

## BACKWATER NO MORE:

Expected growth of vaccine industry through 2012: 10.5% // Merck's vaccine sales in 2007: \$4.3 billion  
 // Sales from Wyeth's Prevnar: \$2.4 billion // Interest in vaccines: restored.

# Prevention's New Profits

■ BY DEBORAH KELLY AND CHARLES SLACK

Until the late 1960s, for millions of children, coming down with mumps meant a week or two away from school with fever, sore throat and painful swollen glands. But in a fraction of cases, the consequences were dire, with complications that could include meningitis, paralysis and sterility. Carried on droplets of saliva, the virus was so infectious that a child could get it just by standing near someone who laughed. With time as the only cure, it seemed to be an affliction that might be with us forever. Then one day mumps messed with the wrong little girl.

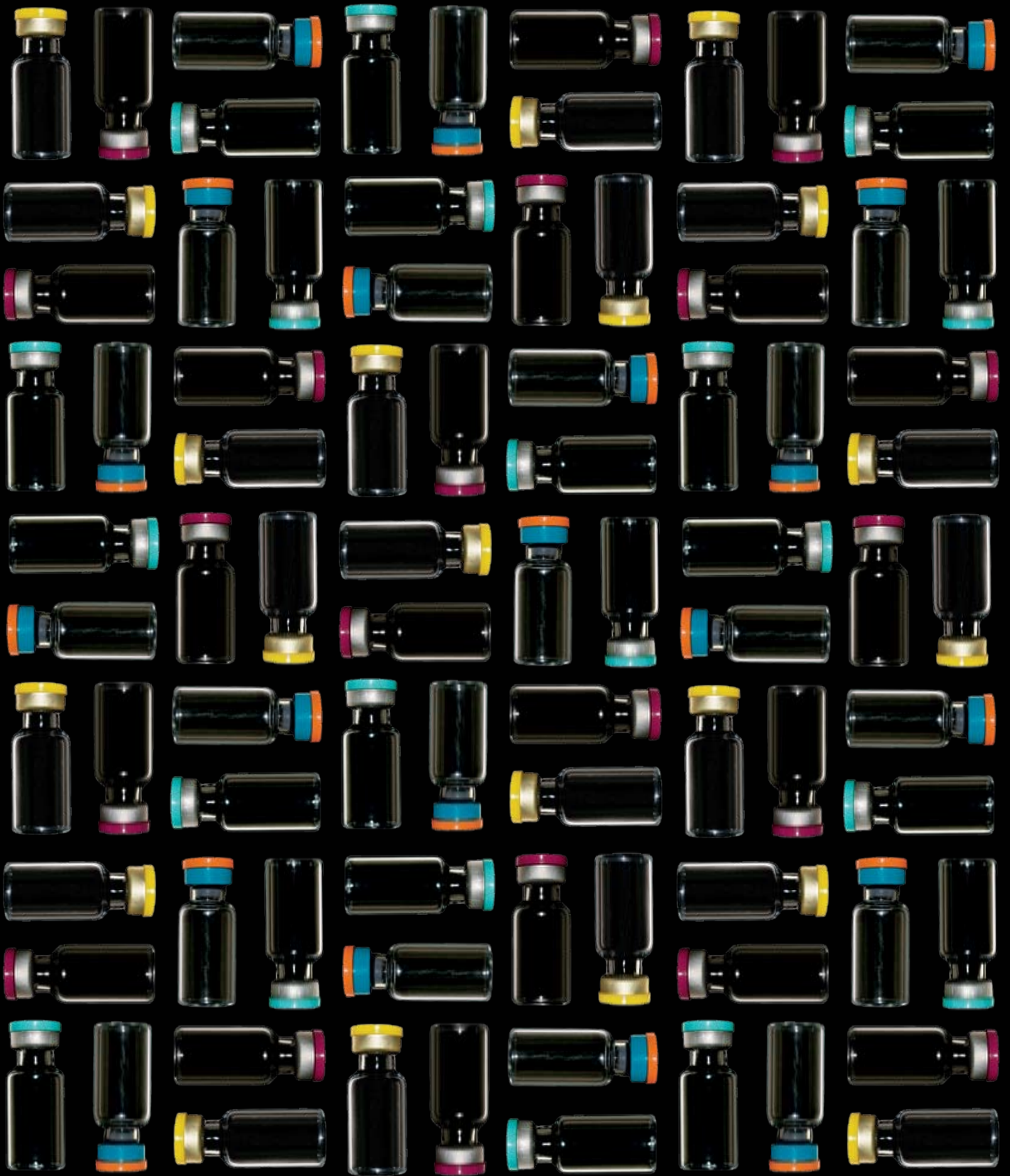
When five-year-old Jeryl Lynn Hilleman awoke with a sore throat and swollen glands, her father, virologist Maurice Hilleman of Merck Research Laboratories, swabbed a sample of the virus from the back of her throat and went to work. By growing and regrowing the virus in fertilized chicken eggs, Hilleman developed a strain that resembled the original but had been weakened so that it was harmless to humans. The modified virus—dubbed the Jeryl Lynn strain—spurred the development of antibodies capable of fighting off the virus. Launched in 1967, it has prevented millions of cases of mumps and hundreds of thousands of serious complications.

But this remarkable success story was only one of many during the 1950s and 1960s, the golden age of vaccines. That was a time of big diseases and even bigger breakthroughs. To a nation living in fear of polio, Jonas Salk's announcement in

1953 of trials for a vaccine made him a hero—and the news two years later that his vaccine had been deemed ready for mass distribution only increased his stature. Measles, rubella and several dangerous flu strains fell in quick succession, and it began to seem as if anything were possible. In 1967, U.S. Surgeon General William H. Stewart announced that it was time to “close the book on infectious diseases.”

Gradually, though, that unbridled optimism gave way to financial and medical realities. As it turned out, vaccines weren't that great a business proposition for private pharmaceutical companies. Vaccines are hugely labor-intensive to develop, and because most combat a single virus, the process must be repeated from scratch for each new strain. Worse, from a profit perspective, is that the better a vaccine performs, the fewer times it's needed. Most provide protection for life; others require a booster shot every few years.

None of this posed much of a problem when drug companies were small and pharmacology's accomplishments modest. But in the 1970s, rapid medical and technological advances led to drugs for treating an array of diseases, including high blood pressure and heart arrhythmias. Patricia Danzon, a professor of health care management at the University of Pennsylvania's Wharton School, says the golden age of vaccines gave way to the era of the blockbuster drug, in which a relative handful of large pharmaceutical companies was always on the lookout for the next big thing.



By the 1980s existing vaccines, while still effective, were an old story, and the field's one big chance to return to the heroic days of yore—by developing an effective vaccine against AIDS—fell short. Indeed, some vaccines came to be considered villains, not heroes. Since the 1990s many parents have become convinced that rising rates of autism are linked to the proliferation of Hilleman's combined measles, mumps and rubella (MMR) vaccine. Though no credible connection between the two has been found, that furor, along with declining profits and the threat of litigation, has made the vaccine business increasingly unappealing, says Paul A. Offit, Hilleman's biographer, who is chief of infectious diseases at the Children's Hospital of Philadelphia. By 2000 there were just five major vaccine manufacturers worldwide, compared with 26 in 1957.

During the past several years, though, the field has shown a resurgence. "We're about to enter a renaissance for vaccines that could easily rival the successes of the 1950s and 1960s," says Gary J. Nabel, director of the Vaccine Research Center at the National Institutes of Health. Merck's Gardasil, for example, is only one of the marvels generating substantial profits. The drug, which protects against certain strains of human papillomavirus that cause cervical cancer, produced \$1.5 billion in sales last year. And more vaccines are on the way. In 2005 there were 68 in Phase I FDA trials, and 21 had

progressed to Phase III. Eventually, there might even be vaccines to prevent such major killers as heart disease, which some researchers now believe may have infectious roots. And while vaccines still represent less than 3% of overall drug company revenue, analysts expect the vaccine industry to grow by more than 10% a year through 2012, compared with 7% for pharmaceuticals overall.

Danzon attributes this comeback to renewed demand, scientific advances and a suddenly favorable business climate. The major pharmaceutical companies, she notes, have at least temporarily run out of blockbuster drugs to pursue. "They've picked all the low-hanging fruit," she says. "Now they're beginning to look harder at drugs with smaller potential revenue." That has brought vaccines back into the picture.

One driving force behind the renewed interest in vaccines can be summed up by a single word: fear. Because vaccines prevent rather than treat diseases, they tend paradoxically to mute the alarms that might arouse public demand for innovation. When children aren't being crippled by polio or killed by measles, people forget about lurking viral threats. "Until recently, vaccines have been undervalued," says Richard M. Haupt, executive medical director for Merck. "We spend less than 5% of our health care dollars on preventive measures, including vaccines. The vast majority of spending is on treatment."

Threats of terrorism have challenged that sense of complacency. Because contagions could be delivered in tiny, easily concealed containers, detection may be impossible, and attempts to treat victims of an attack might prove too little, too late. "The only rational way to combat agents used by bioterrorists would be with vaccines," says Michael Starnbach,

## From Cows to Cures



**1796**

Edward Jenner discovers that cowpox virus injected in humans prevents smallpox. He coins the word *vaccine* from *vacca*, Latin for cow.



**1885**

Louis Pasteur injects his untested rabies vaccine into Joseph Meister, the victim of an attack by a rabid dog. The nine-year-old recovers.



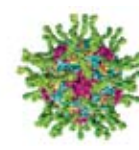
**1921**

A toxoid vaccine is developed to combat diphtheria. Though the poisons produced by the bacteria are neutralized, the body creates antibodies in response to their presence.



**1954**

Jonas Salk tests his polio vaccine on more than 600,000 subjects, using inactivated (dead) polio virus. In 1955 the vaccine is licensed for mass inoculations.



**1955**

Cutter Laboratories mistakenly produces two lots of polio vaccines containing virulent polio virus. At least 164 people are permanently paralyzed and 10 die.



**1961**

An oral polio vaccine, developed by Albert Sabin, is licensed. Unlike Salk's, this vaccine uses a live, attenuated virus, which requires no boosters.

associate professor of microbiology and molecular genetics at Harvard Medical School.

In 2004 President Bush signed into law Project BioShield, which authorizes spending \$5.6 billion over 10 years for safety measures, including stockpiling and improving existing vaccines and developing new ones against anthrax, smallpox and other agents. And Nabel says that since the anthrax attacks in 2001 and outbreaks of West Nile virus, severe acute respiratory syndrome (SARS) and avian flu, it has hit home that more must be done to head off potentially catastrophic scourges. “As the world becomes more crowded, we’re facing threats from biological agents we never imagined,” he explains. “And the natural ones may be worse than the deliberate biodefense threats.”

Even conventional flu vaccines are getting a shot in the arm. After well-publicized shortages, the federal government has tried to quicken the flow, awarding \$1 billion in the spring of 2006 to help drug companies modernize production. Novartis is using a \$220 million contract to build a flu vaccine plant in North Carolina, while GlaxoSmithKline is refurbishing a Pennsylvania plant under a \$274 million federal contract.

**A**s demand for vaccines has increased, so has researchers’ understanding of how the human body fights disease—and of ways to turn that process to further advantage. Unlike bacteria, which are complete cells that live both inside and outside humans and animals, viruses are tiny, incomplete pieces of genetic material that can neither survive nor reproduce away from a host. Essentially a piece of DNA coated in protein, a virus enters the body through an orifice or cut, attaches itself to a cell and injects its genetic material.

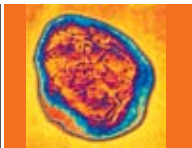
Inside the cell, the virus rapidly reproduces, killing the cell and distributing copies of itself to attack other cells. The

immune system responds by creating antibodies or sending white blood cells to fight the virus. Against relatively weak viruses, the immune system triumphs. In other cases—a virulent case of polio, for example—the body is overwhelmed and the patient dies or suffers lasting injury. Antibiotics, designed to kill invading bacteria, are useless against viruses, which do their damage while hiding inside the body’s own cells.

One of the few good things about this process is that once you survive a viral infection, the antibodies you developed usually make you immune to future attacks of the same disease. That’s the idea behind vaccines: to inject a substance that, though harmless, is close enough in composition to the actual virus to stimulate the development of protective antibodies.

Most vaccines have been made in one of two ways. The first is to use heat or chemicals to kill samples of the virus. Though the virus is dead and thus no longer at risk of reproducing inside cells, its presence is enough to stimulate an immune response. The second method, which Hilleman used to create his mumps vaccine, involves growing and regrowing viruses in animal cells, a process known as attenuation. With each generation, the virus mutates slightly, gradually becoming less dangerous to humans, until it can be safely injected.

Vaccines made from attenuated viruses tend to be more effective than those made from dead viruses. But live viruses



**1963**

A vaccine against measles, developed by Maurice Hilleman, is licensed; it’s the beginning of the end to a scourge affecting hundreds of thousands of children each year.



**1967**

Hilleman’s mumps vaccine, begun with a swab from his daughter’s throat, is licensed, and the first dose, of an estimated 150 million to date, is administered.



**1977**

Five years after routine smallpox vaccinations cease in the United States, the last known natural case is reported in Somalia.



**1999**

The Bill & Melinda Gates Foundation helps form the Global Alliance for Vaccines and Immunizations. The foundation’s contributions to GAVI total nearly \$1 billion.



**2006**

Gardasil, a vaccine against some types of human papillomavirus (HPV), is licensed, offering protection from one known cause of cervical cancer.



**2008**

AIDS researchers from around the world will gather in October in Cape Town to discuss one of the most pressing—and frustrating—vaccine challenges.



Technological advances may soon streamline vaccine manufacturing, but for now it remains a slow, painstaking process, as Merck's Gardasil facility shows. Minimal human contact is crucial, so when operators must intrude into the closed system, they use arm-length gloves molded into the machines (1). "Seed stock"—cells placed in growth medium from which more cells will grow—develops inside this isolator; then the resulting cell "slurry" is frozen at  $-60^{\circ}\text{C}$  (2) to await purification by filtration and chromatography (3). A transfer panel (4) monitors progress in numerous vessels. Once processing is completed, the finished single-strain vaccine is placed in a bulk container (5), stored at  $5^{\circ}\text{C}$ , until it's mixed with other component strains and packaged for shipment.

have the potential to cause disease, and the process of creating vaccines with them is cumbersome and inefficient. For one thing, it requires enormous supplies of fresh animal parts—often, specially bred embryonic chicken eggs. Yet that's still how many vaccines, including those for each year's flu shots, are made. The months required to cultivate and procure eggs bred for uniformity and disease resistance is a major reason the federal government must forecast expected flu strains months before flu season hits—and why its predictions can turn out to be wrong, as seems to have happened this past winter.

Making a vaccine this way is based solely on laborious trial and error. New production methods, in contrast, are much more efficient and precise. Scientists are increasingly using man-made cell cultures rather than chicken or other animal cells to grow flu and other viruses. These cell cultures can reproduce rapidly in the laboratory, reducing the time and expense associated with animal cells. The new method requires re-equipped factories and retrained employees, so the transition is taking time, but it's already helping deliver vaccines more quickly and profitably than before.

Another breakthrough has been the use of recombinant DNA technology to replicate viral DNA. The genetic material, engineered without its disease-causing characteristics, nevertheless spurs the immune system to fight back. In that way vaccines can be created in a single step and administered with an air gun that implants a DNA particle under the skin. The method requires much less training than administering conventional vaccines.

If Gardasil is the poster child for a new golden age of vaccines, it isn't the only success story. In 2006, Merck and GlaxoSmithKline introduced vaccines for rotavirus, a leading cause of life-threatening diarrhea in infants, especially in developing countries. Merck has also introduced a vaccine to prevent shingles that has been approved for use by people age 60 and older. (Merck says its vaccines sales were \$4.3 billion in 2007, compared with \$1.9 billion in 2006.) Another new vaccine, Wyeth's Prevnar, protects children against some types of pneumococcal infections and is the first vaccine to exceed \$2 billion in annual sales.

These developments underscore the idea that an ever-wider range of diseases may respond to vaccines. Researchers are turning their attention to cancer and Alzheimer's disease, as well as to sexually transmitted diseases that, while treatable, can leave patients with lasting damage. "Probably the most common cause of preventable infertility is such sexually transmitted diseases as chlamydia and gonorrhea," says Harvard Medical School's Starnbach. A vaccine against those diseases could save

the health care system millions of dollars that now go toward expensive reproductive treatments, he says.

"We're also beginning to appreciate that some chronic diseases that we haven't thought of as infectious probably are, at least in part," he adds. "Diseases such as multiple sclerosis and heart disease may have an infectious trigger, and you can imagine the enormous public health burden that might be lifted with the development of new vaccines to treat them."

Such possibilities are generating renewed interest in vaccines from major pharmaceutical players. In 2006 U.S. giant Pfizer purchased British manufacturer PowderMed, maker of DNA-based flu vaccines. And in 2007 British company AstraZeneca completed its purchase of MedImmune, a Maryland firm whose products include the nasal flu vaccine FluMist. This interest has increased prices by orders of magnitude, says Edward T. Mathers, executive vice president of MedImmune: "A three-course treatment of Gardasil is about \$360, or about \$120 per dose. Early vaccines were less than \$5 a dose."

A 26-year veteran of the pharmaceutical industry, Mathers considers vaccine technology extraordinarily exciting, offering benefits to society as well as to manufacturers. When compared with the cost of treating the diseases they prevent, the new higher-priced vaccines are still pretty inexpensive, he says. For pharmaceutical companies, he sees a different advantage: When conventional drugs lose patent protection, generic versions flood the market, greatly reducing the original drug's profit potential. But developing a process for manufacturing vaccines is costly and complex, so vaccine makers tend to be less vulnerable to competition.

With such barriers to entry improving the business outlook just when medical and technological advances are pointing toward the feasibility of preventing a widening range of diseases, vaccines have clearly returned to relevance. And if they succeed in heading off some of today's most devastating scourges—Alzheimer's disease, for example, or breast cancer—vaccines could enter an era that surpasses even their first golden age. ■

## → DOSSIER

1. *Vaccinated: One Man's Quest to Defeat the World's Deadliest Diseases*, by Paul A. Offit (Smithsonian Books, 2007). The author, a renowned virologist, recounts the fascinating story of Maurice Hilleman, the developer of eight of the 14 vaccines that are routinely recommended.
2. "Bridging the Knowledge Gaps in Vaccine Design," by Rino Rappuoli, *Nature Biotechnology*, December 2007. The head of vaccine research at Novartis Vaccines & Diagnostics details the possibilities and challenges of new approaches to vaccine development.
3. "One Step Forward, Two Steps Back—Will There Ever Be an AIDS Vaccine?" by Robert Steinbrook, *New England Journal of Medicine*, Dec. 27, 2007. A physician examines the frustrating search for an AIDS vaccine.