

Vaccines

OVERVIEW

Purpose

The purpose of this lesson is to introduce students to the various types of vaccines available. Students will use what they have learned in this lesson and in the previous lessons to identify which types of vaccines are most useful for developing an HIV vaccine. They will be asked to provide rationale for their choices based on safety, effectiveness and the HIV life cycle.

Essential Understandings

- Basic facts about HIV structure, transmission, research, and treatments need to be understood as background to why an HIV vaccine is currently lacking.
- Mutations in viruses force the immune system to adapt and respond, vaccines must also stimulate an immune response. Since there is no history of a human being naturally clearing an HIV infection, a vaccine must produce an immune response which is better than that currently produced by the body

Learning Objectives

- Students will be able to:
 - Summarize key features of vaccine types including advantages and disadvantages
 - Analyze different vaccine types for their suitability in use for HIV vaccine development and support their choice
 - Connect vaccine type choice to HIV structure and life cycle
 - Gain an understanding as to why the making of an HIV vaccine has been so difficult.

Key Concepts

Many different vaccine types exist, some are inappropriate for HIV vaccine trials (live-attenuated, killed/inactivated, and toxoid).

Careful selection of vaccine type ensures that participants will not contract HIV from the vaccine.

Many vaccines that stimulate antibody response utilize viral surface proteins or the genes that code for them.

Prior Knowledge Needed

Basic immunology

HIV Structure and Life Cycle

Materials

Student Handouts from: Understanding Vaccines (NIH Publication pp22-36) found at the end of this lesson, www.niaid.nih.gov/publications/vaccine/undvacc.htm

Vaccine Type Comparison Table

Animations:

- Why is Making an HIV Vaccine so Hard?
<http://www.nwabr.org/education/hivchallenges.html>
- Types of Vaccines
<http://www.nwabr.org/education/vaccinetypes.html>

Prep Time

Time needed to copy Student Handouts

Class Time

1-2 days depending upon the depth of discussions

Timeline

- 1 week before activity:
 - Prepare overheads (if needed) and student handouts

Extensions

- Students can be assigned a particular vaccine type and research in more depth and present to class
- Class can research how each vaccine type has been used in preventing other diseases
- Stop the Virus! HIV Research Strategies Lesson Plan (see Appendix)

Adaptations

- See Day One for IEP and ELL adaptations

Assessment Suggestions

- Monitor answers on table and during discussion
- Evaluate homework paragraphs






Common Misconceptions

- Participants might become infected with HIV from the vaccine
- Positive HIV antibody test results arising after vaccination indicate HIV infection

SUMMARY

- 3.1 *Invitation to Learn*
- 3.2 *Vaccine Type Jig-Saw Activity*
- 3.3 *Debrief and Discussion*
- 3.4 *HIV Animations*
- 3.5 *HIV Vaccine Expository Paragraphs*

Symbols

-  — video
-  — discussion
-  — hands-on
-  — on-line or web based
-  — homework

3.1 Invitation to Learn

1. Facilitate discussion with students about what vaccines they have received.
2. Ask students if they know of people who have had disease whose spread is now controlled by vaccinations such as measles, mumps, and rubella (MMR vaccine) and chickenpox (varicella vaccine). While these diseases have not been eradicated fully, they are well-controlled in the U.S. Programs such as those run by the Gates Foundation and the Rotary Club seek to ensure distribution of these vaccines to children in the developing world.
3. Vaccines work by stimulating the immune system to produce antibodies and immune cells that recognize the antigens—foreign proteins—in the vaccine. These antigens are normally found in harmful pathogens (viruses and bacteria) which cause disease. The idea is to prepare the immune system so that if a person is exposed to the pathogen later, the immune system can respond and prevent an illness from developing.

The immune system has two separate arms. One arm is responsible for the cell-mediated response. In this arm, certain kinds of immune cells called killer T cells are produced that can destroy infected cells. These killer T cells are sometimes called CD8+ T cells. Another kind of immune cell is the helper T cell, and these cells help coordinate the other parts of the immune response. Helper T cells are sometimes called CD4+ T cells and are what are measured when people refer to “CD4 cell counts” in HIV infection.

The second arm of the immune response is called the antibody or humoral response. Here, special cells called ‘B cells’ recognize the antigen and produce antibodies that can attach to it. When these antibodies attach to the antigen on the pathogen they “neutralize” it. This means that the pathogen can no longer infect cells and cause infection.

Once T or B cells have been exposed to a foreign antigen, they produce memory cells that remember that antigen. If the pathogen with that antigen enters the body at a later time, these memory cells can respond quickly and strongly to stop any infection and disease. So, for example, if someone who has been vaccinated against measles is exposed to the measles virus, his or her body will immediately recognize the virus and will destroy it. It is possible to download a poster of ongoing trials of preventative HIV vaccines and view all the current HIV trials underway globally online at: <http://www.iavireport.org/trialsdb/>

(from the International Aids Vaccine Initiative, IAVI - www.iavireport.org/vax/primers/vaxprimer11.asp)

3.2 Vaccine Type Jig-Saw Activity



1. Divide students into six groups. Provide readings from “Understanding Vaccines” NIH Publication (included at the end of this lesson). Each group will read about a different vaccine type and discuss the completion of their column on the table.
2. Reorganize class into mixed groups. Be sure that at least one person from each of the six original groups is present.
3. Students will teach their other group members about the vaccine type they have learned about and assist each other in completing their tables. Direct students to actively teach and discuss, not pass papers around to be copied.
4. The Types of Vaccines animation (see Activity 3.4, below) contains much of the information found in the NIH publication and can be used to support this Jig-Saw Activity.

3.3 Debrief and Discussion



1. Facilitate discussion about content covered in jig-saw activity. Be sure to focus on which vaccine types are suitable for development of an HIV vaccine.
2. Lead students to the conclusion that recombinant vector, subunit, and DNA vaccines are the most promising for preventive HIV vaccines.
3. It must be strongly emphasized that some approaches cannot be used for HIV (live attenuated, inactivated/killed). One of the greatest impediments to healthy volunteers’ willingness to participate in preventive HIV vaccine trials is the fear that they will become infected with HIV from the vaccine.
4. Be sure students can connect learning from previous days to today. Discuss specifically why construction of an HIV vaccine is challenging at this time given both the mutation rate of HIV and the targeting of immune system cells. See Activity 3.4, below, for an animation that specifically explores the challenges of making an HIV vaccine.

3.4 HIV Animations

These animations have been created for this lesson and can be used in a number of ways. The teacher may choose to use them as an introduction to the lesson, as concept reinforcement during the lesson, or as individual homework after the lesson.

1. Why is Making an HIV Vaccine so Hard?

This interactive animation explores the scientific challenges faced by researchers in developing an HIV vaccine. It can be found at: <http://www.nwabr.org/education/hivchallenges.html>

2. Types of Vaccines

What are the different types of vaccines? What are the advantages and disadvantages of each type? Which types are being pursued for an HIV vaccine? Found at: <http://www.nwabr.org/education/vaccinetypes.html>

3.5 HIV Vaccine Expository Paragraphs

Ask students to write 1 paragraph about each of the following:

- The different types of vaccines currently available or in research which are most promising for preventing HIV infection
- The challenges associated with creating an HIV vaccine (see homework reading for additional information)

Vaccine Types

	Live Attenuated	Killed (inactivated)	Subunit (Protein)	Toxoid	DNA Vaccine	Recombinant Vector
Definition and Example						
Advantages						
Disadvantages					Still in experimental stages.	Still in experimental stages (but immune response to the vector can limit use to one to two times.)
Suitable for Preventive HIV vaccine? (Y or N) Provide explanation why.						

Vaccine Types

KEY

	Live Attenuated	Killed (inactivated)	Subunit (Protein)	Toxoid	DNA Vaccine	Recombinant Vector
Definition and Example	Contain a weakened version of the living microbe. Ex: cholera, measles, mumps, rubella, yellow fever	Disease-causing microbe killed with chemicals, heat or radiation. Ex: cholera, flu, hepatitis A, plague, rabies, Japanese encephalitis, Salk polio vaccine	Only the antigens from a microbe are used to stimulate the immune system. Ex: Hepatitis B, pertussis, some pneumonia	A "detoxified" version of a toxin from a bacterium. Ex: tetanus, diphtheria	Give the genes (DNA) that code for antigens directly to cells; those cells then make antigens necessary to stimulate the immune system. Ex: tests include malaria, influenza, herpes, HIV	Uses a virus or bacterium as a carrier ("vector") to deliver DNA to cells. Those cells then make antigens (as with DNA vaccines). Ex: rabies, measles and HIV
Advantages	Good "teachers" of the immune system. They elicit strong cellular and antibody responses. Lifelong immunity with 1-2 doses.	More stable and safer than live vaccines. Doesn't require refrigeration. Easily stored and transported	Low chance of adverse reactions, since most of the microbe is missing. Targeted to very specific parts of the microbe.	Immune system learns to fight off "safe" version of toxin and can then recognize toxic version.	Evokes strong antibody and cellular responses. Relatively easy and inexpensive to produce. Can't cause the disease.	Closely mimics natural infection, which stimulates the immune system well.
Disadvantages	Vaccine could mutate to a virulent form and cause disease. Not good for people with compromised immune systems. Need refrigeration.	Immune response not as strong as for live vaccines. Booster shots required.	Difficult to identify the specific antigens needed for a vaccine.	Only works against bacteria; viruses don't make toxins.	Still in experimental stages.	None given in the reading, but immune response to the vector can limit use to one to two times.
Suitable for Preventive HIV vaccine? (Y or N) Provide explanation why.	No. Too risky to use for a lethal disease that already mutates quickly on its own.	No. There is the possibility of not fully inactivating the virus.	Yes. These have been tried but have been unsuccessful. These would target a humoral immune response (see page 15).	No. Works only with bacteria and HIV is a virus.	Yes. Elicits a "cell-mediated immune response" (see p. 13). Although this is a promising HIV vaccine type, so far the immune responses have been very weak.	Yes. Elicits "cell-mediated immune response" (see p. 13 in handout).

Understanding VACCINES

What They Are How They Work



U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
National Institute of Allergy and Infectious Diseases

Understanding
VACCINES
What They Are How They Work



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Introduction

This booklet contains information about vaccines: what they are, how they prevent disease, how they are made and tested, and what vaccine research might achieve in the future. For more in-depth information about vaccines, consult resources at your local library or ask your health care provider.

The Internet can be a valuable source as well. Start with the National Institutes of Health (NIH) Web site at www.nih.gov for information on the broad range of research supported by NIH. For information on vaccine research, a good place to start is www.niaid.nih.gov, the Web site for the National Institute of Allergy and Infectious Diseases (NIAID). Another good source is MEDLINEplus, an information service of the National Library of Medicine www.nlm.nih.gov/medlineplus/. There is also information on vaccines on the Web site of NIAID's Dale and Betty Bumpers Vaccine Research Center, www.vrc.nih.gov. Finally, a list of Web sources about vaccine concerns, myths, and safety issues appears on page 41 of this booklet.

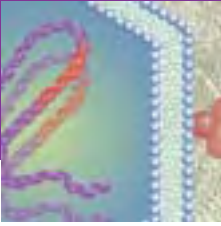
Note: Words in bold are defined in the glossary at the end of this booklet.

What Is a Vaccine?

Chances are you never had diphtheria. You probably don't know anyone who has suffered from this disease, either. In fact, you may not know what diphtheria *is*, exactly. (To find out, see “Diphtheria: Remembering an Old Disease.”) Similarly, diseases like whooping cough (**pertussis**), measles, mumps, and rubella may be unfamiliar to you. In the 19th and early 20th centuries, these illnesses struck hundreds of thousands of people in the United States each year, mostly children, and tens of thousands of people died. These diseases were frightening household words. Today, they are all but forgotten. That change happened largely because of vaccines.

Chances are you've been vaccinated against diphtheria. You even may have been exposed to the bacterium that causes it, but the vaccine prepared your body to fight off the disease so quickly that you were unaware of the infection.

Vaccines take advantage of your body's natural ability to learn how to eliminate almost any disease-causing germ, or **microbe**, that attacks it. What's more, your body “remembers” how to protect itself from the microbes it has encountered before. Collectively, the parts of your body that recall and repel diseases are called the **immune system**. (We'll take a closer look at the immune system in the section “How Vaccines Work.”) Without the immune system, the simplest illness—even the common cold—could quickly turn deadly.



Diphtheria: Remembering an Old Disease

On average, your immune system takes more than a week to learn how to fight off an unfamiliar microbe. Sometimes that isn't soon enough. Stronger microbes can spread through your body faster than the immune system can fend them off. Your body often gains the upper hand after a few weeks, but in the meantime you are sick. Certain microbes are so powerful, or **virulent**, that they can overwhelm or escape your body's natural defenses. In those situations, vaccines can make all the difference.

Traditional vaccines contain either parts of microbes or whole microbes that have been killed or weakened so that they don't cause disease. When your immune system confronts these harmless versions of the germs, it quickly clears them from your body. In other words, vaccines fix the fight but at the same time teach your body important lessons about how to defeat its opponents.

In 1900, diphtheria killed more people in the United States than cancer did. Caused by the toxic bacterium *Corynebacterium diphtheriae*, this upper airway infection often results in a grayish, thick membrane that grows in the throat and obstructs breathing. Other symptoms include fever, hoarseness, and coughing. Most diphtheria deaths resulted not from blocked airways but from the paralyzing **toxin** the bacterium secretes, which can cause the heart or other organs to fail. During the 1990s, an average of only three diphtheria cases among U.S. residents were reported each year.

Vaccine Benefits

You and Your Community

Once your immune system is trained to resist a disease, you are said to be **immune** to it. Before vaccines, the only way to become immune to a disease was to actually get it and, with luck, survive it. This is called **naturally acquired immunity**. With naturally acquired immunity, you suffer the symptoms of the disease and also risk the complications, which can be quite serious or even deadly. In addition, during certain stages of the illness, you may be **contagious** and pass the disease to family members, friends, or others who come into contact with you.

Vaccines, which provide **artificially acquired immunity**, are an easier and less risky way to become immune. Vaccines are one of the few medicines that prevent a disease from occurring in the first place, rather than attempting a cure after the fact. It is much cheaper to prevent a disease than to treat it. According to one analysis, every dollar spent on vaccinating children against **rubella**, or German measles, in the United States saves nearly \$8 in costs associated with treating the disease.

Vaccines protect not only you but everyone around you. If your vaccine-primed immune system nips an illness in the bud, you will be contagious for a much shorter period of time, or perhaps not at all. Similarly, when other people are vaccinated, they are less likely to give the disease to you. So vaccines



*Community immunity:
If a critical number of
people in a community
are vaccinated against
a particular illness, the
entire group becomes
less likely to get the
disease, even those
who are not vaccinated.*

protect not only individuals, but entire communities. That is why vaccines are key to the public health goal of preventing diseases. If a critical number of people within a community are vaccinated against a particular illness, the entire group becomes less likely to get the disease. This protection is called **herd immunity**, or community immunity.

On the other hand, if enough people in a community forgo vaccinations, diseases can reappear. In 1974, the Japanese government stopped vaccinating against pertussis because of public concern about the vaccine's safety and because no one had died from the disease the previous year. Five years later, a pertussis epidemic in Japan sickened 13,000 people and killed 41. In 1989, low vaccination rates allowed a measles outbreak in the United States. The epidemic resulted in more than 55,000 cases of measles and 136 measles-associated deaths.

Harmful Microbes

Vaccines protect against infectious diseases caused by microbes—organisms too small to see without a microscope. Many microbes, such as **bacteria**, are made up of only one cell. **Viruses**, mere snippets of **genetic material** packed inside a membrane or a protein shell, are even smaller.

Humans evolved an immune system because the world is teeming with these organisms. Many of them don't bother us; the bacteria that normally live in your digestive tract are, in fact, beneficial. But other microbes break into and take up residence in your body, using your warmth, nutrients, and tissues to survive and reproduce—and doing you great harm in the process.

Here are a few examples of some of the most serious disease-causing microbes for which vaccines exist.

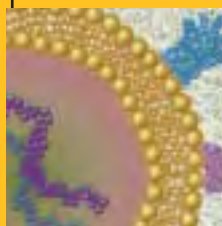
- Variola virus, which causes smallpox, was once the scourge of the world. This virus passes from person to person through the air. A smallpox infection results in fever, severe aches and pains, scarring sores that cover the body, blindness in many cases, and, often, death. There is no effective treatment. In the 18th century, variola virus killed every seventh child born in Russia and every tenth child born in Sweden and France. Although vaccination and outbreak control eliminated smallpox in the United States by 1949, the disease still struck an estimated 50 million people worldwide each year during the 1950s. In 1967, that figure fell to 10 to 15

Vaccine-Preventable Infectious Diseases

million because of vaccination. That same year, the World Health Organization (WHO) launched a massive vaccination campaign to rid the world of smallpox—and succeeded. The last natural case of smallpox occurred in Somalia in 1977.

- The highly infectious poliovirus, the cause of polio, once crippled 13,000 to 20,000 people every year in the United States. In 1 out of 200 cases, this virus attacks the spinal cord, paralyzing limbs or leaving victims unable to breathe on their own. In 1954, the year before the first polio vaccine was introduced, doctors reported more than 18,000 cases of paralyzing polio in the United States. Just 3 years later, vaccination brought that figure down to about 2,500. Today, the disease has been eliminated from the Western Hemisphere, and public health officials hope to soon eradicate it from the globe. In 2001, only 537 cases of polio were reported worldwide, according to WHO.
- The toxic bacterium *Bordetella pertussis* likes to set up home in the human respiratory tract, where it causes whooping cough, also known as pertussis. The wracking coughs characteristic of this

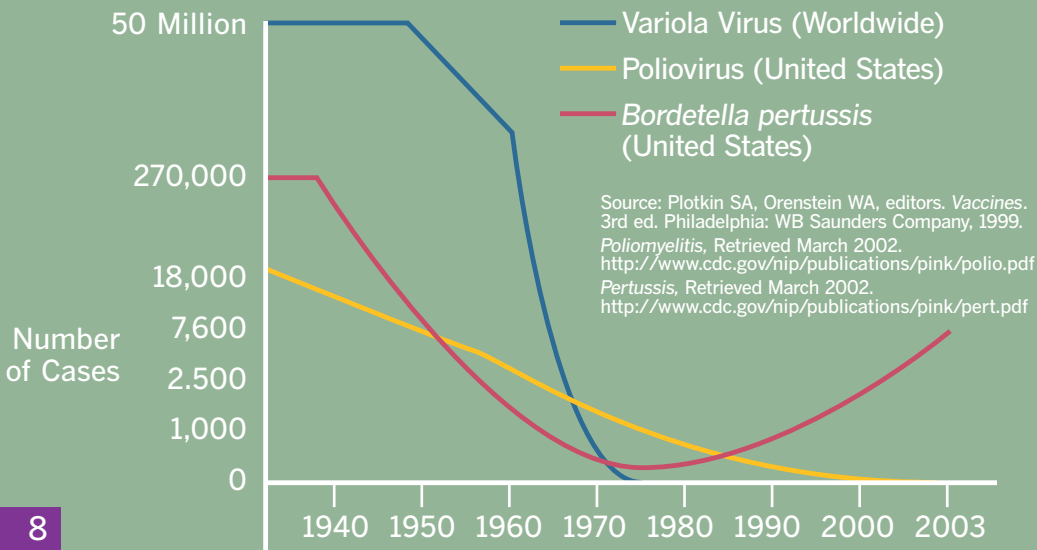
Anthrax
Bacterial meningitis
Chickenpox
Cholera
Diphtheria
Haemophilus influenzae type b
Hepatitis A
Hepatitis B
Influenza
Measles
Mumps
Pertussis
Pneumococcal pneumonia
Polio
Rabies
Rubella
Tetanus
Yellow fever



disease are sometimes so intense the victims, usually infants, vomit or turn blue from lack of air. Before scientists created a vaccine against the bacterium, 115,000 to 270,000 people suffered from whooping cough each year in the United States; 5,000 to 10,000 of those died from it. After the vaccine was introduced in the United States in the 1940s, the number of pertussis cases declined dramatically, hitting a low of about 1,000 in 1976. More recently, pertussis has been on the upswing in the United States, reaching 4,600 cases in 1994 and 7,600 in 2001. The reasons for the increase are complex. The disease strikes in cycles, and the immunity provided by the vaccine wanes over time, leaving some people susceptible in their teen years and as adults.

Other familiar diseases that vaccines protect against include chickenpox, hepatitis A and B, and *Haemophilus influenzae type b (Hib)*. Hib causes meningitis, an inflammation of the fluid-filled membranes that surround the brain and spinal cord. Meningitis can be fatal, or it can cause severe disabilities such as deafness or mental retardation. This disease has nearly disappeared among babies and children in the United States since the Hib vaccine became widely used in 1989.

Vaccines at Work



What do cows have to do with vaccines?

The word “vaccine” comes from the Latin word *vaccinus*, which means “pertaining to cows.” What do cows have to do with vaccines? The first vaccine was based on the relatively mild cowpox virus, which infected cows as well as people. This vaccine protected people against the related, but much more dangerous, smallpox virus.



Dr. Edward Jenner

More than 200 years ago, Edward Jenner, a country physician practicing in England, noticed that milkmaids rarely suffered from smallpox. The milkmaids often did get cowpox, a related but far less serious disease, and those who did never became ill with smallpox. In an experiment that laid the foundation for modern

vaccines, Jenner took a few drops of fluid from a skin sore of a woman who had cowpox and injected the fluid into the arm of a healthy young boy who had never had cowpox or smallpox. Six weeks later, Jenner injected the boy with fluid from a smallpox sore, but the boy remained free of smallpox.

Dr. Jenner had discovered one of the fundamental principles of immunization. He had used a relatively harmless foreign substance to evoke an immune response that protected someone from an infectious disease. His discovery would ease the suffering of people around the world and eventually lead to the elimination of smallpox, a disease that killed a million people, mostly children, each year in Europe. By the beginning of the 20th century, vaccines were in use for diseases that had nothing to do with cows—rabies, diphtheria, typhoid fever, and plague—but the name stuck.

How Vaccines Work

The Immune System

To understand how vaccines teach your body to fight infection, let's first look at how the immune system fends off and learns from a naturally occurring infection. Then we'll examine how vaccines mimic this process.

Imagine you are a dock worker on the piers of Philadelphia. The year is 1793. As you are unloading crates of tea and spices from an oceangoing ship, a mosquito bites you on the arm. Unfortunately, this mosquito carries the virus that causes yellow fever, which the mosquito picked up when it bit a sailor who recently returned from Africa. So now you have thousands of yellow fever viruses swarming into your body. In fact, you have become part of an infamous epidemic that will claim the lives of 10 percent of the people in Philadelphia, and all that stands between you and a fatal case of yellow fever is your immune system.

Your immune system is a complex network of cells and organs that evolved to fight off infectious microbes. Much of the immune system's work is carried out by an army of various specialized cells, each type designed to fight disease in a particular way. The invading viruses first run into the vanguard of this army, which includes big, tough, patrolling white blood cells called **macrophages** (literally, "big eaters"). The macrophages grab onto and gobble up as many of the viruses as they can, engulfing them into their blob-like bodies.



A mosquito bite transmits the yellow fever virus to an unsuspecting dock worker. In 1793, a yellow fever epidemic claimed the lives of 10 percent of Philadelphians.

How do the macrophages recognize the yellow fever virus? All cells and microbes wear a “uniform” made up of **molecules** that cover their surfaces. Each of your cells displays marker molecules unique to you. The yellow fever viruses display different marker molecules unique to them. By “feeling” for these markers, the macrophages and other cells of your immune system can distinguish among the cells that are part of your body, harmless bacteria that reside in your body, and harmful invading microbes that need to be destroyed.

The molecules on a microbe that identify it as foreign and stimulate the immune system to attack it are called **antigens**. Every microbe carries its own unique set of antigens. As we will see, these molecules are central to creating vaccines.

Antigens Sound the Alarm

The macrophages digest most parts of the yellow fever viruses but save the antigens and carry them back to the immune system's base camps, also known as **lymph nodes**. Lymph nodes, bean-sized organs scattered throughout your body, are where immune system cells congregate. In these nodes, macrophages sound the alarm by "regurgitating" the antigens, displaying them on their surfaces so other cells can recognize them. In particular, the macrophages show the yellow fever antigens to specialized defensive white blood cells called **lymphocytes**, spurring them to swing into action.

By this time, about 3 days after the mosquito bite, you are feeling feverish and have a headache. You decide to stay home from work.

Lymphocytes: T Cells and B Cells

There are two major kinds of lymphocytes, **T cells** and **B cells**, and they do their own jobs in fighting off your yellow fever. T and B cells head up the two main divisions of the immune system army.

T Cells

T cells function either offensively or defensively. The offensive T cells don't attack the virus directly, but they use chemical weapons to eliminate the cells of your body already infected with the yellow fever virus. (See "How Viruses Work," p. 18) Because they have been "programmed" by their exposure to the virus antigen, these **cytotoxic T cells**, also called killer T cells, can "sense" diseased cells that are harboring the yellow fever virus. The killer T cells latch onto these cells and release chemicals that destroy the infected cells and the viruses inside. The defensive T cells, also called **helper T cells**, defend the body by secreting chemical signals that direct the activity of other immune system cells. Helper T cells assist in activating killer T cells, and helper T cells also stimulate and work closely with B cells.

The work done by T cells is called your cellular or **cell-mediated immune response**.

B Cells

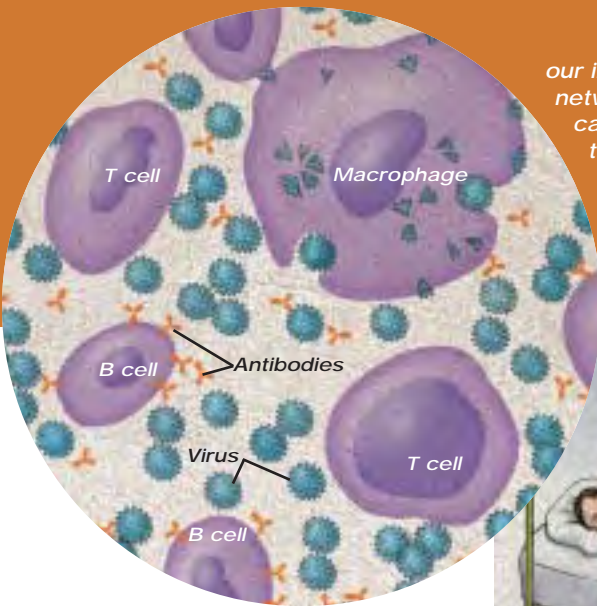
B cells are like weapons factories. They secrete extremely important molecular weapons called **antibodies**. Antibodies usually work by sticking to and coating microbes, and antibodies use the microbe's antigens to grip them. Antibody molecules fit with antigen molecules like pieces of a jigsaw puzzle fit together—if their shapes are compatible, they bind to each other.

Each antibody can usually fit with only one antigen. So your immune system keeps a supply of millions and possibly billions of different antibodies on hand to be prepared for any foreign invader. Your immune system does this by constantly creating millions of new B cells. About 50 million B cells circulate in each teaspoonful of your blood, and almost every B cell—through random genetic shuffling—produces a unique antibody that it displays on its surface.

Before you contracted yellow fever, somewhere in your body B cells were probably circulating with antibodies that, purely by chance, matched antigens from the yellow fever virus. When these B cells came into contact with their matching yellow fever antigen, they were stimulated to divide into many larger cells called **plasma cells** that secreted mass quantities of antibodies to yellow fever virus.

Antibodies in Action

The antibodies secreted by B cells circulate throughout your body until they run into the yellow fever virus. Antibodies attack the viruses that have not yet infected a cell but are lurking in the blood or the spaces between cells. When antibodies gather on the surface of a microbe, it is bad news for the microbe. The microbe becomes generally bogged down, gummed up, and unable to function. Antibodies also signal macrophages and other defensive cells to come eat the microbe. Antibodies are like big, bright signs stuck to a microbe saying, “*Hey, get rid of this!*” Antibodies also work with other defensive molecules that circulate in the blood, called **complement proteins**, to destroy microbes.



our immune system is a complex network of cells and organs. Cells called macrophages gobble up the invading virus and sound the alarm by showing pieces of the invader to T cells and B cells. B cells produce defensive molecules called antibodies that "stick" to the virus.

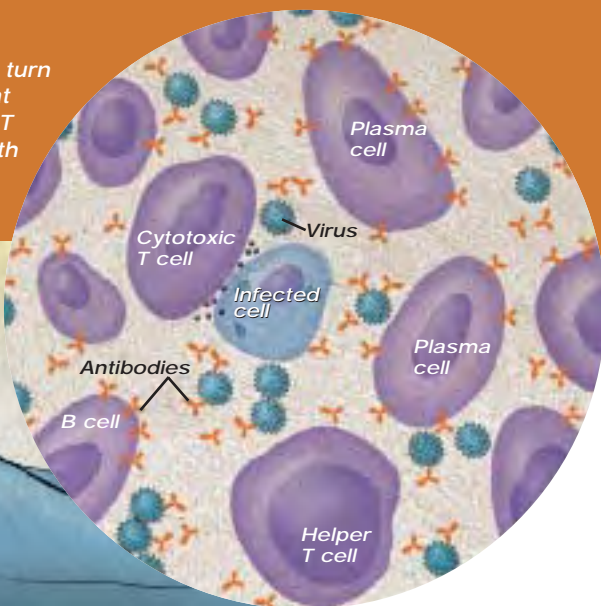


The work of B cells is called the **humoral immune response**, or simply the antibody response. The goal of most vaccines is to stimulate this response. In fact, many infectious microbes can be defeated by antibodies alone, without any help from killer T cells.

Clearing the Infection: Memory Cells and Natural Immunity

While your immune system works to rid your body of yellow fever, you are feeling awful. You lie in bed, too dizzy and weak even to sit up. During the next several days, your skin becomes yellow (or jaundiced) and covered with purple spots. You vomit blood. Your doctor looks grim and tired: He knows that as many as 20 percent of people who contract yellow fever die, and the epidemic is spreading fast through the city.

To overcome the virus, B cells turn into plasma cell “factories” that produce antibodies. Cytotoxic T cells eliminate cells infected with the virus; helper T cells direct the action with chemical signals.



After about a week, however, your immune system gains the upper hand. Your T cells and antibodies begin to eliminate the virus faster than it can reproduce. Gradually, the virus disappears from your body, and you feel better. You get out of bed. Eventually, you go back to working the docks.

If you are bitten by another yellow-fever-infested mosquito, you won't get the disease again. You won't even feel slightly sick. You have become immune to yellow fever because of another kind of immune system cell: **memory cells**. After your body eliminated the disease, some of your yellow-fever-fighting B cells and T cells converted into memory cells. These cells will circulate through your body for the rest of your life, ever watchful for a return of their enemy. Memory B cells can quickly divide into plasma cells and make more yellow fever antibody if needed. Memory T cells can divide and grow into a yellow-fever-fighting army. If that virus shows up in your body again, your immune system will act swiftly to stop the infection.

How Vaccines Mimic Infection

Vaccines teach your immune system by mimicking a natural infection. To show how, let's jump ahead to the 21st century. Yellow fever is no longer a problem in the United States, but you are a relief worker stationed in a part of the world where the disease still occurs, and the Centers for Disease Control and Prevention (CDC) recommends vaccination prior to your departure.

The yellow fever vaccine, first widely used in 1938, contains a weakened form of the virus that doesn't cause disease or reproduce very well. (More on how vaccine makers do that a little later.) This vaccine is injected into your arm. Your macrophages can't tell the vaccine viruses are duds. The macrophages gobble up the viruses as if they were dangerous and, in the lymph nodes, present yellow fever antigen to T and B cells. The alarm is sounded, and your immune system swings into action. Yellow-fever-specific T cells rush out to meet the foe. B cells secrete yellow fever antibodies. But the battle is over quickly. The weakened viruses in the vaccine can't put up much of a fight. The mock infection is cleared, and you are left with a supply of memory T and B cells to protect you against yellow fever, should a mosquito carrying the virus ever bite you.

Next, we'll take a closer look at different types of vaccines—not all of them employ killed or weakened microbes—and learn how each type works.

How Viruses Work

Viruses such as the yellow fever virus are tiny microbes made up of a small number of genes encased in a membrane or protein shell. If you were the size of a cell, a virus would look like a burr attached to your pants leg—a small, round object covered with tiny bristles.

Like burrs, viruses stick to cells. Then they inject their genetic material inside the cells. Once inside, the virus genes take over the cells' resources and molecular machinery, forcing the cells to make more viruses. The newly formed viruses “bud” or are released from the surface of the cells and drift off to infect new cells. Cells infected with viruses can't function properly and usually die. Many are eliminated by killer T cells.

Different Types of Vaccines

Imagine that a new infectious disease emerges from some obscure part of the world and begins to spread across the globe. The infectious agent jumps easily from person to person through the air, and it attacks the lungs, causing terrible coughing, fever, pneumonia, and sometimes paralysis of the respiratory system. Scientists quickly determine that disease *X* is caused by a new species of toxic bacterium. They call it “bacterium *X*.” Unfortunately, bacterium *X* is difficult to fight because it resists most antibiotics.

Everyone agrees a vaccine against bacterium *X* is needed, but how would scientists go about creating one?

First, they would carefully study bacterium *X*. They would figure out what nutrients it requires. They would examine how it damages lung tissue. Geneticists would analyze *X*'s genes. Immunologists would explore how the immune system responds to bacterium *X* and why the body sometimes fails to fight off this microbe. They would identify antigens from *X* that best stimulate the immune system. Other scientists would discover the toxin secreted by bacterium *X*.

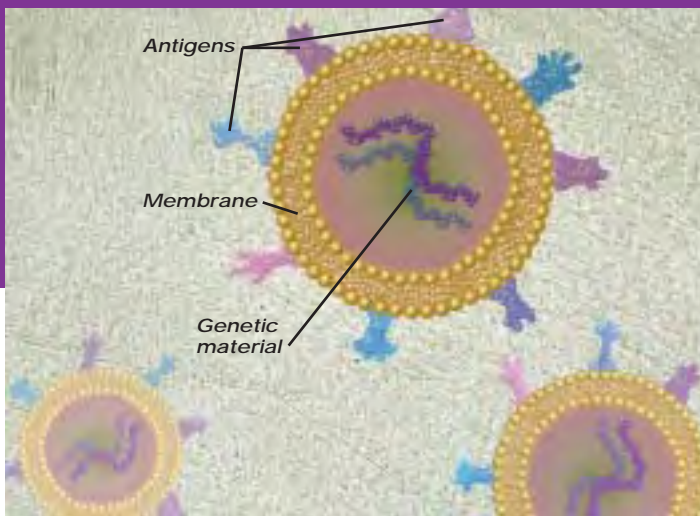
Once scientists had some basic information about *X*, they could begin designing vaccines that might work against it. Following are some of the options that researchers might pursue. They will give you an idea of the main types of vaccine strategies.

Live, Attenuated Vaccines

Some scientists might explore the possibility of a **live, attenuated vaccine** against *X*. These vaccines contain a version of the living microbe that has been weakened in the lab so it can't cause disease. This weakening of the organism is called **attenuation**. Because a live, attenuated vaccine is the closest thing to an actual infection, these vaccines are good “teachers” of the immune system: They elicit strong cellular and antibody responses, and often confer lifelong immunity with only one or two doses.

Despite the advantages of live, attenuated vaccines, there is a downside. It is the nature of living things to change, or **mutate**, and the organisms used in live, attenuated vaccines are no different. The remote possibility exists that the attenuated bacteria *X* in the vaccine could revert to a virulent form and cause disease. For their own protection, people with compromised immune systems—such as people with cancer or people infected with the human immunodeficiency virus (HIV)—usually are not given live vaccines.

Live, attenuated vaccines are relatively easy to create for viruses. Viruses are simple microbes containing a small number of genes, and scientists can therefore more readily control their characteristics. Viruses often are attenuated by growing generations of them in specific types of cells that make it hard for the virus to reproduce. This hostile environment takes the fight out of viruses: As they evolve to adapt to their new environment, they become weaker with respect to their natural host, human beings.



Live, attenuated vaccines use a weakened version of the microbe that has been changed to reduce or eliminate its potential to cause disease. This image shows the live microbe's antigens, membrane, and genetic material.

Live, attenuated vaccines are more difficult to create for bacteria. Bacteria have thousands of genes and thus are much harder to control. However, scientists working on a live vaccine for bacterium X might be able to use **recombinant DNA technology** to remove several key genes from X that allow it to grow and cause disease, thereby creating an attenuated X that could be used in a live vaccine. This has been done for the bacterium that causes cholera, *Vibrio cholerae*, although the live cholera vaccine has not been licensed in the United States.

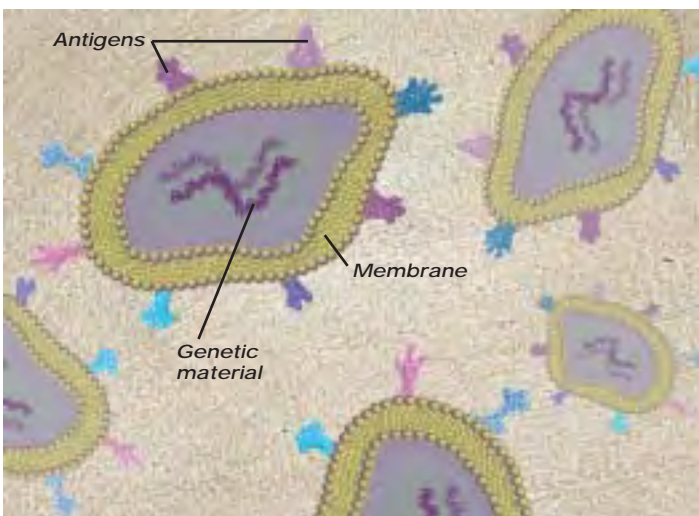
Live, attenuated vaccines usually need to be refrigerated to stay potent. If the X vaccine needs to be shipped overseas and stored by health care workers in developing countries that lack widespread refrigeration, a live vaccine may not be the best choice.

Inactivated or “Killed” Vaccines

An **inactivated vaccine** might be better for bacterium X. Scientists produce inactivated vaccines by killing the disease-causing microbe with chemicals, heat, or radiation. Such vaccines are more stable and safer than live vaccines: The dead microbes can't mutate back to their disease-causing state. Inactivated vaccines usually don't require refrigeration, and they can be easily stored and transported in a freeze-dried form, which makes them accessible to people in developing countries.

Most inactivated vaccines, however, stimulate a weaker immune system response than do live vaccines. So it would likely take several additional doses, so-called **booster shots**, to maintain a person's immunity to bacterium X. This quality could be a drawback in areas where people don't have regular access to health care and can't get their shots on time.

Inactivated or “killed” vaccines contain microbes that have been inactivated with chemicals, heat, or radiation. The microbe's antigens, membrane, and genetic material are still present.

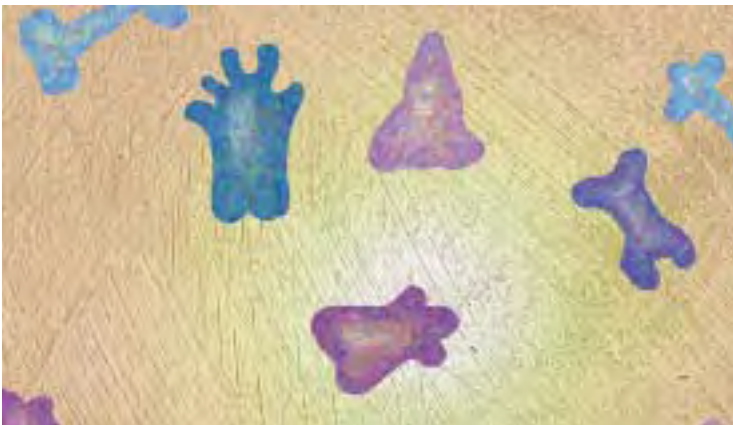


Subunit Vaccines

Scientists would certainly look into the possibility of a **subunit vaccine** for *X*. Subunit vaccines dispense with the entire microbe and use just the important parts of it: the antigens that best stimulate the immune system. In some cases, these vaccines use epitopes—the very specific parts of the antigen that antibodies or T cells recognize and bind to. Because subunit vaccines contain only the essential antigens and not all the other molecules that make up the microbe, the chances of adverse reactions to the vaccine are lower.

Subunit vaccines can contain anywhere from 1 to 20 or more antigens. Of course, identifying which antigens from bacterium *X* best stimulate the immune system would be a tricky, time-consuming process. Once scientists did that, however, they could make subunit vaccines against *X* in one of two ways. They could grow bacterium *X* in cultures, then use chemicals to break it apart and gather the important antigens.

Subunit vaccines contain just the antigens of the microbe that best stimulate the immune system. This image depicts antigens that have been separated from the body of the microbe for use in a subunit vaccine.

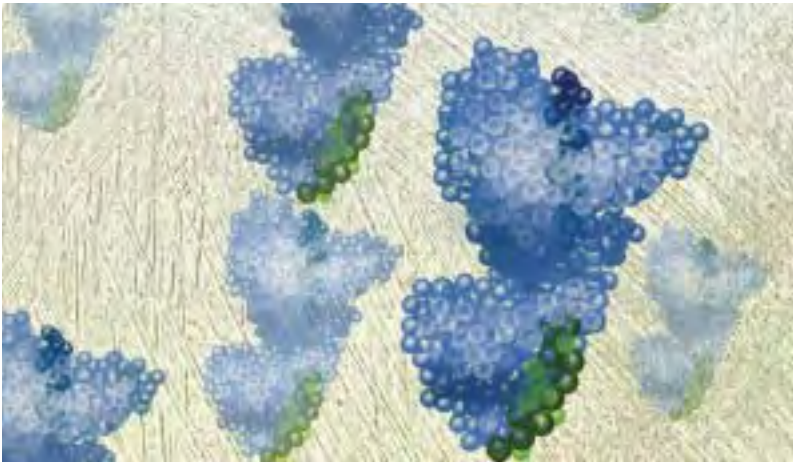


They also could manufacture the antigen molecules from *X* using recombinant DNA technology. Vaccines produced this way are called **recombinant subunit vaccines**. Such a vaccine has been made for the hepatitis B virus. Scientists inserted hepatitis B genes that code for important antigens into common baker's yeast. The yeast then produced the antigens, which the scientists collected and purified for use in the vaccine.

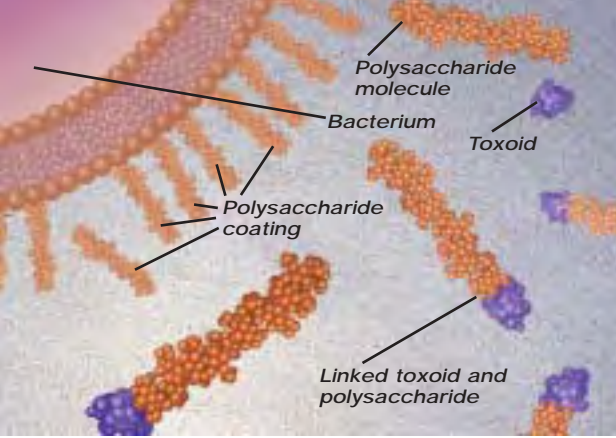
Toxoid Vaccines

Because our imaginary bacterium *X* secretes a toxin, or harmful chemical, a **toxoid vaccine** might work against it. These vaccines are used when a bacterial toxin is the main cause of illness. Scientists have found they can inactivate toxins by treating them with **formalin**, a solution of formaldehyde and sterilized water. Such “detoxified” toxins, called **toxoids**, are safe for use in vaccines.

When the immune system receives a vaccine containing a harmless toxoid, it learns how to fight off the natural toxin. The immune system produces antibodies that lock on to and block the toxin.



Harmless toxoid molecules (artist's representation) are used in toxoid vaccines to immunize and protect people against harmful toxins secreted by some microbes.



Conjugate vaccines link antigens or toxoids to the polysaccharide or sugar molecules that certain bacteria use as a protective coating, thereby allowing the immune system to recognize and attack these “disguised” bacteria. A conjugate vaccine contains the molecules shown in the foreground. The bacterium, part of which is shown in the upper left background, is not part of the vaccine.

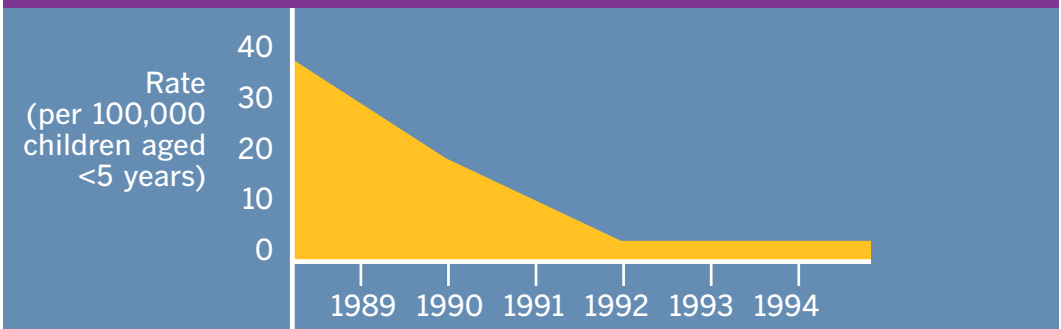
Conjugate Vaccines

If bacterium *X* possessed an outer coating of sugar molecules called **polysaccharides**, as many harmful bacteria do, researchers would try making a **conjugate vaccine** for *X*. Polysaccharide coatings disguise a bacterium’s antigens so that the immature immune systems of infants and younger children can’t recognize or respond to them. Conjugate vaccines, a special type of subunit vaccine, get around this problem.

When making a conjugate vaccine, scientists link antigens or toxoids from a microbe that an infant’s immune system can recognize to the polysaccharides. The linkage helps the immature immune system react to polysaccharide coatings and defend against the disease-causing bacterium.

The vaccine that protects against Hib is a conjugate vaccine.

Incidence rate of invasive *Haemophilus influenzae* type b (Hib) disease among children aged <5 years, United States, 1989-1994



Source: Summary of Notifiable Diseases, United States, 1995. CDC Morbidity and Mortality Weekly Report.

DNA Vaccines

Once the genes from bacterium *X* had been analyzed, scientists could attempt to create a **DNA vaccine** against it.

Still in the experimental stages, these vaccines show great promise, and several types are being tested in humans. DNA vaccines take immunization to a new technological level. These vaccines dispense with both the whole organism and its parts and get right down to the essentials: the microbe's genetic material. In particular, DNA vaccines use the genes that code for those all-important antigens.

Researchers have found that when the genes for a microbe's antigens are introduced into the body, some cells will take up that DNA. The DNA then instructs those cells to make the antigen molecules. The cells secrete the antigens and display them on their surfaces. In other words, the body's own cells become vaccine-making factories, creating the antigens necessary to simulate the immune system.

A DNA vaccine against *X* would evoke a strong antibody response to the free-floating *X* antigen secreted by cells, and the vaccine also would stimulate a strong cellular response against the *X* antigens displayed on cell surfaces. The DNA vaccine couldn't cause the disease because it wouldn't contain bacterium *X*, just copies of a few of its genes. In addition, DNA vaccines are relatively easy and inexpensive to design and produce.

So-called “**naked DNA vaccines**” inject the DNA directly into the body. These vaccines can be administered with a needle and syringe or with a needleless device that uses high-pressure gas to shoot microscopic gold particles coated with DNA directly into cells. Sometimes, the DNA is mixed with molecules that facilitate its uptake by the body's cells. Naked DNA vaccines being tested in humans include those against malaria, influenza, herpes, and HIV.

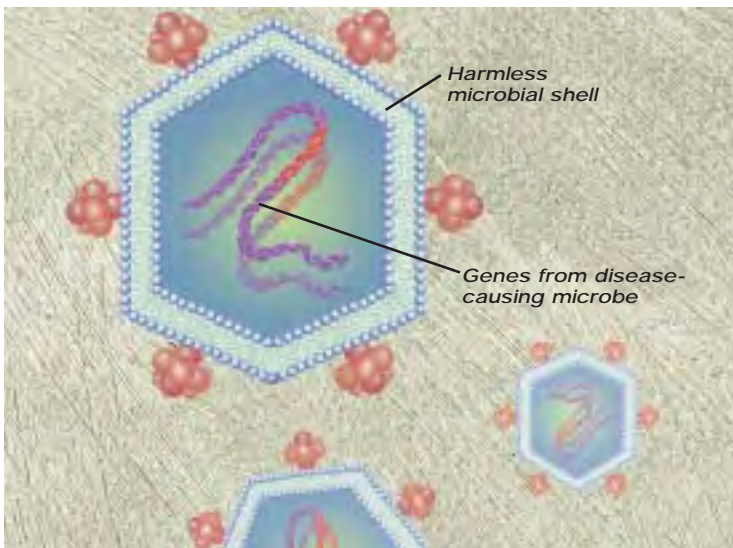


DNA vaccines use a microbe's genetic material; in particular, the genes that code for important antigens. The DNA in these vaccines is a circular form known as a plasmid.

Recombinant Vector Vaccines

Recombinant vector vaccines could be another possible strategy against bacterium X. These experimental vaccines are similar to DNA vaccines, but they use an attenuated virus or bacterium to introduce microbial DNA to cells of the body. “**Vector**” refers to the virus or bacterium used as the carrier.

In nature, viruses latch on to cells and inject their genetic material into them (see “How Viruses Work”). In the lab, scientists have taken advantage of this process. They have figured out how to take the roomy **genomes** of certain benign or attenuated viruses and insert portions of the genetic material from other microbes into them. The carrier viruses then ferry that microbial DNA to cells. Recombinant vector vaccines closely mimic a natural infection and therefore do a good job of stimulating the immune system.



Recombinant vector vaccines use the harmless shell of one microbe to deliver genetic material of a disease-causing microbe. The genetic material contains the code for making vaccine antigen inside some of the body's cells, using those cells as "factories."

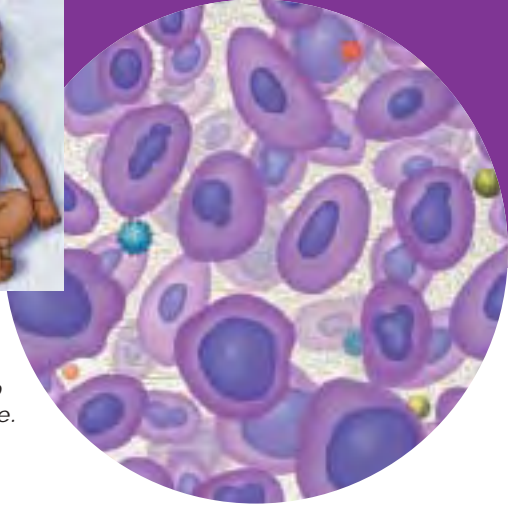
Attenuated bacteria also can be used as vectors. In this case, the inserted genetic material causes the bacteria to display the antigens of other microbes on its surface. In effect, the harmless bacterium mimics a harmful microbe, provoking an immune response.

Researchers are working on both bacterial- and viral-based recombinant vector vaccines for HIV, rabies, and measles.

Many Vaccines Against Bacterium X?

The search for a vaccine against bacterium X would likely result in several promising candidate vaccines. (Researchers working on an HIV vaccine, for example, have developed dozens of experimental vaccines at various stages of testing, including subunit vaccines, DNA vaccines, and recombinant vector vaccines.) But because of the rigorous research and testing each vaccine must go through, it would take years, probably decades, before an X vaccine was approved for use in the United States. In the next section, we'll take a closer look at how vaccines are tested and regulated.

Combination Vaccines



An infant's immune system contains billions of circulating B and T cells capable of responding to millions of different antigens at once.

Some vaccines come in combinations. Most of us are familiar with the DTP (diphtheria, tetanus, pertussis) and the MMR (measles, mumps, rubella) vaccines children in the United States receive.

Combination vaccines reduce visits to the doctor, saving time and money and sparing children extra needlesticks. Without combination vaccines, parents would have to bring their children in for each vaccination and all its boosters, and the chances would be greater that kids would miss their shots. Missed shots put children, as well as their communities, at risk.

Concerned parents have wondered whether combination vaccines might overwhelm or weaken a child's immune system, but the immune system contains billions of circulating B and T cells capable of responding to millions of different antigens at once. Because the body constantly replenishes these cells, a healthy immune system cannot be "used up" or weakened by a vaccine. According to one published estimate, infants could easily handle 10,000 vaccines at once.

For more sources of information on this topic, see "Vaccine Concerns, Myths, and Safety Issues on the Web."

Adjuvants and Other Vaccine Ingredients

Adjuvants are ingredients added to a vaccine to improve the immune response it produces. Researchers are studying many types of adjuvants, but the only type licensed for human use in the United States so far are the so-called “alum” adjuvants, which are composed of aluminum salts. These compounds bind to the antigens in the vaccine, help retain antigens at the site of injection, and help deliver antigens to the lymph nodes, where immune responses to the antigens are initiated. The slowed release of antigens to tissue around the injection site and the improved delivery of antigens to the lymph nodes can produce a stronger antibody response than can the antigen alone. Alum adjuvants are also taken up by cells such as macrophages and help these cells better present antigens to lymphocytes.

In addition to adjuvants, vaccines may contain antibiotics to prevent bacterial contamination during manufacturing, preservatives to keep multi-dose vials of vaccine sterile after they are opened, or stabilizers to maintain a vaccine’s potency at less-than-optimal temperatures.

Some Vaccine Types and Diseases They Protect Against

Vaccine Type	Disease	
	Live, attenuated vaccines	Measles, mumps, rubella, polio (Sabin vaccine), yellow fever
	Inactivated or "killed" vaccines	Cholera, flu, hepatitis A, Japanese encephalitis, plague, polio (Salk vaccine), rabies
	Toxoid vaccine	Diphtheria, tetanus
	Subunit vaccines	Hepatitis B, pertussis, pneumonia caused by <i>Streptococcus pneumoniae</i>
	Conjugate vaccines	<i>Haemophilus influenzae</i> type B, pneumonia caused by <i>Streptococcus pneumoniae</i>
	DNA vaccines	In clinical testing
	Recombinant vector vaccines	In clinical testing

Advantages

Produce a strong immune response

Often give lifelong immunity with one or two doses

Safer and more stable than live vaccines

Don't require refrigeration: more easily stored and transported

Teaches the immune system to fight off bacterial toxins

Targeted to very specific parts of the microbe

Fewer antigens, so lower chance of adverse reactions

Allow infant immune systems to recognize certain bacteria

Produce a strong antibody and cellular immune response

Relatively easy and inexpensive to produce

Closely mimic a natural infection, stimulating a strong immune response

Disadvantages

Remote possibility that the live microbe could mutate back to a virulent form

Must be refrigerated to stay potent

Produce a weaker immune response than live vaccines

Usually require additional doses, or booster shots

When developing a new vaccine, identifying the best antigens can be difficult and time consuming

Still in experimental stages

Still in experimental stages

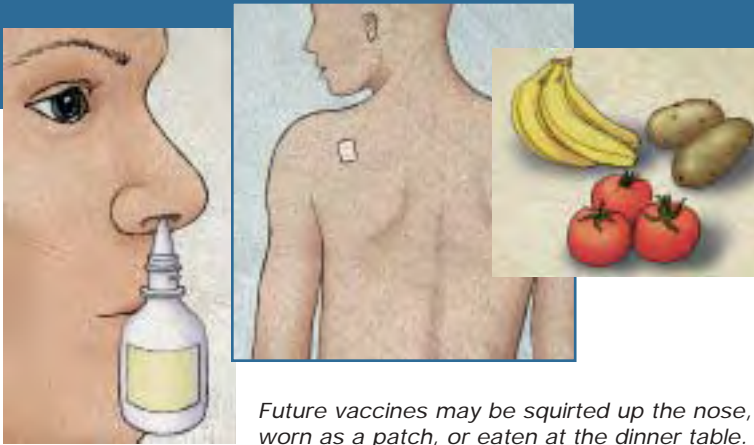
Vaccines of the Future

One day, vaccines may be eaten at the dinner table, applied via a skin patch, or squirted up your nose rather than administered as a shot in the arm—or elsewhere.

Scientists have shown that potatoes genetically engineered to produce an *Escherichia coli* antigen safely triggered an immune response to this bacterium in people who ate small pieces of the potatoes. Similarly, some researchers are modifying bananas to protect against Norwalk virus, a common cause of diarrhea, while other scientists are developing tomatoes containing a vaccine against hepatitis B. Researchers have even engineered a mouse that secretes an experimental malaria vaccine in its milk, and they hope to repeat the experiment with a goat.

Although still a long way off, **edible vaccines** such as these would make it cheaper and easier to immunize people against diseases, especially in developing countries where storing and administering vaccines is often difficult.

The same would be true of vaccines given through a skin patch. Recent tests have shown that a tetanus toxoid administered to mice through a skin patch produces a strong antibody response that protects mice against a lethal dose of the tetanus bacterium. Preliminary tests in humans have established that a skin patch vaccine induces a robust antibody response against *E. coli*, with no serious adverse reactions.



Future vaccines may be squirted up the nose, worn as a patch, or eaten at the dinner table.

A promising live, attenuated flu vaccine might eventually do away with the old flu shot. This vaccine is squirted from a spray bottle into one's nose. This method not only eliminates the needle—making it easier to administer to children—it also closely mimics how the flu virus actually enters your body, which may produce a better immune response. The vaccine, created with NIAID support, has been extensively tested in people and has been shown to work well. In June 2003, the **Food and Drug Administration (FDA)** licensed this vaccine for use in healthy adults and children ages 5 through 49. (For more on the vaccine approval process, see “Making Safe Vaccines,” p. 36)

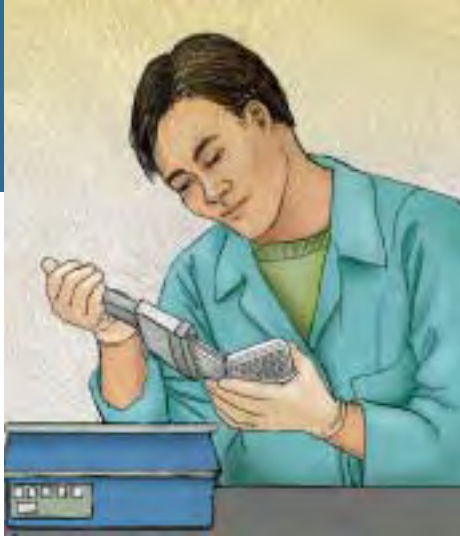
Making Safe Vaccines

No vaccine is perfectly safe or effective. Each person's immune system works differently, so occasionally a person will not respond to a vaccine. Very rarely, a person may have a serious adverse reaction to a vaccine, such as an allergic reaction that causes hives or difficulty breathing. But serious reactions are reported so infrequently—on the order of 1 in 100,000 vaccinations—that they can be difficult to detect and confirm. More commonly, people will experience temporary side effects such as fever, soreness, or redness at the injection site. These side effects are, of course, much preferable to coming down with the illness.

To make vaccines as safe as possible, FDA requires extensive research and testing before allowing a vaccine to be licensed for general use. The time between discovery of a disease agent and production of a widely available vaccine has been as long as 50 years. Today, with improved technology and research methods, the length of time from basic research to availability of a licensed vaccine can sometimes be reduced. If a vaccine is approved, FDA and other government agencies continue to monitor it for safety. Following are some of the key measures taken to ensure vaccines are safe.

Lab and Animal Testing

Also known as **preclinical testing**, this testing is required before the vaccine can be given to people. Researchers test candidate vaccines in cell cultures and in animals such as mice, rabbits, guinea pigs, or monkeys. If the vaccine appears promising in these preclinical experiments, it may go on to be carefully tested in people.



This vaccine researcher uses a multi-channel pipetter to quickly prepare many biological samples for analysis.

Investigational New Drug Application

Before any vaccine candidate can be tested—much less widely used—in people, its sponsors must submit an Investigational New Drug (IND) application to FDA. This application must explain how the vaccine works, describe how it is manufactured, present all preclinical safety data, and propose a plan for human testing. The IND must also demonstrate the vaccine has passed a series of tests for purity and safety.

Studies in Humans

Once vaccine developers have FDA approval for testing their construct in human volunteers, they begin cautiously, starting with a very small **clinical trial** and progressing through three phases of ever-larger studies. (See “Volunteering for a Clinical Study,” p. 39) Phase I studies enroll 20 or fewer people and primarily test for safety. Phase II studies involve 50 to several hundred people.

These studies continue to test for safety as well as try to determine the best dosage and to gather preliminary data on a vaccine's effectiveness. Phase III studies, designed for thorough testing of the vaccine's power to protect against illness, include thousands of people.

FDA License

The application to FDA for a license to market a vaccine is called a Biologics License Application, (BLA). This application must provide the results of all relevant human studies, describe all manufacturing and testing methods, and show the results of safety and purity tests on batches of the vaccine intended for public use. A BLA must also demonstrate that the vaccine manufacturers comply with all government standards, including those for production facilities, personnel, equipment, packaging, and record-keeping. At this stage, FDA also inspects the manufacturing facility.

The BLA is reviewed first by a team of FDA experts, then by an advisory committee made up of scientists, physicians, statisticians, and consumer representatives. The committee votes on whether or not to recommend that FDA approve the vaccine.

Follow-up Surveillance

Once a vaccine is on the market, FDA continues to monitor its safety. FDA periodically inspects the manufacturing facility, and it tests samples of the vaccine for potency, safety, and purity for as long as the vaccine is made. The manufacturer must also safety test each batch, or lot, of the vaccine.

In addition, most licensed vaccines continue to be evaluated with very large studies that look at tens of thousands of people who have received the vaccine. These **Phase IV** studies try to pick up rare or delayed adverse reactions that might not have been apparent in the smaller studies that led to licensure.

Finally, FDA and CDC gather information on licensed vaccines through the **Vaccine Adverse Events Reporting System (VAERS)**. Anyone—doctors, patients, parents—can report adverse vaccine reactions to VAERS. FDA reviews weekly VAERS reports for each lot of vaccine in use, searching for anything unusual.

Volunteering for a Clinical Study

Clinical trials rely entirely on volunteers—people who contribute their time and energy for the advancement of science and improved health care for all. Tens of thousands of volunteers of all ages and walks of life have participated in these trials.

Typically, a volunteer in a vaccine study agrees to be given the vaccine (or a look-alike placebo), visits a clinic frequently for evaluation, undergoes medical tests, and provides blood samples that researchers will use to assess the vaccine. Because no one knows yet how well the vaccine works, participants should not expect the experimental vaccine to protect them against disease.

Volunteers are fully informed about how the study will be conducted, its potential risks and benefits, and measures taken to ensure their safety and privacy. To find out more about clinical studies, visit ***www.clinicaltrials.gov***.

NIAID Vaccine Research

We still need new or improved vaccines to protect against many important disease-causing microbes. Some of these microbes, such as the parasites that cause malaria, have been around forever but have so far eluded scientists' best efforts. Others are newly emerged microbes that researchers are still learning about, such as HIV or West Nile virus. Malaria, HIV/AIDS, and other diseases such as tuberculosis cause immense suffering, especially in developing countries. For this reason, NIAID has made finding vaccines for these diseases a top priority. Another NIAID priority is creating vaccines against the most dangerous potential agents of bioterrorism. Following are some of the vaccine research efforts conducted or supported by NIAID.

Vaccine and Treatment Evaluation Units

NIAID revolutionized the cumbersome, piecemeal approach to vaccine studies by establishing a network of Vaccine and Treatment Evaluation Units (VTEUs) in 1962. These testing sites are based at leading university medical research centers, public health departments, and community clinics across the country. The network can rapidly recruit volunteers for clinical studies, and it played a major role in the studies that led to the licensing of vaccines for Hib and for a new subunit pertussis vaccine. VTEU investigators have also tested and advanced vaccines for pneumonia, influenza, cholera, whooping cough, malaria, and tuberculosis. More recently, they have been called upon to conduct critical studies of smallpox vaccines.

Vaccine Concerns, Myths, and Safety Issues on the Web

Now that vaccines have virtually eliminated many once-feared diseases, the possibility of vaccine side effects or adverse reactions loom larger in some people's minds than the diseases that vaccines prevent, especially now that children routinely receive 11 vaccines by age 2. Most parents today have never seen a case of diphtheria or measles, and some wonder why their children must receive so many shots. Rumors and misinformation about vaccine safety abound. For example, many parents are concerned that multiple vaccines may weaken or overwhelm an infant's immune system or that certain vaccines may cause autism, multiple sclerosis, or diabetes.

For more information on vaccine concerns, myths, and safety issues, try the following sources, which offer current information on these issues.

CDC National Immunization Program

www.cdc.gov/nip

1-800-232-2522

American Council on Science and Health

www.acsh.org

212-362-7044

Immunization Safety Review Committee of the Institute of Medicine

www.iom.edu/imsafety

202-334-1342

Johns Hopkins University Institute of Vaccine Safety

www.vaccinesafety.edu

National Network for Immunization Information

www.immunizationinfo.org

1-877-341-6644

National Partnership for Immunization

www.partnersforimmunization.org

703-836-6110 or 301-656-0003

Vaccine Education Center at The Children's Hospital of Philadelphia

www.vaccine.chop.edu

215-590-9990

HIV Vaccine Trials Network

In 1988, the first HIV vaccine trial in the world began at NIH. That same year, NIAID established the AIDS Vaccine Evaluation Group (AVEG), a network of testing centers at leading universities in the United States devoted exclusively to HIV vaccines. In 1999, NIAID built upon AVEG by creating the HIV Vaccine Trials Network (HVTN), a web of sites in the United States and abroad that test candidate HIV vaccines in clinical trials. The HVTN includes sites in Africa, Asia, South America, and the Caribbean. The international sites allow for studies that examine differences in genetic makeup, nutrition, access to health care, and HIV subtypes in various populations, crucial factors to creating a vaccine that is effective worldwide.

With millions of new HIV infections and deaths from HIV/AIDS occurring worldwide each year—an estimated 5.3 million new infections and 21.8 million deaths in 2000, for example—researchers are working fervently to find a vaccine. A vaccine will be the best tool for halting the spread of HIV infection.

Vaccine Research Center

In 2000, NIAID established the Dale and Betty Bumpers Vaccine Research Center (VRC) on its campus in Bethesda, Maryland, where researchers are working on vaccines against microbes such as HIV, smallpox virus, and Ebola virus. With a roster of about 150 scientists and support staff, the VRC is designed to be a facility where vaccines can be developed from initial concept to final product. The center conducts basic research on microbes and the immune system's response to them, designs candidate vaccines, and tests them in preclinical and clinical trials. VRC scientists also collaborate with researchers around the world in academic, clinical, and industrial laboratories.

Biodefense Vaccines

NIAID is working on new and improved vaccines against possible agents of bioterrorism. To protect citizens from bioterrorist attacks, these vaccines must be safe, easy to administer, and fast-acting—even to the point of providing immunity shortly *after* exposure to the microbe. Researchers supported by NIAID are developing improved vaccines against smallpox, anthrax, plague, and many other possible agents of bioterrorism.

Intramural Vaccine Research

More than 120 scientists at NIAID laboratories in Bethesda, Maryland, and Hamilton, Montana, are studying infectious microbes and the human immune response to them. Many of these scientists are directly involved in vaccine research and have been instrumental in developing currently licensed vaccines, including those for hepatitis A and B. To give just a few examples of intramural vaccine research, the Malaria Vaccine Development Unit, part of the Laboratory of Parasitic Diseases, has been studying the malaria parasite to identify possible antigens for vaccines, and the unit has tested experimental vaccines in Phase I trials. In addition, researchers in the Laboratory of Viral Diseases are working on candidate HIV vaccines.

Conclusion

Vaccines are crucial to maintaining public health: They are a safe, cost-effective, and efficient way to prevent sickness and death from infectious diseases. Vaccines have led to some of the greatest public health triumphs ever, including the eradication of naturally occurring smallpox from the globe and the near-eradication of polio.

In recent years, researchers have increased their understanding of the immune system and how it fights off harmful microbes. Scientists working on vaccines also have advanced technology to draw on, including recombinant DNA technology and the ability to “read” and analyze the genomes of disease-causing organisms. This new knowledge and technology promises to usher in a renaissance in the already vital field of vaccinology. Scientists are hard at work creating improved vaccines, designing new vaccine strategies, and identifying new vaccine candidates to prevent diseases for which no vaccines currently exist.

Glossary

adjuvants—substances sometimes included in a vaccine formulation to enhance the immune-stimulating properties of a vaccine.

antibodies—molecules produced by a B cell in response to an antigen. When an antibody attaches to an antigen, it helps destroy the microbe bearing the antigen.

antigen—a molecule on a microbe that identifies it as foreign to the immune system and stimulates the immune system to attack it.

artificially acquired immunity—immunity provided by vaccines, as opposed to naturally acquired immunity, which is acquired from exposure to a disease-causing organism.

attenuation—the weakening of a microbe so that it can be used in a live vaccine.

B cells—white blood cells crucial to the immune defenses. Also known as B lymphocytes, they come from bone marrow and develop into blood cells called plasma cells, which are the source of antibodies.

bacteria—microscopic organisms composed of a single cell and lacking a defined nucleus and membrane-enclosed internal compartments.

booster shots—supplementary doses of a vaccine, usually smaller than the first dose, that are given to maintain immunity.

cell-mediated immune response (also called cellular immune response)—immune protection provided by the direct action of immune cells (as distinct from that provided by molecules such as antibodies).

clinical trial—an experiment that tests the safety and effectiveness of a vaccine or drug in humans.

complement proteins—molecules that circulate in the blood whose actions “complement” the work of antibodies. Complement proteins destroy antibody-coated microbes.

conjugate vaccine—a vaccine in which proteins that are easily recognizable to the immune system are linked to the molecules that form the outer coat of disease-causing bacteria to promote an immune response. Conjugate vaccines are designed primarily for very young children because their immune systems can not recognize the outer coats of certain bacteria.

contagious—able to transmit disease to other people.

cytotoxic T cells (also called killer T cells)—a subset of T cells that destroy body cells infected by viruses or bacteria.

DNA vaccine (also called naked DNA vaccine)—a vaccine that uses a microbe’s genetic material, rather than the whole organism or its parts, to simulate an immune response.

edible vaccines—foods genetically engineered to produce antigens to specific microbes and safely trigger an immune response to them.

Food and Drug Administration (FDA)—the Federal agency that approves and licenses vaccines and drugs.

formalin—a solution of water and formaldehyde, used in toxoid vaccines to inactivate bacterial toxins.

genetic material—molecules of deoxyribonucleic acid (DNA) or ribonucleic acid (RNA) that carry the directions that cells or viruses use to perform a specific function, such as making a particular protein molecule.

genomes—all of an organism's genetic material. A genome is organized into specific functional units called genes.

***Haemophilus influenzae* type b (Hib)**—a bacterium found in the respiratory tract that causes acute respiratory infections, including pneumonia, and other diseases such as meningitis.

helper T cells—a subset of T cells that function as messengers. They are essential for turning on antibody production, activating cytotoxic T cells, and initiating many other immune functions.

herd immunity (also called community immunity)—the resistance to a particular disease gained by a community when a critical number of people are vaccinated against that disease.

humoral immune response (also called antibody response)—immune protection provided by B cells, which secrete antibodies in response to antigen (as distinct from that provided by the direct action of immune cells, or the cellular immune response).

immune—having a high degree of resistance to or protection from a disease.

immune system—a collection of specialized cells and organs that protect the body against infectious diseases.

inactivated vaccine (also called “killed” vaccine)—a vaccine made from a whole viruses or bacteria that has been inactivated with chemicals or heat.

live, attenuated vaccine—a vaccine made from microbes that have been weakened in the laboratory so that they can’t cause disease. (See **attenuation**.)

lymph nodes—small bean-shaped organs of the immune system, distributed widely throughout the body and linked by lymphatic vessels. Lymph nodes are gathering sites of B, T, and other immune cells.

lymphocytes—white blood cells that are central to the immune system’s response to foreign microbes. B cells and T cells are lymphocytes.

macrophages—large and versatile immune cells that devour and kill invading microbes and other intruders. Macrophages stimulate other immune cells by presenting them with small pieces of the invaders.

memory cells—a subset of T cells and B cells that have been exposed to antigens and can then respond more readily and rapidly when the immune system encounters the same antigens again.

microbe—a microscopic organism. Microbes include bacteria, viruses, fungi, and single-celled plants and animals.

molecules—the building blocks of a cell. Some examples are proteins, fats, and carbohydrates.

mutate—to change a gene or unit of hereditary material that results in a new inheritable characteristic.

naked DNA vaccines—(See **DNA vaccines**.)

naturally acquired immunity—immunity produced by antibodies passed from mother to fetus (passive), or by the body's own antibody and cellular immune response to a disease-causing organism (active).

pertussis (also called whooping cough)—a respiratory infection caused by the toxic bacterium *Bordetella pertussis*. The wracking coughs characteristic of this disease are sometimes so intense the victims, usually infants, vomit or turn blue from lack of air.

Phase IV studies—very large clinical studies that look at tens of thousands of people who have received a licensed vaccine. These studies try to pick up rare or delayed adverse reactions that might not have been apparent in the smaller Phase I, II, and III studies that preceded licensure.

plasma cells—cells produced by dividing B cells that are entirely devoted to producing and secreting antibodies.

polysaccharides—long, chain-like molecules made up of linked sugar molecules. The outer coats of some bacteria are made of polysaccharides.

preclinical testing—required laboratory testing of a vaccine before it can be given to people in clinical trials. Preclinical testing is done in cell cultures and in animals.

recombinant DNA technology—the technique by which genetic material from one organism is inserted into a foreign cell or another organism in order to mass-produce the protein encoded by the inserted genes.

recombinant subunit vaccines—vaccines made using recombinant DNA technology to engineer the antigen molecules of the particular microbe. (See **subunit vaccine**.)

recombinant vector vaccines—vaccines that use modified viruses or bacteria to deliver genes that code for microbial antigens to cells of the body.

rubella (also called German measles)—a viral disease often affecting children and spread through the air by coughs or sneezes. Symptoms include a characteristic rash, low-grade fever, aching joints, runny nose, and reddened eyes. If a pregnant woman gets rubella during her first three months of pregnancy, her baby is at risk of having serious birth defects or dying.

subunit vaccine—a vaccine that uses one or more components of a disease-causing organism, rather than the whole, to stimulate an immune response.

T cells—white blood cells (also known as T lymphocytes) that direct or participate in immune defenses. (See **cytotoxic T cells** and **helper T cells**.)

toxin—agent produced by plants and bacteria, normally very damaging to cells.

toxoids (also called inactivated toxins)—toxins, such as those produced by certain bacteria, that have been treated by chemical means, heat, or irradiation and are no longer capable of causing disease.

toxoid vaccine—a vaccine containing a toxoid, used to protect against toxins produced by certain bacteria.

Vaccine Adverse Events Reporting System (VAERS)—a follow-up surveillance system that gathers information on adverse reactions associated with licensed vaccines. VAERS is a joint effort of FDA and CDC, and anyone—doctors, patients, or parents—can report adverse reactions to VAERS.

vector—in vaccine technology, a bacterium or virus that cannot cause disease in humans and is used in genetically engineered vaccines to transport genes coding for antigens into the body to induce an immune response.

virulent—toxic, causing disease.

viruses—very small microbes that do not consist of cells but are made up of a small amount of genetic material surrounded by a membrane or protein shell. Viruses cannot reproduce by themselves. In order to reproduce, viruses must infect a cell and use the cell's resources and molecular machinery to make more viruses.



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