

Collegiate Case Study



NO. 1 IN THE USA



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Vaccines

Human beings are born with the bare minimum of defenses against infectious diseases. It is the job of a healthy immune system to strengthen itself over time by recognizing and adapting to new threats. When a new, potentially harmful microbe enters the body, the immune system provides defense against it in the form of antibodies. More importantly, the body will remember the attacker and remember how to kill it. This secondary response provides immunity from future infection. Vaccines increase our protection by stimulating the immune system to generate antibodies against specific antigens. Large-scale vaccination of the population, called herd immunity, also provides an important defense against infectious disease. Herd immunity limits outbreaks because there are not enough susceptible people to support an epidemic.

Well before the development of vaccines, humans knew that prior infection to a disease could protect a person from getting that disease again. Recorded history provides many examples of vaccination techniques being used without a full understanding of the mechanisms that allow them to work. As early as the 10th century, Chinese physicians had children inhale dried and powdered smallpox scabs. In 18th Century England, a similar procedure was used when small pox scabs were scratched into children's skin. Unfortunately, in some cases the procedure did backfire and kill the recipient. However, the 1% mortality rate was a vast improvement over the 50% mortality of smallpox.

In 1786 Edward Jenner developed the first vaccine after noticing that milkmaids who contracted cowpox were immune to smallpox. Jenner injected people with a cowpox virus. The resulting mild infection cued the patient's immune system to manufacture antibodies against smallpox. Later, when the patient encountered the smallpox virus, a rapid secondary response ensued. Since Jenner's breakthrough, innumerable lives worldwide have been saved by proper vaccine use. A worldwide program to vaccinate the public in order to build herd immunity eradicated natural smallpox.

Vaccines have been developed for many of the world's most dangerous infectious diseases. Modern vaccines may involve injecting the recipient with (1) a weakened form of microbe itself, (2) a dead microbe, or (3) pieces of microbes, called subunit vaccines. Occasionally, live-microbe vaccines cause disease. In fact, during recent years the live (oral) polio vaccine has caused the only cases of polio in the United States.

Recent USA TODAY coverage shows both the depth and breadth of recent vaccine issues and progress in the science of immunology. This case study will focus on the past success of vaccine, the safety and possible risks of vaccines and the future use of vaccines to fight many different types of diseases.

AS SEEN IN USA TODAY LIFE SECTION,
WEDNESDAY, NOVEMBER 20, 2002, PAGE 9D

Vaccines could halt Third World health crisis

By Anita Manning
USA TODAY

Vaccines, along with improvements in hygiene and sanitation, have saved millions of children's lives in the past decade, says a new report, but unless action is taken to close wide gaps in access to health services, including new vaccines, the consequences could be disastrous.

The State of the World's Vaccines and Immunization report, compiled by the World Health Organization, UNICEF and the World Bank, warns that inequities within and among developing countries could lead to social instability and the spread of disease.

The poorest 20% of the world's population suffer over half of all child deaths from whooping cough, polio, diphtheria, measles and tetanus, says the report, released today in Senegal at a meeting of the Global Alliance for Vaccines and Immunization.

Children in wealthy countries have access to new vaccines against hepatitis, which causes liver disease, and *Haemophilus influenzae*, which causes meningitis. But in poor countries of sub-Saharan Africa, only 50% of children get basic immunization against such common killers as tetanus and measles.

The report urges investment in research and development of vaccines, increasing vaccine capability in developing countries and more equitable access to vaccines for children who need them.

"While new initiatives to fight killer diseases abound, it is the hard cash that is missing," says Daniel Tarantola, director of Vaccines and Biologicals at WHO. "The global campaign for access to medicines and vaccines needs to be backed with political and financial commitment if we want it to get beyond words and make a difference to people."

AS SEEN IN USA TODAY SPORTS SECTION,
TUESDAY, OCTOBER 15, 2002, PAGE 2C

Vaccine use spreading

By Gary Mihoces
USA TODAY

The maker of the horse vaccine for West Nile virus says about 35% of the nation's 6.9 million horses have gotten it. The shots are expected to become part of the routine protection horses get against such illnesses as flu, herpes and tetanus.

"We expect West Nile to be here indefinitely, and it will become part of the combination vaccines that horses receive annually," says Rob Daily, director of the equine business unit at Fort Dodge Animal Health of Overland Park, Kan., a division of Wyeth Pharmaceuticals.

The vaccination involves two shots the first year and at least one recommended booster annually. Fort Dodge says it has sold about 6 million doses.

Fort Dodge has submitted a study to the U.S. Department of Agriculture, which issued the conditional license last year, supporting the vaccine's effectiveness.

Nathan Slovis, an internal medicine specialist at the Hagyard-Davidson-McGee equine hospital in Lexington, Ky., says in some states horses are getting multiple boosters annually.

"It looks like you may have to vaccinate up to twice a year in areas where you have high mosquito populations. In Florida, some people are giving it three, four times a year."

Veterinarians also say that as more horses are exposed to West Nile, they will develop their own immunities. Slovis says that for every horse that becomes ill from the virus, probably 100 that have it are "subclinical, which means they aren't showing any signs."

West Nile illness among horses "is skyrocketing, but it should slow down next year," Slovis says. "We're not going to have a naive population. . . . If they get exposed, their bodies will fight it and they won't have problems."

AS SEEN IN USA TODAY NEWS SECTION, THURSDAY, NOVEMBER 21, 2002, PAGE 1A

Cancer vaccine shows promise

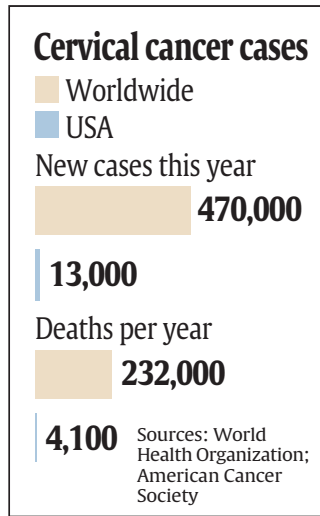
Cervical malignancy could be wiped out

By Rita Rubin
USA TODAY

Scientists have success-fully tested a vaccine against a virus that causes cervical cancer, moving them a step closer to virtually eliminating the second-most lethal malignancy in women worldwide, says a report out today.

Only breast cancer kills more.

Lasting infection from certain strains of a common sexually transmitted virus -- human papillomavirus, or HPV -- causes almost all cervical cancers. The experimental vaccine, which could be available within five years, was effective against the strain that causes about half of cervical cancer cases.



By Karl Gelles, USA TODAY

Scientists first linked HPV to cervical cancer in 1983. Researchers have identified more than 20 high-risk strains, which also are associated with less-common cancers. They are not the same strains that cause genital warts.

The new study tested a genetically engineered vaccine against HPV-16 in 2,392 women 16 to 23 years old. They were randomly assigned to the vaccine or to a placebo and over a six-month period received three shots. They were tested for HPV-16 DNA at enrollment, a month after the third shot and every six months thereafter for, on average, 18 months.

The vaccine contained particles resembling HPV-16's outer coat. These sheep in wolves' clothing can't infect people, but

they can generate high levels of antibodies against HPV-16. The widely used vaccine against hepatitis B, another virus that can cause cancer, liver in this case, uses the same approach.

Though previous trials were promising, they were not designed to show whether antibodies generated by the HPV-16 vaccine actually prevented the virus from causing lasting infections in women. The new study found that no woman who received the vaccine tested positive for HPV-16 more than once; 41 of the women who received placebo shots did. The main reported side effect was soreness at the injection site.

Merck Research Laboratories, which funded the study, is now testing a vaccine against four HPV strains: 16 and 18, which account for 70% of cervical cancers, and 6 and 11, which cause more than 90% of genital warts cases. Merck plans to test that vaccine on tens of thousands of women worldwide, says Kathrin Jansen, senior author of the study and director of vaccine research.

AS SEEN IN USA TODAY MONEY SECTION, MONDAY, DECEMBER 16, 2002, PAGE 1B

Smallpox vaccine costs raise questions

Hospitals, insurers, businesses concerned

By Julie Appleby
USA TODAY

The smallpox vaccination effort could raise costs for hospitals, health insurers and employers, a concern likely to pit them against the government over who will pay for vaccine-related medical care and lost work time.

The American Association of Health Plans, for example, is seeking assurance from the Bush administration that the government, not private insurers and employers, would pay for vaccine-related health costs.

Side effects range from mild fevers to life-threatening brain inflammations. One to two out of every million vaccinated is expected to die.

"We can't imagine that the government would have the expectation that the cost of a national homeland security program should be borne by employers and their employees," says association President Karen Ignagni. The health care industry's concerns include:

- ▶ Will workers' compensation cover lost work time for medical and emergency workers who volunteer to receive the vaccine? Those costs could increase worker compensation costs.

- ▶ Will the government set up an injury compensation fund, similar to one in place for injuries from childhood vaccines? Consumer advocates and labor unions say the smallpox program provides little chance that patients who sue the government for vaccine-related injuries would be compensated.

Secretary of Health and Human Services Tommy Thompson, in a press briefing Saturday, said most states are expected to pay workers' compensation for lost work time for medical or emergency personnel sickened by the vaccine. Modest death benefits are also available. Unions, however, say those amounts are likely to be inadequate.

Thompson also said that health care workers -- and private citizens who seek the vaccine -- would need their own health insurance to pay for any care needed to treat side effects.

"The next question you're going to ask me is, 'Is that fair?' because hospitals' workers' compensation rates might go up . . . or the health insurance premiums might go up," Thompson said. "The truth of the matter is that we have not done anything in that regard yet."

Just as states were given federal money for emergency vaccination plans, Thompson said there might be funds for "any further costs that may result as a result of this vaccination program." A compensation fund for victims is not yet being discussed, he said. Unions, health insurers and hospitals say they want such a fund.

"Let's say we have a young woman who works as a nurse and she . . . dies from the vaccine. Shouldn't we do something like we did for the victims of 9/11, provide the family with some compensation?" says James Bentley of the American Hospital Association.

AS SEEN IN USA TODAY LIFE SECTION, WEDNESDAY THROUGH THURSDAY, NOVEMBER 27-28, 2002, PAGE 17A

Smallpox vaccine carries a dose of risk

If every American gets the inoculation, health experts say thousands could get serious side effects; hundreds could die

By Anita Manning
USA TODAY

President Bush's expected plan to offer smallpox vaccination to about 1 million Americans in preparation for possible bioterrorism raises a host of questions about the risks of a vaccine that could cause life-threatening illnesses in some of the people it is intended to protect.

If, as expected, the White House endorses a plan to vaccinate roughly half a million health care workers and about that many military troops, experts say there will likely be at least some serious illnesses and possibly deaths caused by the vaccine itself. Yet, they say, if nothing is done to protect vulnerable Americans, a single case of smallpox could ignite an epidemic that could kill millions.

The Bush administration is likely to advocate a phased-in approach when vaccinating the civilian population -- starting with selected hospital staff and then expanding to emergency workers, police officers and other first responders.

One advantage of such an approach, observers say, is that it will provide experience and information upon which to base future public health plans, which could include offering the vaccine to everybody on a voluntary basis.

The last known case of smallpox occurred in Somalia in 1977, and the only legitimate stocks of the virus are locked in labs in Russia and at the Centers for Disease Control and Prevention in Atlanta. But scientists and military experts believe that clandestine stockpiles of smallpox exist in Iraq, North Korea and elsewhere.

As talk of war with Iraq heats up, concern about how best to protect the public has grown more urgent.

Smallpox is highly contagious and spreads from person to person through the air. It kills about a third of its victims and leaves many survivors blind or disfigured. The vaccine, which contains a live virus similar to smallpox called vaccinia, has not been used routinely in the USA since 1972, so almost all Americans age 30 or younger are completely vulnerable.

In October, a panel of public health experts, the Advisory Committee on Immunization Practices, endorsed vaccination of health workers in every state to create a pool of immunized doctors, nurses and others who could safely care for the first victims, should terrorists set the virus loose. In addition, the Pentagon is expected to vaccinate U.S. troops in advance of a possible war with Iraq.

For every million people who get the vaccine for the first time, the CDC says, there could be 1,000 reactions severe enough to require medical care, 14 to 52 that are potentially life-threatening, and one or two deaths.

If all Americans ages 1 to 65 were vaccinated today, as many as 4,600 serious illnesses and 285 deaths could result, according to a report published last spring in the journal *Effective Clinical Practice*.

Revaccination not as risky

Among people being revaccinated, side effects are far rarer, experts say. In Israel,

where about 12,000 health care workers, police and other emergency personnel were recently vaccinated, no serious reactions have been reported.

That's not a surprise, says Jerry Hauer, head of the Office of Public Health Preparedness at the Department of Health and Human Services. "The people they're choosing to vaccinate now have been previously vaccinated," Hauer says, so while U.S. officials are keeping a close eye on the Israeli experience, "it makes it difficult to take anything from it right now and try to look at what our experience potentially could be, if the president moves forward with the program."

More than a third of those vaccinated for the first time in a recent study got sick enough to miss work or other activities or had trouble sleeping.

If the vaccine were offered to all Americans as a precaution, about 25%, or roughly 70 million people, would be ineligible to take it because of health conditions such as cancer, AIDS or skin infections like eczema, which could put them at higher risk for serious vaccine side effects. People who have ever had eczema, even if the condition was mild, are at risk of eczema vaccinatum, a condition in which the virus in the smallpox vaccine spreads in the body and causes lesions over the area once afflicted by eczema. It is usually mild but can be severe and, in rare cases, fatal.

Pregnant women and people who live in households with immune-suppressed people or those with a history of eczema are also excluded from vaccination.

The vaccine poses a special risk to millions of people with impaired immune systems, such as those with HIV or who are undergoing chemotherapy or other medical treatments. They could contract potentially fatal vaccinia infection from recently vaccinated relatives or other close contacts.

Although some political leaders and parents groups have pushed for voluntary vaccination for all Americans, others urge caution. They cite historical data that found many of the illnesses associated

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with smallpox vaccine occurred in people who weren't even vaccinated; they contracted the vaccinia virus from household members.

Such infections can be treated -- though it's not clear how effectively -- with vaccinia immune globulin, or VIG, a substance taken from the blood of previously vaccinated people. Currently, there are 700 doses of VIG, which the CDC says is what would be needed if up to 6 million people were vaccinated. More VIG is being produced, and 3,000 more doses are expected to be available by March.

In addition to VIG, a drug called cidofovir, used to treat eye disease in AIDS patients, has been effective in animal studies. The CDC says there are 3,500 doses of it available, enough to treat the reactions expected if 15 million people were immunized against smallpox.

How much protection?

In healthy people, vaccinia virus prompts an immune response that provides full protection against smallpox for about five years, waning thereafter. Some experts say the millions of adults who received smallpox vaccinations as children might still have some level of protection against the disease, possibly enough to prevent death, if not illness.

The vaccine was used successfully in the global smallpox eradication effort of the 1960s and 1970s, but some scientists fear that terrorists could genetically alter the virus to create a vaccine-resistant strain.

While it's technically doable, scientists say, getting genetically altered smallpox into a form that could be used as a weapon, then testing and producing it, could be beyond the capability of terror groups. "We can't rule it out," bioterrorism expert D.A. Henderson said at a recent meeting, "but it seems unlikely, and very difficult."

Current stockpiles of vaccine -- 15.4 million doses that can be diluted five times to make 77 million doses, plus 80 million to 90 million doses of frozen vaccine -- were manufactured decades ago, but recent tests suggest they are still

potent, even when diluted. In addition, the Department of Health and Human Services has contracted to buy 209 million doses of vaccine produced using modern manufacturing methods. Those are going through FDA review. Still, health officials say there is already enough vaccine to protect every American from smallpox should an attack occur.

Despite its risks, many people are ready to roll up their sleeves. A national survey in May found that 59% of those polled said they would get the vaccine, even though it causes side effects.

Philadelphia pediatrician Paul Offit is not among them. A member of the Advisory Committee on Immunization Practices, which makes vaccine recommendations to federal health agencies, Offit says he has seen babies who suffered reactions to smallpox vaccine. He says that, in the absence of a single case of smallpox anywhere on earth, the vaccine is too risky to use.

"A vaccine that I would consider to be unsafe is a vaccine whose risks outweigh its benefits," he says. With smallpox, there is not enough information to make that call. "Its benefits are solely theoretical," he says. "It's a dilemma. This is a vaccine that absolutely has serious side effects, worse than any current vaccine."

Offit favors waiting until there is a confirmed outbreak of smallpox, then vaccinating anyone who may have had contact with the victim or victims, an approach known as "ring vaccination." Studies show that vaccination up to four days after exposure will prevent the disease, or at least minimize its severity. Even if vaccination is delayed up to seven days after exposure, doctors believe it will provide some protection.

New anti-viral medications that could be effective against smallpox are being developed, as are safer versions of the vaccine, Offit says. But it may be years before they're available, and in the meantime, no one knows how urgent is the threat.

"I think we can make a better vaccine," Offit says. "The question is, can we wait?"

Side effects can be severe

Smallpox vaccine side effects and the rates at which they have been found to occur:

Accidental transfer of vaccinia virus from inoculation site to elsewhere on the body
Rate: 529.2 per million first-time recipients; 42.1 per million for others
Common sites: Face, eyelid, nose, mouth, genitalia and rectum

Vaccinia rash
Rate: 241.5 per million first-time recipients; 9 per million for others
Symptoms: A rash, from a few lesions to all over the body
Severity: Usually does not require medical treatment

Eczema vaccinatum
Rate: 38.5 per million first-time recipients; 3 per million for others
Symptoms: Spread of vaccinia virus in people with pre-existing eczema or other skin disorders
Severity: Usually mild but can be severe

Progressive vaccinia
Rate: 1.5 per million first-time recipients; 3 per million others
Symptoms: Vaccine lesion fails to heal and spreads to nearby skin, causing tissue death
Severity: Frequently fatal for immune-suppressed people

Encephalitis, or brain swelling
Rate: 12.3 per million first-time recipients; 2 per million others
Symptoms: Brain swelling that causes fever, vomiting, headache, drowsiness, possibly coma.
Severity: 5% to 25% of affected patients die and another 25% have permanent neurological damage

Source: University of Minnesota, Center for Infectious Disease Research & Policy

For discussion

1. In the United States in 2002, there were 2 cases of rabies, 1 case of plague, and 14 cases of botulism. Discuss whether people should be vaccinated against rabies, plague and botulism.

2. Measles accounts for 10% of global mortality among children aged less than 5 years (approximately 1 million deaths annually). Discuss who, if anyone, should be responsible for providing vaccinations for children in underdeveloped and developing countries.

3. There are about 30 infectious diseases, from anthrax to yellow fever, on the bioweapons list. Assume that there are vaccines against all of them but there is not an infinite amount of money to manufacture the vaccines. What criteria would you use to decide what diseases to vaccinate against and who should receive vaccination?

4. Marie decided against the relatively new chickenpox vaccine and used her parents' method: She wanted her children to get chickenpox in order to develop natural immunity. Her two children did get chickenpox. Her son had a slight itching and skin vesicles, but her daughter was hospitalized for months with streptococcal cellulites and underwent several skin grafts after recovering. Marie's housekeeper contracted chickenpox from the children and subsequently died. Almost half of the deaths due to chickenpox occur in adults.

(a) What responsibilities do parents have for their children's health?

(b) What responsibilities do individuals (e.g., parents) have for the health of society?

(c) What rights do individuals have? Should vaccination be required by law?

(d) Vaccines are given to healthy people, so what risks are acceptable?

5. What would happen if we stopped immunizing?

Future implications

Vaccines have and will continue to play an extremely important role in preventive health care. Although there is a small risk of side effects, evidence supports the effectiveness of large-scale vaccine use to end and prevent dangerous pandemics. (In the U.S. alone, widespread vaccination has controlled the threat of measles, mumps and rubella, not to mention the eradication of smallpox. Polio vaccines can prevent selected diseases from ever occurring, and they are economical.)

The "perfect" vaccine would be swallowed and give lifelong protection. Researchers are developing edible vaccines by genetically modifying plants to produce the antigens necessary for vaccination. Bananas would be ideal because they are eaten raw, do not require expensive refrigeration, and can be grown in the tropics where vaccines are desperately needed.

At present, most vaccines contain the actual disease-causing viruses or bacteria, future vaccines will be genetically modified harmless viruses or bacteria or just DNA. This will avoid the need to grow disease-causing microbes and avoid the risk of infection associated with using the disease-causing microbe in a vaccine.

The large victories have come in the battle against infectious diseases. However, the future of vaccines will include protection against non-infectious diseases as well. Vaccines against pregnancy and cocaine addiction are also being investigated. And vaccines against cancers and Alzheimer's disease are being developed.

Additional resources

Cave, S. and D. Mitchell. *What Your Doctor May Not Tell You About Children's Vaccinations*. New York: Warner Books, 2001.
Provides definitions, balanced coverage of pros and cons, and authoritative references.

Centers for Disease Control and Prevention. <http://www.cdc.gov/nip/> Current vaccine news.

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Fenn, E.A. *Pox Americana*. New York: Hill and Wang, 2001.
An exciting story of politics and disease in the United States between 1775 and 1782.

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An interesting history of the use of smallpox itself as a vaccination against small pox.