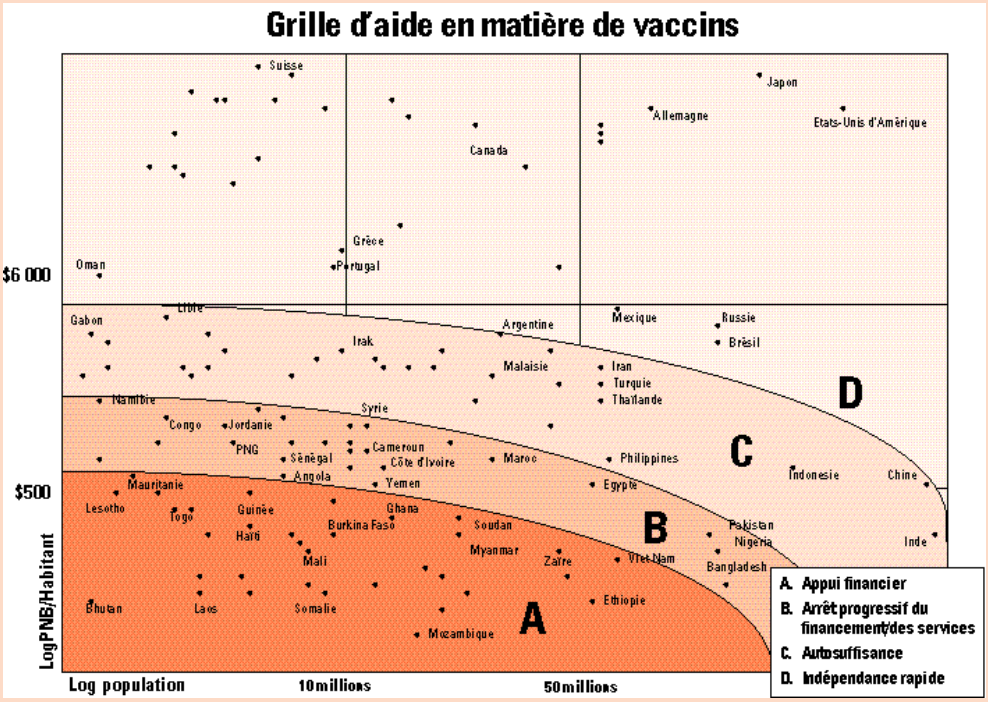
The Vaccine Independence Initiative forces them to engage in a rigorous planning exercise and thereby set out on the road to an efficient management system.



To Each According to Hs Need. ***UNICEF is using this grid to rank its vaccine supply support to countries. The grid separates out countries that still require external support to meet their vaccine needs from those that are or could be self-reliant. Plotted by wealth (per capita gross national product) and population size (which theoretically reflects the feasibility and sustainability of a local vaccine production facility), countries fall into five bands: the smallest, most indigent are clustered towards the bottom left-hand section of the grid (band A) and the more potentially or actually self-reliant in the successively higher bands. UNICEF's new support strategy would assure band A countries of continuing support for current and new vaccines, but would insist that they bear a small proportion of the cost, rising from 10% to 25% over the next three years. Band B countries would be asked to support most of the cost of vaccines (from 80% to 100% over the next three years for current vaccines and 50% to 100% for new vaccines). For band C countries aid would be phased out altogether over the first year, with perhaps a one-time handout. Band D countries would be left to their own devices forthwith. The remaining upper-crust cluster are, of course, already self-reliant.***

One tool the agency is using to sift the truly needy from the potentially self-reliant (if reluctant) is a grid (see above) that groups countries into five bands according to a combination of their wealth and population size and thus, presumably, their vaccine self-sufficiency potential. UNICEF's goal is to shift, over the next three years, the proportions of its vaccine supply cake going to the different categories of countries from the present 30% (about US$20 million) for each of the three bands (A, B and C) to 50% for the "neediest" band A countries, with the remaining 50% going on oral polio vaccine for the polio eradication initiative that is currently in full swing.

Another tool UNICEF strategists have come up with to help countries – particularly band B countries – to make the three-year transition from dependence to autonomy is the Vaccine Independence Initiative (VII). This is a scheme whereby a country works out its vaccine needs over a five- to seven-year period and, with UNICEF acting as broker between the country and vaccine manufacturers, pays for its vaccines through a flexible, revolving fund mechanism. The "added value" of the VII to countries with little experience in handling their own vaccine supply affairs is that it forces them to engage – some of them for the first time – in a rigorous planning exercise and thereby set out on the road to an efficient management system. About a dozen countries have joined or expressed interest in joining the VII, which a UNICEF report

Private, public – face to face or hand in hand?

What vaccine manufacturers want is to make the biggest profit possible out of the vaccines. And never the twain shall meet – unless...unless a common ground can be found. And, believe it or not, it looks as if it has.

That common ground is a mutual understanding of the fact that what drives vaccine production is not only price but also cost and what drives cost most is volume or scale of production. Large volumes of vaccine help to spread fixed costs, thereby increasing efficiency and reconciling the manufacturers' need to pay for development costs with their acceptance of a lower revenue on some sales. Manufacturers need markets offering prices that pay for the full R&D costs but at the same time they can benefit from a tiered pricing system whereby some customers pay full costs and others, like UNICEF, pay less but buy large volumes of vaccine.

The new tender that UNICEF sent out to manufacturers in September this year is based on that understanding. It reminds manufacturers that UNICEF buys a lot of vaccine – it has bought more than eight billion doses over the last ten years. It offers manufacturers access to a large but hitherto untapped market for their new vaccines in the poorest developing countries. It offers them the possibility of an assured long-term agreement to purchase over a given number of years large volumes of one or more traditional vaccines for the WHO's Expanded Programme on Immunization (EPI). And it gives them the possibility of combining their offers for old and new vaccines in a single "bundle." In return, UNICEF asks manufacturers to provide new vaccines at prices that the poorest developing countries can afford.

As this issue went to press, about a dozen manufacturers had responded to the tender with proposals for imaginative vaccine supply arrangements covering a range of the less "traditional" vaccines, including hepatitis B, *Haemophilus influenzae* type b, a diphtheria-tetanus-pertussis (DTP)-hepatitis B combination, a measles-mumps-rubella combination, a DTP-injectable polio combination and diphtheria antitoxin.

Across this new common ground, the two sides – public and private – have apparently started reaching out to each other. For the benefit, and survival, of millions of children.

says is "gaining increasing momentum."

Band C countries, however, which nearly all have the means if not the will to become independent, are being asked to take the plunge into autonomy by the end of 1996. They too, though, are receiving help, and in two areas: to procure vaccines more effectively from international or local suppliers, where they exist, and to ensure proper quality control over procured vaccines and, more especially, locally produced vaccines.

On behalf of the CVI, for example, VSQ teams are looking at the quality and quantity of vaccine being made in developing countries and are offering advice and other forms of collaboration to manufacturers and governments aimed at strengthening local production where this is economically and logistically feasible. Among 63 DTP manufacturers assessed by the teams in 42 countries, for example, at least half were producing vaccine that did not meet WHO standards of quality, according to VSQ scientist Dr Julie Milstien.

On the quality control side, the teams have also visited 10 of 14 "priority" countries (ie. producing vaccine, having access to funding, with a strong potential for successful production but facing problems in meeting their needs for quality vaccines). They found only two countries with a quality control system that ran all their vaccine lots through the full gauntlet of assessments, tests and inspections that the WHO considers essential for quality vaccine production. (The 10 countries visited were Bangladesh, Brazil, Egypt, India, Indonesia, Iran, Mexico, Pakistan, Philippines and South Africa. The four still to be visited are China, Russia, Thailand and Viet Nam.)

These assessments by the VSQ teams have identified five essential, if not easy, steps to successful vaccine production. Countries committed to local production need:

- to take a hard look at costs, not only to produce quality vaccines but also to acquire, set up, use and maintain the necessary infrastructure;
- an independent national control authority with an efficient national control laboratory;
- manufacturers with managerial autonomy;
- manufacturers capable of setting up and running a good management system, with proper strategic planning, well-trained, qualified staff, adequate technology and facilities, and know-how;

Across this new common ground, the two sides — public and private — have apparently started reaching out to each other.

A global vaccine production consortium

It's an idea simple enough to be in the why-didn't-I-think-of-it-first category. There is some doubt about who actually did think of it first, but Dr George Siber, Director of the Massachusetts Public Health Biologic Laboratories, has for the past two or three years been one of the most vocal proponents of a worldwide consortium of vaccine manufacturers, and there are indications that it has a good chance of becoming more than just an idea.

Basically, the consortium would bring together in a loose confederation those vaccine manufacturers who, by virtue of their mandate, would support public health priorities, in particular the CVI's goal of bringing to market affordable, simple vaccines against all the major diseases affecting children. Criteria for membership would include the wherewithal for good management, vaccine quality and technical excellence.

Supporters of the consortium idea believe, according to a recent report by officials of the Global Programme for Vaccines and Immunization (GPV), that it could be "the most sustainable way to implement GPV/CVI self-sufficiency and other goals for vaccine producing countries."

They back this belief with a list of the consortium's potential assets:

- It would provide a mechanism for international validation of high-quality local vaccine production in the developing world.
- It would make it easier at a national, regional and international level to pool research, administrative and legal resources, and also training activities, especially in the creation or improvement of good management and quality assurance and control systems.
- It would give developing country manufacturers a forum for discussion of common problems – and possible solutions.
- It would provide structured assistance – particularly the help of other manufacturers who have already reached a certain level of excellence – to manufacturers and governments willing to take the necessary steps towards quality vaccine production.
- It would provide the international community with a convenient mechanism for channeling and prioritizing funding, and one that ensures management efficiency and accountability.
- It could, eventually, allow easy access by developing country manufacturers to technological and research advances, thereby enhancing capability for the production of new vaccines.

Initially, the consortium would have a two-tier membership: Full members would meet standards of technical excellence, demonstrate long-term economic viability, have a national system for monitoring vaccine quality, be willing to share technology and other means of accessing the development of new vaccines, and be committed to the goals of the consortium. Associate members would have a national control authority and a commitment to ultimate full membership.

About 25 manufacturers have been identified that could be members of the consortium, if they wished, says Dr Julie Milstien, a scientist with the GPV's Vaccine Supply and Quality Unit. "About five of these could form a nucleus of full members. They would have the equivalent of a WHO seal of approval, be internationally recognized as producing good quality vaccine and have a good chance of being around for the next five years."

The consortium's ultimate objective is to help all manufacturers able and willing to achieve quality production to meet the criteria for full membership. However, in the short- and medium-term, it will have to be selective. "That means three things," says Dr Milstien. "The consortium will identify manufacturers whose vaccines are acceptable for purchase. It will help those who are spending money and effort trying to get into the picture actually to achieve their goal. And it will help those who are just never going to make it, to reconsider their options."

The consortium would provide a mechanism for international validation of high-quality local vaccine production in the developing world.

• manufacturers who plan and set priorities for the future.

Dr Milstien puts a lot of the blame for poor quality local production on lack of political commitment. "Governments of countries where local public sector production is a feasible option must, if they are really committed to the idea, be prepared to give it the support it needs." And for Ms Batson, it is only when manufacturers have drawn up a strategic plan that spells out what vaccines are needed, in what quantity and how those targets are going to be met, with what investment, staff and so on, that advice and technical help can be of any use. "In the past," she says, "there has been too much reliance on technical fixes. Compared with setting up and implementing a good management system, the technical fix seems to

be the easy way out. But generally speaking it has not been effective. The developing world is littered with bits of equipment that have never been used, with consultants' reports gathering dust. But for an outfit that is run in an entrepreneurial manner, with a proper strategic plan, a specific technical fix can have maximum impact."

The CVI is also backing efforts by countries, manufacturers and other vaccine-related institutions (including vaccine control laboratories) to form links. One grouping, known by its Spanish acronym SIREVA (Regional Vaccine System for Latin America and the Caribbean) was launched two years ago under the auspices of the Pan American Health Organization. Several SIREVA countries, including Brazil, Chile and Mexico, have brought public sector manufacturers together to plan joint development of certain vaccines. SIREVA is also promoting the creation of a regional quality control network and a regional DTP certification system. There is also much talk these days, in international vaccine circles, of a "global consortium of vaccine manufacturers." The scheme is still at the blueprint stage but is, in Mr Evans' opinion, "creating a tide of enthusiasm." (see Box)

Now, with UNICEF, the WHO and the countries having to get their show together to bring the vaccine supply "revolution" to fruition, what role will the donor community play? Donors too can get into the act, Ms Batson says, by supporting UNICEF's new targeting strategy (for example, by selecting countries for bilateral funding in accordance with UNICEF's tiered or targeted approach). They can also ensure more efficient coordination of such funding by supporting a global vaccine fund. This idea is still at the drawing board stage, but could, according to UNICEF officials, buttress the new approach to vaccine supply. Setting up a nest-egg of, say, $US30 million would, they say, strengthen the agency's negotiating position in long-term deals with manufacturers and act as a buffer against the potential fickleness or inadequacies of bilateral aid.

"Many global funds," says Ms Batson, "end up as slush funds for a range of activities, some not envisaged in the original plans. The beauty of the proposed global vaccine fund would be its transparency: money can be withdrawn and spent for a well-defined, highly specific need, such as for a specific vaccine needed by one or more specific countries to deal with a specific disease-control target. You establish the criteria for use of the funds and you make sure the funds are used according to those criteria. It's all out in the open, clear and logical."

"You establish the criteria for use of the funds and you make sure the funds are used according to those criteria. It's all out in the open, clear and logical."

CVI GOAL – LIFELONG PROTECTION WITH A SINGLE-DOSE VACCINE

Pertussis vaccine trials give DTP shot in the arm

From its inception the CVI has acclaimed DTP as the mainstay of its drive to develop single vaccines against multiple diseases.

You could be excused for yawning if someone brings up DTP at your next luncheon meeting. The old diphtheria-tetanus-pertussis combination that immunization programmes the world over have been pumping into children for the past 50 years does seem like a pretty tired topic. Yet, you'd be wise to listen. To begin with, from its inception the CVI has acclaimed DTP as the mainstay of its drive to develop single vaccines against multiple diseases – for some very good reasons (see Box). What's more, over the past year events have been occurring that could put new life into the old workhorse.

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REPLACING THE OLD DTP with acellular DTP is now an option for some countries. But the old version still saves over half a million lives a year.

For Dr Mark Kane, medical officer with the Expanded Programme on Immunization (EPI) of the WHO's Global Programme for Vaccines and Immunization (GPV) and secretary of the CVI's working group on DTP and DTP-based combination vaccines, "this has been a critical and an exciting time for DTP." The most important event, he believes, is the apparent validation of acellular pertussis vaccines by several trials conducted, respectively, in Italy, Sweden and Germany over the past three years. The trials showed four types of acellular pertussis vaccine to be extremely effective for primary immunization [ie. the first three doses in the first year of life] and "remarkably safe," according to Dr Jann Storsaeter, who was deputy clinical investigator of the Swedish trial and is with the Institute for Infectious Disease Control in Stockholm.

Unlike the standard whole-cell vaccine, which consists of a crude preparation of the entire *Bordetella pertussis* organism and contains an estimated 3,000 different antigens plus a ragbag of other substances not needed for immunity, acellular pertussis (aP) vaccines use only a handful of the organism's antigenic structures, all selected for their immunogenic importance and obtained, purified and detoxified chemically or by recombinant technology. Acellular vaccines, being purer, should be much less likely to cause side-effects than the whole-cell vaccine. Since 1981 they have replaced whole-cell vaccine in Japan for use in children. In the United States two DTaP vaccines have been licensed, although only

Riding on the DTP bandwagon

If ever a vaccine deserved a good service medal, it is DTP – the diphtheria-tetanus-pertussis combination that for almost half-a-century has been protecting millions of children from three common child-killing diseases. Adopted two decades ago by the then newly created Expanded Programme on Immunization (EPI) as the centrepiece of its six-antigen "package," DTP over the years has slashed world figures for reported cases of pertussis by 94% (and diphtheria by 29% and tetanus by 44%). In developed countries the drop has been even more striking: in the United States, for example, before the introduction of DTP in 1949, there were about 200,000 cases a year of pertussis and about 12,000 deaths from the disease vs. less than 5,000 cases and about 10 deaths a year so far in this decade – a 98% drop in cases and a 99.9% drop in deaths.

DTP now protects nearly 80% of the world's children and is generally recognized as the cornerstone of the world's childhood immunization programmes. Of all the current vaccines it is the one most widely produced in the developing world, where manufacturers supply more than half the world's total demand, estimated at over 900 million doses a year. Nor is DTP likely to become obsolete in the near – or even distant – future, since none of the three diseases is believed to be eradicable.

For all these reasons, the CVI believes DTP should be the backbone or core of future combination vaccines. That aim, though, has been hampered by DTP's lack of purity, due largely to its pertussis component, which consists of a crude preparation of the whole *Bordetella pertussis* organism. Using an impure product as the foundation for a long-term combination vaccine development strategy just doesn't seem like good science. Moreover, DTP's impurities have been responsible for the side-effects – mostly minor, but a few severe – that have given the vaccine a bad name and put a break on its routine use in some countries. The advent of acellular pertussis vaccines (aP) – purer and less likely to cause side-effects than the whole-cell version – may give DTP a new lease of life and enable it to play the role the CVI has cut out for it (see text).

Combination vaccines based on acellular DTP (DTaP) are already entering the scene. A DTaP/Hib (*Haemophilus influenzae* type b) combination was first launched in the United States in April 1993. A second combination linking DTaP to HepB (hepatitis B) is ready for registration and a third linking DTaP to HepB and IPV (injectable polio vaccine) is about to enter Phase III clinical trials. And that's only for starters. Some CVI forecasters are talking of a multi-antigen vaccine hitching to the DTP workhorse Hib, HepB, HepA, possibly later HIV (the AIDS virus) and pneumococcal antigens (against pneumonia and meningitis).

And why stop there? Well, for one thing, new technology, such as nucleic acid ("gene") vaccines (see *CVI FORUM* No. 7, August 1994, pages 7 to 10), could offer novel, perhaps better, ways of combining antigens. For another, DTP's scope as an antigen vehicle is limited by the fact that only nonliving antigens, like DTP's three component antigens, can be hooked onto it.

For the moment, though, the future looks bright for DTP and DTP-based vaccines. At least the vaccine industry thinks so, if the recent flurry to form "supergroups" – to disentangle antigens from a complex maze of licensing agreements and ensure their wide availability – is anything to go by.

for fourth or fifth booster doses.

The German study found an acellular vaccine to have a protective efficacy of 89% in 100 children who were household contacts of pertussis cases. The Italian and Swedish studies, which were conducted in over 25,000 infants, showed four acellular vaccines to be much more effective than the traditional, whole-cell pertussis vaccine – between 84% and 85% efficacy for the acellular vaccines in the Italian and Swedish trials, respectively, vs. 36% to 48% for the whole-cell vaccine. Earlier this year, another Swedish field trial in 3,500 children also found an acellular pertussis vaccine to be more than 70% effective and free of serious side-effects.

Just why the whole-cell vaccine made such a poor showing in the Swedish and Italian studies remains an enigma for most experts. Dr John La Montagne, who heads the Division of Microbiology and Infectious Diseases at the National Institute of Allergy and Infectious Diseases (NIAID) in Bethesda, Maryland, USA, believes "it is entirely possible that with whole-cell

Acellular vaccines, being purer, are much less likely to cause side-effects than the whole-cell vaccine.

pertussis vaccines we have a relatively broad spectrum of efficacy...probably 40-90%, depending on the particular vaccine."

GPV pertussis expert Dr Bernard Ivanoff adds: "The results for the whole-cell vaccine used in these studies may not be typical of whole-cell DTP generally. We have calculated, for example, that in 1990, use of whole-cell DTP saved the lives of 600,000 children who would otherwise have died from pertussis. Having said this, the important thing to note from the Swedish and Italian trials is that the acellular vaccines were highly effective and only minimally reactogenic, irrespective of how effective or ineffective the whole-cell vaccine was."

"There's every reason to believe that Europe and North America will switch altogether to the acellular vaccine. The big question is: what will the developing countries do?"

And there, indeed, is the rub. For, the reputation of standard DTP is still tarnished in some countries by a few, mostly unconfirmed, reports of neurological side-effects and by a well-documented high frequency – in 30% to 70% of children – of minor side-effects. For the most part, the vaccine's reactogenicity has been laid at the door of its impure whole-cell pertussis component. Hence, the enthusiasm of vaccine experts at the low frequency of reactions seen with the acellular vaccines in the Italian and Swedish trials – about 20 times less frequent for redness at the injection site after the first dose, nine times less for fever, seven times less for persistent crying and seven times less for local tenderness. The differences were less striking after the second and third doses. As for more serious side-effects, six children went into a collapse-like state (hypotonic hyporesponsive episode), five of them recipients of the whole-cell vaccine, one in the acellular group. Interestingly, the diphtheria and tetanus toxoids that were given to a control group of children in both trials produced as few side-effects as the acellular vaccines, a finding that confirms the pertussis component as the reactogenic culprit.

"These results have considerable ramifications for the CVI and they raise a host of critical questions," says Dr Kane. "There's every reason to believe that Europe and North America will switch altogether to the acellular vaccine. The big question is: what will the developing countries do?" Cost is a major consideration, since DTaP may well cost more than US$1 a dose, vs. the current 15 cents that UNICEF pays for the standard whole-cell DTP. But, as Dr Kane points out, "we really don't know much about likely costs or pricing yet for acellular vaccine."

Which raises the next big question: What will UNICEF do? Continue to buy standard whole-cell DTP or switch to the acellular vaccine?

Technology and local production capability, too, are issues. Nearly two-thirds of children in developing countries receive DTP made locally and more than 50% of the world's DTP is made in developing countries, according to the GPV's Vaccine Supply and Quality Unit (VSQ). However, a recent VSQ survey of DTP manufacturers showed that at least half were producing vaccine not up to WHO standards of quality. "The acellular vaccines require a more sophisticated technology than the whole-cell DTP," says Dr Kane. "Some producers in developing countries, particularly large ones, may try to make the switch. Others may take supplies of the new vaccine in bulk and combine it with their own tetanus and diphtheria toxoids." Which brings up another question: Will the world have a two-tier DTP supply system?

These and related questions will be discussed at two forthcoming meetings: one, organized by the Italian NIH (Istituto Superiore di Sanità) will take place in Rome at the end of October 1995 and deal with the technical implications of the Swedish and Italian studies; the other, organized by the CVI's DTP working group, will be held early next year and address the studies' economic, technological and logistical implications.

CVI GOAL: LIFELONG PROTECTION WITH A SINGLE-DOSE VACCINE

Search for one-dose tetanus vaccine approaches first deadline

"It's still early days yet, but things are definitely on the move." So says Dr Teresa Aguado, secretary of a newly formed working group on single-dose tetanus vaccines.

As its name suggests, the group's main focus is the development of a tetanus toxoid vaccine that can be delivered in a single dose vs. the current three-dose schedule, which is usually administered as part of the diphtheria-tetanus-pertussis (DTP) combination vaccine. However, the technology and know-how that the group is exploring will, it hopes, be applicable to other antigens.

The working group was formed last year through the merger of two groups: one was a subcommittee of the new vaccination approaches committee that used to be part of the former WHO/UNDP Programme for Vaccine Development (PVD) and is now part of WHO's Global Programme for Vaccines and Immunization (GPV); the other unit was the CVI's product development group (PDG) on single-dose tetanus toxoid vaccines.

Embedding the tetanus toxoid antigen in tiny synthetic beads called microcapsules or microspheres was the approach favoured by the CVI's former PDG (see *CVI FORUM* No. 1, April 1992, pages 6-7), and it has been adopted by the new working group. The microcapsules are made of a mix of polymers (most commonly lactic and glycolic acids) that, after administration of a single dose of the preparation, release the toxoid at a rate and schedule determined by the size of the capsules and their chemical composition. They are usually given by injection, but CVI researchers are also examining the possibility of using the oral route. The microencapsulation technique has been widely applied over the past decade for the timed release of drugs and hormones.

"What we're looking for," Dr Aguado says, "is a product that gives a good protective antibody response within weeks of administration of a single dose of vaccine. That means a good priming response very shortly after administration and a strong boosting of immunity one to two months later." Ideally, she adds, boosting should occur again at eight to 12 months.

Research teams collaborating with the working group began work five years ago. After about three years, however, they ran into a roadblock. Initial tests in mice, guinea-pigs and monkeys had shown some of the encapsulated preparations to give strong, protective priming responses – in some cases stronger than the first dose of the existing toxoid vaccine. However, none of the preparations produced adequate boosting, even during the "primary" period a month or two after administration, let alone at eight to 12 months.

Just why, is still not known, despite extensive research to find out. One possibility is that the toxoid may lose its immunogenicity as a result of adverse temperature or acidity conditions within the microspheres. The collaborating research groups are exploring different possible remedies, including chemical modification of the toxoid, the addition of stabilizing agents of one kind or another to the microencapsulated preparation and the use of higher concentrations of toxoid.

"Some of this work has given partial satisfaction," notes Dr Aguado. "But we're not there yet. So the search continues." The working group has given its collaborating teams to the end of this year to produce "their best candidate products" for final

Collaborating teams have to the end of this year to produce their best candidate products for final animal tests to be conducted early next year.

animal tests to be conducted early next year. Among these single-dose candidate vaccines will be a tetanus vaccine developed independently of the working group by an Australian company, CSL of Parkville, Victoria. "Our product is close to the specifications sought by the CVI," CSL Research and Development Director Dr Ian Gust told *CVI FORUM*, "and we're interested in testing it head-to-head with the other candidates."

In an approach inherited from PVD days, the working group is also investigating the use of a live attenuated bacterium, *Salmonella typhi,* as a vector for an immune-stimulating (immunogenic) fragment of the tetanus toxoid. Plans are being made for a Phase I (safety) trial next year of an oral recombinant vaccine comprising a *Salmonella* vector transfected with the gene for the tetanus toxoid C fragment.

A third option being explored by the working group involves replacing the alum adjuvant of the current tetanus vaccine with a more powerful adjuvant. Animal tests of calcium phosphate have given promising but inconclusive results. Human trials planned for next year should produce a more definitive answer. Research on another adjuvant, polyphosphazene, is also under way.

Other research projects the working group is funding are at an even earlier stage. Teams are investigating, for example, how other antigens might be used with the microencapsulation technique: early work has begun on diphtheria toxoid, cholera toxin, malaria parasite peptide molecules, simian immunodeficiency virus-like particles (SIV) and a hepatitis B viral antigen. Yet other projects are probing ways of making microsphere preparations suitable for oral administration. One way, for example, might be to couple a known immunogen, such as a fragment of the cholera toxin, to the microspheres, to increase their chances of accessing the gut's mucosal immune system, which is called into play following oral administration of a vaccine.

All in all, the working group "has cast its net over a wide area," says Dr Aguado, "and it's a question now of pulling in the haul and sifting out the best fish."

"It's a question now of pulling in the haul and sifting out the best fish."

New chief for a new division

CVI FORUM is pleased to announce to its readers the appointment of Dr David Heymann, formerly with the WHO's Global Programme on AIDS, as Director of the WHO's newly created Division of Emerging, Viral and Bacterial Diseases Surveillance and Control.

CVI GOAL – VACCINES THAT WITHSTAND HEAT

A heat-stable oral polio vaccine – waiting for a decision

By mid-July this year, the CVI's four-year, US$750,000 search for a way of making the oral polio vaccine (OPV) less vulnerable to heat seemed close to success. Among different technologies considered, replacing ordinary water with heavy water, or deuterium oxide, in the final blending stage of OPV production looked to be the best solution. Research funded by the CVI's special product development group (PDG) working on the project showed the deuterium oxide capable of increasing the vaccine's heat stability by up to 300-fold at temperatures of 37°C and above, bringing it well within the target of seven days at 37°C without significant loss of potency.

So at the height of last summer it was all systems go for development of a deuterium-oxide stabilized oral polio vaccine (dOPV). Before the end of the year clinical trials would test the safety and efficacy of the vaccine and a panel of experts would review safety data (no problems of toxicity or loss of potency were anticipated). Analysts with WHO's Global Programme for Vaccines and Immunization (GPV) would determine the cost-effectiveness and impact of the stabilized vaccine on efforts to weed out polio from its last strongholds. Surveys in the United Kingdom would probe consumer attitudes to the vaccine (deuterium is a natural nonradioactive isotope of hydrogen but is used, among other things, as a quenching agent in nuclear power stations and its nuclear association could give the product a bad press). Suppliers of deuterium oxide, mainly in Canada, China and India, would put their plants into full production (100 tons a year is the estimated amount needed to stabilize the 350 million to 1 billion doses of vaccine believed necessary for completion of the global polio eradication initiative over the next five years or so). And donors were being sought – including Ontario Hydro of Canada, the world's main supplier of deuterium oxide – to defray the cost of stabilizing the vaccine, estimated at US$0.025 over and above the current cost of standard OPV.

"The critical thing is to get a go-no-go decision by the middle of 1996," PDG Secretary Dr Julie Milstien told *CVI FORUM*. "And the information on which that decision is based has to be as hard and as transparent as possible."

Then, in the last week of July, at their annual meeting at the headquarters of the Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia, USA, CDC and WHO experts reviewing progress in polio eradication expressed "considerable reservations about proceeding with testing and manufacturing of deuterium oxide-stabilized OPV" and brought the whole OPV heavy water operation to a virtual standstill. GPV director Dr Jong-Wook Lee, who attended the Atlanta meeting, said the experts were

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A MORE STABLE VACCINE – how essential for polio eradication?

It was all systems go for development of a deuterium-oxide stabilized oral polio vaccine.

UNICEF/B. Denmers

***A Drop In Time*...saves years of misery and even death from poliomyelitis.**

The experts were impressed with the stunning progress of polio eradication efforts being made with the current oral polio vaccine.

impressed with the "stunning progress" of polio eradication efforts being made with the current OPV and doubted whether there was a real need for a more stable OPV. What is more, beginning next year, the experts noted, all immunization programmes will use vaccine vial monitors, that indicate when a vaccine has lost its potency because of heat or other factors, further reducing the need for a heat-stable OPV. The experts also feared, Dr Lee said, that misinformation about deuterium oxide, "although it would eventually be discredited, could cause substantial damage to the polio eradication effort by reducing coverage in significant population groups."

A special subcommittee of the CVI's Scientific Advisory Group of Experts (SAGE) will discuss the issue during the CVI's fifth Consultative Group meeting in São Paulo at the end of October. Dr Lee said he will decide whether or not to abort work on a stabilized OPV after consulting with sub-committee members and the PDG chairman. As this issue of *CVI FORUM* went to press, the prevailing view among CVI officials was that he would decide to abort or at least direct the PDG to the search for an alternative stabilizing agent.

If so, will the PDG's efforts have been wasted?

Not altogether, says Dr Lee: "They have taught us some important lessons about the process of bringing improved vaccines from the lab into the field. In particular, we have gained valuable experience in working with vaccine manufacturers and licensing authorities and this should stand us in good stead in getting new vaccines introduced into immunization programmes."

Dr Milstien adds that research funded by the group has unearthed insights into how heat cripples the poliovirus. "Work is also continuing," she says, "on ways of making other vaccines, including measles vaccine, more heat-stable."

A new face at the helm of WHO's immunization programme

A gentle but no-nonsense atmosphere pervades the new Geneva office of Danish public health specialist Bjorn Melgaard, 51, who arrived at WHO headquarters this summer to head the Expanded Programme on Immunization (EPI), part of the WHO's Global Programme on Vaccines and Immunization (GPV). Words like "meticulous, methodical, business-like" seem to fit. As do "outgoing, friendly, affable." And "balance" could perhaps be the leitmotiv of his style.

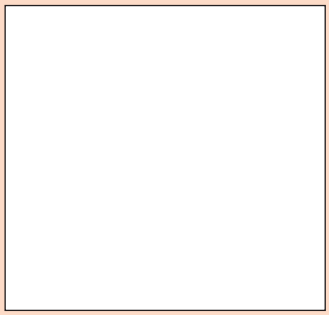
How ready for his new job does he see himself?

"My biggest handicap," he told *CVI FORUM*, "is lack of direct experience of WHO. Not just the administrative side but also WHO's work in developing immunization strategies and expanding immunization activities." He has in fact been involved in field work for other organizations, mainly DANIDA, the Danish International Development Agency, and has only followed WHO's work "from the sidelines."

On the other hand, Dr Melgaard's background in field work may well be his strongest asset. As chief advisor to health ministries in several African and Asian countries, he has built up expertise in national health policy-making and in the planning and management of national health programmes and strategies. As with many Scandinavian health professionals, primary health care has been the cornerstone of his interest. Will he therefore put other items on EPI's agenda – say, eradication campaigns or adding new vaccines to the standard EPI vaccine "package" – on the back burner?

"Certainly not. It's a bit strange to me to find that EPI staff have tended to polarize these two viewpoints. Fortunately, there has also been a move to see how they can mutually benefit each other. Because they *are* mutually beneficial, and certainly not mutually exclusive.

And what about the introduction of new vaccines?



Dr Bjorn Melgaard

EPI, Dr Melgaard said, has to "broaden its approach to disease prevention," which means "bringing new vaccines into the picture." And that means "refining our framework for the introduction of new vaccines to ensure that the necessary research and the introduction machinery is geared to the major health problems." And that, for Dr Melgaard, means first and foremost, acute respiratory infections, which "could and should become the highest priority for EPI work on new vaccines."

Asked to name three changes he would like to bring about in the EPI over the next five years, Dr Melgaard offered the following:

- The EPI should "become a stronger unit through a more solid team spirit and a closer coordination of activities."
- Disease surveillance and information systems generally should become " a major priority for strengthening,"
- EPI strategies should be "more diversified, with each strategy for each activity tailored to the circumstances and needs of each individual country."

During the first few weeks in his new job, many EPI staff members have welcomed Dr Melgaard's management style but questioned his technical credentials. Again, it's going to be a question of getting the balance. Certainly, the future priorities he is staking out for the EPI will call for a good dose of both.

"EPI strategies should be more diversified, with each strategy for each activity tailored to the circumstances and needs of each individual country."

CVI GOAL: VACCINES GIVEN EARLIER IN LIFE

Research on better vaccine takes off, as measles deadlines loom

The quest for a better measles vaccine is well and truly on, its sense of urgency fuelled by imminent deadlines for cutting cases and deaths – targeted to fall below 5% of 1970 levels by the end of this year. Some experts say: "We're making fantastic progress." Others grumble: "We're not moving fast enough." Which camp you're in depends to some degree on whether you're a basic research buff or a "field" aficionado struggling to reach those deadlines.

However successful the battle has been so far using the current vaccine a better vaccine could help to finish the job more quickly.

Both sides agree, though, that however successful the battle has been so far using the current vaccine – annual cases down from the 1970 estimate of 130 million to about 40 million last year and deaths down from the 1970 estimate of six to seven million to about one million for 1994 – a better vaccine could help to finish the job more quickly. The case for a better vaccine is also strengthened by the fact that the measles elimination campaign has cornered the disease into the logistically most difficult countries and population pockets of the world where overcrowding, migration, poverty and other social ills favour transmission of the virus (see *CVI FORUM* No. 7, August 1994, pages 2-6): anything that would make the task easier is welcome (see Box).

How much better must the vaccine be? It should have at least three merits lacking in the present version, which is a live, attenuated "Schwartz" strain of the measles virus, in use since 1963: Its immune stimulating properties should be unaffected by the maternally inherited anti-measles antibodies commonly present in infants under six months of age and so could be administered to such infants together with the other vaccines delivered by the WHO's Expanded Programme on Immunization (EPI); preferably, it should not need to be administered by injection, and so could be more suitable for mass campaigns; and it should not lose potency when exposed to heat.

A lot of basic research is exploring ways to develop such a vaccine. At a workshop organized last August in Bethesda, Maryland, in the United States, by the Division of Microbiology and Infectious Diseases (DMID) of the National Institute of Allergy and Infectious Diseases (NIAID), part of the US National Institutes of Health (NIH), scientists reported on progress in NIH-funded research on measles. One team described research on infectious clones of the measles virus in order, among other things, to make artificial strains for better vaccines. Another group has identified a receptor molecule that the virus uses to attach to cells, opening the way to creation of a mouse model for the disease (mice transfected with the gene for this receptor could be made permissive to infection) that could be used to screen new candidate measles vaccines. Yet others are exploring vaccine vehicles, such as the bacille Calmette-Guerin (BCG) and the vaccinia virus, or the use of the nucleic acid ("naked" DNA or RNA) technique to programme the body to produce its own vaccinating antigens. Animal models too are being developed that enable researchers to probe unexplained problems encountered by vaccines – among them, the immunodepressant effect of some powerful (high-titre) live measles vaccines, and the severe so-called atypical measles syndrome that occurred in the 1960s in some children vaccinated with inactivated viral vaccines and subsequently infected with naturally occurring ("wild") virus.

Dr James Meegan, of the DMID's Virology Branch, is for one decidedly upbeat about advances in basic research: "This virus is always going to be a problem child. But

we're making remarkable progress: three years ago, we had virtually nothing. Now research is really opening up the field."

A working group formed jointly by the WHO's Global Programme for Vaccines and Immunization (GPV) and the CVI has been looking for ways of penetrating or circumventing the maternal antibody barrier. It has funded a study comparing immune responses obtained with the standard vaccine and with three novel systems for delivering immunogenic measles proteins in monkeys. Two of the systems use living viruses – the canarypox virus (called ALVAC) and the vaccinia virus (NYVAC) – genetically manipulated to express the proteins; the third uses so-called ISCOMs (immune-stimulating complexes) both as vehicles for the proteins and as adjuvants to stimulate immunity (see *CVI FORUM* No. 3, page 7, February 1993). The study showed the ISCOM-vectored vaccine, according to a working group report, to have "the greatest potential... [among these candidates for] a vaccine to be used for immunization in the presence of maternal antibody." It gave strong antibody and cellular immune responses even in monkeys who had been injected with anti-measles antibodies, the report said. Certainly, a major asset offered by ISCOMs, the group believes, is that "they could provide a good backbone for carrying several vaccinating antigens."

The working group will back further exploratory research on an ISCOM measles vaccine, which will be undertaken at the National Institute of Public Health and Environmental Protection (RIVM) in Bilthoven, Netherlands. Phase I/II clinical trials could begin in 1998, RIVM officials believe. Among the hurdles the vaccine will face is its safety in regard not only to its inherent toxicity but also to its potential for favouring the development of atypical measles syndrome. Scientists will also look carefully at the duration of the immune response it induces, believed to be short-lived with nonliving vaccines. The cost of ISCOM vaccines, moreover, could, in the view of some experts, be a major obstacle to their suitability as replacements for the present vaccine. Other experts believe they would not be more expensive than some currently used inactivated vaccines, like the injectable polio vaccine, which costs between US$0.70 and US$1 per dose (compared with the current US$0.14 for the standard measles vaccine).

Then there are those who fear that, however exciting, research on a better vaccine may be diverting energy and funds from an effort to increase immunization coverage now, particularly among high-risk groups. Over 95% coverage, for example, may be needed in densely populated areas to fully control the disease, vs. a worldwide coverage rate of around 80%. Some countries – nearly half of the sub-Saharan African countries, for example – have coverage rates below 50%. "Investment in the development of new vaccines should be balanced by investment in developing the human, physical, and financial infrastructures for their delivery," according to two experts, Dr Felicity Cutts of the London School of Hygiene and Tropical Medicine in the United Kingdom and Lauri Markowitz of the Centers for Disease Control and Prevention in Atlanta, Georgia, USA, writing in *The Journal of Infectious Diseases* .

The working group is also searching for more practical ways of administering the measles vaccine. One of the most promising would be by aerosol, either in liquid (droplet) form or as a fine powder. Several manufacturers of state-of-the-art nebulizers have submitted proposals, which the group, together with EPI officials, will examine in the coming months.

Vaccines are not the only items on the working group's agenda. It is also funding work on developing a rapid field test for diagnosing measles. "The elimination strategy that the EPI is conducting needs a way of rapidly detecting outbreaks of measles and we're looking for a simple, cheap, easily performed diagnostic test that will do the trick," says the GPV's Dr Yuri Pervikov, co-secretary of the working group.

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Mass campaigns send measles reeling in many countries

Cuba did it in 1987. The English-speaking Caribbean countries did it in 1990. Chile, Brazil and Peru did it in 1991. All the Central American countries did it in 1992 and 1993, by which time the Dominican Republic had started doing it, followed by Argentina, Colombia, Mexico and Uruguay. Across the water, the United Kingdom began doing it in November last year. And this year Paraguay is doing it.

It, you must have guessed, is a mass measles immunization campaign, reckoned to be the best way of catching any children who may still be susceptible to the infection despite routine immunization in infancy or early childhood. There are a number of reasons why nonimmune children are still around. To start with, the standard vaccine is only about 90% effective, leaving about 10% of vaccine recipients unprotected in each generation or cohort of "new" children. Then, about 25% of children who receive their first doses of vaccines against polio, tuberculosis, tetanus, whooping cough and diphtheria between two and six months of age fail to turn up or cannot be tracked down for their measles shot, which can only be given at six months of age at the earliest (see text). Other children elude vaccination because they live in areas cut off from health care services through geography (roadless terrain, for example), social exclusion (densely populated urban slums) or warfare (breakdown of social services, displaced populations, etc.).

The mass campaigns aim to vaccinate all children in a country between the ages of nine months and 15 years, whether or not they have already been vaccinated or infected with the natural measles virus. Within days, vaccination coverage rates soar to near-100% levels. Following a campaign, health workers make every effort to maintain high coverage rates among new cohorts of infants and among the least accessible population groups. A disease surveillance system also goes into high gear for rapid detection and treatment of new cases.

Countries undertake mass campaigns mainly to wipe out ("eliminate" in WHO-speak) home-grown or indigenous measles. This was the case with the Latin American countries. Or they may do it to nip imminent measles outbreaks in the bud, which was what convinced the UK to take the campaign route. For either reason, they seem to work. Just look at the Americas: 250,000 confirmed cases in 1990 vs. 22,000 in 1994 and less than 3,000 so far (early October) for 1995.

In the UK, health officials noticed in 1994 an ominous increase in measles cases and feared they would be engulfed by an epidemic of about 150,000 cases. At the end of the year they conducted a US$12.5 million campaign (a third of the estimated cost of an epidemic) that immunized six-and-a-half million children aged five to 16 years and, apparently, squelched the epidemic: between January and April this year only 35 cases were confirmed in England and Wales. The campaign, according to a report by health authorities, "interrupted measles transmission and may also have stopped circulation of the virus throughout the population."

Note that the success of the campaign strategy has been achieved with the current standard vaccine that requires subcutaneous injection. With a vaccine that could be given by mouth or intranasally or by aerosol life would be easier for anti-measles campaigners, especially in the Third World, and the cost of campaigns would fall (syringes double the cost of the vaccine itself). Hence, the need to speed the development of such a vaccine (see text).

In particular, the test must differentiate measles from other infections that produce a rash, such as dengue and rubella.

Several companies and institutions have submitted to the WHO proposals for test kits. The two most promising kits are based on detection in blood or serum samples of IgM antibodies, which denote current infection with the measles virus. At the end of this year, prototype kits of these tests will be examined by three independent labs and could, Dr Pervikov says, go into field trials in several developing countries early next year.