# VACCINES AND HOW THEY WORK

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## Infectious Diseases

Infectious diseases have been the bane of human existence throughout history. Evidence of infection has been found in mummified remains from ancient Egypt[1] and elsewhere, and in the oral and written histories of all cultures.[2] The Black Death of the Middles Ages,[3] the decimation of the native peoples of the Americas by imported disease[4] and the worldwide influenza epidemic of 1918[4] are vivid reminders that infectious diseases have profoundly shaped our world and have the potential to do so again.

Infectious diseases are caused by organisms that are able to exploit the human body so that they may grow and reproduce. In general, these organisms are tiny and can exist in our lungs, blood or other body tissues and organs. They gain access to us through the air we breathe, the food and water we ingest, or damage to our skin. Disease-causing agents (pathogens) include bacteria and viruses.[5]

Bacteria are tiny and can be seen only with the aid of a microscope. They typically are rod-shaped or round (see table below). Exposure to these pathogens occurs either by inhalation or oral uptake. However, exposure to the bacteria that cause tetanus is more commonly associated with puncture or laceration injuries or other damage to the skin, and the disease symptoms result from a toxic chemical (toxin) that the bacteria produce and release. The diseases caused by the bacteria listed in the following table can be prevented by vaccines licensed for use in the US.

| Bacteria | Bacteria Shape | Disease Bacteria Causes |
|---|---|---|
| *Corynebacterium diphtheriae* | Rod | Diphtheria |
| *Clostridium tetani* | Rod | Tetanus |
| *Bordetella pertussis* | Rod | Pertussis |
| *Haemophilus influenzae* type b | Rod | Hib disease |
| *Neisseria meningitidis* | Round | Meningococcal disease |
| *Streptococcus pneumoniae* | Round | Pneumococcal disease |

Viruses are smaller than most bacteria, can be seen only with an electron microscope and are much simpler in terms of their biochemical composition and biological activity. Viral diseases that can be prevented by vaccines licensed for use in the US include hepatitis A, hepatitis B, polio, influenza, measles, mumps, rubella (German measles) and varicella (chickenpox). Upon infection, viruses typically enter individual cells that make up the target tissue, e.g., the hepatitis A and hepatitis B viruses enter cells of the liver. Because viruses lurk within the cells of the body, the development of anti-virus vaccines employs strategies different from those used in the development of vaccines against bacterial pathogens. These differences are described below.

## Exposure to Pathogens

Bacteria and viruses are found everywhere in our environment[6] and cannot be avoided. Most cause no health problems and some are even beneficial, such as those that live in the human intestine and aid the digestive process. Some, such as those mentioned above, clearly cause disease, while others occasionally may be responsible for disease in certain individuals. Disease results when a pathogen becomes established in a person and is associated with damage to host tissues as a consequence of its growth and reproduction, or the release of toxins.[7] This occurs in two steps: the host must first be exposed to the pathogen, and secondly, infection must occur. While scientists agree that disease develops as a result of this process, the required amount of the pathogen that the body must be exposed to in order for infection to result is much debated. Indeed the majority of infections do not result in disease.

## GLOSSARY TERMS

Acquired immunity
Acute
Antibody
Antigen
Association
Asthma
Attenuated vaccines
Autoimmune disease
B cell
Bacteria
Booster
*Bordetella pertussis*
Cases
Causal association
Cell-mediated response
Chemokines
Chickenpox
Chronic
*Clostridium tetani*
Combination vaccine
Conjugate vaccine
*Corynebacterium diphtheriae*
Cytokines
Cytotoxic T cell
Diabetes
Diphtheria
Disease
Dysfunction
Epidemic
German measles
*Haemophilus influenzae* type b
Helper T cell
Hepatitis
Hepatitis A
Hepatitis B
Hexavalent vaccine
Immunization
Influenza
Innate immunity
Lymphocytes
Macrophage
Measles
Mumps
*Neisseria meningitidis*
Neonate
Pathogens
Pentavalent vaccine
Pertussis
Pneumococcal disease
Pneumococcal polysaccharide
Pneumonia
Polysaccharide
Polysaccharide vaccine
Protein
Rabies
Recombinant DNA technology
Risk
Rubella
Smallpox
Specific acquired immunity
*Streptococcus pneumoniae*
Subunit vaccines
T cell
Tetanus
Toxin
Type I diabetes
Vaccine
Vaccine schedule
Valent
Varicella
Virus
White blood cells

## ACRONYMS

| | |
|---|---|
| DNA | Deoxyribonucleic acid |
| Hib | *Haemophilus influenzae* type b |
| IOM | Institute of Medicine |
| MHC | Major histocompatibility complex |

## WEB RESOURCES

**American Institute of Immunology**
http://library.thinkquest.org/12429/welcome.html

**Cells Alive**
http://www.cellsalive.com

**Dalhousie University Medical Center**
http://www.medicine.dal.ca/micro/education/pimunit/home.htm

**Davidson College**
http://www.bio.davidson.edu/courses/immunology/bio307.html

**Garland Publishing**
http://blink.uk.com/immunoanimations

**National Cancer Institute**
http://newscenter.cancer.gov/sciencebehind/immune/immune00.htm

**University of California, San Diego**
http://wilson-squier.ucsd.edu/research/sb/ve/immunology

**University of Leicester**
http://www-micro.msb.le.ac.uk/312/BS312.html

### IMMUNIZATION SCHEDULES

**Childhood schedule**
http://www.cdc.gov/nip/recs/child-schedule.htm#printable

**Adult schedule**
http://www.cdc.gov/nip/recs/adult-schedule.htm

Exposure to a single pathogenic bacterial cell is considered by some to be sufficient to result in infection and disease[8] if it is able to evade all of the body's natural defenses (described below) that protect a person from infection. If this occurs, that single cell will be able to grow and divide, ultimately giving rise to sufficient numbers of daughter cells to trigger disease. However, the development of disease following infection is more likely to occur if the host is exposed to large numbers of pathogens versus a single cell. Hence, disease is more likely to occur if the person is exposed to 10,000 pathogenic bacteria than if exposed to 1,000 or 100 bacteria.

## Natural Defenses Against Infection

Human beings are protected against infectious diseases by various physical and biochemical factors.[9-11] 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.[12-14] 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.[15]

## 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.[9-11] Each of these entities has a distinct role to play, and all interact in a coordinated and orchestrated manner to generate a timely and effective immune response to a pathogen or to a vaccine.

When a pathogen or vaccine enters the body 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.[16] 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.

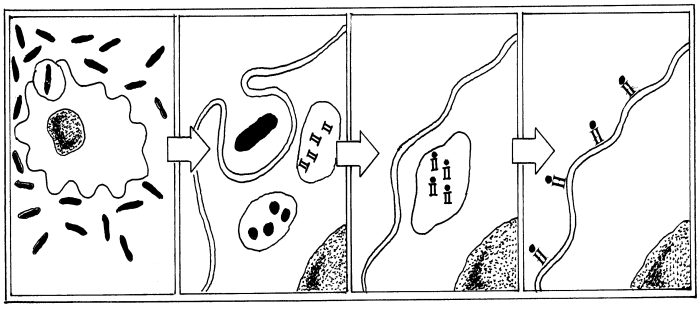
Innate immunity is neither specific nor long lasting. This response occurs each time there is a threat of infection, and is virtually identical for each pathogen that gains entry. Natural immunity is also independent of the number of times a person is exposed to any single agent, that is, even if a person is exposed to a single agent many times, their 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 when the pathogens are not readily eliminated by the natural mechanisms.

Macrophages play a critical role in the establishment of specific acquired immunity.[10,11] (See Figure 1 below.) As macrophages engulf an infectious organism or a certain vaccine, the organism

**Figure 1**



(1) (2) (3) (4)

(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

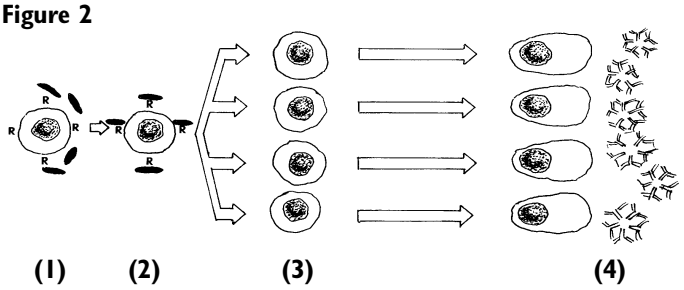
or vaccine is broken down chemically into constituent proteins and other biochemical components. The proteins are further degraded and the resulting small fragments of protein associate with certain molecules, known as major histocompatibility complex (MHC) Class II molecules, that are produced by the 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.[17,18]

Lymphocytes, specifically B lymphocytes (or B cells) and T lymphocytes (or T cells), mediate protective immunity. (See Figure 2.) 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.

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;[17,18] 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. (See Figure 3.) 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.

**Figure 2**



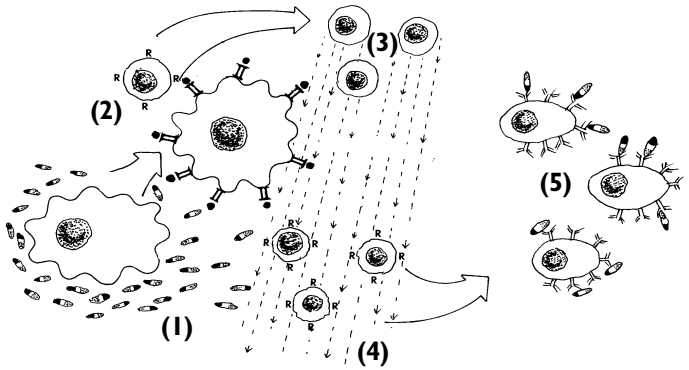

(1) B cell in the presence of an infectious agent

(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

**Figure 3**




(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

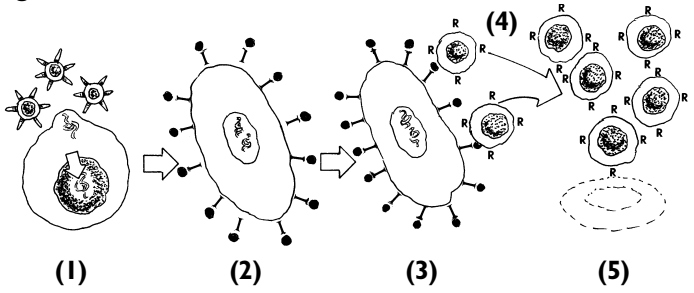
(4) Different B cells recognize different parts of the infectious agent

(5) Each B cell matures into an antibody releasing plasma cell

## 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. (See Figure 4.) This process of replication causes fragments of virus protein to become attached to the cell's own MHC Class I molecules.[17,18] 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.

**Figure 4**




(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 they level 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 their parental cell.[9-11] 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.[9-11] Vaccination establishes a pool of memory cells that can produce pathogen-specific responses 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 kidneys, 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.[9-11]

Immunologists have long recognized that the immune system is capable of recognizing and responding to an enormous number of distinct antigens.[19] This diversity in antigen recognition capacity applies to both B cell- and T cell-mediated immunity,[11,12] and is perhaps best summarized in the context of the B cell response.

The receptors found on the surface of unstimulated B cells are composed mostly of protein. These receptors are assembled from various polypeptides (chains of amino acids that are the building blocks of proteins) during B cell development. The polypeptide components include light and heavy chains (referring to the number of amino acids in each), variable segments, joining segments and diversity segments.[11,12] As the B cell develops, each component is produced within the cell, and each is the product of a separate gene.

There are between four and 1,000 genes that can be used to direct the production of each polypeptide. Although only one of each type of polypeptide is needed to form a receptor molecule on the surface of a single cell, receptors on different B cells are produced from various combinations produced from the many available polypeptide genes. Based on the total number of genes available to produce these molecules and additional diversity enhancing processes associated with their assembly, the immune system is estimated to be able to respond to more than 10 million different antigens.[11,12]

This is, of course, the theoretical upper limit to the number of antigens recognized by the immune system. The actual number is constrained by the number of B cells present, the number of new B cells being added daily (mature B cells survive for only a few days) and various other factors.[20] But even when all of these constraints have been factored in, the ability of the immune system to recognize and respond to antigens is immense. In fact, it has been estimated that even if all of the currently recommended vaccines were given to a child at one time, they would engage less than 1% of the immune system's total antigen response capacity.[20]

Antigen exposure during postnatal development is increasingly thought to be an important prerequisite for normal immune system development. Because exposure to both benign and pathogenic microbes has been a long standing feature of human neonatal experience, such exposures may be necessary in instructing the immune system to ignore or tolerate benign organisms (such as those inhabiting the intestinal tract) while priming the neonate to be able to initiate a functionally robust immune response to potentially dangerous pathogens.[21,22]

## 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 *Clostridium tetani*, 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 formulation and 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.[15] 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 vaccination site and stimulates them to release more and different cytokines. These chemical signals further stimulate and activate macrophages and lymphocytes to acquire additional protective functions.

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 *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 healthy people. The measles, mumps, rubella and some polio vaccines are examples of live attenuated vaccines.[23]

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.[23]

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.[23,24] 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.[23]

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 in children and *Haemophilus influenzae* type b are in common use.[23]

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.[25]

### Vaccination of Children

Based on current immunization recommendations,[26] children in the US typically receive 11 vaccines that are administered through as many as 20 separate inoculations by the age of two years. A national telephone survey in 1999 of expectant parents and parents of children six years of age and younger revealed that 23% of parents questioned the number of immunizations recommended for children and 25% worried that the vaccines might weaken the immune system.[27]

Concerns about the number of immunizations recommended for children and the development of the immune system focus on three issues. The first is the number of inoculations given. The number of recommended inoculations reflects the number of diseases that now can be prevented by vaccination.[20] In 1900, the one vaccine that was given to children prevented one disease, smallpox. By 1960, eight immunizations by age two prevented five diseases. Currently, children can be vaccinated against 11 vaccine-preventable diseases. In most cases, the recommended vaccines require an initial priming immunization and one or more booster immunizations to achieve full, long-lasting protective immunity.

A second aspect of parental concern is the ability of a child's immune system to recognize and respond to all of the antigens that are introduced when a child is vaccinated according to the current vaccine schedule. Vaccines, like the disease agents they mimic, are composed of many different proteins or other molecules that may be recognized by the immune system. Indeed, the smallpox vaccine given to children in 1900 was estimated to consist of about 200 different antigens and the 1960 formulation of the pertussis vaccine used whole cells of *Bordetella pertussis*, which are estimated to consist of approximately 3,000 different proteins.[20] Through advances in how vaccines are developed, the 11 vaccines in current use consist of 123-126 antigens,[20] a small number relative to immune system's capacity to recognize and respond to antigens as described above.

The third aspect of parental concern about childhood immunization is whether exposure to these 123-126 antigens compromises the development of the child's immune system. The Institute of Medicine's (IOM's) Immunization Safety Review Committee recently examined the scientific evidence surrounding this issue.[22] The committee asked whether multiple immunizations were associated with various types of immune dysfunction that might result from impaired immune system development.

The committee found no epidemiological evidence supporting a causal association between multiple immunizations and an increase in the incidence of infections by other pathogens or an increase in the likelihood of developing type 1 diabetes, an autoimmune disease associated with immune dysfunction. There was insufficient information available to assess whether multiple immunizations might increase the risk of allergic disease. Given what is currently known about biological mechanisms associated with the development of autoimmune and allergic diseases, the committee concluded that multiple immunizations could be only theoretically or weakly linked to such immunological dysfunctions. There was stronger evidence of a possible mechanistic link between multiple immunization and susceptibility to other

pathogens, although this was not borne out by the epidemiological data.[22] The findings of this committee are described in greater detail in the *Vaccine Safety Issues* section.

### Vaccination of Adolescents and Adults

The current adult immunization schedule[28] calls for people over 21 years of age to receive regular (every 10 years) booster immunizations against diphtheria and tetanus, annual influenza immunizations for persons 50 years of age and older, and pneumococcal immunization at age 65 years. Influenza and pneumococcal vaccines are also recommended for younger adults and adolescents with chronic illnesses such as heart, lung or liver disease, diabetes and asthma. In addition, adults not previously immunized against measles, mumps, rubella or varicella, or who have no documented history of having these diseases, are encouraged to obtain these immunizations. Adults at risk for hepatitis A or hepatitis B exposure also are encouraged to receive the appropriate immunizations.

The number and frequency of vaccinations recommended in the adult immunization schedule is much reduced relative to those given to children. Except for immunizations that might be required by certain employers, e.g., healthcare providers, or in conjunction with military service, none of the adult recommendations is backed by enforceable mandates.

### Trends in Vaccine Development

Vaccine research and development and the tools of modern biotechnology have resulted in the licensing and use of vaccines that are safe and effective. Researchers continue to seek new approaches to reducing the number of inoculations given and, in some cases, eliminating the use of needles for administering vaccines.

Combination vaccines such as MMR, DTaP, pneumococcal polysaccharide and others have been used in the US for many years,[29] and a new combination vaccine against both hepatitis A and hepatitis B was licensed in 2001.[30] Other combination vaccines are under development. For example, a vaccine that offers protection against diphtheria, pertussis, tetanus, hepatitis B and polio has undergone extensive clinical testing that has shown it to be safe and effective.[31] If licensed and used in the US, this pentavalent vaccine could reduce the number of primary series vaccinations given to children from nine to three. Both pentavalent and hexavalent vaccines are licensed for use in several European countries.[32] Although the introduction of additional combination vaccines could further reduce the number of inoculations given,[33] their development, licensing and manufacturing is complex.[33-35]

Other new and emerging developments related to vaccine administration include the potential use of inhaled or intranasal vaccines. Because many diseases result from inhaling pathogens, vaccines delivered to the lungs could produce a strong immune response capability in the lungs, thus providing highly effective protection against disease. Intranasal vaccines against influenza,[36,37] hepatitis B,[38] meningococcal disease[39] and others[40,41] are under active investigation. Additional needle-free approaches to vaccination include the use of skin patches[42] similar in design to those used to prevent motion sickness, using compressed air to painlessly propel microscopic vaccine-coated particles into the skin,[43] and incorporating vaccines into edible plants.[44] These and other approaches are still under development, but offer hope that someday syringes and needles will be relegated to museums.

### 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 preventive. 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.

### Vaccines and the Quality of Life

In addition to their ability to prevent disease among both immunized and non-immune members of the community, vaccines can make substantial contributions to the quality of life of families and communities. Disease prevention results in substantial cost savings whether measured by personal, family, insurer or community expenditures. Vaccines reduce the need for visits to physicians' offices, hospital admissions, medication use and other medical care. In addition, effective immunization programs that protect individuals and limit the transmission of disease within a community, contribute to better school attendance by healthier students, the maintenance of a healthy and reliable workforce, and reduce the amount of time devoted to visits to doctors offices, clinics or caring for ill children, family members or others. Communities embracing the use of vaccines to protect the health of its members are also likely to endorse other preventative practices and policies, e.g., car seat usage, programs to reduce drug, alcohol and tobacco use and others, that further enhance community health and the quality of life.[45]

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