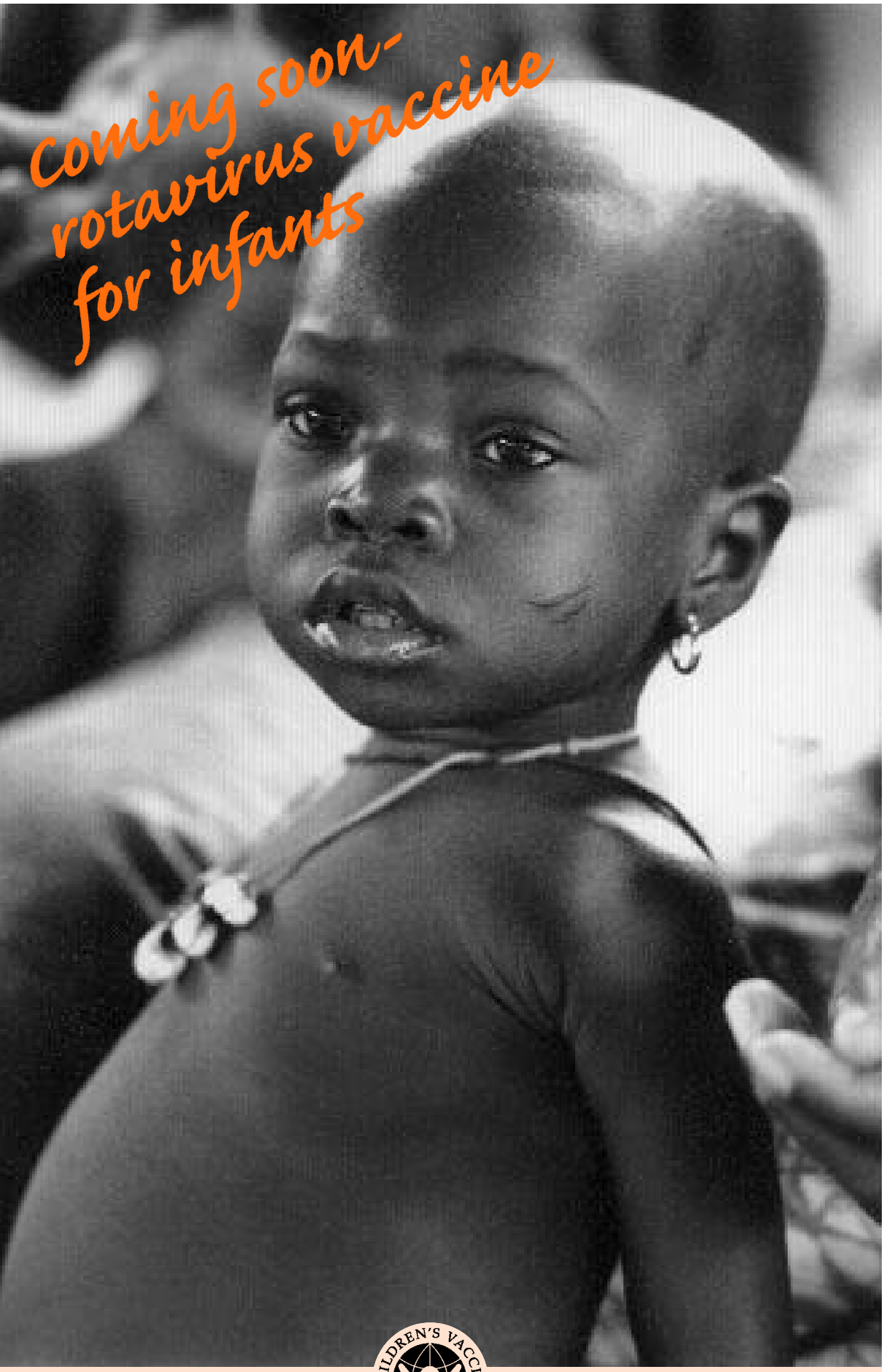
C V I F O R U M

Coming soon- rotavirus vaccine for infants



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CHILDREN'S VACCINE INITIATIVE

A global vaccine for a global disease– an end to rotavirus diarrhoea?

The Children's Vaccine Initiative (CVI) is a coalition of international agencies, national governments, non-governmental organizations, and public- and private-sector vaccine companies. It was established in 19991 to promote,coordinate and accelerate the development and introduction of improved and new vaccines and thereby enhance the protection of the world's children against infectious diseases.

Cover Photo UNICEF/M. Murray-Lee

Every day, on our beautiful blue planet, an estimated 11 million people, mostly children under five, suffer a bout of diarrhoea, 200,000 of them become so severely dehydrated they have to be hospitalized and nearly 7,000 of them die[1]. Every day.

There are many causes of diarrhoea, but the one that accounts for most episodes (up to an estimated 370,000 a day or 134 million a year), hospitalizations (50,000 a day, 18 million a year) and deaths (2,000 a day, 800,000 a year),[2,3,4] is a relatively common, highly contagious, spherical microbe called rotavirus.

Dubbed "the democratic virus" because it infects just about all children by the age of five throughout the world, developing and developed, poor and rich, rotavirus is clearly a major cause of child disease and death– and a costly one: in the U.S. alone it is estimated to be running up an overall bill of about $1.4 billion a year, mostly from hospitalizations.

"There is no question in my mind," says Jong Wook Lee, CVI Executive Secretary, "that we're talking here about a burden of disease that is of staggering proportions and that is just crying out for speedy action."

Roger Glass of the viral gastroenteritis section at the U.S. Centers for Disease Control and Prevention in Atlanta, Georgia, and a world authority on rotavirus agrees, but adds: "Trouble is: most countries, particularly in the developing world, just don't realize they have a problem."

One reason they don't realize it is that, unless you're something of an infectious disease expert, diarrhoea is just diarrhoea, its cause buried in a multiplicity of possible factors. To find rotavirus you have to look for it, in stool samples, for example, and look deliberately–in hospitals, for example, where one child in three with severe diarrhoea will probably be infected with rotavirus.

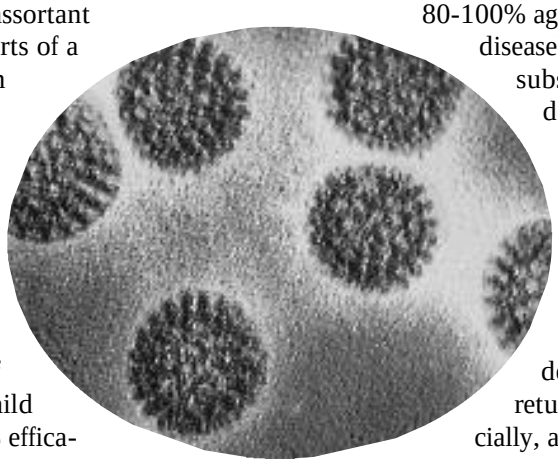
Also, up to very recently, realizing the burden of disease caused by rotavirus may not have mattered all that much. Now, the need to evaluate that burden is becoming urgent because the first rotavirus vaccine could well be on the market next year, if licensing authorities find it safe and effective, and others will surely follow. As Peter Paradiso, senior director of scientific affairs at Wyeth-Lederle Vaccines & Pediatrics (WLVP), the U.S. manufacturer of the vaccine closest to market, says: "We need to get a handle as soon as possible on the likely demand for this vaccine so that we can plan the production capacity that will be needed to meet that demand–and I'm talking about global, not just U.S., demand."

The WLVP vaccine, code name RRV-TV (to be called Rotashield™ in the U.S. and Rotamune™ in the rest of the world), is a live, orally administered "Jennerian" vaccine: that is, it uses an animal virus, or a part of it, to protect people from the human virus, just as 18th century vaccine pioneer Edward Jenner used an animal (cowpox) virus, with immune-stimulating structures (antigens) similar to those of the human smallpox virus, to protect people against smallpox.

In fact, RRV-TV, originally developed by Albert Z. Kapikian and his team at the U.S. National Institutes of Health, is a genetically engineered cocktail vaccine containing a rhesus monkey rotavirus strain, combined (reassorted) with parts of human rotavirus strains. It is a "tetravalent" vaccine, designed to provoke an immune response against the four commonest human rotavirus strains, which account for over 90% of rotavirus disease cases, at least in the western hemisphere. Studies conducted over the past six years in 18,000 children in the U.S., Finland and Venezuela have shown RRV-TV to be safe and effective: three doses given before six months of age prevented severe rotavirus diarrhoea in 70-95% of vaccinated children and all degrees of rotavirus diarrhoea in 48-83%. In January this year,

WLVP submitted its vaccine for regulatory approval to U.S. and European control authorities and hopes to have a decision early next year.

About a year further back on the development path is a vaccine designed by a U.S. research group headed by H Fred Clark, then of the Wistar Institute in Philadelphia, and manufactured by Merck & Co., Inc. This is a live, oral, reassortant vaccine combining parts of a bovine rotavirus strain with part of a human strain. In a U.S. trial in 1992 involving 325 children, a single-strain (monovalent) version of this vaccine showed a 73% protective efficacy against all forms of rotavirus diarrhoea–mild and severe–and 100% efficacy against hospitalization for rotavirus diarrhoea. A recent ten-centre trial, also in the U.S., of a four-strain (tetravalent) version in about 400 children has shown virtually identical efficacy to the monovalent version. So far, no trials have been conducted with this vaccine in a developing country and, according to Merck's Alan Shaw, Senior Director of Virus and Cell Biology, "before going into places where the socioeconomic and sanitation background is less uniform, we want to iron out some minor issues of formulation and do tests here in the States, to get a product that's simple to use and simple to store."



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Rotavirus–the most important cause of diarrhoea worldwide

WLVP's RRV-TV and Merck's tetravalent product are the only two vaccine candidates in the late stages of development and their manufacturers are the only two likely to compete for world demand for a rotavirus vaccine in the immediate future. But second- and third-generation vaccines are in the offing (see Box) and other manufacturers are watching developments.

Stanley Plotkin, Medical and Scientific Director of Pasteur Mérieux-Connaught (PMC), says: "We have nothing on our list at the moment, but would certainly be interested in setting up a programme should the conditions warrant it."

Then there's SmithKline Beecham Biologicals (SKBB), who produced the first rotavirus vaccine, a single, live bovine strain (code name RIT 4237), originally used as a veterinary vaccine. RIT 4237 performed well in trials conducted in the 1980s in Finland (55-62% protective efficacy against all and 80-100% against severe rotavirus disease), but fared poorly in subsequent trials in developing countries and was abandoned. SKBB's Walter Vandersmissen, Director of Government Affairs, says the company is currently debating whether to return to the field, "especially, as current thinking has changed–instead of looking for over 90% efficacy against all rotavirus disease, a vaccine that can protect extremely well against severe and somewhat less well against all disease seems to be more acceptable now, and by those standards our original vaccine was by no means a bad performer, at least in the industrialized setting." If SKBB comes back, though, it is uncertain whether they will want to resuscitate RIT 4237, pepped up perhaps with a bit of modern reassortant technology to ensure its global efficacy, or go straight for a second- or third-generation product.

Nobody claims the two front-runners–the WLVP and the Merck vaccines–are perfect: they don't, for example, prevent rotavirus infection, only disease. And they reach high protective efficacy rates only for severe disease. For sure, only about 7-10% of rotavirus diarrhoea cases are severe, but it is severe disease that accounts for the hospitalizations and deaths caused by this virus. And as the CDC's Dr Glass points out, "It is in its ability to prevent severe disease that a rotavirus vaccine will have a major impact–on child mortality and on health costs."

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Roy Widdus, CVI Coordinator, believes the two near-market vaccines have a lot going for them. In addition to safety and efficacy against severe disease, he says, "if these vaccines perform well in studies currently being planned in a variety of developing country settings, either one of them could be a vaccine for children everywhere, as universal as rotavirus infection is itself." They are both administered orally, are relatively stable and can fit in with existing routine immunization schedules. And three doses given in infancy appear to protect for at least two years–"past the period during which a child is most likely to die from rotavirus disease."

What's more, because it would fulfil a global need, a rotavirus vaccine would be a particularly attractive commercial proposition. Both WLVP and Merck are thinking globally. "We don't right now have the capacity to meet global needs," says WLVP's Dr Paradiso, "but we're thinking along those lines and discussions are under way with the CDC and WHO." Merck's Dr Shaw says the vaccine itself is not all that complicated to produce, but "if we're looking at what is needed for the world's birth cohort of 140 million kids, we're talking about an oil-tanker volume of bulk vaccine–but nothing's impossible."

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Peter Evans, chief of the vaccine supply and quality unit of the WHO's Global Programme for Vaccines and Immunization (GPV), agrees that the potential market for a rotavirus vaccine is huge. But he is concerned about the time–traditionally, over 15 years–it could take for a new vaccine to trickle down from the private industrialized market to the public developing country market.

"With up to three-quarters of a million lives being lost every year because of this virus, it would be a tragedy if we couldn't speed up the sequence for this vaccine. But to do that we have to be asking the right questions now so that those who have to, can make some critical decisions as early in the game as possible."

Decisions, for example, about the price of the vaccine. WLVP and Merck both say it's too early to talk about the ultimate price. But clearly, if the vaccine is going to reach all the children who need it, some kind of differential or tiered pricing system is going to have to be worked out for the poorest countries buying through UNICEF. "Certainly, the market is large and varied enough to support several price levels," says Mr Evans.

Countries will also have to decide whether or not to introduce the vaccine into their routine immunization programmes. How many countries make that decision will depend to a large extent on whether they get

UNICEF/A. Pannirk

Oral administration is a big plus-point of rotavirus vaccines likely to be available soon.

a green light from the GPV's Expanded Programme on Immunization (EPI). The EPI's Mark Kane says: "We are very interested in using this vaccine because we are convinced most developing countries have a major burden of rotavirus disease. But we need more evidence, from different sites, that it will work well against severe disease throughout the developing world."

It is true that only one trial of the RRV-TV vaccine has been conducted in a developing country, Venezuela (but that trial showed it to be 88% effective in preventing severe rotavirus disease). And, as Dr Glass admits, "we may not be able to extrapolate the results of trials in industrialized countries to the developing world because of differences in the epidemiology of the disease." In many parts of the developing world, for example, rotavirus disease does not occur in a distinct seasonal pattern as it does in elsewhere. It also affects younger infants more often and more severely, seems to be caused by a wider variety of rotavirus strains and by a heavier infective dose of virus, and occurs more often with other microbial infections.

However, the GPV's vaccine research and development unit (VRD) is backing several studies in developing countries, starting with Venezuela again (but for effectiveness, as distinct from efficacy, in a "real-world" public health care setting involving some 45,000 children), and also in Bangladesh, China, India and Indonesia. Further studies will also determine the distribution of rotavirus strains in many parts of Africa, the Americas, Asia and Europe.

But for health policy makers in a developing country pondering whether they need a rotavirus vaccine, perhaps the most critical issue is just how big a toll–in deaths, disease and medical costs–rotavirus is exacting. Studies on rotavirus disease burden are therefore being planned for several countries, including China and Guinea-Bissau. Already India has a fully-functioning rotavirus surveillance system in five cities, another is starting business in South Africa, and yet another in South America, including Argentine, Brazil and Chile.

Officials will, of course, also want to know how cost-effective a rotavirus vaccine would be. This will depend on a country's disease burden, the effectiveness of the vaccine and its price. CVI analyst Mark Miller estimates that a rotavirus vaccine with a 60-85% protective efficacy rate could prevent 470,000 deaths annually, 350,000 of them in low-income countries alone. If the vaccine ultimately cost $1 a dose for the neediest countries and had a 60% efficacy rate, it would, Dr Miller estimates, prevent a death for less than $1,500, which "would be a good public health buy," he says, "for countries that could afford the vaccine."

"Fine," some hesitant officials may ask, "but to what extent do existing control measures, such as oral rehydration salts (ORS), and public health measures to provide clean water, to improve sanitation and to promote breast-feeding, obviate the need for a vaccine?" Not at all, according to the evidence. For one thing, ORS is a treatment, not a prevention, and does nothing to reduce the incidence of rotavirus disease in a country. For another, public health measures have "failed to achieve the anticipated gains," according to one report[5] (although they might not be expected to do so, since rotavirus infection is as prevalent in industrialized as in developing countries).

One hurdle a rotavirus vaccine may have to overcome is earning public support. Since rotavirus is only one, albeit the most important, of many causes of diarrhoea, and since the vaccine, at least the first generation versions, will not prevent all rotavirus diarrhoeas, parents may not notice much impact from vaccinating their children. WLVP's Dr Paradiso doesn't think this is a problem. "We've entered an era where a vaccine doesn't necessarily prevent all the causes of a disease. Take the vaccine against *Haemophilus influenzae* type b, which prevents only one cause of meningitis and pneumonia. I think parents will see the rotavirus vaccine's impact in saving their infants under two years of age. But it mustn't be presented as an anti-diarrhoeal vaccine–rather as a rotavirus vaccine that will keep kids out of hospital or from dying."

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"A rotavirus vaccine with a 60-85% protective efficacy rate could prevent 470,000 deaths annually, 350,000 of them in low-income countries alone."

Dr Glass believes that "health officials, hospitals, paediatricians are likely to see a 30% fall in hospitalizations for severe diarrhoea and a decrease in deaths as well. Clearly, this vaccine will have a tremendous impact as a public health tool and public health officials are bound to notice the difference within one-to-two years."

For the CVI's Dr Lee "the important thing now is to anticipate what information is still lacking, to marshal that information quickly and to make it available to those who have to make the critical decisions prior to adoption of the vaccine in developing countries. The momentum is there. We mustn't let it falter."

[1] The World Health Report 1997.
[2] R.I. Glass et al., *Science*, *272*: 46-48, 1996.
[3] R.I. Glass et al., *Science*, *265*: 1389-1391, 1994.
[4] Institute of Medicine, *Prospects for immunizing against rotavirus*, p. 308-318, *in* New vaccine development. Vol. 2, National Academy Press, Washington, D.C., 1986.
[5] *Current Status and Future Priorities for Rotavirus Vaccine Development, Evaluation and Implementation in Developing Countries*, CDC, Atlanta, Georgia, USA, 1996 (unpublished).

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Rotavirus vaccines of the future

About a dozen research groups are working on vaccines that may improve on the first-generation versions about to hit the market.

Some of the newer candidate vaccines emerging from this work have entered human trials, for example:

- In Australia, a team at the Royal Children's Hospital working under Ruth Bishop, discoverer of the rotavirus, have started early human trials on a vaccine based on a so-called "nursery" strain derived from a newborn baby (neonates infected with rotavirus generally do not come down later with rotavirus disease, suggesting that the strains infecting the neonates are provoking immunity that protects them against subsequent disease).
- Another human strain vaccine, code-named 89-12, is being tested for safety, immunogenicity and optimal dosage by a team under Dale Spriggs at the Virus Research Institute, a U.S. biotech firm in Cambridge, Massachusetts. A study of a cohort of children naturally infected with this strain showed that it conferred 100% protection against subsequent rotavirus disease in these children.
- A team headed by Albert Z. Kapikian at the U.S. National Institutes of Health, in Bethesda, Maryland, in collaboration with the University of Rochester, has started human trials with a candidate vaccine made of a mutant human rotavirus strain that is "cold-adapted" and "temperature-sensitive," i.e. it grows in cold temperatures and ceases functioning at 38°C.
- In China, a group headed by Bai Zhi-Sheng at the Institute of Biomedical Products in Lanzhou is testing for safety and immune-stimulating capacity (immunogenicity) in infants a live oral vaccine, code-named LLR, that uses a lamb rotavirus strain.
- The Biken Institute, at Osaka University's Research Foundation for Microbial Diseases in Japan, is backing the development of a candidate vaccine, code-named BIRVI, by Osamu Nakagomi of the Akita University School of Medicine. This vaccine would be chemically inactivated and administered by injection.

Other approaches to making a rotavirus vaccine are being explored–still in laboratory animals–that use, for example:

- "virus-like particles" (VLPs)–clumps of different rotavirus protein molecules that form when the genes encoding them are cloned in an insect virus called baculovirus to produce a nonliving or "subunit" rotavirus vaccine; these VLPs look exactly like rotavirus particles but carry no genetic instructions;
- a live microbe, harmless to humans, such as an animal species of *Salmonella* or the vaccinia (cowpox) virus, used as a vector to carry immunogenic rotavirus molecules;
- the so-called naked DNA technique, whereby rotavirus genes coding for immunogenic rotavirus proteins, produce ("express") these proteins within an animal (or human) host when the genes are administered to the host;
- plants carrying rotavirus genes encoding rotavirus proteins: when the plants are eaten by a child, say, the genes make proteins (antigens) in the child's body that induce it to mount a protective immune response against subsequent disease;
- microcapsules containing rotavirus antigens: the microcapsules are delivered orally or by injection and release the antigens according to a pre-programmed schedule.

A plan for immediate action, a vision for the future

In April this year, the CVI's task force on strategic planning met in Geneva to update the "strategic plan" first drafted in 1992-93 as a blueprint for the activities of the international vaccine community working together as the "CVI coalition." In the interview below, task force chairman John La Montagne talks about some of the key points that have emerged from the task force's year-long work and how he sees the CVI's "unique role" in the vaccine community. As director of the Microbiology and Infectious Diseases Programme at the National Institute of Allergy & Infectious Diseases, part of the U.S. National Institutes of Health, in Bethesda, Maryland, Dr La Montagne oversees a budget of $350 million, of which about $120 million for vaccine research.

Q When the CVI was created at the time of the 1990 World Summit for Children there was much talk of its visionary goal–high-quality vaccines accessible to all the world's children, protecting them against all the major infectious diseases and administrable in one or two, preferably oral, doses. In your discussions, was that vision still before your eyes?

A It certainly was. The vision is definitely still there. But clearly it's going to take a long time to realize it. The CVI was created at a time when everyone was basking in the achievements of immunization programmes that had raised vaccine coverage from 3% to around 80% in the space of 15 years. But the vaccines delivered by those programmes–against polio, tetanus, measles, tuberculosis, pertussis, diphtheria–were based on simple concepts and were relatively easy to produce. Today's vaccines are much more complex and tomorrow's are likely to be even more so.

Q And even more expensive?

A Yes, but still extremely cost-effective relative to the huge public health benefits they're going to bring. Because there is no doubt about it, these new vaccines are ushering in a new age, in which prevention of disease on a vast scale is closer than ever to being achieved. But it's going to take a lot of resources. And it will take place over a number of stages. Our job over the past two days was to bring the CVI's strategic plan up to date in relation to the stage we've reached today and pinpoint what can and should be done to move the field forward over the next 10- to 15-year stage.

Q More precisely...

A Well, we endorsed the crucial contribution the CVI has been making to work in such areas as improving the quality of vaccines being produced throughout the world, the management of the world's vaccine supply and its financing for poor countries, the selective promotion of local vaccine production where viable, raising the awareness of vaccines as the best health buys you can get, and making vigorous efforts to get the newer vaccines widely introduced as quickly as possible, while pushing ahead with the development of the multi-disease, few-dose vaccines of the future. All those activities have to continue.

NIAID

John La Montagne

Q Did you identify any specific targets?

A We set the year 2005 as the deadline for getting four already licensed but still under-utilized vaccines into wide use–those against *Haemophilus influenzae* type b or Hib, hepatitis B, rubella and measles. And by wide use, we mean at least up to the 80% coverage level of the traditional vaccines. Achieving that goal would save an estimated 2.9 million lives a year. If you add three vaccines that are just around the corner to prevent another

"Without the CVI, you'd have a far less efficient, a far less dynamic vaccine community."

three diseases–rotavirus diarrhoea (see pages 2-6), pneumococcal pneumonia and meningococcal meningitis–you would save a further two million lives.

Q *How realistic are those targets?*

A They are attainable–not without difficulty, though. Not enough is known, for example, about the extent of Hib disease in South-East Asia, but what evidence there is suggests that this vaccine could almost wipe out Hib pneumonia in developing countries–and that may be as much as one fifth of all types of pneumonia–as it has wiped out Hib meningitis in the industrialized world.

"With the tools we now have plus those we're about to get, we will never have been in such a strong position in our endless confrontation with infectious diseases."

Q *Talking of the industrialized world, there has been criticism voiced that the CVI is solely interested in the developing world. How does the task force view this issue?*

A We specifically stressed that the CVI should not devote its efforts exclusively to developing countries. There are vaccine problems in industrialized countries. Vaccine coverage, for example, is not what it should be in, say, Australia, Germany, Italy, Japan and the United States. Part of the problem is that people's fears about side-effects of vaccination increase as the diseases they are preventing fall in incidence. On the other hand, the advent of vaccines with fewer side-effects, like the new acellular pertussis vaccines, does a lot to allay these fears. But helping to sustain vaccine coverage rates throughout the whole world should now, we insisted, be part of the CVI agenda.

Q *Isn't that putting too much on the CVI's plate?*

A Not really. The CVI's unique strength has been in acting as a neutral arbiter or prod among the different segments of the vaccine continuum–research and development, production, quality control and regulatory functions, introduction and use in the community, analysis of impact. Applying that strength to activities and targets affecting the whole world, developing and developed, is really an integral part of the CVI's mandate, not an added-on task.

Q *What about the CVI's weaknesses? Are there any?*

A Yes, and we talked about one at the meeting. The CVI has not been doing such a good job in actively getting across its unique identity, although that identity is now coming across much more strongly as the CVI's activities are beginning to make a visible impact.

Q *How do you see that identity?*

A The CVI is a lubricant that keeps the world's vaccine machine–the immunization programmes, the research and development process, the financing mechanisms, and so on–working smoothly in synergism. A lubricant, let's say, laced with a stimulant to give it some pep. Without a lubricant, your machine can't function. Without the CVI, you'd have, well, a far less efficient, a far less dynamic vaccine community. The research community and public immunization programmes and private industry, for example, would still be dancing their polite minuets in public without really joining hands to move the whole field forward. I for one am convinced that if the five organizations that founded the CVI had not done so–and remember they did it out of a clearly perceived need–we wouldn't be where we are today.

Q *Just where are we today?*

A We're at a real turning point. With the tools we now have plus those we're about to get, we will never have been in such a strong position in our endless confrontation with infectious diseases. And we're fortunate, in two major respects. First, vaccines are gaining increasing public support, thanks to the threat of emerging infections. That threat–plus the alarming spread of antibiotic-resistant strains of micro-organisms–is forcing people to see that infectious diseases have not gone away. That the big battle has still to be fought. And second, we're at a real turning point in vaccine development. Biology is producing an incredible amount of information at an almost exponentially growing pace. The genes of an increasing number of disease-causing microbes are being sequenced as we sit here. And this work is being applied to the design of new vaccines. Never before have we had such an array of vaccine candidates–something like 240 are in the research and development pipeline, versus 160 or so three years ago. More and more people are entering the field. Never before has there been such a need for coordination and cohesion among the many players of the CVI coalition. This is the role the CVI was set up to play, with its secretariat at the hub of the myriad activities being pursued throughout the coalition as it moves forward into the twenty-first century.

A public-private handshake promises new vaccines for the world

A meeting "to find common ground between the public and private sectors in order to ensure the global supply of new vaccines" might have been expected to indulge in mere wishful thinking. Although this was the topic of the meeting organized in February by the CVI and the Rockefeller Foundation at the Foundation's conference centre in Bellagio, at the tip of Lake Como in North Italy, the result "was a surprise–refreshing, stimulating, vital, a real watershed meeting," according to one participant. Mr Jacques-François Martin, chief executive officer of Biocine SARL, the French branch of Chiron Vaccines, and at the time chairman of the Biologicals Committee of the International Federation of Pharmaceutical Manufacturers Associations, puts it this way: "This was the first meeting I've ever attended where the whole range of issues related to vaccine supply was addressed. It was also exceptional in the breadth of consensus that we achieved in our analysis of the strengths and weakness of the vaccine supply system. This meeting really gave a jump-start to that system."

Rockefeller Foundation

"A place for taking stock…"

For Dr Jong Wook Lee, CVI Executive Secretary and Director of the WHO's Global Programme for Vaccines and Immunization (GPV), the meeting produced "a new relationship between the public and private sectors. Both sides realized it could be possible to help each other, with each achieving its own goals. The wall between the two has crumbled and a continuous discussion has started."

What happened?

Well, for one thing, as Dr Lee said in his opening speech, the meeting had "the right people in the right place at the right time."

Start with the place: "Cut off from the world outside," said Dr Lee, "it was a place where we could take stock of a subject that has been evolving rapidly over the past few years." (see *CVI FORUM* No. 11, October 1995, *Public sector, private sector, discord or dialogue?)*

The time? "We had been accumulating all the bits and pieces of a public-private sector relationship," says Ms Amie Batson of the GPV's Vaccine Supply and Quality (VSQ) unit. "There was the creation of the CVI in 1990, the WHO-UNICEF analysis of the vaccine industry in 1993, and more recently a new UNICEF tender and procurement strategy targeted to countries in relation to their wealth and size. Clearly, the time was ripe to pull all these pieces together to produce a bedrock, a solid foundation, on which we could go forward together."

And the people? About 30 individuals from key and in some ways very disparate professions–private and public sector vaccine manufacturers, biotechnicians, public health leaders, international health and development officials and experts, scientists, technology transfer experts, lawyers, licensing and international trade experts and officials, and market analysts. "What made things click," says Ms Batson, "was the catalysing, refreshingly enthusiastic presence of some faces quite new to the usual health and development circles–people from the legal world, from the technology transfer community, from academia."

The meeting was also unusual in addressing not just generalities but some concrete issues.

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Issues like: If a vaccine is identified that would be valuable for what is seen as only a limited market, how could it be taken through the development process and made available to those who need it? Or how to make a vaccine with a complex intellectual property structure more accessible to the public sector. Or how to bolster the commitment of countries that have signed the World Trade Organization's Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS)–which the meeting unanimously agreed are essential to a productive public health-industry relationship.

The three-and-a-half day discussions culminated in a ten-point call for:

▶ Greater use of the UNICEF-WHO system that groups countries according to their wealth and size: with this "banding" system, assistance is targeted only to those countries in greatest need, which account for about a quarter of the world's child population, leaving market forces to operate in the rest of the world wherever they function effectively.

▶ A coherent system of managing intellectual property rights, such that their value in stimulating innovation is appreciated, that they are legally respected throughout the world and that the risk of their hampering access to new technologies is minimized by an appropriate technology licensing system.

▶ Ways to be sought whereby the few local vaccine producers in developing countries likely to seek entry into the global vaccine market might access new technologies.

▶ An unrelenting effort to ensure that vaccines are of the highest quality–essentially, by ensuring that every vaccine-producing country has a fully functioning national control authority.

▶ Earlier forecasting of vaccine demand.

▶ Greater efforts to get the vaccines that are available but not being fully used, such as those against *Haemophilus influenzae* type b (Hib), hepatitis B and yellow fever, adopted much more widely.

▶ Communication, economic impact studies, enlistment of donor and government backing, and other activities aimed at motivating manufacturers to develop vaccines against diseases, like dengue haemorrhagic fever, that are public health problems in a number of developing countries but do not as yet offer commercially attractive markets.

▶ Greater advocacy to convince public health policy makers that vaccines–including the more expensive new vaccines–are the best buys among health tools.

▶ A bigger pool of funds for the purchase of these and upcoming vaccines.

Overall, the meeting seems to have set the scene for a more proactive role for the CVI. "We all agreed," said Mr Martin, "that with the traditional vaccines, we've done the easiest part of the job. For the new vaccines, we're going to need a tenfold greater effort. Can the CVI muster that kind of effort and the resources it will call for? As far as we in industry are concerned, now that we are accepted as credible partners, we are ready to play a major role, within the CVI, to find the necessary resources."

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Hib and pneumococcal vaccines: keeping up the momentum

Most people believe the CVI's unique strength lies in its ability to get the right people from the most diverse parts of the vaccine world to work together efficiently on specific goals. One of the toughest testing grounds for this talent is trying to get new vaccines as quickly as possible into the world's routine immunization programmes.

At a meeting in Geneva in March, the CVI brought 30 experts together to take stock of progress in introducing two recently developed so-called conjugate vaccines–one licensed, the other in a late stage of development–and devise ways of speeding things up. The two vaccines are those against *Haemophilus influenzae* type b (Hib) and *Streptococcus pneumoniae* (pneumococcus)–for which the CVI and its partners have drafted "introduction agendas." (For more details on the Hib conjugate vaccine, see *CVI FORUM* No. 12, August 1996, pages 2-9, and on the pneumococcal conjugate vaccines,

CVI FORUM No. 13, December 1996, pages 2-11, and 15). The meeting reviewed and updated key elements of these agendas.

On introducing the Hib conjugate vaccine, the participants agreed on these points:

▶ Knowing just how heavy a burden Hib is putting on countries is the perhaps the most pressing need–and a prerequisite to estimating world demand for the vaccine. Information about the Hib disease burden is available for much of the western hemisphere, Africa and the Middle East, but is lacking in Eastern Europe, the Newly Independent States (of the ex-Soviet Union) and Asia.

▶ One obstacle to wide adoption of the vaccine by some countries will be its price, and innovative tiered pricing mechanisms will have to be found to overcome it. Studies on potential cost-saving strategies–such as lower doses or cheaper dose regimens, or less potent vaccines–should be pursued as a longer-term approach.

▶ Showing how cost-effective the Hib vaccine could be–saving a year of healthy life at $50, according to one CVI estimate–is critical to convincing countries to adopt the vaccine.

▶ World capacity for producing Hib vaccine could not, today, meet the needs of the 140 million "new" children entering the world each year. Accurate projections of demand for the vaccine will therefore be needed to enable industry to plan its production capacity.

▶ Countries adopting or starting to think about adopting the Hib vaccine in their routine immunization programmes should be monitored to find out what influences their decision and what impact the vaccine has on the disease burden and on existing immunization programmes.

▶ The CVI should hold a series of regional meetings to air problems and devise regional strategies.

On introducing a pneumococcal conjugate vaccine, the meeting highlighted these points:

▶ Studies of pneumococcal disease burden are needed and should look, among other things, at the role of microbial drug resistance and infection with HIV, the AIDS virus, and the extent of adult pneumococcal disease in developing countries.

▶ The best way to determine the burden of pneumococcal pneumonia may be by using the vaccine as a probe in an efficacy study, as the Hib vaccine was in a trial in the Gambia (see *The Lancet*, April 26, 1997, pages 1191-1197). In other words, since the vaccine is designed to prevent only pneumococcal disease, the extent to which it prevents all pneumonia will give an indication of the proportion of all pneumonia due to the pneumococcus.

▶ Immunizing pregnant women to protect their offspring against pneumococcal disease is difficult but doable–witness neonatal tetanus vaccination, which now reaches about two-thirds of women worldwide–but has so far not been studied for protective effectiveness in the field. Further studies should be conducted on this approach.

▶ For countries wishing to introduce the vaccine and determine its impact, a standard protocol should be designed that would call, among other things, for the collection of information about the possible effect of vaccination on asymptomatic carriage of the pneumococcus and changes in the respective prevalence of different strains (serotypes) of the organism.

▶ To shorten the traditional time sequence of new vaccine adoption–starting with industrialized and "trickling down" over subsequent years or even decades to developing countries–early decisions should be made about price tiering and other financial mechanisms, funding assistance to the poorest countries, and long-term forecasting of global needs that would enable industry to plan production capacity.

▶ Better diagnostic tests are needed, as are "surrogate markers" of protection–such as antibody levels in the blood–that indicate whether a vaccinated person is in fact protected against infection.

Showing how cost-effective the Hib vaccine could be—saving a year of healthy life at $50, according to one CVI estimate—is critical to convincing countries to adopt the vaccine.

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Future Meetings

Pertussis in the adult

28-29 October, 1997, National Institutes of Health, Bethesda, MD, USA

This symposium is organized by John Robbins of the U.S. National Institutes of Health in Bethesda and James Cherry of the University of California School of Medicine in Los Angeles. Participants will explore the possibility of eliminating pertussis in the U.S. by including the new, safer acellular pertussis vaccines in immunization programmes for adults (as well as for children). The adult population now constitutes a major reservoir for the causative organism, *Bordetella pertussis*, and thereby contributes to its transmission among children and adolescents.

For further information: tel: +1.301/4960850; fax: +1.301/4964757.

CVI Consultative Group Meeting 1998

The CVI would welcome offers to host the 7th meeting of its Consultative Group at the end of 1998 (possibly in November). This meeting brings together about 200 representatives of the international vaccine community to assess progress and plan future directions in the attainment of the CVI's objectives.

Contact: Ms Molly Abruzzese, CVI.

Announcement

NIBSC annual report

Copies of the latest (1995-96) annual report of the UK National Institute for Biological Standards and Control (NIBSC) are available free of charge from the CVI Secretariat. The report summarizes the work of the NIBSC during the biennium, highlights recent scientific achievements of its staff members and illustrates the contribution the Institute makes to securing high national and international standards of quality, safety and efficacy of vaccines and other biological substances used in medicine.

PICTURE POSTSCRIPT

UNICEF/Jeremy Hartley

"What's rrotavirus?" (see pages 2-6)