Bumps on the Vaccine Road

Science surveyed a large sample of the world's top vaccine researchers, who told us lack of leadership, funding, and tough scientific problems are slowing the vaccine search

Science's "Frontiers in Medicine" section on vaccines begins on this page. The section, a combined effort of the Editorial and News departments, focuses on the scientific and technological issues involved in making vaccines as well as on the political and economic obstacles that are preventing more rapid vaccine development.

A decade ago, the Institute of Medicine (IOM) set up a committee to decide which vaccines the world needed most desperately. Topping the list were vaccines against malaria, the respiratory illnesses caused by *Streptococcus pneumoniae* and respiratory syncytial virus (RSV), and the severe diarrhea caused by rotavirus and *Shigella*—all major killers in developing countries. At the time, there was great optimism that government and industry could pool their resources and quickly develop vaccines against at least some of these threats. Indeed, the IOM committee selected the vaccines on its priority list in part because "success was reasonably foreseeable within the next decade" for each of them.

Vaccine researchers have had their triumphs in recent years, but a decade after the IOM report, there are no effective vaccines for any of the major killers the IOM focused on. "We didn't live up to what the IOM said we could do," laments Boston University's Anthony Robbins, a veteran vaccine advocate who currently is the director-designate of the U.S. government's National Vaccine Program Office (NVPO). Not only that, the search for a vaccine against AIDS, which was just emerging as an important public health threat a decade ago, has been dogged by frustration (see p. 1373), as has the hunt for an improved tuberculosis vaccine.

Why have these vaccines remained so stubbornly out of reach? To find out, *Science* surveyed an international sample of more than 100 of the field's leading researchers, public health officials, and manufacturers. All told, 67 people from 18 countries on six continents responded. And when it came to describing the obstacles that hinder vaccine development, the respondents—be they from Russia, Indonesia, Egypt, Europe, India, or Brazil—had remarkably similar views. The scientific unknowns are the highest hurdles, they said, but they also stressed that the field lacks the strong leadership and funding to speed progress.

The survey also asked respondents to list, in order of priority, the most urgently needed new vaccines, listing the developing and developed countries separately; the results are shown in the table on this page. Predictably, the vaccines that ranked the highest often reflected the needs of a respondent's country. Yet a strong consensus put an AIDS vaccine at the top of the list for both developing and developed countries. In addition, three vaccines that received the highest priority in the IOM study still ranked high a decade later: malaria, RSV, and pneumococcal.

But will these vaccines be available a decade from now? As the experience of the IOM report shows, vaccine development is a field in which it's difficult to feel confident about predictions. To find out what the next decade might hold, *Science* questioned the researchers who responded to our survey to tease out a sense of the major obstacles to the development of new vaccines and the prospects for future research.

ILLUSTRATION: E. CARROLL

The bottom line

Predictably, money—or rather, lack of it—was one of the most frequently mentioned obstacles. Even though vaccines are among the most cost-effective medical interventions ever devised, they are not big moneymakers. A recent study for UNICEF estimates that the entire global vaccine market is only $3 billion. By comparison, the antiulcer drug Zantac, the best-selling pharmaceutical, last year took in $3.5 billion by itself. "The major stumbling block [in vaccine R&D] is there's not enough money to bring basic science up through development of a vaccine," says Scott Halstead, the Rockefeller Foundation's deputy director of the Health Sciences Division.

Companies can make money on a vaccine—if it's used in developed countries. Companies sell vaccines for one price in industrialized nations and provide them at a deep discount to groups such as UNICEF, which donate vaccines to poorer nations. As a result, for diseases that don't afflict developed countries, there is scant commercial interest in vaccines. Malaria, which the World Health Organization (WHO) estimates causes 300 million to 500 million clinical cases a year and as many as 2.7 million deaths, is a telling example. "Ten years ago, when we wanted industry support, it was terribly difficult to find a company," says malaria vaccine researcher Ruth Nussenzweig, chair of the parasitology department at New York University (NYU). "They'd turn their backs when the word 'malaria' was announced."

And that lack of interest isn't the only way relations between rich and poor countries affect vaccinology. Take the case of a potential new pneumococcal

SCIENCE SURVEY: MOST URGENTLY NEEDED VACCINES*

Developing World

Vaccine	Times ranked #1	Times in top 3	Cases/Deaths** (millions)
1. HIV	28	43	2***/0.48
2. Malaria	17	49	300–500/1.5–2.7
3. Improved tuberculosis	3	18	3.4/2

Developed World

Vaccine	Times ranked #1	Times in top 3	Cases/Deaths** (thousands)
1. HIV	41	49	81***/79
2. Respiratory syncytial virus	6	22	3737/4.6
3. Conjugated pneumococcal	3	19	153–576/40

*Sixty-seven researchers responded; vaccines were ranked according to how many times they were named as the most urgently needed preparation and also how many times they appeared in the top three rankings.
**Estimates of annual cases and deaths from most recent years available.
***HIV-infected, as opposed to AIDS cases.

SOURCE: CDC/WHO/NIAID/IOM/WORLD BANK/JAMES CHIN

vaccine. A handful of companies are developing a vaccine that relies on "conjugating" a piece of the bacillus to a different, harmless organism to trigger an immune response in infants. Several survey respondents said they fear reliance on this sophisticated technology will make the vaccine unaffordable in the developing world.

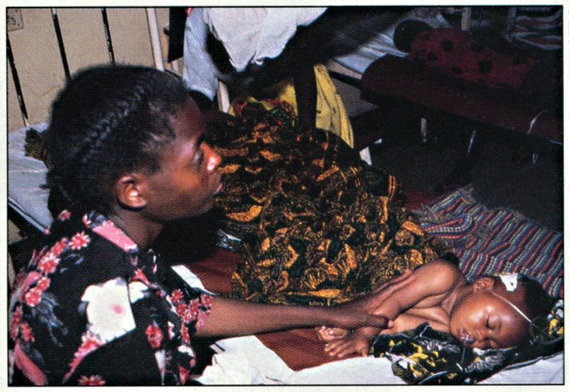
And even if the vaccine were available in the developing countries, it might not do much good there, because it is not being tailored to the type of disease that predominates in the developing world. Invasive pneumococcal disease causes pneumonia, which kills about 10% of children under the age of five in developing countries and is the leading cause of death, notes the 1993 "Jordan Report," an annual update on vaccine development issued by the National Institute of Allergy and Infectious Disease (NIAID). *S. pneumoniae*, the cause of pneumococcal disease, is also responsible for as many as 40,000 deaths in the United States each year and as many as 576,000 cases of pneumonia.

But in developed countries, *S. pneumoniae* is not primarily a pneumonia threat. On the contrary, it's infamous as the leading cause of earache—and earache is what industry is designing a vaccine against. Myron Levine, head of the University of Maryland's Center for Vaccine Development, warns that the types of *S. pneumoniae* used to make a vaccine that prevents earaches might not protect against invasive pneumococcal disease. "The place where there's the greatest need is not the place driving the development," says Levine.

If the incentives to develop vaccines for developing nations weren't low enough, recent policies in industrial countries may have lowered them further. Industry contends that the U.S. government's recent drive to convince pharmaceutical companies to lower vaccine prices is counterproductive—because it cuts the profits that industry might use for subsidizing R&D. "Politicians need to recognize that when they cut vaccine prices, they are also cutting vaccine research programs," asserts R. Gordon Douglas, who heads Merck's vaccine division. "If the Clinton Administration had not done this," claims Douglas, "you'd have seen another $100 million going into biotech vaccine companies last year."

Rudderless vessel

The absence of strong market incentives increases the need for effective leadership from public-sector organizations devoted to vaccine development. And there isn't a shortage of organizations. At WHO, the new Global Programme for Vaccines supports vaccine research and delivers vaccines to the developing world. The Children's Vaccine Initiative (CVI), launched in 1990, aims to develop new, improved vaccines for the developing world (see story on p. 1376). The U.S. National Institutes of Health (NIH) is the world's single largest funder of vaccine research, spending more than $300 million annually. NIH's sister agency, the U.S. Centers for Disease Control and Prevention (CDC), spends another $528 million on vaccine purchase, research, and testing.



ANDY CRUMP/WHO/TDR

A lot of bad air. A child languishes, ill from malaria. The disease causes 300 to 500 million cases a year worldwide; there is no fully effective vaccine.

But even with this supply—some would say oversupply—of organizations involved in vaccine research and distribution, one of the chief concerns of the respondents to *Science*'s survey is the quality of leadership. There are far "too many 'experts' who are uneducated in the field and who are self-serving," charges NIH's John Robbins, who was instrumental in developing the recently licensed vaccine for *Haemophilus influenzae*. Isao Arita of Japan's Agency for Cooperation in International Health adds that he sees a "lack of leadership to set up research strategies and to promote teamwork."

STEVE TURNER

Barry Bloom of the Albert Einstein College of Medicine in New York City contends that although these large programs have merits individually, they do not mesh well. "The whole shooting match is fragmented," argues Bloom. Mary Lou Clements, who heads the Center for Immunization Research at Johns Hopkins University in Baltimore, adds that "in contrast to the [U.S. Department of Defense], which has primary responsibility for developing vaccines from the preclinical stage all the way through testing for the vaccine's efficacy and licensure, no other single agency takes responsibility for all stages of vaccine development."

Bloom's solution is a single U.S. government office with the power to coordinate all vaccine issues—essentially a stronger version of the existing NVPO (see story on p. 1375 and Policy Forum on p. 1378). Such increased coordination in the United States, he says, would change the pattern that prevails in the international arena. "There's the law of the jungle right now. Everybody's fighting for power and money."

Researchers believe urgently needed vaccines are stuck in the pipeline because of the leadership vacuum. NYU's Nussenzweig says that although individuals and organizations have pushed for malaria vaccines in the past, no one is now driving the search. "The leadership—I don't see it," says Nussenzweig. She notes that WHO, the Rockefeller Foundation, and the U.S. government all have either "drastically" cut back or eliminated their malaria programs. The U.S. Agency for International Development, once the largest funder of malaria vaccine research, was rocked by a series of scandals in the late 1980s and now funds hardly any.

Duke University's Samuel Katz, who chaired the IOM committee a decade ago, says the RSV vaccine is also mired in the leadership swamp. During tests of experimental RSV vaccines in infants in the 1960s, researchers found to their surprise that a strong immune response against the virus can, for unknown reasons, actually enhance the disease. As a result, explains Katz, there's "reluctance and extreme caution in clinical studies today."

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—Barry Bloom

In particular, he says, an RSV vaccine being developed by Lederle-Praxis Biologicals has been stymied because scientists at NIAID who conducted the studies in the '60s—and who, he says, have much influence at the FDA —have consistently argued against testing it in infants. Though Katz thinks caution is appropriate, he maintains that in this case, it has had an unfortunate result. Says Katz: "Lederle-Praxis has a good vaccine, but because of quarrels with the NIH it isn't being tested quickly enough. Who adjudicates that sort of thing?"

Leadership and money by themselves, of course, will not remove the largest obstacle that stands in the way of many of the most urgently needed vaccines: scientific unknowns. The vaccines at the top of today's scientific wish lists are often there because they're difficult to make. "The relatively easy ones we've solved," says polio vaccine developer Jonas Salk, who now is working on AIDS vaccines. With TB, HIV, RSV, and malaria, no researcher has yet demonstrated which immune responses provide protection. RSV and HIV vaccines lack good animal models. The protozoan that causes malaria has a complex life cycle, presenting the immune system with myriad challenges. HIV mutates rapidly to duck the immune system—and, potentially, any vaccine.

Salk believes one of the main scientific obstacles is that many scientists researching and developing vaccines "don't have a clue" what's required to make an effective vaccine. "It is chaos....There's going to be a need for more awareness not of the pathogen, but of the host," says Salk, who believes few vaccine makers focus on understanding the immune responses needed for protection.

A few points of light

Although the challenges of finding money, leadership, and scientific answers are daunting, there may be a few bright lights on the horizon. An International Vaccine Society, the first of its kind, was recently formed; Salk thinks the society "might provide some intellectual and scientific leadership." WHO's recent restructuring of its vaccine program aims to incorporate CVI; a meeting slated for 31 August in Geneva will specifically address the integration of CVI into WHO's existing vaccine programs. The Japanese recently launched a campaign to raise $100 million to support CVI, and, with help from the United Nations Development Fund, a new International Vaccine Institute, based in South Korea, is being set up to help countries in the region coordinate R&D for priority diseases.

The NVPO's Roy Widdus, director of the '80s IOM study, adds that the vaccine industry has been going through a rebirth in the last few years, as companies made money from sales of hepatitis B and *H. influenzae* vaccines. Start-up biotechnology companies also have become serious players in vaccine R&D. "There's a lot more interest from industry than there was in the mid-'80s," he says.

Those developments might help grease the vaccine machine and make the next decade a productive one for vaccinology. IOM, at NIAID's behest, also will convene a new committee soon to establish priorities for vaccine development once again. Perhaps this time around, more of the successes that appear "reasonably foreseeable" within the next decade will actually be seen.

–Jon Cohen

AIDS VACCINES

Are Researchers Racing Toward Success, Or Crawling?

In 1990, AIDS researchers and stock analysts hailed Repligen Corp., a Massachusetts biotechnology firm, as a leader—many said *the* leader—in the race to develop a vaccine against HIV. Not only was Repligen collaborating with top AIDS researchers and publishing impressive scientific papers, the start-up had won financial backing from pharmaceutical giant Merck & Co. A 1990 investors' guide from Shearson Lehman Hutton predicted that if human tests of the vaccine went well, Repligen and Merck might ask the U.S. Food and Drug Administration to license it as early as the end of 1994.

Fast forward to 19 July 1994. On that day, Repligen announced that, because of a "lack of available funding," it was axing its HIV vaccine research and development program. One way of interpreting this startling turnaround is to assume it's a normal development in a long-distance race; after all, the early leaders in the New York City marathon seldom stay the course. A more skeptical view, however, holds that there never was a "race" to make an AIDS vaccine.

That view may seem as surprising as Repligen's fade-out, but a growing number of AIDS researchers have come to this depressing conclusion. Jaap Goudsmit, a leading AIDS researcher at the University of Amsterdam, says of the alleged race, "I haven't seen it." Wayne Koff, former head of the AIDS vaccine program at the National Institute of Allergy and Infectious Diseases (NIAID), who is now developing an AIDS vaccine at New York's United Biomedical Inc., says the idea of a "race" is largely "a game" played at scientific meetings. "There's a lot of noise and a lot of posturing"—and little else, says Koff.

The reason pharmaceutical companies aren't pouring dollars and energy into AIDS vaccines the way they would into a hot new mood-elevating drug is simple: The AIDS vaccine market in developed countries is likely to be much smaller than early estimates indicated. As a result, only a handful of companies are committed to the search, mostly biotech start-ups. And most of these companies are taking the same narrow approach, which limits the chances of success, say Koff and Goudsmit.

Not everyone accepts this downbeat view. But even congenital optimists must have found it difficult to smile about the AIDS vaccine "race" in June, when two NIAID advisory panels decided that even the two most promising experimental vaccines are not ready for large-scale testing (*Science*, 24 June, p. 1839). NIAID director Anthony Fauci says the discussions by those panels "laid naked what a paltry effort" is being made to develop AIDS vaccines. "When all of the clothes get ripped away, what do we have?" asked Fauci.

Not a super market

Economics clearly isn't the only factor that is discouraging companies from entering the search for an AIDS vaccine. Another is the fact that the science is very tough. Animal models used to test AIDS vaccines have severe limitations; the genetic diversity of HIV may require an effective vaccine to be based on many viral strains; and no researcher has successfully demonstrated which immune responses correlate with protection from HIV.

ROCKEFELLER FOUNDATION

A rocky start. The Rockefeller Foundation invited these vaccine experts to Bellagio, Italy, where they criticized the way the search for an AIDS vaccine is being conducted.

Yet even with these high scientific hurdles, you might think the market for AIDS vaccines would have companies salivating. And early estimates did get their juices flowing. In Shearson Lehman's 1990 report, analysts estimated the market in the United States and Europe would include more than 67 million people, including homosexuals, intravenous drug users, health-care workers, prisoners, and college-age heterosexuals. If, on average, 15% to 20% of these people took a vaccine priced at $150, it could be a $1.6-billion-plus market.

Yet those estimates are rapidly deflating. In July the Rockefeller Foundation released a report, "Accelerating the Development of Preventive HIV Vaccines for the World,"