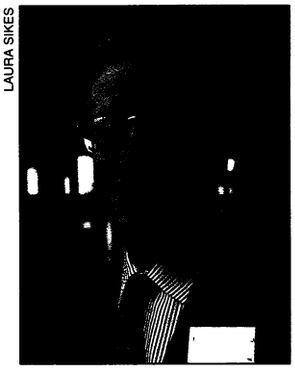
agency; and developing a National Vaccine Plan to establish priorities for vaccine research, distribution, and use.

The National Vaccine Plan, finally released this March, has underwhelmed vaccine researchers. Even those who helped draw up the plan concede its limitations. "It's not earth-shattering. It's obvious. But at least we have a plan. We know, for instance, that by 1996, we want more than 90% of our kids to be vaccinated. We've anticipated the problems, and we know some of the ways around them," says Barry Bloom of the Albert Einstein College of Medicine in New York City, a member of the NVP advisory committee that helped develop the plan.

The problems of the NVP, however, go deeper than the indifferent reception its plan is receiving. Robbins points out that NVP has "very little authority" over the agencies it is supposed to coordinate. As an HHS office, NVP has no jurisdiction over DOD or USAID; the agencies that are within HHS are loath to surrender turf. Walter Orenstein, director of the National Immunization Program for CDC, expresses his agency's attitude: "NVP should not be playing a true program implementation role; that should be at the agency level."

With little money and less clout, all NVP has to offer is a neutral arena in which government agencies and industry can discuss vaccine issues. "Providing a forum for discussion, as innocuous as it sounds, has been quite useful," says John La Montagne, director of the division of microbiology and infectious diseases at the National Institute of Allergy and Infectious Diseases. He cites NVP's report on the 1989–90 measles epidemic as an example of consensus reached through NVP. That report identified several factors behind the measles outbreak, including a low vaccination rate among children under 2 years of age and a 5% failure rate among those who did receive the vaccine; the report recommended immediate measures to improve the effectiveness of measles vaccination. Despite some successes, La Montagne says, it may be "time for NVP to fade out."



LAURA SIKES

And fade it could. For the past 2 years, Congress has put NVP's discretionary fund of about $6 million in the hands of CDC. So far, CDC has had to consult NVP on how to spend the money. This year, however, Congress may change that consultative relationship and allow CDC to swallow up NVP. On 19 July, an amendment to the U.S. Senate Labor, Health and Human Services, and Education appropriations bill proposing transfer of 30 of NVP's 35 staff to CDC was passed by the appropriations committee. The committee clearly intends NVP "to be put out of business," says Robbins.

Even if NVP hasn't been the answer to problems in national vaccine policy, most experts say a coordinating body is needed. "If the U.S. is going to have a really good immunization program, without gaps in it, it needs such a group," insists Douglas. In 1993, an Institute of Medicine (IOM) committee on the Children's Vaccine Initiative, the international drive to improve childhood immunizations (see story on this page), recommended forming a meatier organization: a "National Vaccine Authority," or NVA, with a budget of $55 million to $75 million per year. Besides coordinating academic, government, and industrial vaccine efforts, NVA would conduct vaccine research, development, and pilot production. The IOM, however, failed to say how NVA would be funded or where in the federal hierarchy it might be located. The proposal has gone nowhere.

Roy Widdus, a full-time consultant to NVP, says that if what is wanted is a truly national program to "meet international and domestic public health needs, the only place it could sit is in the White House." But that powerful location also poses problems, says Widdus, because "it is too far removed from implementation of programs at the agency level." Vaccine expert Bloom suggests another possibility: transforming NVP's advisory committee into a National Vaccine Commission (see Policy Forum on p. 1378). Such a move, he argues, has the advantage of creating a body independent of government, while including experts from the major federal agencies, as well as industry researchers, health-care providers, and health economists.

"NVP was a very good idea, but I don't think it seized the opportunity it had."

—R. Gordon Douglas

These widely varying ideas about what form national policy leadership on vaccine research and distribution should take belie consensus on one point: Almost everyone in the field agrees that until there is a robust body responsible for setting U.S. national vaccine policy, one of the best creations of medical research—the vaccine—will continue to be underutilized.

–Rachel Nowak

DEVELOPING COUNTRIES

Childrens' Vaccine Initiative Stumbles

Vaccine researchers call it the Holy Grail of childrens' health. The quest for the Grail began 4 years ago when the biggest international agencies in the vaccine field set out to develop a "supervaccine" that could protect the world's children against all major childhood diseases in a single dose. "The fundamental idea was so good" that most vaccine researchers rallied to the cause immediately, says Philip Russell, a Johns Hopkins University vaccinologist. The Children's Vaccine Initiative (CVI) was launched in 1990 to great fanfare from world leaders, donors, and eminent scientists at the World Summit for Children in New York.

Underlying the fanfare was the hope of resolving one of the most serious problems in public health: the deaths, every year, of more than 2 million children from measles, *Haemophilus influenzae*, and other diseases that could be prevented by vaccination. The reason for the toll is that at least one child in five—including many U.S. children under age 2—is not fully vaccinated. That was plenty of motivation to begin the quest for the vaccinologists' Holy Grail. Yet 4 years later, the CVI has produced little in the way of tangible results.

So far, CVI has raised less than $10 million of the estimated $300 million needed by the year 2000 to catalyze research and development for new and improved childrens' vaccines, with the ultimate goal of producing a supervaccine. Since its inception, insiders say, CVI has lacked a strong leader; sponsors and donor agencies have squabbled over how much should be spent on research and over who should be in charge. Muddling the picture further, the U.S. government, which should be a key player, has provided little leadership. Supporters of the initiative are hopeful, however, that the infighting is dying down, and CVI may soon gather momentum.

The initiative was launched to combat the fundamental problem that prevents vaccines from reaching millions of children around the world. To provide protection against measles, tetanus, pertussis, diphtheria, tuberculosis, and polio, health-care workers must vaccinate a child at least six times during the first 2 years of life, which is impossible in most developing countries. To make matters worse, many vaccines require refrigeration and must be administered by injec-

tion, both difficult to achieve in poor countries.

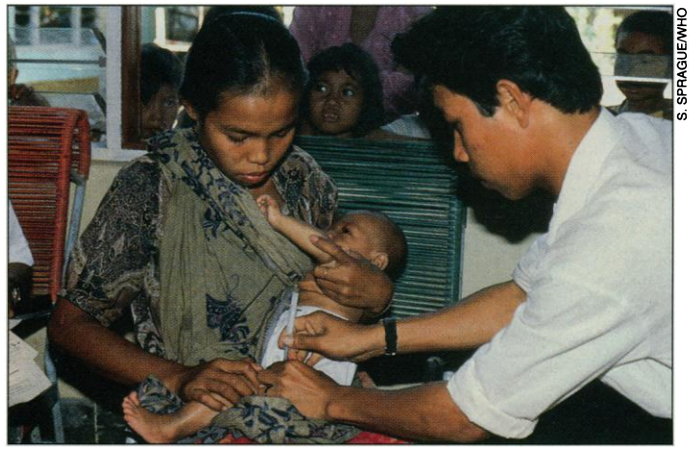
To CVI's backers, the solution is a preparation that combines as many vaccines as possible into one shot or oral dose to be administered shortly after birth. Ideally, the preparation would be cheap and would last a week without refrigeration. "Obviously, this is a goal that is difficult to achieve—maybe even impossible, like the Holy Grail," says Stanley Plotkin, a vaccinologist who is medical and scientific director of Pasteur-Mérieux Connaught Laboratories in Paris. Yet there was no shortage of knights errant, and the CVI was launched in an atmosphere of high hope by the United Nations Children's Fund (UNICEF), the United Nations Development Project, the Rockefeller Foundation, the World Bank, and the World Health Organization (WHO).

But the quest wasn't made any easier by the squabbling that broke out soon after CVI was launched over how much funding should be devoted to research. When so many children in the world don't get today's vaccines, some argued, why should funding agencies spend scarce dollars developing tomorrow's vaccines? Experts in the field say that point of view has been argued most strongly by UNICEF, the U.S. Agency for International Development (USAID), and some WHO administrators, including Ralph Henderson, assistant director-general of WHO, who was director of WHO's Expanded Programme on Immunization (EPI). Henderson told *Science*: "I had been generally opposed to research within EPI in its initial stages because I felt our main issue was to apply existing knowledge, not to generate new knowledge."

That view seems short-sighted to some CVI advisers, including Russell, and to D. A. Henderson, a senior science adviser to the U.S. Public Health Service who led WHO's successful campaign to eradicate smallpox in the 1970s. This group says research is badly needed on which new vaccines should be developed first; how they can be made; and how to combine them, deliver them, and monitor their quality in the developing world. Says D.A. Henderson: "Research into quality control and production is hard to fund. These are not sexy, Nobel Prize problems. But they are critical to the success of CVI." The drug companies cannot be relied on to carry out this kind of research, say insiders in the field, because there's too little profit in it (see story on p. 1371).

While the debate over funding research raged, there was "an endless contest" between WHO, UNICEF, and the Rockefeller Foundation about whether WHO should take control of the CVI, says Russell. In a bureaucratic stalemate, Russell and others say, neither WHO nor UNICEF wanted to take the lead—but neither wanted to see the other in charge. Worse, no agency put a strong leader at CVI or threw its weight behind fund raising. Potential donors were lost; the result "was a tragedy," says Russell.

The tragedy wasn't alleviated by policy shifts in the United States. Vaccine development has always proceeded according to a "two-tiered" system in which profits on vaccines in the industrialized countries subsidize research and distribution in developing countries. Last year, Congress and the Clinton Administration inadvertently dealt a major blow to CVI when a bill was passed requiring the U.S. Centers for Disease Control and Prevention (CDC) to buy vaccines at reduced prices for American children whose vaccines are not covered by health insurance. By cutting profits, this measure could reduce the private sector's incentive to conduct research on new children's vaccines for developing countries. Lederle-Praxis Biologicals president Ronald J. Saldarini claims the new program "absolutely threatens" CVI's goals.



S. SPRAGUE/WHO

Making a point. An indonesian infant is vaccinated against Hepatitis B, but globally more than one in five young children are not fully vaccinated.

U.S. policies have also hurt CVI more directly: So far, the U.S. government has contributed little cash to the global CVI effort, supporting only efforts to immunize children with existing vaccines. In addition, there has been a vaccine policy vacuum in the United States. An Institute of Medicine report concluded last year that "the absence of a domestic strategy has, in the committee's judgment, impeded full U.S. participation in the CVI."

But that gloomy picture might soon brighten. As *Science* went to press, representatives of U.S. agencies responsible for vaccines were planning to meet in Washington, D.C., in August to develop a national strategy for CVI. On the international front, CVI has received a boost from a reorganization of WHO in April. Three divisions involved with vaccines were merged into a new Global Programme for Vaccines (GPV), which was given responsibility for the global CVI. At the same time, WHO selected a new director for both GPV and CVI—Korean physician Jong Wook Lee, who says CVI is "top priority."

Scientists inside and outside WHO say they are hopeful this will be a turning point for CVI. Specifically, it could be a turn toward a more realistic view of the Holy Grail, since CVI's backers say they have decided to work toward a supervaccine in small steps. According to Barry Bloom of the Albert Einstein College of Medicine in New York City, a more practical goal for the end of the decade is to develop an arsenal of new vaccines that can be given to children in a several ways—for example, in shots, nasal sprays, pills including antigens that dissolve at different rates, and, eventually, by ingesting or being injected with naked DNA.

Even those steps pose scientific challenges. No one knows, for example, how many antigens a baby's immune system can handle in one shot. There are also challenges in adjusting the doses of different antigens so that an immune response doesn't wipe out the other antigens before they confer immunity. What is more, some antigens are less stable than others, requiring different bases of sugar and proteins to make them last without refrigeration, according to Francis Andre, vice president and director of medical and scientific services for Smithkline Beecham Biologicals in Brussels, Belgium.

Despite those scientific obstacles, some new combinations of existing vaccines are emerging. Pasteur-Mérieux is selling a vaccine in Europe that uses DTP (the diphtheria, tetanus toxoid, and pertussis vaccine) as a base and mixes in the inactivated polio vaccine; Smithkline Beecham Biologicals has completed clinical trials in Europe of a vaccine that marries DTP with hepatitis B; and Lederle-Praxis Biologicals in New Jersey is selling a DTP vaccine in the United States combined with a vaccine against *Haemophilus influenzae*.

Developments like these, along with the fact that CVI, even in its underachiever mode, has managed to focus attention on the need for new children's vaccines, give CVI backers a sense that they can succeed, if only because "we're stubborn and persistent and right," says Russell. But it remains to be seen whether that combination of qualities will be enough to move the quest for the Holy Grail of childrens' vaccines forward, even in small, cautious, realistic steps.

–Ann Gibbons