Background Information on Vaccines

BMJ

The legacy of Edward Jenner

More vaccines of different types are reaching ever more people

Two hundred years after the pioneering clinical experiments of Edward Jenner, who inoculated humans with cowpox to prevent smallpox, we find ourselves at the threshold of a golden age of vaccinology. Much attention has recently been directed at the advances in modern biotechnology that are giving rise to exciting new vaccine candidates. Nevertheless, a long and arduous journey lies between being an innovative concept and becoming a licensed product that can serve as a public health tool. In fact, few concepts survive to become products. Less well appreciated are the advances in clinical vaccine testing that allow a vaccine to progress towards licensing; the epidemiological techniques devised to appraise its effectiveness after licensing, when the vaccine is used under real life conditions; and the tactics used to achieve high levels of vaccine coverage, particularly in less developed countries.

Biotechnology has opened entire new approaches to vaccine development, such as the rational and precise attenuation of bacteria and viruses to serve as live vaccines,[i] the direct inoculation with plasmid DNA encoding protective antigens ("naked DNA" vaccines), and the microencapsulation of antigens to enhance immunogenicity and modulate the kinetics and type of immune response.[ii] Consequently, at various stages in the pipeline we find vastly improved vaccines against infectious diseases for which vaccines already exist - for example, acellular pertussis vaccines containing purified antigens [iii] and a recombinant, single dose, live oral cholera vaccine [i] together with new vaccines against diseases for which immunoprophylaxis was previously unavailable (malaria, rotavirus [iv], and Lyme disease). Notably, several rotavirus vaccines that are advanced in clinical trials follow a "Jennerian" approach in which an animal (rhesus monkey or bovine) rotavirus strain is genetically manipulated (reassortant viruses) to express human rotavirus neutralisation antigens.[iv]

Vaccines are tested in a series of stepwise clinical trials. Phase 1 trials, performed in small numbers of adults, are early dose-response tests to detect common adverse reactions and provide an initial glimpse of whether relevant immune responses are generated. Most vaccine candidates never progress beyond phase 1. Phase 2 trials, which assess the vaccine in increasingly larger numbers of subjects, are typically placebo controlled to measure the rate of adverse reactions versus background rates of complaints. The level of shedding of a live intranasal influenza vaccine or of a recombinant live attenuated *Vibrio cholerae* 01 oral vaccine would also be examined in phase 2 trials, as would their propensity to be transmitted to household contacts and to survive in the environment.[v] For vaccines that will ultimately be used in infants and children, phase 1 and 2 trials must be undertaken in progressively younger subjects.

Particularly demanding is the design of phase 2 clinical trials to evaluate the reactogenicity and immunogenicity of the new multivalent combination vaccines in infants. As additional vaccines - such as hepatitis B, *Haemophilus influenzae* type b conjugate, and multiple component acellular pertussis vaccines - enter infant immunisation regimens, a way must be devised to administer them along with the fewest inoculations along with existing parenteral vaccines. The ultimate objective is to combine vaccine antigens into a single inoculation. This raises the theoretical possibility of interactions,[vi] so phase 2 trials must show that acceptable immune responses to all antigens can

indeed be stimulated without undue reactogenicity. Phase 1 and 2 trials of candidate AIDS vaccines also require special considerations.

In some cases, as with vaccines to prevent influenza,[vii] shigella dysentery,[viii] or *Plasmodium falciparum* malaria,[ix] preliminary assessments of efficacy can be obtained through carefully performed experimental challenge studies with wild type organisms in fully informed adult volunteers. Such modern day challenge studies are a direct legacy of Edward Jenner's experiments, although today the study protocols undergo stringent ethical review, and children, such as Jenner's young subject, James Phipps, would not be allowed to participate.

Large scale, randomised, controlled field trials remain the gold standard for showing the efficacy of a vaccine.[iii,x] Such trials tend to be expensive, require several years to complete, and are subject to the vagaries of year to year variation in the incidence of the disease. Moreover, in prelicensure efficacy trials the protective activity of a vaccine is measured under ideal conditions, with extra staff and with only fully vaccinated subjects included in calculations of efficacy. Therefore the practicality of use of the vaccine within a programme is not readily estimated. Estimating efficacy after licensing usually involves case-control studies, which are relatively inexpensive and simple to perform but have inherent limitations that can distort the estimation of efficacy.[xi] A few controlled postlicensure trials have directly measured the effectiveness of vaccine under real life, programmatic conditions.[xii]

Enhanced postlicensure epidemiological surveillance has proved its value by showing herd immunity effects (as with *H influenzae* type b conjugate vaccine) and consequences in those who are not the targets of the vaccine - for example, the rare occurrence of vaccine associated paralytic poliomyelitis in household contacts of infants who have received Sabin live oral polio vaccine.

The ultimate triumph of vaccines is disease eradication. In the mid-1970s smallpox vaccine deployed following special epidemiological strategies succeeded in eradicating the disease that Jenner attempted to prevent in the 1790s. Polio has been eradicated from the western hemisphere, and worldwide eradication is now a realistic goal. The World Health Organisation's expanded programme on immunisation, descended from the smallpox eradication programme, has devised practical solutions to maintaining a "cold chain" and delivering vaccines under field conditions in less developed countries. During the past decade the percentage of the world's infants who receive the basic vaccines of the expanded programme (BCG, DPT, oral polio, and measles) has risen from about 40% to over 80%.

Vaccines have come to be recognised by public health authorities as one of the most cost effective interventions available. Across the world, in both industrialised and developing countries, more vaccines of different types are being administered to increasingly larger segments of the population. This is the greatest tribute to Edward Jenner, who started it all 200 years ago.

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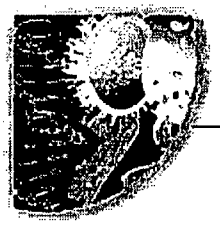

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EXPLORING
IMMUNIZATION **A Brief History of Vaccination**

It has been 200 years since a country doctor from England named Edward Jenner first discovered a way to vaccinate against the most dreaded disease of that time, smallpox. On May 14, 1796, Jenner applied the first vaccine by using cowpox to immunize James Phipps against smallpox.

Previous attempts for vaccinate date back to the 6th century. The first written record of vaccination, *The Correct Treatment of Smallpox*, attributed the art to a Buddhist nun practicing during the 11th century. And, it is widely accepted that vaccination was used in ancient times, in China, India and Persia.

Edward Jenner's work with cowpox vaccination was the first scientific attempt to control an infectious disease by means of a deliberate, systematic inoculation. Jenner's work laid the foundations of modern vaccinology. However, nearly a century elapsed before a French chemist, Dr. Louis Pasteur, previously noted for his studies of fermentation and bacteria, disproved the theory of spontaneous generation and advanced the germ theory of infection.

Pasteur was able to prove that protection against a disease could be afforded by the infection of weakened germs which cause silent and relatively harmless infections. The milestone in immunization for which Pasteur is most noted occurred in 1885. A boy named Joseph Meister was bitten by a rabid dog, and, for the first time in history, was successfully treated with a vaccine that prevented the development of rabies.

During the remainder of the 19th century, vaccine research continued. In addition to the early discovery that vaccines could be made with weakened germs, it was discovered during this time that vaccines could also be made with killed germs. Thus, at the turn of the century, there existed two human virus vaccines: Jenner's smallpox vaccine and Pasteur's rabies vaccine. Three human bacterial vaccines, typhoid, cholera and plague (all killed) also existed.

However, vaccination was not without its opponents. The thought of deliberately and routinely introducing a deadly virus - in any form - into a human being was met by many with horror and outrage. By the turn of the century, these opponents had organized against the new vaccines. Bitter battles were waged in the medical and scientific community, as well as in the arena of public opinion over the merits of vaccines. But, by the time World War I broke out, general vaccination was becoming routine. Soon thereafter, tetanus toxoid, a vaccine based on an inactivated toxin, was introduced.

The Golden Age of vaccine development began in 1949. New discoveries and improved techniques led to an explosion of creative activity in vaccinology. That interest, commitment and study continues today. Two of the most famous products developed during this period were the inactivated polio vaccine of Dr. Jonas Salk and the live polio vaccine of Dr. Albert Sabin. Other discoveries included now widely used vaccines against measles, mumps, rubella, hepatitis B and *Haemophilus influenzae* type b.

Recent vaccine development efforts have moved away from vaccines containing whole organisms and toward safer subunit vaccines containing only the components necessary to solicit satisfactory immune responses. Genetic engineering has been highly useful in this process. In the next decade, with its dominant hope for the development of an AIDS vaccine, the emphasis on safety will be paramount.

The 1990s and the early days of the 21st century may well mirror the 40 years after Pasteur's important rabies experiment, with public reaction forcing scientists to find even more ingenious and secure ways to protect humans against disease.

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Evolution of Vaccine Development

English physician Edward Jenner's observation that milkmaids stricken with a disease called cowpox were rarely victims of smallpox prompted him to devise the first vaccine 200 years ago. One of the world's great medical successes, a modern-day version of this vaccine led to the total eradication of smallpox by 1980. Since Jenner's time, advances in the science of virology, bacteriology, and immunology have led to an enhanced understanding of how the human body defends itself against invading microorganisms. The development of vaccines against more than 20 infectious diseases has revolutionized our approach to public health. Since 1980, at least 15 new or improved vaccines have become available. Today, tremendous advances in molecular biology enable scientists to devise new approaches to developing vaccines against diseases that continue to plague the world's population.

Scientists in the laboratories of the National Institute of Allergy and Infectious Diseases (NIAID) and NIAID-supported investigators at research institutions around the country are pursuing novel approaches to the development of new and improved vaccines. The Institute has fostered the development of vaccines against such diseases as influenza, pneumococcal pneumonia, pertussis, rubella, rabies, bacterial meningitis, hepatitis B, and adenovirus-associated respiratory disease. NIAID also supports innovative scientists who are using vaccine technology to combat autoimmune disorders and allergies.

Vaccines are made in a variety of ways, depending in part on the nature of the organism and the disease it causes. Animal viruses, weakened microbes, killed microbes, and toxins are the most common components of the vaccines that have been in use throughout much of the 20th century.

Animal Viruses

Unknown to Jenner, his vaccine worked because the cowpox virus he used, which does not cause severe disease in healthy humans, shares some proteins with its more virulent cousin, the variola virus that causes smallpox. These proteins, called antigens, stimulate the body's complex immune response, including the production of memory cells. The next time that an individual encounters that same antigen, the immune system is primed to destroy it quickly, before it can cause disease.

Jenner's approach to vaccines is still being used today. NIAID

investigators are using viruses that cause diseases in animals to make vaccines designed to offer protection against rotaviruses, the leading cause of infant diarrhea worldwide, and against parainfluenza viruses, which cause severe respiratory tract infections in children.

Weakened Microbes

In the late 19th century, the French microbiologist Louis Pasteur used another approach to create a vaccine against human rabies. The vaccine he developed, using weakened live rabies virus, was later refined, but his idea has been used to create many highly effective vaccines. Microbes weakened by growing them for many cycles in animals or in tissue cultures in the laboratory can be used to infect individuals without causing serious symptoms of the disease. Scientists have also created vaccines from naturally weakened strains of microbes that have been isolated from humans.

The oral polio vaccine is made from live, weakened virus as are vaccines for mumps, measles, and rubella. In addition, NIAID-supported researchers are using weakened viruses to create vaccines designed to protect against diseases caused by rotaviruses, respiratory syncytial virus, parainfluenza and influenza viruses.

Killed Microbes

A number of other vaccines have been developed from whole organisms that have been killed. Safe and relatively easy to produce, these inactivated vaccines do not cause infection in people who receive them, but they are able to stimulate the immune system. However, the immunity produced may be less complete and shorter lasting than that produced by a live vaccine or by natural infection. Such vaccines in use today include those against polio, whooping cough, and influenza.

Toxins

Some bacteria cause disease by producing toxins that invade the bloodstream. Around the turn of the century, the identification of the tetanus and diphtheria toxins led to another type of vaccine that stimulates the production of antibodies against these toxins. The diphtheria and tetanus vaccines are made from inactivated toxins and have been used successfully to prevent these diseases since the early 1900s. Improved vaccines against whooping cough (caused by the pertussis bacterium) that are made up of inactivated pertussis toxin and other toxic bacterial products of the pertussis organism have recently been demonstrated to be both safe and effective in preventing whooping cough in babies and young children.

Subunit Vaccines

Recent research has focused on developing vaccines that use only part of the infectious agent. Such subunit vaccines, which are now available for meningitis, pneumonia, typhoid, and hepatitis B,

produce the desired immunity without stirring up separate and potentially harmful immune reactions to the many antigens carried, for instance, on a single bacterium. Other subunit vaccines under development include those for respiratory syncytial virus and parainfluenza virus infections.

Conjugate Vaccines

Bacterial diseases such as pneumonia and meningitis cause considerable illness, disability, and death among babies and children in the United States. Some of the bacteria that cause these diseases have an outer coat that cannot be recognized by the immature immune systems of young infants, and therefore vaccines made from these bacteria are not effective in babies. In addition, these vaccines are of limited benefit to the elderly who have a diminished immune response.

NIAID-supported researchers and scientists at the National Institute of Child Health and Human Development devised a way to produce vaccines that link together proteins or toxins from a second organism to the outer coat of the bacteria. This enables a baby's immune system to respond to the combined vaccine and produce antibodies, immune system proteins that bind to the bacteria and prevent disease. The first of this new breed of conjugate vaccines was licensed in December 1986 to protect against *Haemophilus influenzae* type b (Hib), the major cause of bacterial meningitis in babies and young children. In 1990, two conjugate vaccines were licensed to protect against Hib in babies as young as 2 months. The widespread use of these vaccines has virtually eliminated Hib meningitis in the United States.

Vaccines Through Biotechnology

Through genetic engineering, scientists can isolate specific genes and insert them into the DNA of certain microbes or mammalian cells grown in the laboratory, which become living factories, mass producing the desired antigen. Then, using another product of biotechnology, a monoclonal antibody that recognizes the antigen, researchers can separate the antigen from all the other material produced by the microbe or cell. This technique has been used to produce safe vaccines that stimulate the human immune system against such organisms as the hepatitis B virus.

In another approach, scientists have inserted genes for desired antigens into the DNA of related but harmless viruses such as the vaccinia virus, a relative of the cowpox virus that was used in modern smallpox vaccines. When the re-engineered vaccinia virus is inoculated, it stimulates an immune reaction to both the vaccinia and the products of its passenger genes. These have included, in animal experiments, genes from the viruses that cause hepatitis B, influenza, rabies, and AIDS. Scientists similarly are using bacteria such as salmonella as vaccine vectors to carry portions of microbes.

Instead of adding a gene, some scientists have snipped a key gene out of an infectious organism. Thus crippled, the microbe can

produce immunity but not disease. This technique has been tried with the cholera bacterium and with herpes simplex virus.

DNA vaccines employ a new approach in which genes from disease-causing microbes are isolated and injected directly into a person. Some of these genes enter host cells, which then synthesize the proteins encoded by the injected genes. The foreign proteins elicit an immune response that may protect against subesequent infection by the microbe. A DNA vaccine against AIDS is now being tested in people.

A totally different approach to vaccine development lies in chemical synthesis. Once scientists have isolated the gene that encodes an antigen, they are able to determine the precise sequence of amino acids that make up the antigen. They then pinpoint small key areas on the large protein molecule, and assemble it chemical by chemical. Wholly synthetic vaccines are being explored for malaria and diarrheal diseases prevalent in developing countries.

Vaccines remain among the most powerful tools we have for disease prevention. Advances in biotechnology have ushered in a new era in vaccine development. NIAID has maintained a leadership role in the basic research and development of new and improved vaccines and will continue to nourish this exciting renaissance in vaccine development.

NIAID, a component of the National Institutes of Health, supports research on AIDS, tuberculosis and other infectious diseases as well as allergies and immunology.

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Vaccines--How and Why?

By: Bonnie A. Maybury Okonek and Pamela M. Peters, Ph.D.

History

Long before the causes of disease were known and long before the processes of recovery were understood, an interesting thing was observed: if people recovered from a disease, rather than succumbing to it, they appeared to be immune from a second bout with the same illness. Perhaps it was these types of observations that led the Chinese to try to prevent smallpox--a deadly disease characterized by pus-filled blisters--by exposing uninfected individuals to matter from smallpox lesions. This process, known as "variolation," took a variety of forms. One form consisted of removing pus and fluid from a smallpox lesion and using a needle to place it under the skin of the person to be protected. Another method involved peeling scabs from lesions, drying and grinding them to a powder, and letting an uninfected person inhale this powder. The third method involved picking up a small amount of the scab powder with a needle and then using the needle to place the powder directly into the individual's veins. Lady Mary Wortley Montagu, wife of the British Ambassador to Turkey, observed this third method in the early 1700s and brought it back to England. Although the effects of variolation varied, ranging from causing a mild illness in most individuals to causing death in a few, the mortality and morbidity rates due to smallpox were certainly lower in populations that used variolation than in those that did not.

One person who experienced variolation as a child in the late 1700s was Edward Jenner, a young boy who survived the process and grew up to become a country doctor in England. As a country doctor, Jenner noticed a relationship between the equine disease known as "grease" and a bovine disease known as "cow pox." He saw that farmers who treated horses with grease lesions often saw the development of cow pox in their cows, complete with blisters similar to those seen in smallpox infection. Unlike lethal smallpox, however, the cowpox blisters eventually disappeared, leaving only a small scar at the site of each blister.

At the same time, Jenner was interested when a milkmaid told him that she could not catch smallpox because she had had cowpox. Jenner noted that there were many people like the milkmaid - people who milked cows and who did not get smallpox even when exposed repeatedly. With this in mind, Jenner undertook a daring experiment in 1796: he infected a young boy with cowpox in hopes of preventing subsequent smallpox infection. After allowing the boy to recover fully from cowpox, Jenner - in an experiment that would be considered unethical by today's scientific community - intentionally infected the boy with smallpox by injecting pus from a smallpox lesion directly under his skin. As Jenner had predicted, the boy did not contract smallpox.

Although Jenner wanted to report his first case study in the Transactions of the Royal Society of London, his study was rejected. Despite this, Jenner went on to collect 23 case histories over

the next months and published his own book detailing his observations. The book was called "An inquiry into the causes and effects of the variolae vaccinae, a disease discovered in some of the western counties of England, particularly Gloucestershire, and known by the name of The Cow Pox." It soon became clear that Jenner's experiments had paid off, and that intentional infection with cowpox protected people from much more serious infection with smallpox. As a result, within a few years thousands of people protected themselves from the deadly smallpox disease by intentionally infecting themselves with cowpox.

Jenner's process came to be called "vaccination," after "vacca," the Latin word for cow, and the substance used to vaccinate was called a "vaccine." Now, some 200 years later, we have progressed from a time when vaccination was a rare event, and Jenner's theories about vaccination were not widely accepted, to the late 1900s when vaccines are so commonplace that most children receive multiple vaccinations before they reach their first birthdays. The result of such widespread vaccination has been a marked decrease in diseases which once ravaged the world's population. An example of this is smallpox: once a major cause of death world-wide, the smallpox virus is now found only in freezers in high-containment laboratories at the Centers for Disease Control and Prevention (CDC) in Atlanta and the Institute for Viral Preparations in Moscow.

How Vaccines Work

Disease causing organisms have at least two distinct effects on the body. The first effect is very obvious: we feel sick, exhibiting symptoms such as fever, nausea, vomiting, diarrhea, rash, and many others. Although the second effect is less obvious, it is this effect that generally leads to eventual recovery from the infection: the disease causing organism induces an immune response in the infected host. As the response increases in strength over time, the infectious agents are slowly reduced in number until symptoms disappear and recovery is complete.

How does induction of the immune response occur? The disease causing organisms contain proteins called "antigens" which stimulate the immune response. The resulting immune response is multi-fold and includes the synthesis of proteins called "antibodies." These proteins bind to the disease causing organisms and lead to their eventual destruction. In addition, "memory cells" are produced in an immune response. These are cells which remain in the blood stream, sometimes for the life span of the host, ready to mount a quick protective immune response against subsequent infections with the particular disease causing agent which induced their production. If such an infection were to occur, the memory cells would respond so quickly that the resulting immune response could inactivate the disease causing agents, and symptoms would be prevented. This response is often so rapid that infection doesn't develop - you are immune from infection.

How to Make Vaccines

Obviously, a live, virulent organism cannot be used as a vaccine because it would induce the very disease it should prevent. Therefore, the first step in making a vaccine is to separate the two effects of disease causing organisms. In practice, this means isolating or creating an organism, or part of one, that is unable to cause full blown disease, but that still retains the antigens responsible for inducing the host's immune response. This can be done in many ways. One way is to kill the organism using formalin; vaccines produced in this way are called "inactivated" or "killed" vaccines. Examples of killed vaccines in common use today are the typhoid vaccine and the Salk poliomyelitis vaccine.

Another way to produce a vaccine is to use only the antigenic part of the disease causing organism, for example the capsule, the flagella, or part of the protein cell wall; these types of vaccines are called "acellular vaccines." An example of an acellular vaccine is the Haemophilus influenzae B (HIB) vaccine. Acellular vaccines exhibit some similarities to killed vaccines:

neither killed nor acellular vaccines generally induce the strongest immune responses and may therefore require a "booster" every few years to insure their continued effectiveness. In addition, neither killed nor acellular vaccines can cause disease and are therefore considered to be safe for use in immunocompromised patients.

A third way of making a vaccine is to "attenuate" or weaken a live microorganism by aging it or altering its growth conditions. Vaccines made in this way are often the most successful vaccines, probably because they multiply in the body thereby causing a large immune response. However, these live, attenuated vaccines also carry the greatest risk because they can mutate back to the virulent form at any time. Such mutation would result in induction of the disease rather than in protection against it. For this reason, attenuated vaccines are not recommended for use in immunocompromised patients. Examples of attenuated vaccines are those that protect against measles, mumps, and rubella. Immunity is often lifelong with attenuated vaccines and does not require booster shots.

Some vaccines are made from toxins. In these cases, the toxin is often treated with aluminum or adsorbed onto aluminum salts to decrease it's harmful effects; after such treatment the toxin is called a "toxoid." Examples of toxoids are the diphtheria and the tetanus vaccines. Vaccines made from toxoids often induce low level immune responses and are therefore sometimes administered with an "adjuvant" - an agent which increases the immune response. For example, the diphtheria and tetanus vaccines are often combined with the pertussis vaccine and administered together as a DPT immunization. The pertussis acts as an adjuvant in this vaccine. When more than one vaccine is administered together it is called a "conjugated vaccine." Toxoid vaccines often require a booster every ten years.

Another way of making a vaccine is to use an organism which is similar to the virulent organism but that does not cause serious disease, such as Jenner did with his use of the relatively mild cowpox virus to protect against the similar, but often lethal, smallpox virus. A more recent example of this type of vaccine is the BCG vaccine used to protect against Mycobacterium tuberculosis. The BCG vaccine currently in use is an attenuated strain of Mycobacterium bovis and requires boosters every 3 - 4 years.

In addition, biotechnology and genetic engineering techniques have been used to produce "subunit vaccines" - vaccines which use only the parts of an organism yet which stimulate a strong immune response. To create a subunit vaccine, researchers isolate the gene or genes which code for appropriate subunits from the genome of the infectious agent. This genetic material is placed into bacteria or yeast host cells which then produce large quantities of subunit molecules by transcribing and translating the inserted foreign DNA. It is important to note that these subunit molecules are encoded by genetic material from the infectious agent, not from the host cell's genetic material. These "foreign" molecules can be isolated, purified, and used as a vaccine. Hepatitis B vaccine is an example of this type of vaccine. Subunit vaccines are safe for immunocompromised patients because they cannot cause the disease.

Vaccines are effective in preventing disease not only in individuals, but also in communities. This type of protection is called "herd immunity." When a disease spreads from one human to another, it requires both an infected individual to spread it and a susceptible individual to catch it. Herd immunity works by decreasing the numbers of susceptible people. When the number of susceptible people drops low enough, the disease will disappear from the community because there are not enough people to carry on the catch-and-infect cycle. The greater the proportion of vaccinated members of the community, the more rapidly the disease will disappear. This is the reason that school children are often required to be vaccinated before attending school. This required vaccination has resulted in the marked decrease of many once-common diseases including pertussis (whooping cough), polio, smallpox, and others. Look for the story of the Polio Vaccine in a future Classic Collection chapter. Viva la Vaccine!

For further information please see:

- Graphics-
  Making Vaccines
  Memory Cells and Immunity (S-345)
- Classroom Activities-
  Demonstrating an Epidemic
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The Role of US Government Agencies in Vaccine Research and Development

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Abstract

Gregory Folkers and Anthony Fauci (National Institute of Allergy and Infectious Diseases) discuss the role of US government agencies and the NIAID in particular, in the fight against infectious diseases and the part that vaccine research plays in this fight. From long term strategic decisions to specific research projects, Fauci and Folkers illustrate the federal commitment to vaccine development and how it has and can impact both national and international health. (Nature Med 1998; 4(5 Suppl): 491–494)

Introduction

In this century, vaccines have without question been among our most powerful tools for preventing disease, disability and death and controlling health care costs. Recognizing the extraordinary benefits of vaccines, US government agencies charged with protecting and improving the public health have traditionally made vaccine research and development a top priority. Together with academic and industrial partners, government-supported scientists have helped develop many of our most useful vaccines, as well as several that will become available in the near future. These include new or improved vaccines that protect against rabies, *Haemophilus influenza* type b, pneumococcal pneumonia, pertussis, influenza, measles, mumps, rubella, hepatitis A and B, typhoid fever and rotavirus[1,2].

Successes and Challenges

Safe and effective vaccines, along with the operational expertise and political commitment to

administer them, have facilitated some of the greatest successes in public health. Globally, smallpox has been eradicated, poliomyelitis is on the verge of elimination, and other serious diseases such as measles have been dramatically reduced in many regions. Each year, vaccines against these three diseases alone save an estimated 7–8 million lives. By using measles vaccine in National Immunization Days and more widespread administration of currently available vaccines against rubella, hepatitis B, and *Haemophilus influenza* type b, another 3 million deaths could be prevented every year[3].

In the US, dramatic progress has been made against many serious diseases (Table 1). Age-appropriate vaccine coverage in the period June 1996 to June 1997 reached an all-time high, meeting or exceeding each of the targets set in President Clinton's 1993 Childhood Immunization Initiative[4].

The impact of vaccines in the United States		
Disease	Peak incidence (year)	1996 cases
Diphtheria	206,939 (1921)	2
Measles	894,134 (1941)	508
Mumps	152,209 (1968)	751
Pertussis	265,269 (1934)	7,796
Polio, paralytic (wild poliovirus)	21,269 (1952)	0
Rubella (German measles)	57,686 (1969)	238
Rubella, congenital syndrome	20,000 (1964-5)	4

Table 1. Impact of vaccines in the US.

Despite these encouraging developments, infectious diseases remain the leading cause of death worldwide, and the third leading cause of mortality in the US. Of approximately 52 million deaths worldwide from all causes in 1996, more than 17 million were due to infectious diseases, including approximately 9 million among children. In 1996 alone, an estimated 4.5 - 6 million deaths were attributed to two diseases, tuberculosis and malaria, for which no effective vaccines are available[5]. Vaccines also are lacking for many other serious infectious diseases that exact an enormous toll worldwide, such as sexually transmitted diseases (other than hepatitis B), respiratory syncytial virus and dysentery due to *Shigella* spp[2].

In addition to endemic diseases, we face the ongoing threat of new and re-emerging diseases and the widespread development of antimicrobial resistance, which underscore the need for a strong commitment to the development of new and improved vaccines. At least 30 newly recognized diseases and syndromes have been identified since 1980, including the acquired immunodeficiency syndrome (AIDS) and its etiologic agent, the human immunodeficiency virus (HIV). As a vivid reminder of the ever-present threat of disease emergence, the first known human cases of H5N1 avian influenza were identified in Hong Kong in 1997[6]. The multinational response to this outbreak has been extraordinary, including the US government's collaboration with industry in producing a recombinant vaccine for use in at-risk laboratory and health care personnel.

Resistance to antimicrobial agents has been observed in virtually all classes of organisms, resulting in a diminished capacity to treat many serious infections. For example, more than one-third of nosocomial *Staphylococcus aureus* infections in the US are resistant to methicillin, leaving

vancomycin as the only reliable therapy [7]. We were given pause for thought in recent months when *S. aureus* isolates with increased resistance to vancomycin were identified for the first time in Japan and the US[7,8]. The threat of malaria also has been exacerbated by the widespread development of drug resistance. Among the 100 countries and territories where *Plasmodium falciparum* malaria is endemic, only Central America and Egypt have not recorded cases of chloroquine-resistance[9]. Resistance to fansidar and mefloquine is also common in many areas. As is the case with many diseases that disproportionately affect the developing world, an effective malaria vaccine is essential if this disease is to be controlled.

Collaborations and Commitment

Most currently available vaccines, as well as those in the development "pipeline," have resulted from collaborations between partners in the public and private sector, including federal and state governments, small and large companies, academic research institutions and non-governmental organizations [10-12].

The importance of vaccine development and the necessity for strong cross-sector partnerships have been recognized at the highest levels of government, both internationally and in the US. Last year, for example, the participants in the Denver Summit of Eight stressed their shared commitment to developing an HIV vaccine. Both Congress and President Clinton have made immunization, including vaccine research and development, a top priority, and the President has articulated the goal of developing an HIV vaccine within ten years. At the National Institutes of Health (NIH), funding for vaccine research and development has increased approximately 65 percent overall from fiscal year 1993 to fiscal year 1999[13]. NIH and other national research agencies are partners in the Children's Vaccine Initiative (CVI), launched in 1990 with the goal of developing safe, affordable and heat-stable vaccines that can protect children against the infectious killers of childhood with a minimum of doses given orally early in life[3]. Congress has twice targeted funds in support of the CVIs work in facilitating the development, production, technology transfer, procurement and introduction of new vaccines. More recently, NIH helped establish the Multilateral Initiative on Malaria (MIM), an international consortium of government agencies, research organizations and donor agencies working to mobilize the scientific resources and political will needed to develop malaria control strategies and notably, a vaccine[14].

The private sector also has demonstrated a renewed commitment to vaccine development, thanks in part to revisions in product liability laws and new technology transfer legislation which have facilitated interactions between government, academia and industry[15,16,17]. Moreover, recent advances in gene cloning and expression, peptide synthesis and other technologies have created unprecedented opportunities for developing patentable "bioengineered" vaccines that promise a substantial return on research and development costs[15].

The Government Players in Vaccine Research

Within the federal government, more than 20 different agencies have a role in vaccine research[10-12]. Among these, the Centers for Disease Control and Prevention (CDC), the Department of Defense (DoD), the Food and Drug Administration (FDA), the United States Agency for International Development (USAID) and the NIH are the federal agencies with the largest investment in vaccine development[10-12].

The roles of these different agencies in vaccine development are related and complementary, and span the spectrum from basic research to licensure and program implementation[10-12]. For example, CDC conducts epidemiologic studies and surveillance needed to define health priorities, and develops recommendations for vaccine use through the Advisory Committee on Immunization Practices (ACIP). DoD performs research into vaccines that will protect against pathogens likely to be encountered by military personnel. USAID supports research on vaccines of particular relevance to young children in developing countries. The FDA establishes standards for the processes, facilities and pre- and post-licensing studies needed to insure the safety and effectiveness of vaccines. And the NIH supports much of the basic and clinical research in fields such as immunology and microbiology that leads to vaccine development. In addition, the NIH supports Vaccine Evaluation Units (VEU) and AIDS VEUs around the country, with broad capabilities to conduct prophylactic and therapeutic studies in children, adults and the elderly, as well as specific high-risk populations.

At the NIH, we have identified three broad goals in vaccine research:

- Identifying new vaccine candidates to prevent diseases for which no vaccines currently exist
- Improving the safety and efficacy of existing vaccines
- Designing novel vaccine approaches, such as new vectors and adjuvants.

The federal government also has an important coordinating function through the National Vaccine Program Office which is responsible for the coordination of government and nongovernment activities on research, licensing, production, distribution and use of vaccines[10-12]. As noted above, several government agencies are partners in the CVI, a global coalition working to maximize protection against infectious diseases through the development and use of safe, effective, easy-to-deliver and widely available vaccines. Coordination of national malaria vaccine efforts is conducted through the Malaria Vaccine Coordinating Committee, which has developed new collaborations among federal agencies. In addition, programs such as the National Cooperative Vaccine Discovery Group bring together experienced investigators from academia, industry and government to facilitate the conceptualization, discovery and development of HIV vaccines. These consortia follow leads from basic studies of virology, microbiology, molecular biology, immunology, genetics and structural biology to design vaccine strategies[18].

Decisions regarding the federal government's vaccine priorities are made on the basis of current morbidity and mortality data, recommendations by advisory groups such as the National Vaccine Advisory Committee, and evaluations made by the Institute of Medicine (IOM) of the National Academy of Sciences. In this regard, a new IOM study on Vaccine Research *Priorities for the 21st Century*, to be published in 1998, will provide a useful roadmap for developing vaccines for both infectious and non-infectious diseases such as cancer and autoimmune diseases.

Setting the Stage for Product Development

NIH and other agencies actively pursue research portfolios that involve interaction with industry and academia and the transfer of technology to the private sector for commercialization. Historically, an important focus of these efforts has been to further explore concepts that may not be of immediate financial interest, including those for which the principal market might be less developed nations, but nonetheless are of great potential public health importance.

For example, 25 years ago, when very little was known about viruses that cause gastrointestinal diseases, NIH researchers helped identify rotavirus as the leading cause of severe diarrhea in infants and young children[1]. They embarked on the development of a rotavirus vaccine, and after a series of pivotal discoveries developed a rhesus rotavirus-tetravalent (RRV-TV) vaccine to protect against the four clinically important strains of the virus. Having demonstrated the feasibility of this approach, which probably would not have been pursued alone by industry, the NIH team signed a Cooperative

Research and Development Agreement (CRADA) with a leading vaccine manufacturer in 1987, which began commercial development of the RRV-TV vaccine. Subsequently, the vaccine has proven safe and efficacious in both developed and developing countries. Widespread use of the RRV-TV vaccine promises to reduce the enormous global burden of rotavirus diarrhea, which claims the lives of an estimated 870,000 children annually[19].

The government also plays a critical role in vaccine development by providing scientists with reagents that might not otherwise be shared because of proprietary interests. Of growing importance are repositories such as the AIDS Research and Reference Reagent Program of the NIH, which now stocks over 1,100 reagents for public distribution, including viruses, proteins/peptides, cell lines, recombinant DNA clones and antibodies[20]. Other repositories provide genetically altered mice and research materials relevant to malaria and other diseases. The critical role of such repositories was cogently demonstrated most recently during the Hong Kong outbreak of H5N1 avian influenza. Fortuitously, as part of NIH's long-standing research into respiratory viruses, the specific antiserum needed to identify the H5N1 avian influenza strain was available in sufficient quantities from the NIH to quickly develop test kits for detecting the avian influenza virus. CDC, WHO, the Hong Kong Department of Health and other collaborators used these kits in their extraordinarily successful public health response to the outbreak[21].

DOE

A number of government agencies, including DoD and NIH, support projects to sequence the genomes of medically important pathogens. Sequence information can be used in many ways, including identifying antigens to incorporate into vaccines. The success of the first microbe sequencing project—the delineation of the complete *Haemophilus influenzae* genome in 1995—encouraged the current government-sponsored efforts to sequence the full genomes of many other pathogens, such as *Plasmodium* spp., *Mycobacterium* spp., *Chlamydia trachomatis*, *Vibrio cholerae* and *Neisseria gonorrhoeae*[22]. These sequencing efforts have beenfacilitated by technologies such as DNA chip technology and microarrays that enable the rapid, simultaneous analysis of tens of thousands of genes and hold particular promise in the development of libraries of immunologically important genes. Among many possible uses, such gene libraries will provide a powerful tool to rapidly identify DNA vaccine candidates.

Successful Partnering

Vaccines are complex products, and the process whereby a vaccine is developed and tested requires many steps (Fig. 3). The various partners in vaccine development bring perspectives, resources and skills that are sometimes unique, but more often overlapping and complementary. Industry provides expertise in product development and manufacturing, while many governmental efforts focus on creating and expanding the scientific base in disciplines that underlie product development[10-12].

A prototypic example of a successful partnership across sectors is the development of acellular pertussis vaccines[23]. In the 1930s, the US recorded more than 200,000 cases of pertussis each year. With the development and widespread use of whole-cell pertussis vaccines, morbidity and mortality related to pertussis declined dramatically wherever the vaccines were widely used. However, despite their proven record, concerns about the side effects of whole-cell vaccines resulted in a decrease in their use in many parts of the world, and a concomitant increase in pertussis cases[1].

These and other concerns stimulated the search for an effective acellular vaccine that would have fewer side effects, thereby removing barriers to the immunization of infants and perhaps adults as well. Basic research in government and university laboratories helped provide the insights that enabled industry to develop candidate vaccines. Phase I and Phase II clinical trials of these products, supported by industry and government, were conducted at academic medical centers. International efficacy trials, funded and overseen by industry and government through CRADAs and other

mechanisms, and facilitated by public health officials through intergovernmental channels, helped provide the safety and efficacy data necessary for licensure[23]. These new vaccines are at least as effective, and less reactogenic than "whole-cell" pertussis vaccines. Acellular pertussis vaccines are now recommended for all doses in the childhood immunization schedule in the US[24]. The widespread availability of these well tolerated vaccines will remove a major disincentive to pertussis immunization in the US and abroad.

The integration of expertise brought to the vaccine development process by various partners will continue to be crucial to dealing with the challenges posed by infectious diseases. As we prepare for the public health challenges of endemic, emerging and re-emerging diseases, it is imperative that a robust commitment to basic research and cross-sector collaboration be maintained. Only with such collaborations can we successfully translate basic research findings and technological advances into improved health through immunization.

As we approach the 21st century there is a growing awareness that we are increasingly living in a global community. The concept of the US government playing a contributory role in the fostering of global health has been the subject of increased attention. This was evident in the justification of the FY 1999 National Institute of Allergy and Infectious Diseases budget before the House Appropriations Subcommittee on the Departments of Labor, Health and Human Services, Education, and Related Agencies[25]. In this regard, the contribution of the federal government to vaccine research and development will be critical.

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Acknowledgements
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Basic Information about AIDS vaccines

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HIV Vaccine Glossary

Why an AIDS Vaccine

Although recent treatment advances have led to an encouraging downturn in the number of new AIDS cases and AIDS-related deaths in this country, the epidemic continues to accelerate elsewhere in the world. In 1997 alone, approximately 5.8 million people globally were newly infected with HIV, including approximately 590,000 children under age 15.

According to a detailed, country-by-country analysis of HIV prevalence released earlier this year by UNAIDS, approximately 5.8 million people worldwide were newly infected with HIV in 1997 alone. More than 90 percent of these new infections occurred in developing countries, where antiretroviral therapy is beyond the reach of all but the privileged few. Alarmingly, in 27 developing countries, HIV prevalence more than doubled between 1995 and 1997. The prevalence of HIV infection is highest in the African nations of Botswana and Zimbabwe, where more than 25 percent of adults are now HIV-infected.

Globally, one in every 100 adults 15 to 49 years of age is HIV-infected; at least 80 percent of these infections are due to heterosexual transmission. By the end of 1997, an estimated 30.6 million people worldwide were living with HIV/AIDS, including 1.1 million children younger than 15 years of age. Since the beginning of the HIV/AIDS epidemic, at least 8.2 million children younger than 15 have been orphaned because of the premature deaths of HIV-infected parents.

Current worldwide statistics can be found at the WHO.

Other information sources:

- Intensifying the Global Response to HIV/AIDS - Statement by Dr. Peter Piot, Executive Director UNAIDS to the United states House of Representatives International Relations Committee, September 16, 1998
- UNAIDS Report July 1998 - HIV preventive vaccine trials in developing countries
- UNAIDS report October 1998
- The Need for a Vaccine Against HIV-AIDS - Edward

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Smallpox: The beginning of vaccines, the end of a disease

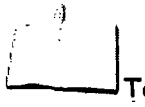
Throughout history, there has never been anything small about smallpox, except perhaps the variola virus that causes it. A very old, deadly, and virulent disease, smallpox was often portrayed as the Grim Reaper himself. It occurred in two forms: variola major, which killed 20% or more of its victims, and variola minor, which killed 1%.(1) In its typically widespread epidemics, one percent was often rendered in the thousands.

Smallpox began somewhat like the flu, with chills, high fever, nausea, and aches. Within a few days, however, its characteristic rash of unsightly, painfully swollen pustules declared itself. The disease spread with devastating ease from one individual to another by way of droplets from the nose and mouth (for example, in sneezing), contact with the dried scabs of the pustules, or even contact with clothing or articles used by people with smallpox. It took about 12 days from exposure to the time the disease became evident; consequently, care givers of people with smallpox often caught the disease and then followed the first wave of victims to the grave within a matter of weeks.

The numbers of people killed by smallpox in previous centuries are so large that they are numbing. Some authors credit smallpox with the collapse of both the Aztec and Incan empires,(2) civilizations that had prospered for centuries in South America, Mexico, and nearly halfway into the North American continent. Some historians think smallpox emerged when humans first began to grow their own food, around 12,000 years ago.(3) From that time forward, every human era was marked by the presence of smallpox. Anthropologists have determined that eruptions evident on the skin of an Egyptian mummy of the 20th dynasty (1200-1100 B.C.) originated in smallpox.(4) From the earliest days of Europe, epidemics hung like a perpetual thundercloud over human society. As Thomas Babington Macaulay, a 19th-century British historian and statesman,(5) observed, "The havoc of the [bubonic, or "black"] plague had been far more rapid: but plague had visited our shores only once or twice within living memory; and the smallpox was always present...."(6) In 1519, the Spanish brought the disease to Mexico, where three and a half million Indians died.(7) In the 17th and 18th century, entire tribes in North America were wiped out by smallpox.(8) In the North American colonies, those who could, would flee to the countryside when the first case in a new epidemic appeared.(9) Epidemics often followed the course of a river or trails taken by traders and explorers. Many people who survived this highly contagious disease bore its mark forever in unsightly scars, and many were left blind. However, survivors truly triumphed, because having the disease and surviving it made them immune to having it again. Recognizing a similar, cross-over effect in milkmaids who contracted cowpox--they appeared to be immune to smallpox--Dr. Edward Jenner began late 17th- and early 18th-century efforts to rid humanity of this scourge.

On May 14, 1796, Dr. Jenner performed an experiment that demonstrates how desperate people were to find some way to prevent this terrible scourge. He innoculated (vaccinated) a boy with matter taken from pustular cowpox lesions. Several weeks later, he challenged the success of the first inoculation by vaccinating the boy with smallpox. It was a tremendous risk, but it worked. The boy didn't develop smallpox. . Following publication of the results in June, 1798, Jenner predicted the eventual eradication of smallpox. It took more than two centuries to prove him correct.

Jenner was hardly the first to observe that inoculation could prevent disease. Folk methods had been tried in many cultures, most of them relying herbs, magic, religious objects, prayers, incantations, and ultimately, luck. In some countries where more than one God was worshiped, there were gods to whom one prayed specifically for protection against smallpox.(11) Medical practitioners in a number of ancient cultures had made observations about resistance to smallpox and had experimented with methods of immunization. Around 1700, nearly a century before Dr. Jenner's experiment, the practice of variolation--inoculation of a healthy person with pus from an infected person's smallpox lesions--was first tried in England, but the practice is believed to have originated in Africa and was learned from slaves.(12) In 1716, Cotton Mather, a member of the clergy, author, scholar, and physician in Boston,(13) sent Dr. John Woodward, an English physician, a vivid description of inoculation, as it had been described to him by one of his slaves, Anesimus.(14) The difference between the African method and Jenner's method was that Jenner involved a third party (cows) and a milder form of the disease (cowpox). His work opened the door to immunization as we know it today.



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Why we don't need smallpox vaccinations today

Through massive vaccination efforts, smallpox has been wiped out. This historic victory occurred in this century, in the lifetimes of today's grandparents, parents, and children.
The one weakness of the variola (smallpox) virus is that it survives by being passed from one person to another. Public health officials worldwide joined together in the 1970s to take advantage of this weakness. They undertook to interrupt the cycle of smallpox through an intensive immunization and monitoring effort. In effect, by immunizing humans, they were removing the human incubator from the cycle, one vaccination at a time.
This was a huge task, involving many densely populated countries with limited health, technology, and communications facilities. Nevertheless, the effort succeeded. The last case of variola major occurred on Bhola Island in Bangladesh in October, 1975. The last case of variola minor was in Ethiopia in August, 1976. Although smallpox had been a nearly constant companion for twelve millennia, no one grieved over its quiet departure.
Because smallpox has been eradicated, smallpox vaccination has ceased everywhere. Travelers no longer need certificates to prove vaccination against this disease.(15) The children born at the end of this century may be puzzled by the small, round scars on their parents' and grandparents' upper left arms, the last scars left by smallpox.

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Pneumococcal disease

Streptococcus pneumoniae (pneumococcus) bacteria is a leading cause of illness in young children. In the elderly, such infections can be deadly.
The terms *pneumoniae, pneumococcus*, and *pneumococcal* refer to the *S. pneumoniae* bacteria, not to the illness *pneumonia*, although pneumococcal bacteria can indeed cause a form of pneumonia. *S. pneumoniae* sets up camp in the upper respiratory tract: nose, sinuses, ears, and throat. From there, they launch widespread invasive infections in the blood, central nervous system, brain, upper and lower respiratory tracts, and ears. They have a particular affinity for the environment in the respiratory tracts and ears of little children. The ear infections they cause account for more than 24 million visits to pediatricians each year. The chart below shows the annual tally of human miseries that begins with *S. pneumoniae.*

Table. Annual number of cases of diseases associated with Streptococcus pneumoniae bacteria, and the groups in the United States most at risk of having

*these diseases**

Disease	Affecting	Group(s) most at risk of having the disease	Number of cases each year
Meningitis	Brain, central nervous system	Certain Native American tribes; Alaskan natives, especially children under age 2 yrs.; other children age 6-24 months; all adults 65 yrs. or older	3,000
Bacteremia	Blood	Certain Native American tribes; Alaskan natives, African Americans; all children, all adults 65 yrs. or older.	50,000
Pneumonia	Lungs	Certain Native American tribes; Alaskan natives, all ages; all children; all adults 65 yrs. or older	500,000
Otitis media	Ears	Children under age 4 yrs.	7,000,000

*Source: Advisory Committee on Immunization Practices. Prevention of pneumococcal disease. Morbidity and Mortality Weekly Review April 4, 1997; 46(RR-8):1-25.

The highest incidence rates for invasive pneumococcal disease (such as meningitis or bacteremia) in any U.S. population have been reported among specific American Indian groups, such as the Apache.

Alaskan Natives of all ages have an eight- to ten-fold higher risk of meningitis or bacteremic pneumonia than do any other groups in the U.S. population.

Black adults have three to five times greater incidence of bacteremia, compared with white adults.

The worst of the *S. pneumoniae* infections, of course, are those that get into the bloodstream or central nervous system. Pneumococcal infection causes death in 40,000 people per year, making *S. pneumoniae* the number one killer among all vaccine-preventable bacterial diseases. About half of the lives lost to pneumococcal infections could be saved through use of the pneumococcal vaccine.

Meningitis and bacteremia are the most lethal of the pneumococcal diseases. The highest proportion of deaths from pneumococcal infections occurs among the elderly and people who have underlying medical conditions. As many as 91% of adults who have invasive pneumococcal infection have at least one of the conditions described in the chart below.

Table 2. Underlying health problems that place people at greater risk of pneumococcal infections or severe pneumococcal disease*

Type of health problem	Age group affected	Explanation/examples
Chronic cardiovascular disease	Adults (especially elderly)	Congestive heart failure Cardiomyopathy
Chronic pulmonary disease	Adults (especially elderly)	Chronic obstructive pulmonary disease (COPD) Emphysema
Chronic liver disease	Adults (especially	Cirrhosis

	alcohol abusers)	
Some diabetes mellitus complications	Adults	Cardiovascular dysfunction Kidney dysfunction
Asthma, but only as indicated	Adults	Only if associated with chronic bronchitis, emphysema, or long-term use of systemic corticosteroids
Asplenia	Children and adults	Spleen surgically removed Spleen in place but not functioning due to disease such as sickle cell anemia
People who are unresponsive to the pneumococcal vaccine or who have certain types of reduced immune resistance	All ages	Congenital (inherited) immunodeficiency HIV infection Some cancers: leukemia, lymphoma, multiple myeloma, Hodgkins' disease, generalized malignancy Organ or bone marrow transplantation Certain drug treatments: alkylating agents, antimetabolites, systemic corticosteroids Chronic kidney failure or nephrotic syndrome

* Source: Advisory Committee on Immunization Practices. Prevention of pneumococcal disease. Mortality and Morbidity Weekly Review April 4, 1997; 46(RR-8):1-25.

People in this group are at the highest risk of all for pneumococcal infection, because of the vital role that the spleen plays in filtering impurities (in the case of pneumococcal disease, encapsulated bacteria) from the blood.

Children with sickle cell disease or who have had their spleen removed are at increased risk for widespread, severe pneumococcal infection in the blood and death from that infection.

S. Pneumoniae is the most common source of bacterial pneumonia in people with HIV infection.

Since introduction of a vaccine to prevent *Haemophilus influenzae* type b (Hib disease), *S. pneumoniae* has also taken the lead as the most common cause of bacterial meningitis in the United States. Nevertheless, among children, death from pneumococcal infection is relatively uncommon, except in those who have meningitis, those whose immune system is compromised (for example, by AIDS or by chemotherapy treatments), and those who have had spleen removal and develop severe bacteremia.

The pneumococcal vaccine is given in one injection. Repeat doses are not needed in people who received a first dose at age 65 or older, but vaccination can be repeated after five years in people over 65 who had the first dose before turning 65. Some people find it convenient to get this vaccine at the same time as an influenza injection, but the injections are separate and in different arms. Pneumococcal vaccine can also be combined with other vaccines in the same way. The vaccine is especially appropriate for: children over age 2 years, people 65 years or older, people aged 2 to 64 years who are at increased risk of pneumococcal disease because they have chronic illness, especially those listed in Table 2; and people aged 2 to 64 years who live in settings where risk of pneumococcal disease is increased (for example, Alaskan Natives, Native Americans, and people in nursing homes). The vaccine is not recommended for routine use in healthy children who attend day-care facilities.

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Get the facts on other vaccine-preventable diseases

The home page of the National Immunization Program offers information about the following diseases and vaccines:
Pertussis (whooping cough) Varicella (chicken pox, shingles)
Diphtheria Meningococcal
Tetanus Influenza
Diphtheria-tetanus-pertussis (DTP) vaccine Cholera
Acellular pertussis vaccine Bacillus Calmette Guérin (tuberculosis vaccine)
Polio Japanese encephalitis
Measles Typhoid
Mumps (Bubonic) plague
Rubella Rabies
Haemophilus influenzae type b Vaccinia (smallpox)
Hepatitis A Yellow fever

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National Vaccine Program Office
Centers for Disease Control and Prevention (CDC)
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Are vaccines safe?

Yes, vaccines are very safe. Today, the United States has the safest, most effective vaccine supply in history.

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I'm hearing so many different things about vaccines. I don't know whom to believe.

Studies have shown that most parents rely on their child's physician for advice on vaccination decisions. In particular, pediatricians and family practitioners have taken special, intensive training in infant and child health. No one knows your child's health and medical needs better than the health professional who routinely cares for your child.

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Are vaccines effective?

Vaccines are both effective and cost-effective. "Effective" does not mean that every individual who has vaccination is 100% protected. No vaccine can

accomplish that kind of guarantee. Effective means that most vaccinated people will be protected, particularly when a high proportion of people in a population are immunized. That is why protection from disease involves more than one step. As explained in the Immunization Concepts section of this page, three steps are needed: immunization of the individual, community immunity, and practical measures to prevent disease outbreaks.

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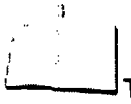
Is it true that vaccines can cause side effects?

There is some risk associated with *any* medical procedure or medication, and immunization is no exception. Side effects of immunizations range from redness and warmth of the skin where a vaccine was injected, to more serious effects, including damage to the central nervous system or death. However, the risk of such a serious event is extremely small. As a rule, the risk of contracting the disease, and of dying or suffering serious or permanent complications of that disease, is far greater than the risk of dying from the immunization.



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Is it true that polio vaccination causes polio?

It is true that in *extremely rare cases*, one of the two types of polio vaccine can cause polio. This type of polio is referred to as vaccine-associated paralytic polio, or VAPP.
The two types of vaccine are *oral polio vaccine* (OPV), which was introduced in 1961 and contains live but weakened polio virus, and *inactivated polio vaccine* (IPV), in which the virus is killed. OPV, as the name implies, is given orally. IPV is injected. With each type, four doses must be given.
About eight or nine people per year develop VAPP as a result of the OPV vaccine. The estimated rate of cases is one per 2.4 million doses distributed, or one case to every 750,000 children receiving their first dose of OPV.
In hopes of eliminating this risk altogether, the Advisory Committee on Immunization Practices (ACIP) published recommendations on January 24, 1997, for a transition period in which use of OPV would be reduced, and use of IPV would be increased.

Specifically, ACIP recommended:

1. Use of IPV, followed by OPV. On this schedule, resistance to polio would develop as a result of the IPV injection; therefore, it would be safe to have OPV in the second, third, or fourth dose.
2. OPV alone, for certain cases. For example, ACIP stated that this schedule would be better for children who begin the primary vaccination schedule after 6 months of age.
3. IPV alone, for certain cases. For example, ACIP recommended IPV alone for children with immune suppression.

The preferred method recommended by ACIP is two doses of IPV, followed by two doses of OPV. Implementation of these recommendations should reduce the risk for VAPP and would help providers to make the transition to using only IPV, says ACIP.
To visit the home page of a consumer group dedicated to reducing the risk of VAPP, click here.

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Can I or my child get AIDS, or the HIV virus, or chronic fatigue syndrome from vaccines?

No. There is no evidence that vaccine supplies today are contaminated or that they are capable of causing HIV, AIDS, chronic fatigue syndrome, or other health problems.


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Do vaccines cause fibromyalgia, rheumatoid arthritis, arthritis, or lupus?

After decades of vaccine use in the U.S., current research shows no definitive evidence proving vaccines cause chronic illness.
According to the Arthritis Foundation, there is no known link between vaccines and fibromyalgia, rheumatoid arthritis, or lupus, and while the number of persons with these conditions has been rising, the statistics do not support alarm over these increases.(1) In considering the increases, it's important to remember that rheumatoid arthritis (a type of arthritis that causes systemic inflammation, as well as joint problems), arthritis, and lupus are primarily diseases of middle and older age. A very large segment of the American population--the so-called "baby boomers"--are now entering the ages when these diseases occur, so an increase in the numbers of cases is to be expected.
Perception of increases in fibromyalgia incidence may be because this disease has only recently been defined, and it is just in the past decade that physicians have known that the various symptoms of fibromyalgia (chronic muscle aches and pains, "trigger points" of pain, and chronic, sometimes overwhelming fatigue) do constitute a specific disease. Thus, it is not possible to know whether the number of cases detected these days represents an increase over that which occurred previously.
Arthritis, on the other hand, is not a "new" disease. Evidence of osteoarthritis (arthritis confined to the joints, where one bone meets another) has been found as far back as the mummies of ancient Egypt. Its incidence increases with age. In a comprehensive 1994 study of adverse events associated with vaccination, the Institute of Medicine reviewed the possibility of a link between diphtheria and tetanus vaccines--these vaccines are generally given in combination--and arthritis. The Institute found that it is *biologically possible* for these immunizations to be associated with arthritis, primarily because the tetanus toxoid has the potential to induce serum sickness, which is a source of a *temporary* form of arthritis. However, the Institute also found that the evidence available in scientific studies up to 1994 was inadequate to determine whether this biologically possible link actually occurs. Since those findings were reported, one group of researchers found a link between rubella vaccine and temporary, acute arthritis, arthralgia (joint pain) or myalgia (muscle pain) when the vaccine was administered within 12 months of giving birth.(2)Another group found no evidence of any increased risk of developing chronic arthritis, arthralgia, or myalgia within the 12 months following vaccination; the women in this study were of childbearing age.(3)
Similarly, the Institute found that a link between hepatitis B vaccine and acute or chronic arthropathy (inflamed, painful joints) also is biologically plausible, but the studies available are inadequate to accept or reject a causal link to vaccination. A link between the disease, hepatitis B, and arthropathy has been proven.(4)


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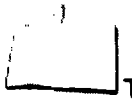
Who should not have vaccinations

If you have questions or concerns about the appropriateness of a particular immunization for yourself or your child, you should consult with your health care

provider, who knows your individual circumstances best.
In general, any person who has had an anaphylactic (shock) reaction to an immunization should not have that vaccine again. A mild to moderate local reaction, such as soreness, redness, or swelling after injection of a vaccine, is not an indication for withholding a vaccination.
Any person who has had an anaphylactic reaction to an ingredient contained in a vaccine (for example, egg protein, which is contained in influenza and yellow fever vaccines)(6) should not have that vaccine.
The Advisory Committee on Immunization Practices recommends that "All vaccines can be administered to persons with minor illness such as diarrhea, mild upper-respiratory infection with or without low-grade fever, or other low-grade febrile illness."(7) Anyone who currently has a moderate or severe illness, with or without a fever, should delay vaccination until restored to health.
Live vaccines, such as oral polio vaccine, should not be given to people whose immune system is suppressed by congenital immunodeficiency, HIV infection or AIDS, leukemia, lymphoma, generalized cancer, cancer therapies, or high-dose corticosteroids. (8)
The complete general recommendations on immunization are spelled out in the Recommendations of the Advisory Committee on Immunization Practices,(9) which are available on the CDC National Immunization Program home page.

**For additional information on this topic, click here to go to the National Immunization Program site.*



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Do vaccines cause cancer?

As explained by the National Immunization Program in its Vaccine Safety Fact Sheet, after decades of vaccine use in the United States, current research shows no reliable evidence proving that vaccines cause chronic illness. The term "chronic illness" includes cancer.

Questions have been raised from time to time, by various researchers, about the role of components or unique substances that may be found in vaccines and cancer. The most current questions are addressed in a technical document, "Selected Issues on Immunizations."

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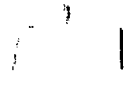
Do vaccines cause autism?

Autism is a neurologic condition--a problem that occurs in the brain and central nervous system. It is usually identified at the ages of 18 months to 30 months, the same ages at which some vaccinations are given. For example, a child who is receiving vaccinations on the recommended schedule would receive three doses of diphtheria, tetanus, and acellular pertussis (or pertussis) vaccines, plus a "booster" of the DtaP or DTP combination; three doses of oral polio vaccine; at least one dose of the measles/mumps/rubella combination; two or three doses of the *Haemophilus influenzae* type B vaccine; and the hepatitis B vaccine by 30 months.(10) The symptoms are absence or delay of speech development and lack of interest in interacting with others. Sometimes autism results in loss of already acquired speech and social skills, which gives the impression that some external event may have caused damage that leads to autism. There is no scientific evidence to date that autism and immunizations are linked. According to very recent findings of experts in the field of neurology, autism appears to result from prenatal dysgenesis; that is, a specific set of brain abnormalities that occur while the fetus is developing in the womb. (11)



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Can I get animal diseases from vaccines that are made using animal cells?

This question arises from time to time because animal cells are used in the manufacture of some vaccines. Today, manufacturers are required to test cell lines used for the presence of a variety of infectious agents, to prevent contamination of vaccine products. There is no evidence that currently available vaccines are contaminated with infectious agents that cause disease.

Although it is quite biologically possible for animal viruses to be transmitted to human beings, it is not a simple matter. Viruses that establish themselves and then thrive in one species are dependent upon the genetic and biochemical make-up of that species to continue to survive. They may--but do not always--find an acceptable genetic and biochemical environment in another animal species. To cross species, the virus may have to evolve--possibly over thousands of years and millions of spontaneous "trial-and-error" mutations--to become sufficiently adaptable to cross to another species, and adequately matched to the environment of the second species to survive there. New strains of influenza, which can develop in birds, adapt in pigs, and then be transmittable to humans is one example of a virus that can do this. This topic is more fully discussed in the Vaccine Safety.

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Can't I just "wait and see" on my child's vaccinations?

Delaying a child's vaccinations is inadvisable for several reasons. First, the recommended schedule for childhood vaccinations is not an arbitrary schedule. In developing vaccines, scientists must take into account:

- The ages at which the vaccine is safe for a child, taking into account a number of developmental factors, including height and weight
- The age at which certain diseases are most likely to strike
- The situations in which the child might be exposed to diseases, for example, by entering day care or kindergarten
- The period of time in which the vaccination continues to provide protection or a booster shot becomes necessary

Second, disease outbreaks occur even in vaccinated populations, and children who are not vaccinated are at risk of getting the disease and of infecting others. Some diseases that are typically not too severe in children can have serious consequences in adults. Varicella (chicken pox), for example, is usually (although not always) not severe in children, but it can be quite serious in adults. Between January and April, 1997, state health departments reported three fatal cases in which women of ages 23, 25, and 32 died. The two younger women had previously been in good health. The 23-year-old contracted the disease from her children (ages 2 and 5), who were not vaccinated against the disease. The 32-year-old woman, who had Crohn's disease (a condition that can be managed with diet and medication) caught chicken pox from 4-year-old niece, who also had not been vaccinated against the disease.(12)
Mumps can cause sterility in men. While rubella (German measles) is usually mild in children and adults, up to 90% of infants born to mothers infected with rubella during the first three months of pregnancy will develop congenital rubella syndrome, resulting in heart defects, cataracts, mental retardation, and deafness. (13) A decision to withhold vaccinations from your child puts your child, other children, adults, and even your future grandchildren at risk of diseases that can be prevented.
Third, unless you qualify for a religious or philosophical exemption (the laws vary among states), your child's entry into school could be delayed until you comply with your state's school vaccination requirements. If you do qualify for an exemption, you must take responsibility for the health of your own child and

for the children and adults who come into contact with your child. An unvaccinated child will be at risk of becoming infected even when other children are not yet ill but are incubating the infection and able to spread the disease. In the event of an outbreak of vaccine-preventable disease in the community, schools usually require that children who are not protected by vaccination remain at home, from the first case through the last--which may mean 30 to 60 days at home. Any child with an infectious disease should be isolated at home to prevent its spread to others. Keep in mind that there are many people in any community whose resistance to disease is low: for example, people who are being treated for cancer, people who have immune disorders, and elderly people. To protect these people, a parent of an unvaccinated child must take constant precautions. Realistically, since the symptoms of many childhood illnesses look much like cold or flu symptoms, even the most cautious parent will not always be able to recognize symptoms that merit isolation.

**The Advisory Committee on Immunization Practices is a panel of experts who convene regularly to review current vaccine schedules and new and improved methods of administering vaccines. Based on their recommendations, vaccination schedules may change. For information on the current recommended schedule of vaccinations for children, call the National Immunization Program's hotline at 1-800-232-2522 (English) or 1-800-232-0233 (Spanish), or click here to go to the National Immunization Program's homepage.*

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Can epidemics occur today? In the United States?

They can and they do. In every country and every region where immunization levels drop, fresh outbreaks of disease follow. Thanks to the protection provided by immunizations, few young people living in the United States today have any idea of what it's like to live through an epidemic of a highly infectious, deadly disease. Our grandparents may well remember the dread they felt when their child--or a neighbor's child--developed a summer cold, which often signaled a developing case of polio. Fortunately, we now have vaccines to prevent polio and many other diseases. All of the generations of people who lived on earth before this century lived under constant threat of diseases that spread rapidly into epidemic proportions, sweeping away entire families, tribes, or towns. Even today, millions of people who do not have immunization in their community experience this threat.

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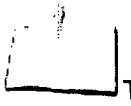
Are we safe from epidemics?

We are safe from many diseases, in large measure because we have the technology and good fortune in this country to develop and distribute vaccines quickly and routinely, and because the majority of our population has been vaccinated and community immunity is in effect.

The diseases that we have controlled through vaccination still exist, and there is no safety in hiding, especially in today's world. Increasingly, national borders are blurred and the separation created by geographic distances is minimized. We may travel more in a week, and rub shoulders with more people, than our grandparents did in a lifetime. Travel and travelers are increasingly a source of exposure to diseases. Early data analysis showed, for example, that in 1996, 488 confirmed cases of measles were reported in the U.S., and a substantial proportion of these cases had been "international importations" (cases brought into the U.S. by persons who had traveled). The sources of the imported cases included Germany, Greece, Japan, Austria, India, the Philippines, China, Italy, Russia, England, Kenya, Liberia, Nepal, Somalia, Tahiti, and Turkey.(14)

Another set of outbreaks was linked to school-aged American children who were not required to receive a second dose of measles vaccine to attend school. To read the complete text of these reports, click here.

We conduct business around the world, travel to distant nations where vaccinations are not widely available, vacation in exotic places where we may plunge into jungles, climb isolated mountains, and explore hidden caves--or we work with people who do these things. As our suburbs expand into fields and woods, we are pressing into the abodes of living things we have not encountered in many years, or may never have encountered, and some of them harbor viruses that can cause sickness in people. A chance encounter may be just that--a chance to acquire a disease that can result in sickness and death.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Why must my child have so many shots?

As we have increased the number of vaccinations that are available, the number of shots a child receives has indeed gone up. The miracles of technology have created a "crisis of opportunity." While there is no known consequence of having so many injections,[15] no one wants to subject children to unnecessary discomfort. For this reason, vaccine developers are working on alternative and less discomforting methods of administering vaccines. Among those being tried are combination vaccines, which will reduce the number of injections required. New ways to give vaccines, such as by mouth or by inhaling an aerosol, are also being explored. Also, pediatricians and vaccine experts are working together to develop new schedules that will reduce the number of injections that are needed at any one visit or altogether.


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Aren't there some chemicals and other substances added to vaccines?

Yes, chemicals are added to some vaccines in very small amounts and for specific purposes (for example, to boost the action and strength of the vaccine). Details on the additives used are available in a fact sheet posted on the CDC National Immunization Program site.


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I got a flu shot and I still came down with the flu. Why?

Influenza vaccine has an excellent track record in preventing disease. It is 70% to 90% effective in healthy people younger than 65, if a good match has been made between the vaccine and the circulating viruses, and if the vaccinated individual's immune system is functioning properly.(16)
There are several possible explanations for getting a flu-like illness after an influenza immunization.

- One is that you didn't have the flu at all--that you acquired another virus, disease, or condition that caused flu-like symptoms, which are common to a number of other ailments. There are many viruses that can cause flu-like symptoms that wouldn't be prevented by influenza vaccine. Diseases like fibromyalgia, rheumatoid arthritis, and chronic fatigue syndrome can cause aches, pains, and fatigue that resemble the flu.
- Second is that for any of a number of reasons, your immune system didn't respond properly, or as folks sometimes say, "Your vaccination

didn't 'take'."
- Second is that for any of a number of reasons, your immune system didn't respond properly, or as folks sometimes say, "Your vaccination didn't 'take'."
- A fourth possibility is that the vaccine you received was not strong enough or had not been stored properly. This has occurred occasionally.
- And yet a fifth is that you had already been exposed to the flu before you received the vaccine.

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If you didn't find the answer you need in this section...

Call the CDC National Immunization Program hotline at 1-800-232-2522 (English) or 1-800-232-0233 (Spanish), or visit the National Immunization Program's home page .

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Do you have a question you think should be answered here?

Submit your question on our comments line. We are unable to answer inquiries individually, but will do our best to respond by improvements and additions to this web site. Click here to go to the comments line.

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Footnotes

1. Arthritis Foundation. Letter of May 15, 1997: "There is no evidence that defects in vaccine administered to newborns and children are contributing to a current explosion of chronic neurological and immune system dysfunction in the American population including lupus and rheumatoid arthritis. This certainly is not true in lupus, rheumatoid arthritis, or juvenile arthritis....Certainly the term explosion is not justified. The current scientific data reveals that the causes of lupus and rheumatoid arthritis are a combination of genetic susceptibility and then a variety of factors stimulating the immune process....I am not aware of any findings linking childhood immunizations with lupus or rheumatoid arthritis."

2. Tingle AJ, Mitchell LA, Grace M, et al. Randomised double-blind placebo-controlled study on adverse effects of rubella immunisation in seronegative women. *Lancet* 1997;349:1277-1281.

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11. Rapin I. Current concepts: Autism [review article]. *New England Journal of Medicine* July 10, 1997; 337(2):97-104. The full text of this review article can be purchased through the Journal's online service at http://www.nejm.org.

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National Vaccine Program Office
Centers for Disease Control and Prevention (CDC)
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http://www.cdc.gov/od/nvpo/qa.htm

Better Than a Cure

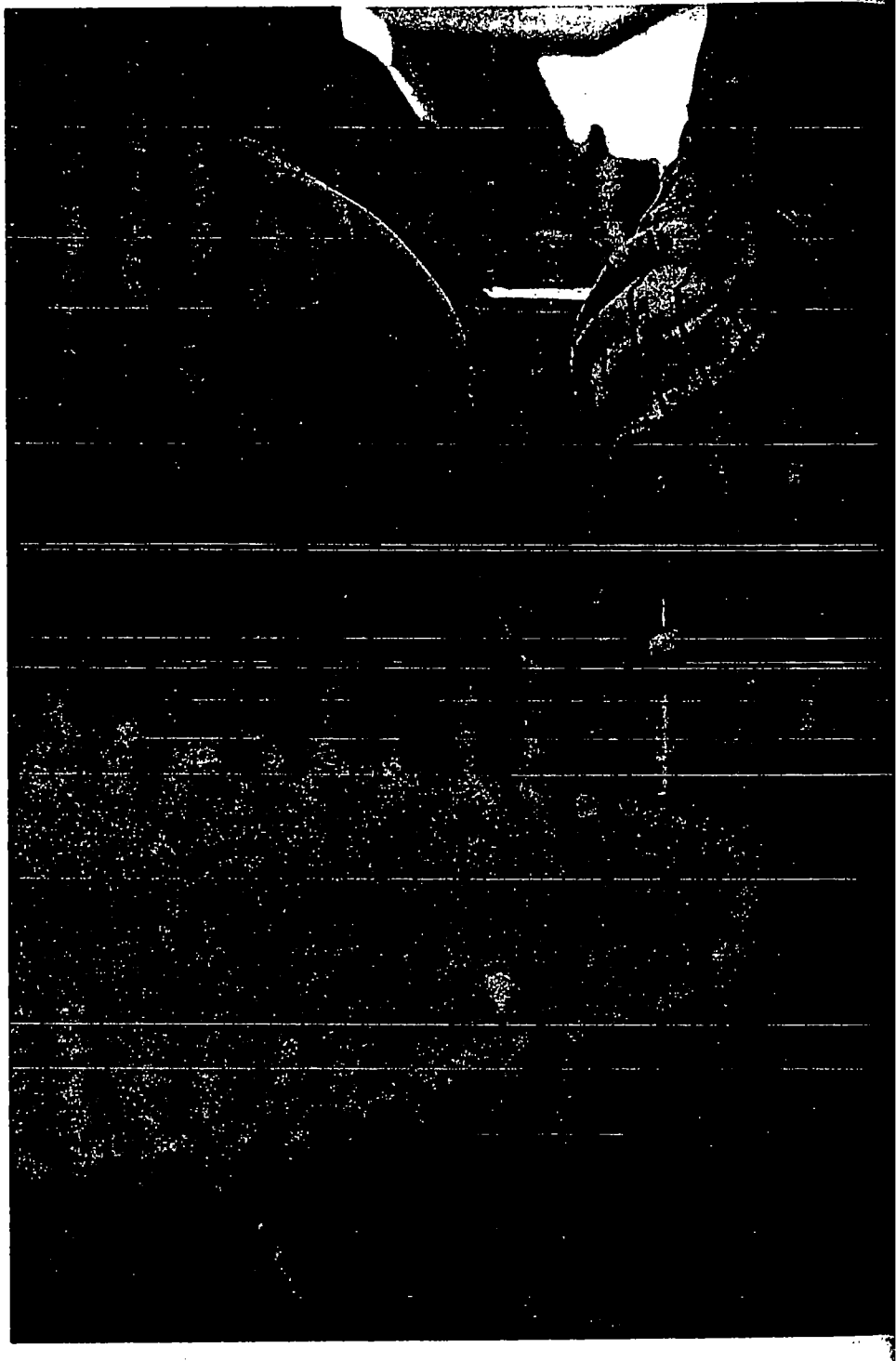
by Tim Beardsley, *staff writer*

When cholera started killing thousands of Rwandan refugees in camps in Zaire last summer, nobody was more frustrated than Jerald C. Sadoff of the Walter Reed Army Institute of Research in Washington, D.C. As chair of a World Health Organization (WHO) committee on vaccines for diarrheal diseases, Sadoff had been trying unsuccessfully for months to raise about $200,000 for research into vaccines against a newly identified strain of cholera. It took pictures of sickness and death beamed around the world from the camps to focus international attention on the disease; relief agencies eventually spent $140 million in emergency aid to contain the outbreak. "It did seem ironic," Sadoff recalls.

The episode highlights some of the difficulties faced by vaccine science. The benefits of immunization are invisible, yet governments as well as ordinary citizens are most easily persuaded to reach into their purses for medical research when they see suffering. Likewise, even though it is in the public interest for people to be well immunized, healthy individuals are unwilling to pay much for vaccines. Most pharmaceutical companies therefore avoid making them. In consequence, the global effort to develop new and more effective vaccines is small in comparison with other areas of medical research.

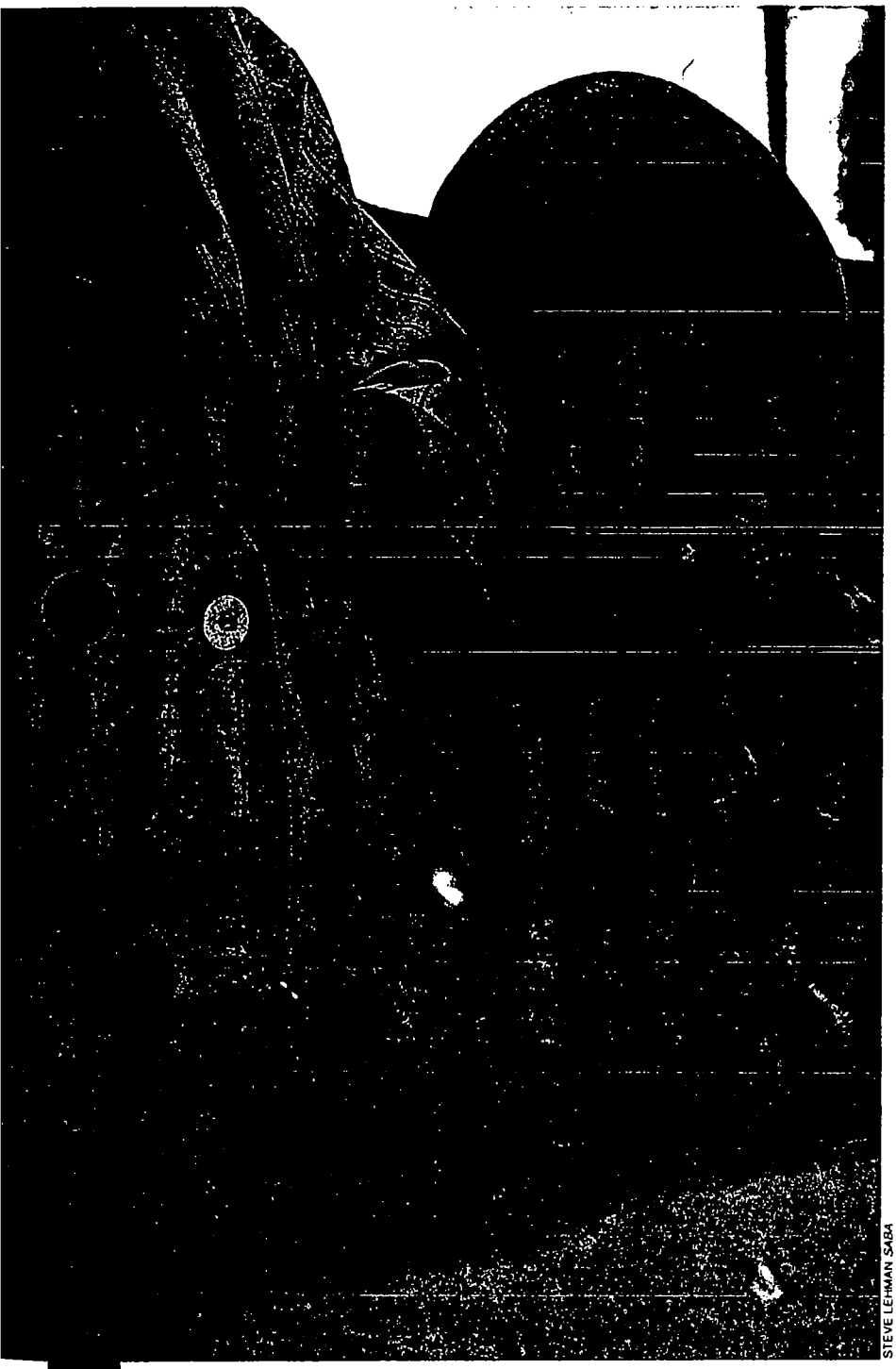
Infectious disease is still the number-one cause of death worldwide. Microbes of one kind or another kill more than 13 million every year, mostly infants. Acute respiratory infections take the biggest toll among the young; in 1992 they killed about 2.8 million children younger than five years. Diarrheal diseases took another 2.2 million, and malaria carried off a million.

Vaccines offer the best hope for reducing the appalling toll. Immunization is, simply, the best medicine. Not even antibiotics can touch it in terms of cost-effectiveness. According to David Parker and Terrel Hill of UNICEF, immunization against measles, tetanus and tuberculosis costs from $2 to $15 per "discounted year of healthy life" gained (a statistical measure of the value of a vaccine). Other common interventions cost from $25 to $1,000 for the same



VACCINATIONS against measles are administered to Rwandan refugees at a camp in Tanzania. Such immunization campaigns assume an especially high priority in situations where there is crowding and poor sanitation. Vaccines save lives and prevent disease more cost-effectively than

The World Health Organization wants industry to step up its efforts to develop new vaccines. Can big business and a public health bureaucracy see eye to eye?



STEVE LEHMAN SABA

...y other form of medication. The technical means for developing new vaccines for a variety of fatal illnesses are improving steadily. Money for vaccine research remains a limiting factor, however, and often vaccines fail to reach those whom they would benefit most.

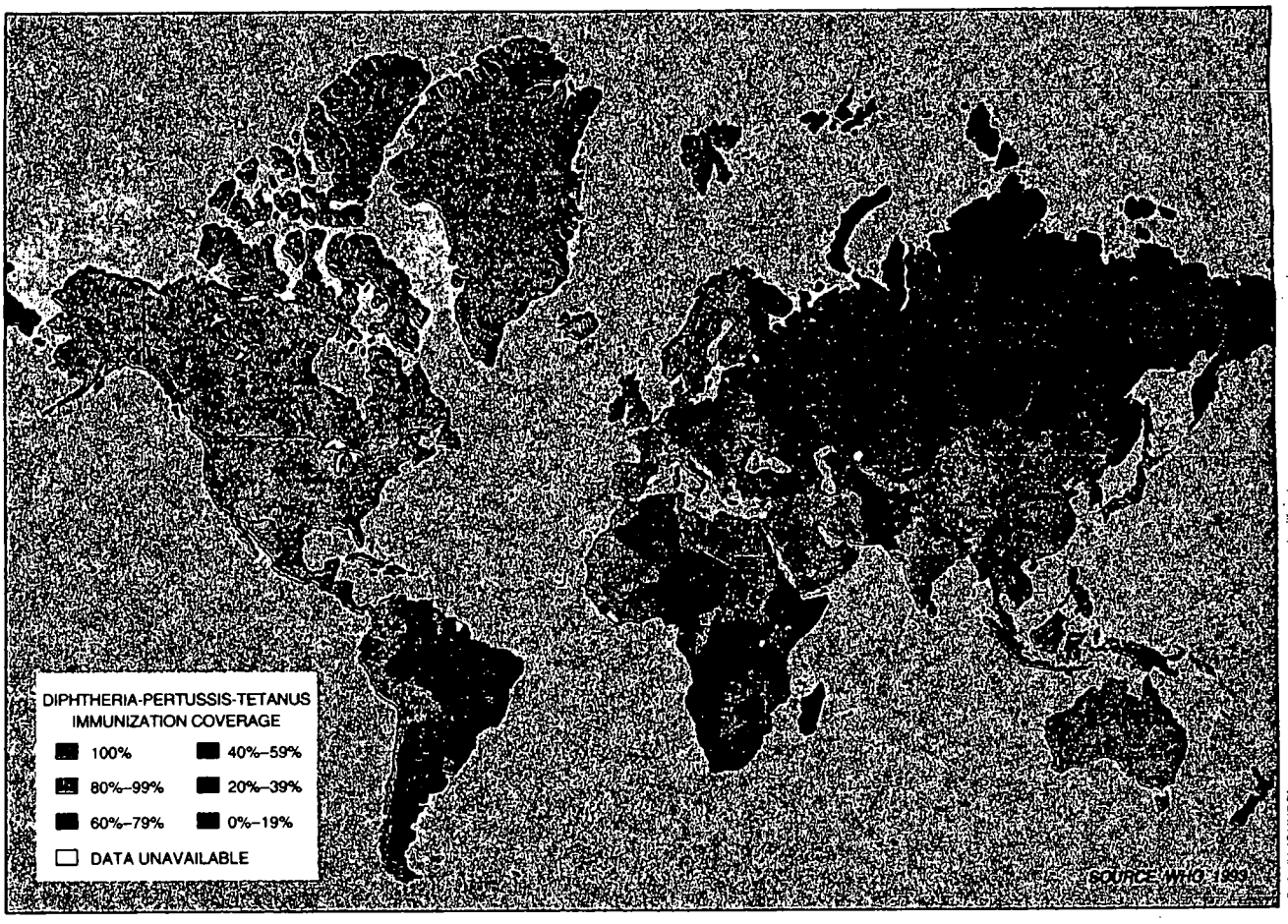
benefit. Moreover, vaccination is extremely safe. Although some serious reactions have been linked to the current generation of pertussis (whooping cough) vaccines, the risk is tiny in comparison with the threat posed by contracting the disease itself, which in the 1980s killed more than 500,000 a year worldwide. Pertussis vaccines now in clinical trials should be even safer.

Some public health experts have worried that the large reductions in death rates brought about by immunization might in poor countries be offset by children dying at greater rates from other causes, such as starvation. But the available data do not support that notion, Parker and Hill say. They even suggest that decreasing death rates from disease seem to lead to lower birth rates, presumably because women feel the need to have fewer children when more survive.

Much could be achieved merely by ensuring that today's vaccines reached all the people who could benefit from them. That step alone would save about two million lives every year, WHO calculates. Even in the U.S., an estimated 500 children die every year from diseases that could have been prevented by vaccination. Influenza, hepatitis B and pneumococcal pneumonia kill more than 500,000 adults annually in the U.S.; many of those deaths could have been avoided if available vaccines were more widely used.

There seems to be no argument among the players in the vaccine business that even larger gains against microbes are achievable with new and improved products. In the past, vaccine development was as much an art as a science. But scientific advances in recent years have pointed to fresh approaches, some of which are already proving themselves. "From an immunologic perspective, the state of knowledge is such that the art of vaccination can soon be grounded on a rational rather than an empirical basis," declares the 1993 edition of *The Jordan Report*, a survey of vaccine developments published once a year by the National Institute of Allergy and Infectious Diseases (NIAID).

At present, only about 20 different types of vaccine are in widespread use.



IMMUNIZATION RATES vary widely. The map shows the proportion of infants receiving all three doses of diphtheria-pertussis-tetanus vaccine. The vaccine is one of five the World Health Organization recommends for use globally. Rates for poliomyelitis, measles and tuberculosis tend to track those shown here; for hepatitis B, coverage is more patchy.

Yet there is no shortage of leads for novel products. A survey conducted by the NIAID has identified 192 vaccine candidates that are ready for early testing in people or animals. New disease targets aside, there is plenty of room for improvement in existing products. Measles vaccine, for example, does not work in infants younger than nine months, so many children die from the illness before that age. Typhoid vaccine is unreliable. The bacillus Calmette-Guérin (BCG) vaccine against tuberculosis is only partly effective; as a result, more than three million people die of that infection every year, most of them young adults. With the spread of multidrug-resistant strains, that total seems likely to increase.

Purely practical considerations connected with delivering vaccine to its recipients are often a major hurdle. Most vaccines are sensitive to heat, so a refrigerated "cold chain" stretching from the manufacturer to the patient has to be established. The challenge can be daunting in regions where temperatures may reach more than 40 degrees Celsius and where the kerosene fuel for portable refrigerators is of varying quality and availability. The cold chain is one reason why in developing countries the cost of delivering a vaccine is far greater than the cost of the vaccine itself.

From Bench to Bush

One of the biggest problems with current products is simply that most have to be given several times to be effective. A full course of all the WHO-recommended vaccines, for example, requires five visits to a provider. Inevitably, many children do not receive all the required doses, especially in remote places. Yet although workers in the field agree that reducing the number of necessary doses is one of the most promising ways to improve protection, manufacturers have been slow to develop such vaccines, in the opinion of Philip K. Russell, a former head of the U.S. Army medical research and development command, who is now president of the Albert B. Sabin Vaccine Foundation.

Russell is not alone in believing that the progress of vaccines from the research laboratory to the field—"from bench to bush," in the argot of the business—has not been as rapid as it should be. Many vaccine researchers feel the same way. "There has existed for some time the belief that even more could be accomplished if ways could be found to bring greater cohesion" to vaccine development, the recently published *U.S. National Vaccine Plan* states.

The obstacles are complex. Manufacturers have to be convinced that the investment necessary to develop a new product—which may be anywhere from $10 million to more than $100 million—is likely to produce a good return. Vaccines, they say, are much harder than the average drug to manufacture. Some involve the use of dangerous microorganisms. "You can't imagine the number of steps it takes to make a new vaccine," says R. Gordon Douglas, Jr., president of the vaccine division at Merck & Co. To make a batch of poliomyelitis vaccine takes at least nine months, he notes.

A product is likely to generate hefty returns, however, only if it can be sold in rich countries or if the market will be

extensive. Many potential disease targets are not economically justifiable. "Take Crimean hemorrhagic disease—who's going to develop a vaccine for it?" Douglas asks rhetorically. Many international development agencies, including the U.S. Agency for International Development, have been hesitant to get involved in early-stage vaccine research, Russell observes. Most agencies have seen their primary role as delivering existing vaccines to the needy. "One of the sad problems is that implementers and researchers and manufacturers hardly ever got together, and when they did they didn't talk the same language," remarks John R. La Montagne, head of vaccine research at the NIAID.

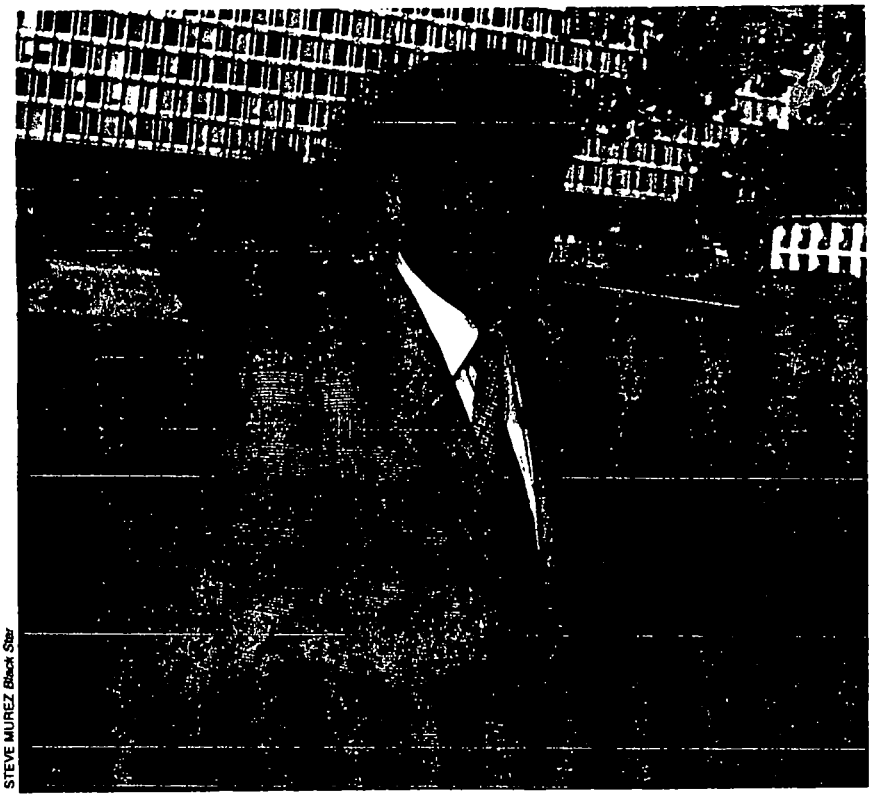
Vaccine Czar

The task of breaking that logjam has fallen to Jong Wook Lee, a soft-spoken former vaccine researcher from South Korea, who is director of the new WHO Global Program for Vaccines and Immunization. The program, which is run out of a cramped annex behind WHO headquarters in Geneva, brings the organization's vaccine research and delivery operations together for the first time. It will, Lee predicts, wield enough influence over manufacturers to persuade them to cooperate. "We are flinging open the door to industry," he announces.

Even if Lee's program meets only some of its targets for the remainder of the decade, the effort could save millions of lives. "Never in the field of human medicine will so much be owed by so many to so few," he beams in a rare immodest moment.

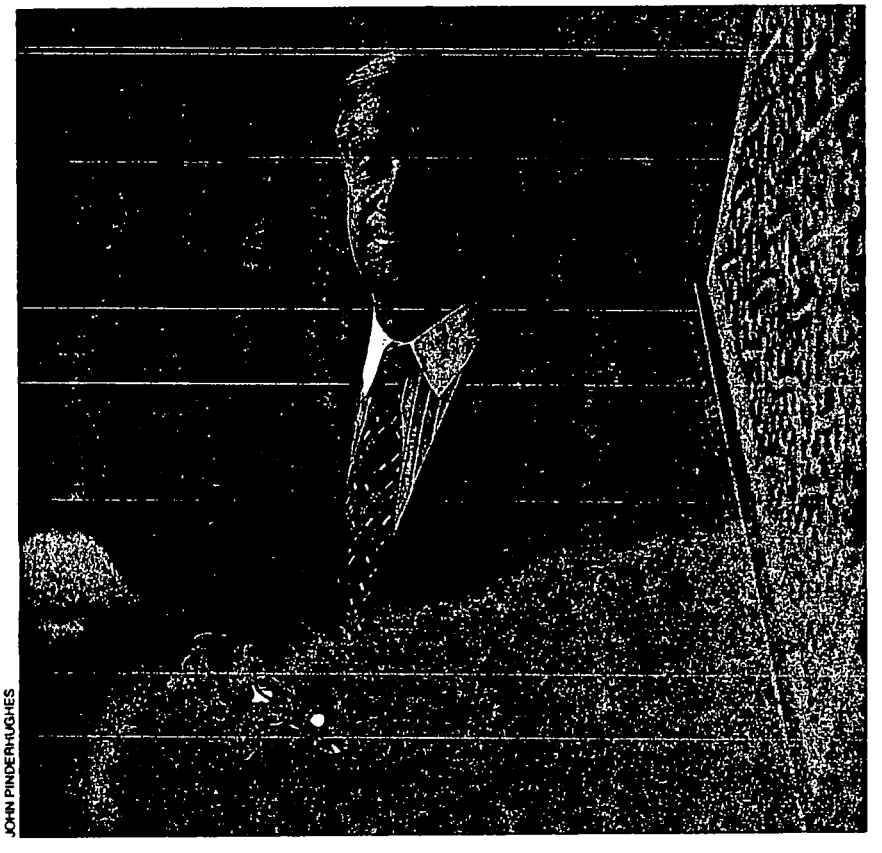
If Lee's ambitions seem unrealistic, it is worth remembering that WHO, in collaboration with UNICEF, has a successful history when it comes to getting vaccines to where they are needed. The organizations eradicated smallpox in 1977 and boosted global immunization levels for six major killing diseases from 5 percent in 1974 to more than 80 percent in 1990. Lee's program estimates that vaccination against just three of those six—measles, neonatal tetanus and pertussis—is now preventing almost three million deaths a year. Although immunization rates have started to flag in recent years in some countries, most of them in western and central Africa, Lee has plans to reverse that trend.

WHO has also made impressive strides against polio and estimates that vaccination prevents 550,000 cases of that crippling disease annually. WHO's American wing, the Pan American Health Organization, announced last September that an unrelenting surveillance ef-



STEVE MUREZ *Black Star*

JONG WOOK LEE is head of the new Global Program for Vaccines and Immunization at WHO and also runs the Children's Vaccine Initiative. Lee declares he is "flinging open the door to industry" in order to speed the development of new vaccines.



JOHN PINDER-HUGHES

R. GORDON DOUGLAS, JR., president of Merck & Co.'s vaccine division, is angry about price controls Congress has imposed on vaccines supplied to the government. "This means we're not doing all the things we're capable of," he states.

fort combined with "vaccination days" for the entire juvenile populations of high-risk countries has already eradicated polio from the Western Hemisphere: the last recorded case there occurred in Peru in 1991. Lee's team at WHO believes polio could follow smallpox to extinction in the wild by the year 2000 (stocks of virus may exist in laboratories after then). Lee is planning to ease that passage by stepping up surveillance and vaccination efforts in countries where polio is still well known.

Close collaboration with industry on vaccine development is a new venture for WHO, however. And history suggests there are dangers. In August 1990, WHO, the World Bank, UNICEF, the U.N. Development Program and the Rockefeller Foundation launched a campaign called the Children's Vaccine Initiative (CVI). The CVI was intended to catalyze the creation of heat-stable, affordable vaccines that could be administered orally

Many Ways to Make a Vaccine

As long ago as the early 18th century, people sought protection against smallpox by pressing infectious "matter" from patients' lesions into breaks in their own skin. The highly dangerous practice was intended to cause a mild case of the disease and so bestow immunity.

Immunization became a more reasonable proposition in 1798, when Edward Jenner demonstrated how the illness could be prevented by inoculations of cowpox, a related but less dangerous disease. The principle of using a related pathogen to provoke immunity is still being explored today in vaccines designed to protect children from rotaviruses, which cause often fatal diarrhea in millions of children. But many other approaches to vaccination are used as well.

Killed whole organisms and weakened toxins.

Several widely used vaccines, including those targeted at influenza and pertussis, are based on killed microbes. Injectable poliomyelitis vaccines also work this way. A variant of this approach, used in diphtheria and tetanus immunization, is to inject people with chemically modified versions of toxins produced by the infectious agent. Such toxoids, as they are called, allow the immune system to learn how to inactivate the poison from a real infection.

Subunit vaccines.

Vaccines consisting of molecular subunits of pathogens can avoid some of the complications of using whole organisms. Subunit vaccines are now available for meningitis, pneumonia and hepatitis B; vaccines employing this approach against respiratory syncytial virus and parainfluenza virus, both major killers, are in development. Subunit preparations are also being investigated as candidates for protection against infection with HIV (the AIDS virus) as well as malaria.

HANK MORGAN Photo Researchers, Inc.

Altered pathogens.

Some diseases require a more powerful immune stimulus. In such cases, favorable results can sometimes be obtained with live microorganisms that have been weakened, or attenuated, so that they do not produce significant illness. This is still the basis of the oral polio vaccine and the combined vaccine against measles, mumps and rubella. Modified pathogens might be even more commonly used in the future. Genetic engineering has made it possible to introduce immune-stimulating proteins from a range of pathogens into tried and trusted carrier organisms such as vaccinia (derived from the cowpox virus with which Jenner countered smallpox) and various bacteria.

Conjugates.

Vaccines for some bacterial diseases, such as pneumococcal pneumonia and meningitis, cannot be used in babies, because their immune systems do not recognize as foreign the sugars in the bacterial cell walls. During the past two decades, however, researchers have learned how to combine these sugars with protein carriers. The resulting "conjugate" vaccines work well even in infants. In 1986 the first conjugate vaccine, against *Hemophilus influenzae* type B, was licensed in the U.S., and current versions are effective in children as young as two months. Conjugate vaccines for pneumococcal pneumonia and meningococci groups A and C are under development. "They could have a tremendous impact in a number of diseases," says John R. La Montagne of the National Institute of Allergy and Infectious Diseases.

Adjuvants and microspheres.

Many improvements in vaccines expected over the next decade are likely to be the result of better adjuvants or carriers. Adjuvants are substances that potentiate an immune response. The only adjuvant licensed for use in humans at present is alum, an aluminum salt, but other chemicals, including some complex organic ones, are being studied. Among them are muramyl dipeptide, squalene, lipid spheres known as liposomes and cagelike organic structures called immunostimulatory complexes (ISCOMs).

An approach that has long captured the imagination of researchers puts immunogenic chemical fragments into minute polymer spheres that only slowly let the immune system "see" their contents as they diffuse out. The scheme might be able to confer long-lasting immunity for some diseases with a single inoculation. Recently workers have successfully stabilized tetanus toxoid in polyester microspheres, thus pointing the way to a one-dose tetanus vaccine.

Oral vaccines.

Most vaccines are thought to exert their effects in the bloodstream. Oral polio vaccine, however, seems to work by triggering a different kind of immune response that can be elicited only when immunostimulatory molecules reach special cells in the lining of the gut. Immunity generated this way is termed mucosal immunity. Many researchers believe vaccines designed to stimulate mucosal immunity—which would probably be administered orally—might protect against diseases that have so far proved resistant to vaccination. Sexually transmitted diseases, including HIV infection, are a major focus of research interest, as are pathogens that enter the body through the gut, such as *Vibrio cholerae* (which causes cholera) and *Shigella* (dysentery).

Naked DNA.

The most recent and surprising development was the demonstration that DNA, when injected into muscle, can by itself

early in life and would protect against a wide range of diseases.

The plan was to cajole manufacturers [redacted] to making innovative products by establishing priorities for research, organizing clinical trials and raising money. Ciro A. de Quadros of the Pan American Health Organization says the initiative has secured international agreement on procedures for manufacturing vaccines and checking their quality, an important step toward being able to make novel combinations. It also stimulated a promising project that demonstrated how deuterium oxide, better known as heavy water, can be used to make a polio vaccine that is stable for up to a week at 37 degrees C. (The product is now in industrial development.)

Russell believes that the CVI's greatest achievement was to persuade manufacturers to make vaccines that combine protection against hepatitis B and *Hemophilus influenzae* type B (Hib)—a common and dangerous cause of meningitis—with the existing combination vaccines for diphtheria, pertussis and tetanus. "There was tremendous embedded resistance" from people who saw no need to disturb the status quo, Russell recalls. "If you look at the CVI as a global intellectual movement, it's been a substantial success."

Others have a different assessment. "European industry was quite upset with the CVI because it ignored our achievements," explains Walter S. Vandersmissen, director of government affairs for SmithKline Beecham in Brussels. "It was a dream, and we tried to instill a sense of realism. Today not much has been achieved." The ambitions were slowly scaled back, but friction still developed between the CVI and WHO when workers for those agencies started giving conflicting advice to governments. Moreover, the CVI failed to raise more than a few million dollars toward a planned $300-million fund for vaccine development.

Mounting disagreements among the CVI's sponsors over what the initiative should be doing were finally resolved last August. The sponsors agreed to let the initiative be advised by the same committee that oversees WHO's new program, thus effectively bringing them under one command. Lee was given the additional appointment of executive secretary of the CVI, which makes him almost a global vaccine czar. The CVI will now concentrate on raising awareness of research results and gaining political commitments to improved vaccines, according to Roy Widdus, an adviser to Lee on the project.

Whether the new WHO effort can forge a consensus on vaccine development will depend on the ability of Lee and his team to better the record of the CVI in building constructive links with industry. Lee acknowledges that WHO has in the past been coy, even "a little paranoid," about close relations with manufacturers, fearing that its impartiality might seem to be tainted. But he now has good reason to want to change that stance.

Last year WHO received the results of a confidential study conducted by Mercer Management Consulting on the economics of the $3-billion global vaccine industry. A central finding was that the $60 million that UNICEF spends ev-

confer immunity. Workers at Vical, a biotechnology company in San Diego, Calif., collaborating with Merck and U.S. Navy investigators, have shown that such "naked DNA" can immunize mice against malaria and influenza. The DNA, which encodes a protein displayed by the pathogen, apparently stimulates host tissues to synthesize proteins that the immune system recognizes as foreign.

By continuously stimulating the immune system, naked DNA vaccines could produce responses as strong as those induced by attenuated organisms. In particular, they seem able to stimulate the arm of the immune system that employs *T* cells to kill invaders. Naked DNA technology "has an immensely powerful capability," says Philip K. Russell of the Albert B. Sabin Vaccine Foundation.

SOME VACCINES IN DEVELOPMENT

Disease/Pathogen	Technology
Respiratory syncytial virus	Attenuated virus; subunit in microspheres
Influenza	Attenuated virus and naked DNA
Group B streptococci	Conjugates
[redacted]fluenza	Subunits and attenuated virus; inactivated virus in microspheres
Meningococci group B	Modified polysaccharide
Measles	Subunits in ISCOMs and in vaccinia; attenuated virus; naked DNA
Pneumococcal pneumonia	Subunits and conjugates
Typhoid	Subunits and conjugates
Cholera	Inactivated and attenuated pathogens; subunit combinations
Shigella	Bacterial vector; subunits and conjugates
Tuberculosis	Mycobacterial vector; subunit
Malaria	Subunit and naked DNA
Dengue	Yeast, yellow fever and vaccinia vectors; attenuated and chimeric viruses
Rotavirus	Attenuated and modified viruses
Tetanus	Single dose: toxoid in microspheres
Schistosomiasis	Subunit
[redacted] immunodeficiency	Subunits; vaccinia vectors; inactivated virus

SOURCES: Global Program for Vaccines and Immunization, World Health Organization; The Jordan Report, National Institute of Allergy and Infectious Diseases

ery year to buy vaccines for poor countries—at discount prices—was enough for the deals to be profitable for manufacturers, provided they could charge higher prices elsewhere. The study thus made clear that UNICEF—which acts as the purchasing arm of WHO—could exert pressure on manufacturers. "We are writing the guidelines, so we have leverage," Lee declares. "No one country can perform this function, and industry cannot ignore the process."

Building Bridges

Lee is keen to stimulate vaccine production in developing countries as well as in the industrial world. About 60 percent of the global supply of diphtheria-pertussis-tetanus vaccine—a relatively simple product—is made in developing countries; Lee explains that he would be quite happy to see manufacturers outside the industrial world grab a larger slice of the pie for other products. "In the developing world, they are not just driven by profit motivations," he says.

At present, technical problems mean some vaccines manufactured in developing countries "may be completely useless," Lee admits. But WHO has introduced standards of good manufacturing practice that should eliminate such variations. Lee argues that if manufacturers in Asian countries can make cars suitable for the U.S. market, Asian pharmaceutical companies can probably make vaccines to WHO's standards.

Lee is also spearheading an effort to encourage more countries to make or buy vaccines rather than appeal to the charity of UNICEF. At present, UNICEF purchases fully 40 percent of the world's pediatric vaccines for countries that have not made their own arrangements. Some of those countries could buy for themselves, Lee says, and a few—including China and India—will be told to start doing so immediately. Others will be given a grace period. The move is likely to be well received by manufacturers: because many poor countries are unlikely to establish their own plants, Lee's policy means more vaccines will be sold at higher prices.

Vaccine makers have noticed the new industry-friendly stance in Geneva. "It's a major change for a group that has a tendency to denigrate the profit-making sector," reflects Thomas M. Vernon, Jr., executive director for medical, scientific and public health affairs at Merck. "There has been a wind of change," Vandersmissen agrees. "Now industry can frankly state its point of view, including financial concerns."

Within the past year the Global Program for Vaccines and Immunization has awarded $400,000 to industrial and academic researchers to investigate how a heat-stable oral polio vaccine might be manufactured. It has also entered into contracts worth more than $300,000 with companies in the U.S. and Europe to develop improved vaccines for group A and C meningococci and for tuberculosis and leprosy, as well as a single-dose tetanus toxoid using microsphere technology [*see box on pages 92 and 93*]. The amounts are small, but manufacturers can "feel they are partners," says Paul-Henri Lambert, head of the vaccine R&D division.

U.S. vaccine producers, however, are unlikely to become suppliers for UNICEF. According to Ronald J. Saldarini, president of Lederle-Praxis Biologicals, another major U.S. vaccine manufacturer, the prices are simply too low. "I can't afford to supply" UNICEF, he states. Merck's Douglas blames the U.S. government for making it hard for domestic manufacturers to bid on UNICEF contracts. Merck would do so, he says, if it could charge lower prices than it charges the federal government for vaccines. But back in 1982, Merck executives were lambasted by a congressional committee for proposing to do just that, and the company wants to avoid a repeat episode. Overseas manufacturers that have supplied UNICEF programs were encouraged to do so by their governments as a matter of foreign policy, Douglas maintains.

Constraints on vaccine prices also lie at the heart of a separate bitter argument U.S. manufacturers have with their government. The amount of vaccine that U.S. producers sell to the Public Health Service can fluctuate drastically from year to year as a consequence of the rules used to apportion purchases. Yet under the Vaccines for Children program [*see box on opposite page*], which started last October, the price the government pays is capped, with increases only for inflation. The combination is anathema to industry. Barry R. Bloom, a researcher at the Albert Einstein College of Medicine in Bronx, N.Y., argued recently in *Science* for the creation of a national vaccine commission to try to bring some stability to the rocky relations between the U.S. government and its suppliers. The commission would assess vaccine supply and demand and be able to respond to emergencies, such as an outbreak of infectious disease. "If there were an outbreak of yellow fever in New Orleans, we would be out of vaccine in two weeks," Bloom declares. "We are not prepared."

Others are not convinced that a commission would help. Saldarini of Lederle-Praxis sees no need for another government committee. "I'm committeed out," he complains. In any event, Congress recently directed the nearest thing the government had to a central authority on vaccines—the National Vaccine Program Office—to cut 30 people from its staff of 35. Russell calls the effective dismantling of the office "a disaster."

Lee seems anxious to avoid similar disasters in the international arena. But

PETER CHARLESWORTH SABA

MOBILE VACCINATION CLINIC near Chang Rai, Thailand, is visited by hill tribe villagers. In such remote areas lacking electricity and modern refrigeration, distribution efforts are complicated by the need to keep the vaccines cool.

Born in the U.S.A.

Even in a rich country such as the U.S., getting vaccines to infants is difficult. Almost all American children are fully vaccinated by the time they enter school, since vaccination is a condition for enrollment. Still, many do not receive all their shots by the recommended age. Henry D. Mustin and his colleagues at the University of Washington published in a recent issue of the *Journal of the American Medical Association* a study showing that in a nationally representative sample only 46 percent of white infants and 34 percent of black infants had received adequate immunizations by the age of eight months. According to the Centers for Disease Control and Prevention, 67 percent of U.S. youngsters have received all the recommended doses of diphtheria-pertussis-tetanus, measles-mumps-rubella and poliomyelitis vaccines by the time they are two years old. But only 55 percent had received the three recommended *Hemophilus influenzae* type B shots, and only 16 percent had been properly vaccinated against hepatitis B. The vaccine-policy joke (there is only one) is that there are counties in Texas where the cattle are better immunized than the children are.

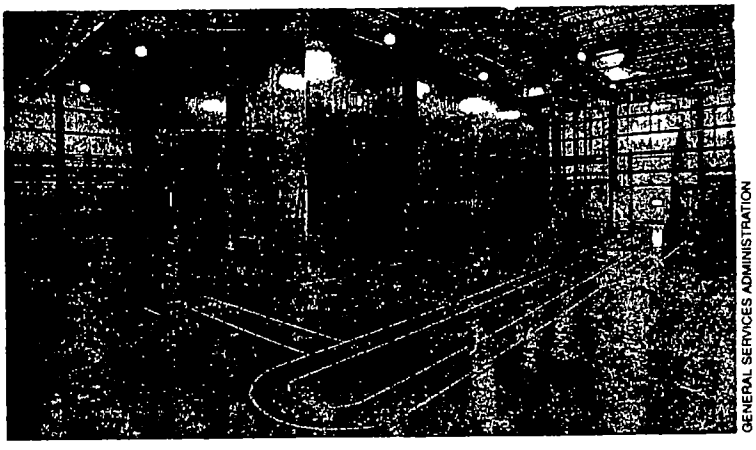
Missed vaccinations can have serious consequences. Poor measles vaccination rates resulted in a 55,000-case outbreak in the U.S. in 1989–1991, causing 136 deaths. Concern about the low rates prompted the government to implement last year the Vaccines for Children (VFC) program, which was intended to make it easier for uninsured or inadequately insured children to obtain free vaccines from private physicians. (Private pediatricians typically charge $270 for a full course of 11 shots, although vaccinations have also been free for the asking in public health clinics.) But the program has gotten off to a shaky start.

Initially the government had proposed distributing vaccines for the program to private physicians from a single warehouse in Burlington, N.J. Officials realized belatedly, however, that they could not establish the necessary tracking and handling system by the program's October 1 starting date; consequently, that plan was scrapped. Some states with experience in vaccine distribution have agreed to disburse VFC vaccines to physicians themselves, but as of early November, 24 states had still not done so.

U.S. vaccine manufacturers bitterly oppose the VFC program because it has increased the fraction of domestic vaccine bought by the government (at a half-price discount) from about 50 to 80 percent. At the same time, Congress put a cap on prices, so makers cannot compensate for the fall in revenues. The result, they say, will be less research and fewer new products.

R. Gordon Douglas, Jr., of Merck notes that the projected shortfall is already constraining the company's choices about which projects to pursue. "These decisions will affect health 10 years from now, and I can only tell you that this means we're not doing all the things we are capable of," he insists. Christine M. Grant of Connaught Laboratories, which is owned by Pasteur-Merieux, remarks that the price-capping provisions of the program "send a message that is 180 degrees opposed to support for research and development." Ronald J. Saldarini, president of Lederle-Praxis Biologicals, charges that the VFC program "is an attempt to virtually nationalize the industry and take us out of the private sector."

Even if the VFC program is fully implemented, Douglas argues that it will not significantly increase the number of children in the U.S. who receive their immunizations on time. The reason some children fall behind is not cost, Douglas maintains, but a lack of education and ready opportunities in impoverished inner-city areas. Douglas's proposed solution to U.S. vaccination woes is to require that every health insurance package cover preventive services for children.



GENERAL SERVICES ADMINISTRATION

The VFC vaccine distribution center that wasn't

whether the new WHO/CVI combined bureaucracy can really spur the development of more effective vaccines is still an open question. Despite Lee's overtures to industry, difficulties remain. Lambert says industry's penchant for secrecy about its plans—especially when it scents profits—is still a problem. Vandersmissen argues that WHO would be most effective if it concentrated on organizing clinical trials.

Lee has his own measure of progress in relations with industry. "When we invite, they always come," he observes with satisfaction. "They are never too busy." But in the long term, success will depend on other factors, not least on how much money the program can raise. "Unless some other source of funds is found, none of this can really work," Bloom says. The Global Program for Vaccines and Immunization now has a budget of less than $30 million; Lee would like to increase that to $50 million.

More important still will be whether WHO adopts economically sustainable policies that will keep the industry connection strong. It is still too early to judge the program, but Lee at least appears to have a clear vision. "Whatever else," he admonishes, "we must not kill the goose that lays the golden eggs."

FURTHER READING

THE JORDAN REPORT: ACCELERATED DEVELOPMENT OF VACCINES IN 1993. National Institute of Allergy and Infectious Diseases, National Institutes of Health, 1993.

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PRESIDENT BILL CLINTON vows to speed the pace of AIDS vaccine research and make cutting-edge drugs more widely available to the infected through the Medicaid program.

AIDS Moonshot?

Under President Clinton's command, researchers step up the search for an HIV vaccine

Medical science is still far from conquering AIDS, but a number of recent events give reason for hope. Within the past 18 months, clinical studies have shown that protease inhibitors and other powerful new drug treatments can virtually halt replication of HIV, the virus that causes AIDS. These successes have led to marked improvements in the condition of many suffering from the disease. The drugs are expensive, however, and nobody knows how long they will hold the virus at bay. To halt the spread of HIV around the world, researchers believe that it is necessary to discover a vaccine, and an affordable one at that.

MORE EXPLORATIONS

President Bill Clinton gave AIDS vaccine research a shot in the arm on May 19, 1997, when he called for scientists to develop a vaccine for the disease within ten years--and invoked the spirit of John F. Kennedy's 1961 declaration that the U.S. would set a man on the moon within ten years. Although activists criticized Clinton for not promising new money to support the initiative, having a vaccine as a presidential goal is likely to help boost funding for vaccine research in future federal budgets. In the meantime, the Administration says it plans to propose extending federal Medicaid coverage to buy costly and potent drugs for infected low-income people who have not yet developed the symptoms of full-blown AIDS. Medicaid recipients are now excluded from early access to these drugs.

Although some researchers are concerned about the demoralizing consequences if Clinton's timetable proves impossible, many are optimistic that the campaign might spur drug companies to step up their efforts to protect against HIV. Manufacturers have tested dozens of potential vaccines in small groups of people. These small trials are aimed at establishing that the preparations are safe and that they stimulate the immune system. But the results so far have not persuaded pharmaceutical companies to organize large "phase 3" trials involving

thousands of volunteers--the kinds of tests which will be necessary to prove that a vaccine is safe for widespread use and effective and preventing infection.

Researchers do not yet understand what aspects of the immune response are necessary to confer protection against HIV; some even worry that no highly effective vaccine is possible. And development efforts have slowed since 1994, when the National Institutes of Health decided that small tests had produced insufficient evidence to justify large-scale U.S. trials of two candidate vaccines based on an HIV protein called gp-120.

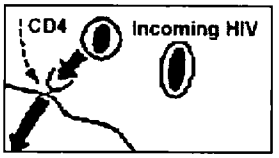
AIDS vaccines have largely fallen out of the spotlight since then, but very recent findings suggest possible ways to overcome some of the widely-recognized obstacles to developing an effective vaccine. One of the big problems bedeviling such efforts is that there are multiple strains of HIV, and different ones predominate in different regions. As a result, a vaccine that works acceptably in one part of the world might be useless elsewhere. Recently, however, Kent Weinhold of Duke University Medical Center demonstrated that several vaccine candidates in development could actually elicit immune responses to a variety of HIV strains. In the tests, immune-system cells known as cytotoxic T lymphocytes, taken from a group of volunteers, were exposed to cells harboring various strains of HIV. Having thus been "trained" to recognize the characteristic proteins of HIV, the lymphocytes often were then able to kill HIV-infected cells.

The vaccines that Weinhold investigated were based on a modified canarypox virus (a virus that causes disease in canaries but not in humans) that had been genetically engineered to contain a gene from HIV. These vaccines are more sophisticated than the gp-120 vaccines that NIH declined to test in 1994. In the newer tests, vaccinated volunteers were injected first with the canarypox preparation, and subsequently given a booster shot consisting of just HIV's gp-120 protein, a protein that HIV uses as a gateway to enter the human cells. Consequently, the body's immune cells were exposed to HIV proteins from two different sources--both the ones manufactured by the canarypox virus, and the gp-120 protein that was injected directly--to assist the cells in identifying and destroying the invading AIDS virus.

The encouraging results from laboratory tests do not yet prove the vaccines will work in people. "The only way to establish protection is to do a phase 3 trial," notes Carole A. Heilman, associate director of the division of AIDS at the National Institutes of Health. But the latest finding show that the new candidates have potential. "There seems to be more activity going on in AIDS vaccines in general," Heilman comments.

David B. Weiner the University of Pennsylvania recently announced another encouraging discovery. He and his colleagues were able to make two chimpanzees resistant to HIV infection (like humans, chimps are susceptible to the virus) by vaccinating them with a preparation based on "naked" DNA encoding HIV genes. Conventional vaccines employ killed or modified pathogens, or proteins made by them, rather than DNA. In contrast, a DNA vaccine like the one used by Weiner works by allowing the body's cells to make viral proteins in a harmless,

non-infectious form; the immune system then gets sensitized to them, which helps prevent subsequent infection by the actual virus. Weiner's result provides evidence that a naked DNA vaccine might work in people, although there are substantial differences between chimpanzees and humans: most notably, chimps usually do not become sick with AIDS when infected with HIV.



DEADLY LIFECYCLE

Scientists have also learned a lot in recent years about the molecular-level interactions between HIV and the receptors on cells of the body, which provide the virus with its foothold for entering the cells. "We can work to find the best immunogens," Heilman declares. Moreover, researchers have acquired new tools in the form of genetically-engineered small animals, such as rabbits, that are susceptible to infection with HIV. (Non-primates are normally immune to infection with HIV and its close viral relatives.) These animals will speed the testing of anti-AIDS therapies and vaccines.

Plans are moving ahead to test various types of HIV vaccine in humans in intermediate and large-scale trials; studies are now being planned in Uganda, Thailand and the U.S. And despite the past gloom in the field, Heilman says there is no reason to believe that President Clinton's goal is out of reach. Most successful vaccines are the end result of trail and error modifications, she notes. But HIV researchers have a more sophisticated understanding of their quarry than did previous generations of immunologists. "This is not very different from how vaccines generally are developed," she points out: "Everything is consistent with our enthusiasm."

--Tim Beardsley, staff writer

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