

## HOW VACCINES WORK

### Natural Defenses Against Infection

Human beings are protected against infectious diseases by various physical and biochemical factors.<sup>1-3</sup> Our first level of protection against disease is our skin and its acidic secretions, tears and the mucous membranes that line our nose, mouth and other passages connecting our internal and external environments. These factors and others, when functioning properly, keep pathogens at bay.

If an infectious agent, a pathogen, gets past the first line of defense, our bodies have a second tier of defense provided by natural or innate immune mechanisms.<sup>3-5</sup> In this case, our own cells and the chemicals they produce seek out, identify and eliminate the pathogen. These very general and non-specific responses are critical to the maintenance of good health.

On occasion, a pathogen can get past our bodies' primary protective mechanisms if it is present in very large numbers or if it has evaded or suppressed these processes. Stronger protection is needed and we respond by mounting an acquired immune reaction specific to the pathogen. These responses involve a variety of types of cells found in the blood and tissues, and can require a week or more to become established. Acquired immunity consists of antibody and cell-mediated responses.

An acquired immune response can result in either short-term or long-term protection against a specific pathogen and, perhaps, against some of its close relatives. In the case of long-term protection, re-exposure to the same pathogen weeks, months or years later reactivates the response mechanisms laid down during the original exposure. This reactivation leads to rapid, effective elimination of the agent, often without clinical symptoms or signs of infection. When specific immunity results from unintentional exposure to agents in the environment, we refer to the resulting protection as being passively acquired immunity. Intentional exposure to such an agent or its components through vaccination is known as actively acquired immunity.<sup>6</sup>

### Natural Innate Immunity

Understanding how vaccines work requires some appreciation of the cells and other factors that play a role in the acquisition of immunity. The immune system is a complex network of molecules, cells and tissues that is widely dispersed throughout the body.<sup>1-3</sup> Each of these entities has a distinct role to play, and all interact in a coordinated and orchestrated manner to generate a timely and specific immune response to a pathogen or to a vaccine.

When a pathogen or vaccine reaches the internal environment through inhalation, ingestion, a wound or injection, the cells in the surrounding tissues release chemicals called chemokines and cytokines that attract various types of white blood cells to the area of injury, leading to the destruction of the pathogen.<sup>7</sup> White blood cells are found in everyone's blood and are responsible for keeping our bloodstream and tissues free of pathogens, abnormal cells and other unwanted material. Several types of white blood cells are critical to the natural immune response. One type of white blood cell is called a macrophage. It is among the first of the responding cells to arrive at the site of injury where it engulfs and destroys the pathogen.

Other types of white blood cells, called lymphocytes, also are attracted to the site. These cells, along with the macrophages release other chemokines and cytokines that direct the immune response. The local accumulation of the various types of cells contributes to the inflammation or redness that is often observed at sites of infection and injury. These cells and processes constitute the natural immune response and are often sufficient to clear or eliminate the infection.

Natural immunity is neither specific nor long lasting. This response occurs each time there is a threat of infection, and is virtually identical for each pathogen that gains entry. Natural immunity is also independent of the number of times to which

## GLOSSARY TERMS

Acellular vaccines	Immunity
Acute	Inactivated vaccines
Allergy	Incidence
Antibody	Inflammation
Antigen	Influenza
Asthma	Lymphocytes
Attenuated vaccines	Macrophage
B cells	Major histocompatibility complex
B lymphocytes	Measles
Booster	Meningococcal disease
Cases	Mumps
Cell-mediated response	Pathogen
Chemokines	Pertussis
Chronic	Pneumococcal disease
Conjugate vaccines	Poliomyelitis
Cytokines	Polysaccharide vaccines
Cytotoxic T cells	Recombinant DNA technology
Diphtheria	Rubella
Disease	Specific acquired immunity
DNA	Subunit vaccines
<i>Haemophilus influenzae</i>	T cells
Hepatitis A	Tetanus
Hepatitis B	Valent
Immune response	Virus
Immune system	White blood cells

## ACRONYMS

MHC	Major Histocompatibility Complex
DNA	Deoxyribonucleic acid

## WEB RESOURCES

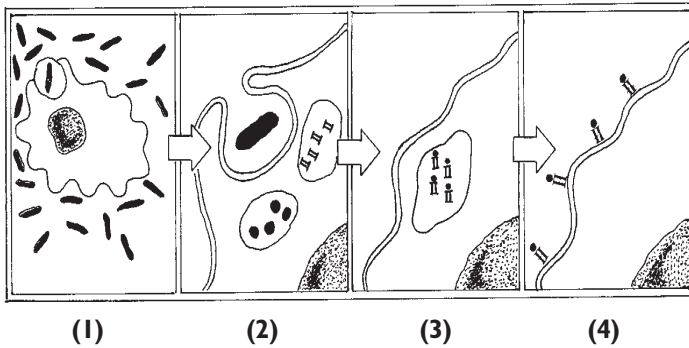
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we are exposed to any single agent, that is, even if we are exposed to a single agent many times, our response to each exposure is the same.

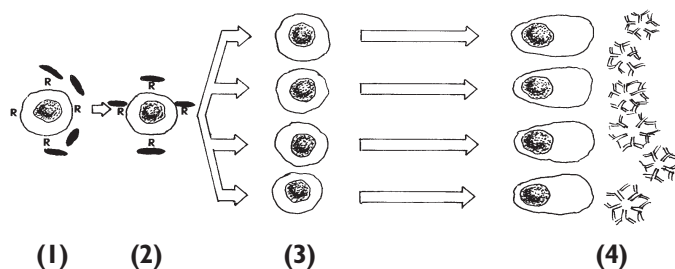
### Acquired Immunity – Antibody Response

Induction of a specific, protective immune response, i.e., acquired immunity, enhances the natural response by directing certain interactions among the cells participating in the immune response. Conditions for these interactions are met when the number of pathogens is large or persistent, or when they are not readily eliminated by the natural mechanisms.



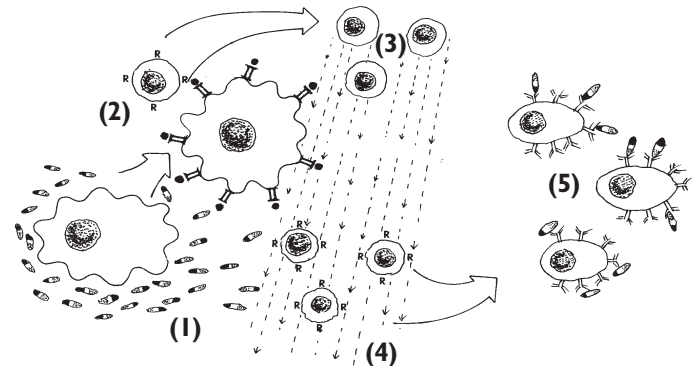
- (1) A macrophage in the presence of an infectious agent
- (2) The macrophage engulfs and breaks down the infectious agent into small fragments
- (3) The fragments bind to MHC Class II molecules that are produced by the macrophage
- (4) Complexes of antigen fragments and MHC Class II molecules are transported to the macrophage surface

Macrophages play a critical role in the establishment of specific acquired immunity.<sup>2,3</sup> As macrophages engulf an infectious organism or a certain vaccine, it is broken down chemically into constituent proteins and other biochemical components. The proteins are further degraded and the resulting small fragments of protein associate with certain molecules, known as major histocompatibility complex (MHC) Class II molecules, that are produced by the macrophages. These complexes, consisting of the protein fragment or antigen and the MHC Class II molecule, are arrayed on the surface of the macrophage where the antigen can be “presented” to certain lymphocytes.<sup>8,9</sup>



- (1) B cell in the presence of an infectious agent
- (2) Receptors on the B cell adhere to the infectious agent
- (3) The now activated B cell divides to produce many virtually identical copies of itself
- (4) The B cells mature into plasma cells that release antibodies that can adhere to the infectious agent, leading to its destruction

Lymphocytes, specifically B lymphocytes (or B cells) and T lymphocytes (or T cells), mediate protective immunity. Both types of cells circulate freely in the blood and large numbers reside in the spleen, lymph nodes and other tissues where antigen exposure is likely. B cells have structures on their surface membranes known as receptors that simultaneously recognize and adhere to proteins that make up the pathogen or vaccine. This contact is sufficient to activate the B cell causing it to divide rapidly, forming hundreds if not thousands of virtually identical cells. Many of the B cells ultimately mature into plasma cells, all of which release large amounts of antibody molecules that can specifically attack the pathogen.



- (1) Macrophages, B cells and T cells are attracted to the site of an infection
- (2) The macrophage engulfs the agent and presents fragments to helper T cells
- (3) Activated helper T cells release cytokines that promote B cell activity
- (4) Different B cells recognize different parts of the infectious agent
- (5) Each B cell matures into an antibody releasing plasma cell

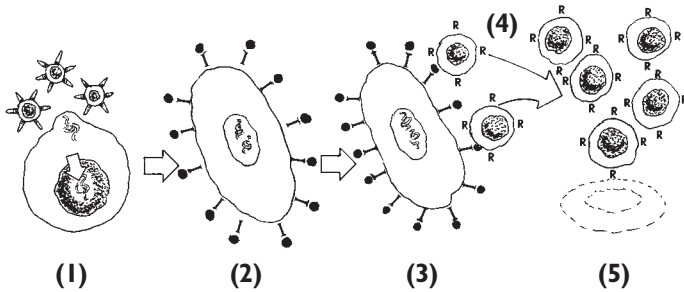
There are at least two distinct populations of T cells and these are distinguishable, in part, by the types of receptors found on their surfaces. The receptor on the helper T cell simultaneously recognizes and briefly adheres to the antigen and MHC Class II complex presented by macrophages or other antigen presenting cells;<sup>8,9</sup> the other T cell population is discussed below. This contact, although transient, is sufficient to activate the lymphocyte causing it to release more or different cytokines. The cytokines stimulate cells, particularly antigen-stimulated B cells, to divide and become functionally mature. Because a pathogen or vaccine may have hundreds or thousands of distinct antigens, many different B cells are stimulated simultaneously.

This results in the production and release of many different antibodies that recognize many of the distinct antigenic components of the pathogen. Antibody molecules encountering the pathogen attach to it, providing a handle by which macrophages, other cells or other types of molecules attach to the pathogen resulting in its destruction. In other cases, aggregations of many antibody-linked pathogens are eliminated in the urine or stool.

### Acquired Immunity – Cell-Mediated Response

Antibody-mediated immunity is most effective when the pathogen occurs in the tissues and does not become established within individual cells. Other pathogens penetrate into individual cells where they can avoid interactions with antibodies and thus persist for long periods of time, causing acute or chronic disease. Viruses are particularly adept at this. When viruses

infect human cells, they take over the machinery of the cell, using it to produce more copies of themselves, i.e., they replicate. This process of replication causes fragments of virus protein to become attached to the cell's own MHC Class I molecules.<sup>8,9</sup> This complex attaches to the surface of the cell where the antigen is presented to T cells bearing receptors for the antigen and the Class I molecule. These T cells are called cytotoxic T cells because of their capacity to specifically destroy cells harboring the virus.



- (1) Virus infects a cell
- (2) Fragments of the virus bind to MHC Class I molecules produced by the cell
- (3) The virus antigen fragments are presented to cytotoxic T cells
- (4) Activated cytotoxic T cells divide to produce many virtually identical copies of themselves
- (5) Activated cytotoxic T cells destroy other virus-infected cells

Again, the transient interaction between the antigen-presenting cell bearing the antigen-MHC Class I complex and the cytotoxic T cell is sufficient to activate the latter. The cell divides rapidly producing many, virtually identical activated cytotoxic T cells that have the capacity to destroy virus-infected cells bearing the same antigen/MHC Class I molecular complex. These T cells are thus responsible for specific cell-mediated immunity to the pathogen. This process is referred to as the cell-mediated response.

## Remembering the Pathogen

The cellular interactions that produce antibodies and cytotoxic T cells occur relatively rapidly. The amount of antibodies in the blood and the number of cytotoxic T cells increase over the course of several days or weeks before leveling off. As the infection is cleared or the response to immunization diminishes, some of the B cells become memory B cells and preserve on their surfaces receptors specific for the antigen that originally stimulated its parental cell.<sup>1-3</sup> Thus, if the individual is subsequently re-exposed to the same agent, the B memory cell is poised to respond by quickly dividing and releasing antibodies. Similarly, certain pathogen-specific cytotoxic T cells also persist as memory T cells that are available to respond more quickly and effectively should the individual be exposed again to the same agent.<sup>1-3</sup> Vaccination establishes a pool of memory cells that can produce pathogen-specific antibodies fast enough to largely prevent development of the disease and to minimize its impact on the individual.

## Development of the Immune System

At birth, many of our biological systems, e.g., lungs, liver, heart and kidney, are fully formed and fully functional. The

immune system, however, is not. The various cells and tissues that comprise the system are in place, and natural immune responses are possible, but the immune system does not become fully functional until it has been exposed to antigens.<sup>1-3</sup>

During fetal and postnatal development, the immune system is still learning its job and, like children themselves, has a great learning capacity. Consequently, at least part of the reasoning behind immunizing young children is to take advantage of the immune system's ability to learn to recognize and respond to potential health-threatening agents. Infant and childhood vaccination also takes advantage of the system's ability to build memory to protect against important pathogens likely to be encountered during childhood or later in life. It is unlikely that the capacity of a child's immune system is compromised by immunization. Indeed, evidence suggests that insufficient antigenic stimulation of the developing immune system may contribute to the increased incidence of asthma and allergy observed among children.<sup>10</sup>

## Maintaining Immunity

Some vaccines need to be administered periodically throughout the lifespan, e.g., tetanus, or even annually, e.g., influenza. Vaccines against tetanus trigger antibody responses to a specific toxic protein made by the tetanus-causing organism. Over time, the production of specific antibodies wanes to the point that there is no longer sufficient antibody or memory B cells present to protect against the toxin produced as a result of a natural infection. The waning of the response is gradual and hence, re-immunization with the tetanus vaccine is recommended at ten-year intervals after the final childhood immunization (at approximately five years of age).

Vaccines against influenza (the flu) offer a further example of the complexities of protective immunization. The influenza virus changes on a continuing basis, making it difficult to identify a stable antigen to be used in a vaccine to elicit long-lasting protective immunity. The virus also is promiscuous; it can infect a variety of non-human animals such as ducks, chickens and swine. As the virus moves from host to host, it can undergo further changes. Thus, the antigen associated with the flu-causing virus differs from year to year, necessitating the administration of a different vaccine each year.

## Vaccines

Vaccination is intended to elicit a specific immune response that will protect the immunized individual from the pathogen should he or she be exposed to that agent at a later date. Such intentional exposures use inactivated or other forms of the agent that stimulate the protective response without triggering the disease.<sup>6</sup> The ability of a vaccine to do this is sometimes enhanced when it is combined with an adjuvant, a substance that attracts additional inflammatory cells to the site of injury and stimulates them to release more and different cytokines. These chemical signals further stimulate and activate macrophages and lymphocytes to acquire additional protective functions. The underlying processes and mechanisms are similar regardless of whether protective immunity is passively or actively acquired.

Because of the unique properties of viruses and other intracellular pathogens, vaccines against such infectious agents ideally should elicit vigorous antibody- and cell-mediated responses. Effective vaccines stimulate the production of antibodies that destroy the pathogen prior to its entry into cells, and elicit cytotoxic T cells that can destroy cells in which the pathogen resides. Together these responses protect against disease.

### Types of Vaccines

Each vaccine is unique in terms of its composition and formulation. These differences reflect not only the different infectious agents from which the vaccines are derived, but also how the vaccines are used and the mechanisms through which their effects are mediated. The following describes various vaccine formulations in current use and gives examples of each. Each vaccine is further described and characterized in the section *The Value and Safety of Recommended Vaccines*.

Live attenuated vaccines consist of a weakened form of the infectious agent itself. The attenuated form can reproduce, thus assuring that the vaccinated person will be exposed to the agent long enough to develop a specific protective immune response. However, because the disease-causing agent is weakened, it is unable to elicit the disease in normal, healthy people. The measles, mumps, rubella, and some polio vaccines are examples of live attenuated vaccines.<sup>11</sup>

Inactivated vaccines may consist of intact bacteria or viruses (often referred to as whole cell vaccines) or extracts of those agents sometimes referred to as acellular, subunit, or fractional vaccines. The components of these vaccines are not able to reproduce, do not cause disease, and are typically given in multiple doses to elicit immune protection. Inactivated vaccines include some of those for influenza (flu), rabies, hepatitis A and B, pertussis and tetanus.<sup>11</sup>

Acellular and subunit vaccines are typically composed of protein extracted from the infectious agent. For example, tetanus disease is due to a toxic chemical produced by the tetanus pathogen. A weaker form of this chemical, referred to as tetanus toxoid, is the principle component of the tetanus vaccine. Other subunit vaccines include those for hepatitis B and diphtheria.<sup>12</sup> The

hepatitis B vaccine is the first to be produced using recombinant DNA technology, an approach that holds great promise for speeding the development of safe and effective vaccines.

Some subunit vaccines consist of polysaccharides (long chains of sugar molecules) isolated from a specific infectious agent. Pure polysaccharide vaccines, such as some of the older vaccines against pneumococcal and meningococcal diseases and against *Haemophilus influenzae* type b, often have limited ability to elicit effective protective immunity.<sup>11</sup>

The response to polysaccharide-based vaccines is enhanced when the polysaccharide molecules are conjugated (bound chemically) to a carrier protein. Such conjugated vaccines elicit strong protective immunity that can be further enhanced by additional (booster) immunizations. Conjugate vaccines against pneumococcal disease and *Haemophilus influenzae* type b are in common use.<sup>11</sup>

Both pure polysaccharide and conjugate polysaccharide vaccines consist of multiple antigenic components from the target pathogen. The number of components is often used to describe the vaccine. For example, a pure polysaccharide vaccine against pneumococcal disease that contains 23 different antigenic components is referred to as a 23-valent vaccine.<sup>13</sup>

### Vaccines and Disease Prevention

Vaccines are designed to protect us from the consequences of infectious disease. This is accomplished by exposing the individual to inactivated or other forms of the pathogen, giving rise to antibodies, B cells and T cells that protect the individual from the debilitating and often life-threatening consequences of infectious disease. Vaccines are unique among modern medications in that they offer effective protection against the onset and progression of specific infectious diseases. Most other medications are therapeutic, i.e., they are used to treat the disease and/or its symptoms; few are preventative. Vaccination is also unique in harnessing the cells, tissues and molecules of an individual's immune system to mediate this protection through a variety of natural mechanisms and processes that are fundamental to human biology. The development and use of safe, effective vaccines has and will continue to contribute significantly to our increasing life expectancy and to the quality and richness of our lives.

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