

A confluence of unrelated problems has created widespread shortages of medicine's best preventive against infectious diseases

# U.S. Vaccine Supply Falls Seriously Short

## PUBLIC HEALTH

This special report on public health examines the causes of the current vaccine shortage in the U.S. and the bold efforts of the Gates Foundation to improve global health. Following is an analysis of the U.S. and Russian research programs on smallpox, which are generating heated debate over the virus's destruction. A sidebar describes a ghoulish search for live smallpox in bodies frozen in the Arctic permafrost.

## ► VACCINES GATES SMALLPOX ARCTIC DESTRUCTION?

more varicella (chickenpox) vaccine. A few months earlier, the doctor continued, shortages had forced him to delay vaccinating children against hepatitis B and pneumococcal disease. "What's going on?" he asked Orenstein.

Orenstein knew the answer, and it wasn't reassuring. During the past 6 months, shortages have occurred with eight of the 11 childhood vaccines. Demand has also outstripped supplies of adult vaccines against influenza, tetanus, and pertussis. "I've been in immunization for 24-and-a-half years, and I've never seen anything like this," says Orenstein.

Indeed, CDC's National Vaccine Advisory Committee (NVAC) was so concerned that last month it held a 2-day meeting on the topic in Washington, D.C. The immediate shortages stem from a mix of factors, some as mundane as retooling a manufacturing plant or misjudging demand and others as fundamental as the need for companies to

make money. But the comments of representatives from industry, academia, and the government also revealed a more troubling picture: The entire edifice for the manufacture and supply of vaccines in the United States is so fragile that even minor perturbations can lead to a collapse.

### Dwindling supplies

Vaccines are nowhere near as profitable as drugs. According to GlaxoSmithKline, the world's largest vaccinemaker, worldwide vaccine sales in 1999 totaled \$4.3 billion. In contrast, the cholesterol-lowering drug Lipitor now grosses upward of \$6 billion a year. Not only do people use vaccines far less frequently than drugs—typically, a child receives a battery of shots and is protected for life—but vaccine prices are heavily influenced by the federal government.

Vaccines are also trickier to manufacture than drugs. "Vaccines require the use of biological organisms, viruses, and bacteria, which will not always grow or respond on demand," notes Wayne Pisano, an executive at Aventis Pasteur who works at the

company's Swiftwater, Pennsylvania, branch. "It's not a matter of opening a tap and pouring out vaccine."

These economic forces have helped drive many companies out of the vaccine market. In 1967, says Kathryn Zoon, director of the branch of the Food and Drug Administration (FDA) that oversees vaccines, FDA had licensed vaccines made by 26 different manufacturers. By 1980, the number had fallen to 17. Today it stands at 12, of which only four are large pharmaceutical companies.

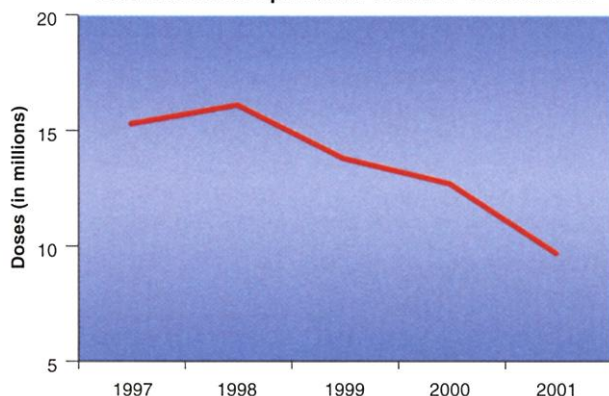
The U.S. government has intervened in several ways to try to ensure adequate vaccine supply. In 1983, CDC began to stockpile vaccines, and 3 years later Congress created a no-fault compensation program for people injured by vaccines. That step dramatically limited the liability of vaccine-makers—a key reason many cited for leaving the business. But the current shortages underscore the limits of these fixes. Some critics in fact say other government vaccine programs have actually exacerbated the problem by substantially decreasing the profit margin for most companies.



**Painful predicament.** Clinicians have struggled to purchase childhood vaccines that prevent eight different diseases.

CREDIT: RUSS CARMACK/THE NEWS TRIBUNE/AP

U.S. Tetanus-Diphtheria Vaccine Distribution

**Snowball effect**

The current wobbliness of the U.S. vaccine supply first became apparent during the flu season 2 years ago. "We had a very rude wake-up call," says Nancy Cox, who heads CDC's influenza branch. The program had been working so well for several years, explains Cox, that "people stopped paying attention to the fact that the influenza distribution system was fragile."

Making a flu vaccine poses unique challenges. The most daunting is that manufacturers must reformulate it each year to combat the new strains of influenza virus in circulation. Some strains do not grow well, complicating the process that transforms them into vaccines. And the seasonality of flu forces companies to deliver the vaccine on a tight timeline.

In 2000, the four licensed manufacturers had exceptional difficulty growing one strain of influenza. Coincidentally, FDA cited two manufacturers, Wyeth Lederle (a division of American Home Products) and Parkdale Pharmaceuticals, for quality-control infractions. Parkdale decided to drop its flu vaccine program. About the same time, CDC increased the pressure on the remaining manufacturers by broadening the "primary target group" to include anyone over 50, rather than 65.

This flu season, the trio of Wyeth, Aventis Pasteur, and Evans Vaccines (a subsidiary of PowderJect Pharmaceuticals) produced 87 million doses for the U.S. market. Although that was a record supply, about one-third of it was not available by October, when demand for the flu vaccine typically peaks (see graph at right).

Equally troublesome was Wyeth's decision in January 2001 to stop making vaccines against tetanus and diphtheria. The company was increasing production of a new and significantly more profitable vaccine that protects children from pneumococcal disease, says spokesperson Douglas Petkus, leaving it without "the capacity" to continue production of older products.

Wyeth's withdrawal left Aventis as the only national producer of the diphtheria-tetanus vaccine. Pisano says that the company did not have enough advance notice of Wyeth's plans to crank up extra production. As a result, supply of this vaccine, which is given in combined form to adolescents and adults, has dropped by an estimated one-third since 1998 (see graph at left).

For infants, the tetanus and diphtheria vaccines are combined with yet another product, acellular pertussis, creating what is known as DTaP. In 2000 Wyeth scotched DTaP from its production line, as did North American Vaccine, which also ran into quality-control problems with FDA. Aventis Pasteur and GlaxoSmithKline still make DTaP, but neither was able to increase production to meet demand after two of their competitors left the market. CDC estimates that the current supply of DTaP meets only about three-fourths of demand. (Ironically, Wyeth has struggled to fill orders for its pneumococcal vaccine because of a higher-than-expected demand.)

The vaccine shortage escalated in August 2001 when Merck, which makes six vaccines that protect against nine diseases, voluntarily decided to change its manufacturing procedures. A few weeks later, Merck stopped production again for scheduled modifications to its production facility. CDC estimates that Merck, the sole manufacturer of both varicella and measles-mumps-rubella vaccines, supplied 65% less varicella vaccine this winter than the previous year and only about half the needed measles-mumps-rubella vaccine.

**Tweaks or overhauls?**

Stockpiles are the best hedge against shortages, vaccine experts concluded nearly 20 years ago. Theoretically, the stockpile creates an artificially large marketplace, and manufacturers that run short of a vaccine can "borrow" product from the stockpile. But the reality is quite different.

CDC initially focused on critical vaccines that only one manufacturer produced. To increase efficiency, CDC also selected vaccines that have a predictable marketplace, reducing the likelihood of wasting these perishable products. Currently, the stockpile contains just three vaccines: polio, measles-mumps-

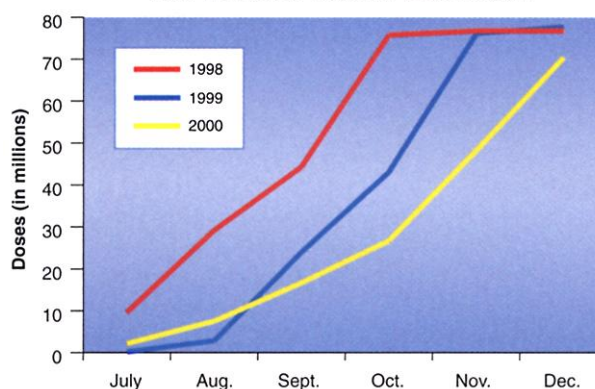
rubella, and a small amount of diphtheria-tetanus. But since the early 1980s, a half-dozen new vaccines have come online. "We need to get stockpiles of all the other vaccines," acknowledges Orenstein.

Expanding the stockpile is probably the best immediate solution to offset vaccine shortages, says Boston University's Jerome Klein, a pediatrician and NVAC member. "It's a quick fix that legislators can understand."

But even that answer is not as simple as it appears. Demand for a new vaccine, like the one that prevents pneumococcal disease, is difficult to predict until it has been on the market for a few years. The stockpile is not practical for flu vaccine, which changes annually. Most vaccines also have a shelf life; to stay current, the stockpile must rotate out its inventory every 6 months.

Orenstein suggests that the government may have to "overpurchase" vaccines each year, knowing that some will go to waste. "Society needs to be prepared for [the waste] if we want that insurance," he says.

U.S. Influenza Vaccine Distribution



Although most eyes have turned to the federal government to solve the supply problems, industry charges that one intervention helped create the shortages. Congress launched the Vaccines for Children program in 1993 to increase immunization rates among the poor. As part of this program, the government purchases about 35% of childhood vaccines on the U.S. market, says Orenstein, and supplies states and other public programs with another 17%. That means manufacturers sell 52% of the childhood vaccines used in the United States at a price, negotiated by the federal government, that is significantly lower than that paid by private purchasers.

Although the Vaccines for Children program does not aim to manipulate the market, it does give the government huge negotiating power. Vaccinemakers and their lobby, the Pharmaceutical Research and Manufacturers of America, argue that the price caps—which limit increases that companies can charge for their products—in particular



## Gates Foundation Rearranges Public Health Universe

SEATTLE, WASHINGTON—A large AIDS meeting held here last month had an unusual keynote speaker: Bill Gates. The world's richest man had never spoken at a medical research conference, and a few years ago many in the audience would have wondered why he was there. But since 1999, the Microsoft CEO and his wife Melinda have created the world's largest philanthropy, with current assets of \$24.2 billion, and improving the health of the world's poor is at the top of its agenda. So far, the Bill and Melinda Gates Foundation has spent \$2.5 billion on global health—more than twice the annual budget of the World Health Organization.

The foundation has rearranged the public health universe so speedily that many have yet to comprehend the change. "They're having a huge impact," says Barry Bloom, dean of Harvard School of Public Health in Boston, which, along with his own lab, has received some of the Gates Foundation's largesse. "There is no other money like that anywhere in the world." The \$400 million investment in AIDS projects, for instance, is having a major ripple effect, says epidemiologist Peter Piot, who heads the Joint United Nations Programme on HIV/AIDS, by "shaming many 'donor' governments" into spending more.

Gates's interest in public health grew out of his own reading on the topic, in particular a 1993 World Bank report, *Investing in Health*. "Every page screamed out that human life was not being treated as being nearly as valuable in the world at large as it should be," Gates told the audience at the 24 February meeting. But when Gates and his wife decided to spend their vast wealth on creating a more equitable world, they realized they needed help.

In the beginning, Bill's father, a Seattle lawyer with the same name, and a family friend, former Microsoft executive Patty Stonesifer, oversaw grants and quizzed experts. The few foundation staffers worked in a modest space atop a pizza shop. But as the foundation's assets quickly grew, they hired one of those experts, family planning and child health specialist Gordon Perkin, to run the foundation's global health program. They also brought in William Foege, former head of the Centers for Disease Control and Prevention (CDC). "Probably 80% of our grants were made with a staff of five or less," laughs Perkin, sitting in the sleek offices the foundation recently occupied near the Seattle waterfront. For many of the grants, he explains, they asked for short, clear proposals and simply tried to ascertain whether the applicants were the world's best in their field. "It was an immensely satisfying challenge," says Perkin.

The foundation's interests have stretched from AIDS to reducing maternal mortality, bolstering nutrition, and improving treatment and prevention for several tropical diseases, including malaria, tuberculosis, lymphatic filariasis, dracunculiasis, schistosomiasis, and trachoma. Nearly half of the global health money has gone to vaccines, including a whopping \$750 million to the Vaccine Fund. This fund, in turn, supports the Global Alliance for Vaccines and Immunization and its drive to close the "vaccine gap" between rich and poor children—3 million of

whom die each year from diseases that vaccines can prevent.

In keeping with its recent growth spurt, the young foundation is increasing its staff and restructuring how it awards grants. Global health is now split into three divisions. Perkin heads the reproductive and child health program. The HIV/AIDS and tuberculosis program is run by Helene Gayle, a well-known AIDS epidemiologist whom Gates lured from CDC. Sally Stansfield, an epidemiologist who has worked extensively on public health in Cambodia and Ethiopia, is acting director of grants that involve vaccines and infectious diseases. "There is no single human who can master all of the decisions," says Stansfield. "It is really important to know the



**Helping hand.** Melinda Gates vaccinates a Thai child against polio. Below, selected Gates Foundation grants.

Grantee	Project	Amount
Vaccine Fund	Immunization of poor children	\$750 million
International AIDS Vaccine Initiative	AIDS vaccine R&D	\$126 million
Global Fund to Fight AIDS, Tuberculosis and Malaria	Increase in treatment and prevention	\$100 million
Program for Appropriate Technology in Health	Elimination of meningitis in sub-Saharan Africa	\$70 million
Save the Children Federation	Global neonatal survival initiative	\$50.5 million
African Comprehensive HIV/AIDS Partnerships	HIV treatment in Botswana	\$50 million
Harvard Medical School	Tuberculosis control	\$44 million
London School of Hygiene and Tropical Medicine	Establishment of malaria center	\$40 million

subculture and the players in each area."

The newly structured foundation will place even more emphasis on accountability and aggressively pursue projects that mesh with its agenda. "We'll have a little more bandwidth now," says Stansfield. That targeting will inevitably make it "less responsive to what comes in the door," says Gayle, a transition that may rankle some. "It's tough when you're seen as a large, caring foundation—and I think people do perceive Gates as both caring and not just rich—and an important idea is not part of our priority."

Although Bill and Melinda choose how to spend the foundation's money, Perkin, Gayle, and Stansfield evince a sense of wonder about having the opportunity to affect public health in such a dramatic way. "If I stop and think about it," says Stansfield, "the excitement is heart stopping."

Bloom suspects that if the Gates Foundation can demonstrate that its money has improved public health, the foundation will have an impact far beyond the projects it supports. "If Gates can do it," says Bloom, "there are a lot of other people who can do it, too."

—J.C.

serve as a disincentive and help explain why so few companies are in the business.

Orenstein disagrees. Besides guaranteeing a large marketplace and a fair price, he says, the government creates huge markets for products it endorses, such as the new pneumococcal vaccine required of all school-age children. As for the influence of price caps, Orenstein notes that the 1993 program set limits only for existing vaccines—but that shortages have also occurred with newer ones that had no price controls.

One cost-free tactic that won widespread support at last month's meeting was greater communication among everyone involved. Shortages could be averted if manufacturers gave their competitors better advance warning before dropping a product, says Aventis's Pisano, or if the government were allowed to share confidential supply informa-

tion with the private sector.

Confronted with the obvious failure of market mechanisms, some have long favored a radical overhaul of the system. The current crisis, coupled with the increased concerns about bioterrorism following 11 September, have revived a 1993 proposal by the Institute of Medicine (IOM) for a National Vaccine Authority that has at its center a government-owned vaccine manufacturing plant. The authority would oversee production and distribution of all vaccines, monitor supply and demand, and fill in gaps with government-made products. "We are not talking about competing with the private sector," stresses IOM president Kenneth Shine at the meeting. Senators Edward Kennedy (D-MA) and William Frist (R-TN) and other lawmakers have shown serious interest in the idea, which is widely

opposed by industry representatives.

Instead, companies would prefer tax incentives, especially to refurbish manufacturing plants for older and cheaper "commodity" vaccines. The federal government, for example, pays 15 cents a dose for diphtheria-tetanus vaccine, whereas the new pneumococcal vaccine sells for \$58.75.

Companies need to be able to make money on vaccines, says Klein. He and others say the most pressing problem is convincing the public to pay a fair price for vaccines that can save millions of lives. "You have to be as willing to pay for DTaP as you are for Viagra," he says. Unfortunately, it may take a resurgence in vaccine-preventable diseases to drive home the importance of these critical medicines.

—JON COHEN

With reporting by Katie Greene.

## PUBLIC HEALTH SMALLPOX

# Dead Virus Walking

Smallpox, humankind's greatest scourge, was banished from the wild decades ago. New fears that bioterrorists may try to resurrect the virus have thrown two controversial research programs into high gear

**KOLTSOVO, RUSSIA**—Stalin's gulags have long since vanished from Siberia, but one remote outpost lays claim to the mantle of horror. The world's worst killers, among them Ebola, hantavirus, and Marburg, are kept here in a maximum-security facility, the State Research Center of Virology and Biotechnology. An urgent overhaul has turned this prison, better known as VECTOR, into a fortress. A new fence topped with razor wire encircles the lab complex, forming a no man's land between it and the old concrete wall. Entrance is via a checkpoint run by the military, but even that won't get you into VECTOR's inner sanctum. Only a handful of the staff can enter Building 6, wherein resides—Hannibal Lector-like—the most notorious inmate of all: smallpox.

During a millennia-long reign of terror, smallpox killed hundreds of millions of people before a concerted worldwide eradication campaign finally routed it in the late 1970s. The enormity of the public health threat is such that if smallpox were to escape from its cell here on the outskirts of Siberia's largest city, Novosibirsk, VECTOR would put in motion a government-approved plan to quarantine the 1.5 million inhabitants.

VECTOR is one of only two places on Earth where it is permitted to keep live smallpox virus, also known as variola.

The other repository—the U.S. Centers for Disease Control and Prevention (CDC) in Atlanta—guards its stock just as zealously. To access the virus storage, two CDC researchers have to enter the facility simultaneously with different keys.



**Pandora's box?** Peter Jahrling takes smallpox samples out of deep freeze.

Armed security guards and cameras keep a close watch.

Over the past few years, both labs have taken the virus out of the freezer for limited studies. And now, spurred on by the events of 11 September and the fear of new bioterrorist attacks, both labs are about to ramp up their research programs. Their goal: to develop modern-day diagnostics, safer vaccines, and new drugs against the disease.

The researchers are in a hurry, because the variola virus may not be long for this world. In January, the executive board of the World Health Organization (WHO) recommended giving the virus—which had been slated for destruction several times before—another stay of execution to allow researchers more time to study it (*Science*, 25 January, p. 598). "It's clear we cannot destroy the virus at this stage," declares virologist Antonio Alcami of the University of Cambridge, U.K., a mousepox expert and adviser to WHO's variola panel. But the decision to hold onto smallpox must be approved by the World Health Assembly (WHA) in May. Although nobody expects it, WHA could vote to proceed with the virus's scheduled destruction by the end of 2002. More likely, it may set a new deadline, say, 3 years from now.

That's why, starting later this month, CDC will devote one of its two maximum-containment laboratories exclusively to smallpox research, "for as long as it takes," says James LeDuc, who leads the studies. "That's a huge commit-