THIS CHAPTER MEETS THE FOLLOWING IMMUNIZATION COMPETENCIES FOR HEALTH PROFESSIONAL (PHAC, 2008): http://www.phac-aspc.gc.ca/im/pdf/ichp-cips-eng.pdf

 # 1: The Immune System and Vaccines

- Competency: Explains how vaccines work using basic knowledge of immune system.

 # 4: The Types of Immunizing Agents and Their Composition

- Competency: Applies the knowledge of the components and properties of immunizing agents as needed for safe and effective practice.

1.0 THE IMMUNE SYSTEM

- Refer to Appendix 14.1 for a comprehensive glossary of terms.

1.1 Introduction

The body is protected from infectious agents and other harmful substances by a variety of cells and molecules that make up the immune system. Immunity is the ability of the human body to tolerate the presence of material indigenous to the body (self), and to eliminate foreign (non-self) material. The primary function of the immune system is to prevent or limit infections caused by microorganisms.

Pathogens are foreign substances such as viruses, bacteria, toxins, and parasites are surrounded by antigens. When introduced into the body, antigens are capable of inducing a response by the immune system. Allergens are foreign substances that induce allergic responses. This discriminatory ability provides protection from infectious disease, since most agents or associated toxins are identified as foreign substances by the immune system.

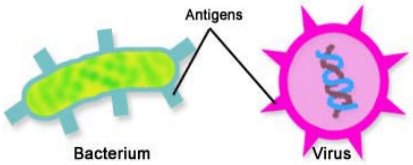


Figure 1: Antigens (used with permission from BCCDC)

1.2 Cells of the Immune System (see Figure 2 - Lymphatic System)

The immune system depends upon the activities of three categories of white blood cells (WBCs) that are derived from bone marrow:

1. Phagocytic cells: Macrophages and dendritic cells are phagocytic cells that reside in the blood and tissues waiting to engulf foreign substances.
2. T cells: After leaving the bone marrow, some WBCs reach the thymus gland where they differentiate and become thymus-derived lymphocytes or T cells.
3. B cells: WBCs that do not reach the thymus gland become B lymphocytes or B cells.

Their granules contain histamine, which increases the blood flow to the area of infection. Mast cells play a role in hay fever and anaphylactic responses to insect stings.

1.3 Lymphatic System

Some of the WBCs migrate to guard peripheral tissues, some reside within the tissues, and others circulate in the blood stream and in a specialized system of vessels and nodules in the lymphatic system. The lymphatic system drains extracellular fluid and frees cells from tissues. The extracellular fluid and cells are transported through the body via the lymphatic vessels as lymph, and eventually emptied back into the blood system. The lymphatic vessels closely parallel the body's veins and arteries. Lymph nodes are found throughout the lymphatic vessels and provide meeting areas for interaction between the immune system cells.

The lymphatic system contains the following:

Primary lymphoid organs:

- Bone marrow
- Thymus
- Lymphatic vessels

Secondary lymphoid organs:

- Spleen
- Lymph nodes

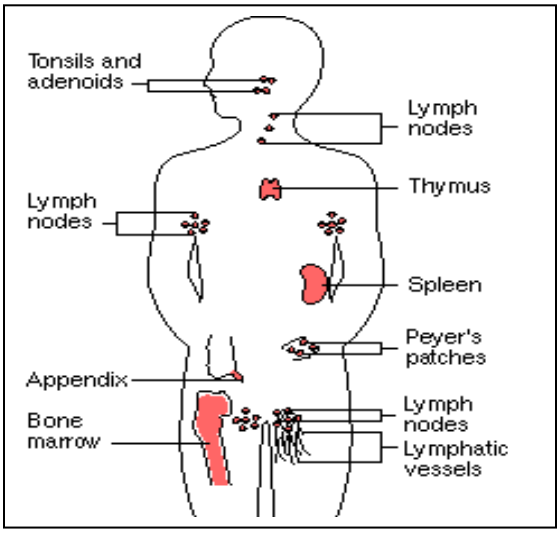


Figure 2: Lymphatic System
(Figure used with permission from BCCDC)

1.4 Types of Immunity (see Figure 3)

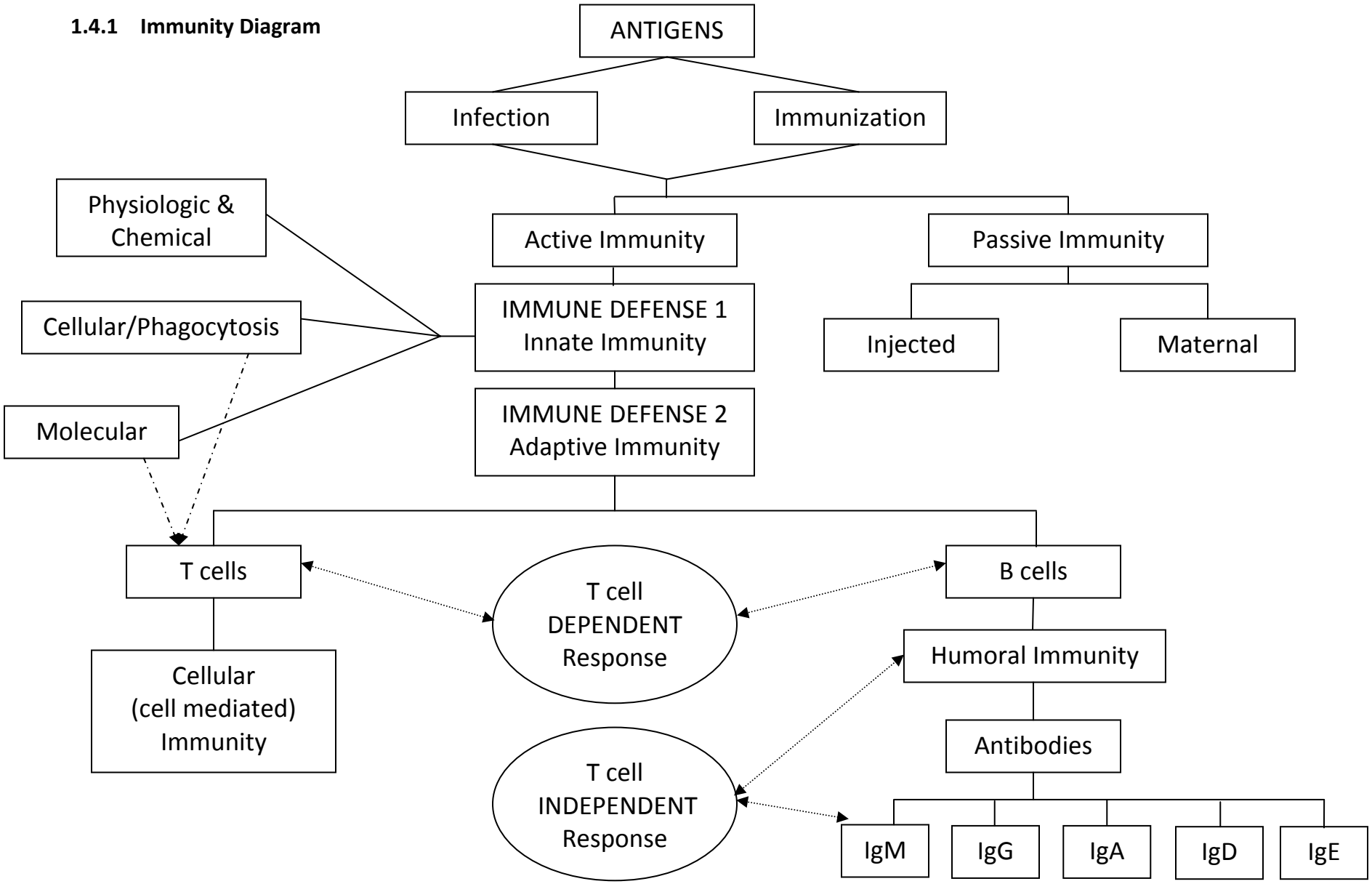
Passive Immunity:

- Antibodies from another person or animal that can be injected or transfused;
- Called passive because the individual did not create the antibodies, but instead received pre-formed antibodies;
- Protection is effective, but duration is short lived and no memory is created; and
- Examples of passive immunity are maternal antibodies (trans-placental and breast milk) and injected antibodies (e.g., rabies, varicella, and tetanus immune globulins).

Active Immunity:

- When the body is exposed to a foreign substance the cells of the immune system "actively" respond. Active immunity is further divided into categories:
  - Innate Immunity - protective mechanisms we are born with; and
  - Adaptive Immunity - cell mediated immunity and humoral immunity. The immediate immune response may destroy some or all of the antigens, whereas the long-term response establishes immune memory (future recognition of the antigen).

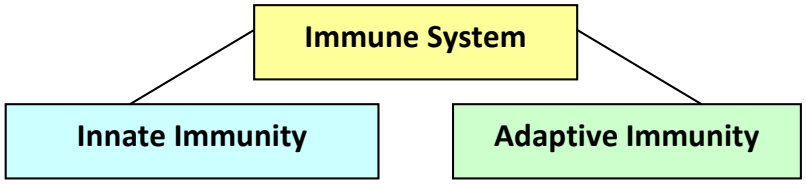
1.4.1 Immunity Diagram



1.5 Active Immunity

There are two distinct components of the immune system that work synergistically for active immunity: innate immunity and adaptive immunity.

Figure 3



The body's immune response can be understood by following the course of an infection as described below:

- Most pathogens are kept outside of the body by protective mechanisms such as tears or skin that act as barriers;
- When there is an injury to tissue, bacteria or viruses can enter the tissue and cause infection;
- Innate cells (macrophages, dendritic cells) respond by recognizing viruses and bacteria as foreign and specialize in engulfing these invaders (phagocytosis). These innate cells and protective barriers are part of innate immunity because they "innately" respond to foreign substances;
- In addition, dendritic cells display the antigens on their cell surface and travel to the lymph nodes; and
- In the lymph nodes the dendritic cells present the antigen to the T cells. The T cells then activate the B cells to make antibodies. The T cells and B cells are part of the adaptive immunity because they are "adapting" to the foreign substance and creating memory against future infections.

1.6 Innate Immunity - "First" Immune Defense

Innate immunity consists of protective mechanisms we are born with, and are the first line of defence against anything recognized as non-self (all antigens). The produced immune response is unspecific to particular antigens and no memory of any antigen that is encountered is retained. However, innate immunity is the crucial first step in most adaptive immune responses (section 1.7). The following are the protective mechanisms of innate immunity (see Table 1):

- Physical and Chemical Mechanisms
- Phagocytosis
- Molecular Response
- Inflammatory Response

Table 1: Innate Immunity Characteristics

Physical and Chemical Mechanisms	Phagocytosis	Molecular Response	Inflammatory Response
Physical barriers: • Intact skin • Cilia • Mucous membrane barrier (sneezing, coughing) **Chemical barriers**: • Tears • Acid (pH) • Saliva • Bile	**Macrophages:** • Engulf and kill invading organisms **Dendritic cells:** • Engulf pathogen • Display antigen on cell surface • Travel to lymph node to present antigen to T cells • Critical link between the innate and adaptive immune responses.	**Cytokines:** Cytokines are small proteins made by a cell that affect the behaviour of other cells. Examples: • Cytokines cause vasodilation (heat and redness). • Some types of interferon are antiviral cytokines which help healthy cells resist viral infection. **Chemokines:** Chemokines are proteins secreted by macrophages that attract cells out of the blood stream and into the infected tissues. **Complement:** The complement system is a group of approximately 20 proteins that coat bacterial surfaces and promote bacterial destruction by macrophages.	The accumulation of fluid and cells at the site of infection causes the redness, swelling, heat, and pain known as inflammation. Inflammation is beneficial because it: • Recruits cells out of the blood stream, • Increases the flow of lymph to take away microbes and antigen-bearing cells to the lymphoid tissue which will lead to adaptive immunity, and • Brings the T cells and B cells back to the site of infection.

1.7 Adaptive Immunity - "Second" Immune Defence

Adaptive immunity is the second line of defence against anything recognized as non-self and it provides protection against re-exposure to the same pathogen. Adaptive immune responses are slower to develop compared to innate immune responses.

Characteristics of adaptive immunity:

- Specificity: The immune response is specific to each antigen that is encountered (e.g., antibody for measles antigen has no effect on rubella antigen);
- Memory: With subsequent exposure to an antigen there is a rapid and strong immune response. This is called an anamnestic response; and
- Tolerance: The immune response is able to differentiate between self and non-self so that body tissues are not destroyed.

Adaptive immunity is divided into two categories:

1. Cell mediated immunity (section 1.8).
2. Humoral (antibody) immunity (section 1.9).

1.8 Adaptive Immunity - Cell Mediated Immunity (CMI)

Cell mediated immunity describes any immune response where T cells have the main role. The activation of T cells is an essential first stage in virtually all adaptive immune responses. This is called the "T cell-dependent immune response". T cells do not recognize microorganisms in the extracellular fluids. Instead, T cell receptors bind to fragments of antigens (epitopes) that are presented on the surface of antigen presenting cells (APC).

There are three main types of APC:

1. Macrophages
2. Dendritic cells
3. Naïve B cells

When T cells recognize an antigen presented by the APC, they can differentiate into several different types of T cells:

- Cytotoxic T cells: Kill cells infected with intracellular pathogens such as viruses
- Helper T cells:
  - Activate antigen and stimulate B cells to differentiate and produce antibodies;
  - Activate macrophages to become more efficient at killing the pathogen; and
  - Control intracellular bacterial infections (e.g., tuberculosis) that grow in intracellular membrane-bound vesicles of macrophages. The macrophages can't kill the bacteria but instead display the bacterial antigen on the surface so that it can be recognized by T cells.
- Regulatory T cells: Suppress lymphocytes and control the immune response.

1.9 Adaptive Immunity - Humoral Immunity

Humoral immunity is mediated by B cells that are formed in the bone marrow. B cells react against foreign substances in the extracellular spaces of the body by producing and secreting antibodies (Abs). These Abs are present in the biological fluids of the body (the humours); hence the term humoral immunity. B cells are not activated by most antigens without "help" from helper T cells.

Many microorganisms multiply in the extracellular spaces of the body, and most intracellular pathogens spread by moving from cell to cell through the extracellular fluids. These extracellular spaces are protected by humoral immunity where antibodies either:

- Kill the extracellular organism and the intracellular organism as it is moving from cell to cell; or
- Bind the pathogen and present it to T cells.

B cells display immunoglobulin molecules (antibodies) on their surface membranes, which act as receptors for the antigens. B cell antibody receptors can either bind to helper T cells that have interacted with an APC or bind to extracellular microorganisms such as bacteria. Once an antigen binds to an antibody with the best "fit", the B cell differentiates into plasma cells or B memory cells.

- Plasma cells: These cells operate as factories to manufacture the chosen antibody and then secrete those antibodies; and
- B memory cells: These cells mediate immunological memory. They respond rapidly on re-exposure to the antigen that originally induced them.

Except for the phenomenon of cross-protective immunity, each antibody can recognize and bind to only one specific antigen and no other.

T cell-dependent antigens:

- Cellular immunity and humoral immunity work synergistically;
- T cell-dependent antigens require the interaction of T cells and B cells to generate the production of antibodies; and
- The antibodies produced in response to T cell-dependent antigens are primarily IgG and the response produces immunologic memory.

T cell-independent antigens:

- Specific to humoral immunity;
- In some situations, B cells can create antibodies without the help of T cells;
- Many common extracellular bacteria (e.g., Haemophilus influenzae type b) are surrounded by a polysaccharide capsule that enables them to resist ingestion by phagocytes and therefore avoid stimulating the T cell response; and
- Antibodies produced are of the IgM class and immunologic memory is not created.

1.10 Antibodies

1.10.1 Classes of Antibodies

Seroconversion is the phase of an infection when antibodies against an infecting agent are first detectable in the blood. To test for immunity against a particular disease an antibody titre may be ordered to assess the amount of circulating antibody specific to that pathogen. Antibodies as a class are known as immunoglobulins. There are five classes of antibodies that are produced by plasma cells: IgM, IgG, IgA, IgD and IgE. The immune response to injected vaccines involves IgG and IgM. Each class performs particular functions:

Immunoglobulin M (IgM)

- A valuable diagnostic marker for infectious diseases because it is usually the first immunoglobulin made following antigen exposure and is relatively short-lived;
- Effective in activating complement system;
- Participates in the lysis (bursting apart) of cells; and
- Generally remains in the blood; does not diffuse into the surrounding tissues due to its large size.

Immunoglobulin G (IgG)

- The most abundant class of antibody, constituting approximately 80% of all antibodies in serum;
- Produced slowly upon primary exposure to an antigen;
- Produced rapidly during secondary or subsequent exposure, becoming the major antibody present;
- The principal humoral component of immunological memory; and
- The only antibody that crosses the placenta. It helps protect the newborn from infection through passive immunity.

Immunoglobulin A (IgA)

- Represents approximately 10% to 20% of the immunoglobulins in serum;
- Most abundant immunoglobulin in tissues;
- Prevents or interferes with the attachment of viruses and bacteria to the mucosa of respiratory and digestive systems;
- Protects against enterotoxins released by certain bacteria; for example, forms an antibody-antigen complex with cholera toxin, preventing it from binding to specific receptors on the intestinal membrane;
- Plays a role in eliminating food antigens from the circulatory system; and
- The main secretory immunoglobulin; found in exocrine secretions (e.g., breast milk, saliva, tears, respiratory and digestive secretions, urine).

Immunoglobulin D (IgD)

- Constitutes only a very small fraction (0.2%) of immunoglobulin in the body;
- Acts as an antigen receptor on the surfaces of B cells; and
- Unknown activity.

Immunoglobulin E (IgE)

- Minute concentration in serum;
- Involved in mediating allergic reactions;
- Elevated in people with hypersensitivity to allergens, as well as those with eczema, asthma, or other respiratory problems; and
- Especially useful against parasitic infections (e.g., worms).

1.10.2 Antibody Function (see Figure 4)

Antibodies have three main functions:

1. Neutralization: Antibodies bind to pathogens (e.g., viruses, bacteria) and block their access to cells, and then the antibody-antigen complex is engulfed by a macrophage.
2. Opsonization: Encapsulated bacteria (e.g., Hib, pneumococcal, and meningococcal) evade the innate immune system because they are not recognized by macrophages or dendritic cells. However, encapsulated bacteria can be recognized by antibodies. The antibody coats the bacteria to enable the ingestion by macrophages and dendritic cells through the process of opsonization.
3. Complement Activation: Antibodies bind to certain bacteria in the plasma. A region on the antibody is a receptor to complement proteins which will help lyse the bacteria or attract the macrophages to it.

Figure 4: Antibody Function

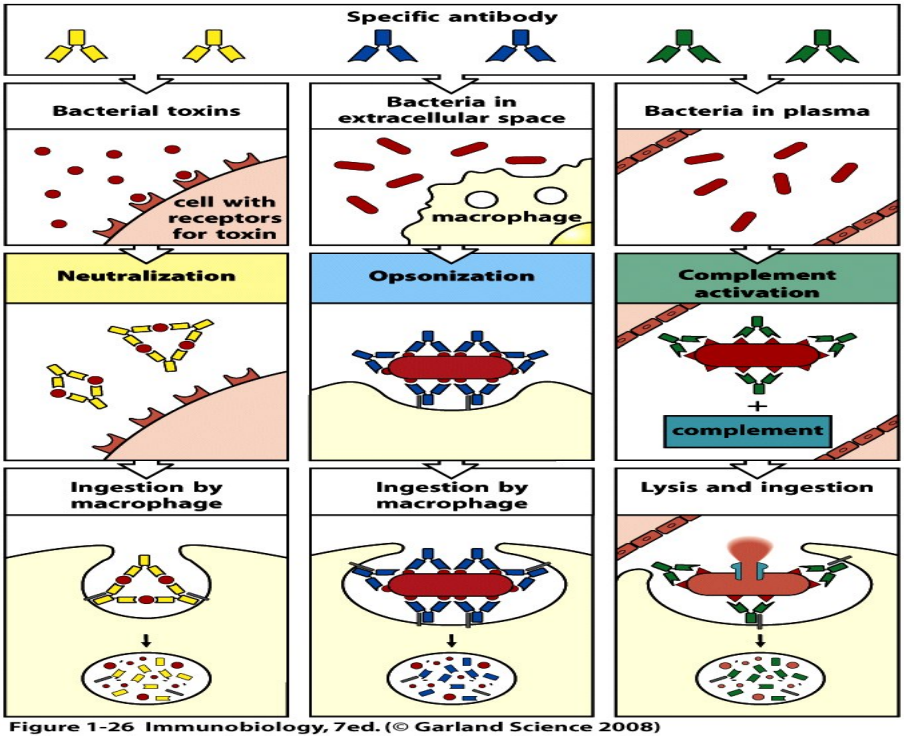


Figure 1-26 Immunobiology, 7ed. (© Garland Science 2008)

(Original Source: ©2008 From Janeway's Immunobiology, 6E by Murphy et al., cited in BCCDC Immunization Manual, 2009).

1.11 Fetal and Infant Immune System

The development of the immune system occurs early during fetal development.

Table 2: Fetal Immunity

Passive Immunity (passage of maternal antibody -IgG only)	Active Immunity
• Beginning at 8 weeks gestational age (GA) • IgG levels correlate with GA: o low until 20 weeks o by 40 weeks, it doubles that of 32 wks	• B cells and T cells present by 14 weeks' GA • Relatively sterile environment in utero. There is an enormous unchallenged capacity

Newborns (even premature infants) can actively distinguish self from non-self.

Table 3: Neonatal and Infant Immunity

Birth	Passive Immunity (maternally acquired antibodies)	Active Immunity
• Instant challenge • Within hours, GI tract heavily colonized	• Circulating placental IgG lasts 6 months or longer • Secretory IgA in breast milk and colostrum	• B cell responses are good. Until two years of age, children do not respond well to T cell-independent antigens (e.g., polysaccharide vaccines) • Full T cell subsets. Infants respond well to T cell-dependent antigens (i.e., conjugate proteins)

2.0 IMMUNIZING AGENTS

Immunizing agents are classified as passive or active.

2.1 Passive Immunizing Agents

The prevention of illness through the transfer of pre-formed IgG antibodies is called immunoprophylaxis. While the protection is immediate, it is temporary and it can only be offered if the exposure is recognized. Protection is also time-sensitive. Post-exposure immunoprophylaxis must be initiated within a short time frame, usually within days of exposure to the infection. Passive agents may not be completely free of blood borne pathogens despite all current safeguards and technology in place.

2.1.1 Types of Passive Immunizing Agents

1. Standard immune globulin - pooled antibody from thousands of donors. It is now primarily used for post-exposure prophylaxis against measles.
2. Hyperimmune globulins - made from donated plasma of persons with high levels of a specific IG (e.g., Hepatitis B Immune Globulin).
3. Hyperimmune serum - produced in animals (e.g., botulinum and diphtheria antitoxins).

Table 4: Passive Immunizing Agents

Agent		Indication/Action
Standard Immune Globulin	Immune globulin (Ig) (human)	Exposure to measles for susceptible individuals who cannot receive live attenuated measles-containing vaccine. Exposure to Hepatitis A for individuals who cannot receive Hepatitis A vaccine.
Hyperimmune Globulins	Varicella-zoster immune globulin (VarIg)	VarIg is recommended for high risk susceptible people with significant exposure to varicella.
	Rabies immune globulin (RabIg)	Post-exposure prophylaxis against rabies in susceptible exposed individuals.
	Tetanus immune globulin (TIg)	TIg neutralizes tetanus toxin in the body fluids and tissues.
	Hepatitis B immune globulin (HBIg)	Provides immediate and effective short-term passive immunity to hepatitis B.
Hyperimmune Serums	Botulism antitoxin (equine) (BAT)	Recommended for established or suspected botulism.
	Diphtheria antitoxin (equine) (DAT)	Neutralizes diphtheria toxin in the body fluids.

2.2 Active Immunizing Agents

Protection acquired through active immunizing agents is produced by one's own immune response. Protection takes longer than with passive immunizing agents, but is stronger and may be permanent. Some examples of active immunizing agents are presented in Table 5.

Table 5: Active Immunizing Agents

Replicating Vaccines	Viral	MMR Varicella MMRV Rotavirus
	Bacterial	Typhoid (oral)
Non-Replicating Vaccines	Viral	Polio (injectable) Hepatitis A Rabies
	Recombinant (viral) (subunit)	Hepatitis B Human papillomavirus
	Bacterial	Typhoid (injectable)
	Protein toxoid (subunit)	Diphtheria Tetanus
	Proteins (subunit)	Acellular pertussis Influenza (viral)
	Polysaccharide (subunit)	Pneumococcal Meningococcal Typhoid (injectable)
	Conjugate (subunit)	Act-HIB® (*H. influenzae*) Meningococcal Pneumococcal

2.2.1 Replicating Vaccines - Live Attenuated Vaccines

These vaccines contain whole, living virus or bacteria that induce immunity by actively replicating within the host. Attenuated means the vaccine strains are weakened so that infection is usually inapparent or very mild. Because these vaccines replicate, the immune response is both cell mediated and humoral and therefore protection is long-lasting, probably life-long.

2.2.1.1 Limitations of Replicating Vaccines

- Circulating antibodies can interfere with vaccine virus replication;
- Sensitive to exposure to heat and light;
- Use with caution/contraindicated in immunocompromised persons; and
- Live vaccines must be given on the same day or 28 days apart because circulating interferon may interfere with the replication of the second live vaccine.

2.2.2 Non-Replicating Vaccines

Because these vaccines do not replicate, protection takes longer to achieve as more vaccine doses are needed to create a protective immune response. After the scheduled numbers of vaccine doses are given, the immune response is strong and may be permanent. With some vaccines, antibody levels may fall over time and as a result booster doses may be needed.

1. Inactivated Vaccines: Inactivated vaccines contain killed bacteria or viruses.

2. Recombinant Vaccines: Vaccine antigens produced using genetic engineering technology.

3. Polysaccharide Vaccines: Polysaccharide vaccines are composed of long chains of sugar molecules that make up the surface capsule of encapsulated bacteria. The immune response to a pure polysaccharide vaccine is typically T cell-independent.

4. Conjugate Vaccines: By linking a polysaccharide to a protein (diphtheria toxoid protein is commonly used) the immune response becomes T cell-dependent and immunogenicity is improved in infants and young children < 2 years of age. This process is called conjugation; hence the term 'conjugate vaccines'.

5. Subunit Vaccines: Subunit vaccines contain purified products that usually come from the bacteria or virus that causes natural infection, but may also be synthesized in the laboratory using recombinant technology.
   a. Proteins: Purified, inactivated proteins from the outer coating of viruses or bacteria. Aluminum salt is added as an adjuvant to enhance the immune response.
   b. Protein Toxoid: Vaccines made from inactivated bacterial toxins. Aluminum salt is added as an adjuvant to enhance the immune response.

3.0 VACCINE IMMUNE RESPONSE

3.1 Introduction

Vaccines interact with the immune system and produce an immune response similar to that produced by the natural infection, but they do not subject the recipient to the disease and its potential complications. Vaccines produce immunological memory similar to that acquired by having the natural disease. The antigen is the part of the vaccine that stimulates the immune response.

The immune or antibody response to non-replicating vaccines (inactivated/subunit) is different from the response to replicating vaccines (live attenuated).

3.2 Antibody Response to a Non-Replicating Vaccine

Inactivated/subunit vaccines will need more doses to build an adequate and lasting immune responses (see Figure 5). It is for this reason that recommended immunizations schedules should be adhered to.

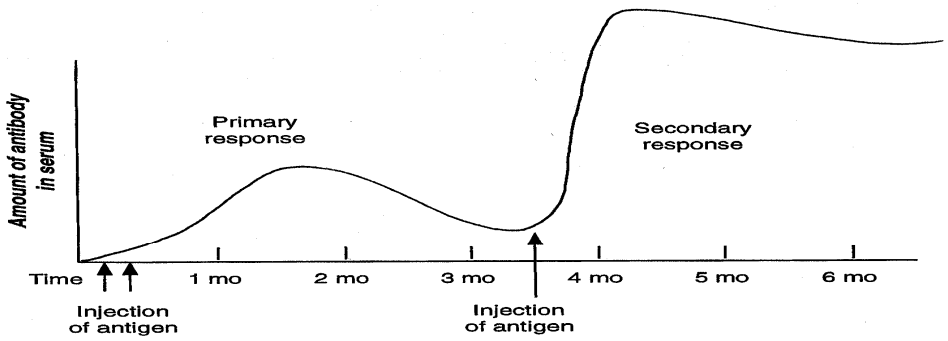
Primary immune response:

- Occurs after first exposure to an antigen;
- Antibody following the first exposure to an antigen is primarily IgM;
- Response is of brief duration and low intensity; and
- Memory cells are established to respond to future antigen exposures.

Secondary (memory) immune response:

- Antibody following the second and subsequent immunogenic challenges is primarily IgG; and
- Memory cells are already present at time of repeat exposure and make the specific antibodies more rapidly.

Figure 5: Immune Response to Non-Replicating Vaccines.



3.3 Antibody Response to a Replicating Vaccine

The immune response to a live attenuated vaccine is virtually identical to that produced by a natural infection as cell-mediated and humoral immunity are fully activated. Replicating vaccines will need fewer doses to create lasting memory.

3.4 Antibody Response to Conjugate and Polysaccharide Vaccines

Conjugate vaccine immune response:

- Conjugate vaccines stimulate T cells and B cells, resulting in a T cell-dependent immune response;
- The antibodies produced include IgG, providing longer protection and immunologic memory; and
- Conjugate vaccines are highly immunogenic in children less than 2 years of age.

Polysaccharide vaccine immune response:

- Polysaccharide vaccines stimulate B cells without the help of T cells, resulting in a T cell-independent immune response;
- The antibody made in response to these vaccines is mostly of the IgM class and immunologic memory is not produced; and
- Polysaccharide vaccines are not immunogenic in children less than 2 years of age.

3.5 Factors that Influence the Vaccine Immune Response

1. **Vaccine-related factors**:
   a) Nature of the antigen:
      - Live, inactivated/subunit, conjugate and polysaccharide vaccines each generates immune responses of a different intensity and duration.
   b) Dose of the antigen:
      - A certain threshold dose of antigen is required to elicit an immune response.
   c) Presence of vaccine adjuvants:
      - Vaccine adjuvants are added to the inactivated and subunit vaccines to enhance the immune response through three mechanisms: the “depot effect” increases the immunologic half-life of the antigen at the injection site; adjuvants induce the production of cytokines to assist T cells; and adjuvants induce dendritic cell maturation.

2. **Host-related factors:**
   a) Circulating antibodies:
      - Antibody from any source (e.g., maternal, transfusion) can interfere with live vaccine replication. For example: potential antibody interference is the reason to defer MMR vaccine until 1 year of age when maternal antibodies have declined; and
      - Administration of immune globulins (Ig) may interfere with live vaccine replication.
   b) Age of the client:
      - Protection should precede the age of greatest risk (e.g., human papillomavirus vaccine is ideally given before an individual is sexually active);

- Children less than 2 years old do not mount a protective immune response to T cell-independent antigens such as polysaccharides; and
- Conjugate vaccines will produce an immune response in young children.

c) Genetics:
- Deficiencies in the terminal components of complement and properdin result in an impaired immune response.

d) Nutritional factors:
- Malnutrition results in reduction of cell-mediated immunity.

e) Co-existing disease or immunosuppression related to medical treatment or therapy.

f) Previous exposure to antigen/vaccine (anamnestic response).

3.6 Vaccine Antigen Load

3.6.1 Capacity of the Immune System

The immune system has the capacity to respond to extremely large numbers of antigens:

- There are 10^9 to 10^{11} different antibody specificities;
- 2 billion helper T cells are replenished each day; and
- Each infant has the theoretical capacity to respond to about 10,000 vaccines at any one time. Using this estimate, if 11 vaccines were given to an infant at one time, then about 0.1% of the immune system is needed to respond.

3.6.2 Vaccine Antigen Load: "Then and Now"

Even though the number of vaccines given to a child has increased over the past 45 years, the number of antigens has decreased. There are fewer antigens per vaccine because of improved purification processes; and improved knowledge of antigen concentrations needed to induce protective immunity.

Table 6: Number of Immunogenic Proteins and Polysaccharides Contained in Vaccines over the Past 100 Years in USA *(Adapted from source)*

1960 – 1 vaccine		1980 – 2 vaccines		2000 – 6 vaccines	
Vaccine	**Proteins**	**Vaccine**	**Proteins**	**Vaccine**	**Proteins/Polysaccharides**
Diphtheria	**1**	Diphtheria	**1**	Diphtheria	**1**
Tetanus	**1**	Tetanus	**1**	Tetanus	**1**
Pertussis (whole cell)	**3000**	Pertussis (whole cell)	**3000**	Pertussis (acellular)	**2–5**
Polio	**15**	Polio	**15**	Polio	**15**
Total	**3017**	Measles	**10**	Measles	**10**
		Mumps	**9**	Mumps	**9**
		Rubella	**5**	Rubella	**5**
		Total	**3041**	Hib	**2**
				Varicella	**69**
				Pneumococcus	**8**
				Hepatitis B	**1**
				Total	**123–126**

(Source: Offit, P.A., Quarles, J., Gerber, M.A., Hackett. C. J., Marcuse, E.K., Kollman, T.R., et al. (2002) Addressing Parents' Concerns: Do Multiple Vaccines Overwhelm or Weaken the Infant's Immune System? *Pediatrics* Vol. 109 (1) pp. 124 -129 (DOI: 10.1542/peds.109.1.124)

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Offit, P.A., Quarles, J., Gerber, M.A., Hackett. C. J., Marcuse, E.K., Kollman, T.R., et al. (2002). Addressing Parents' Concerns: Do Multiple Vaccines Overwhelm or Weaken the Infant's Immune System? *Pediatrics* Vol. 109 (1) pp. 124 -129 (DOI: 10.1542/peds.109.1.124).

5.0 RESOURCES

The following documents are not endorsed by the Ministry of Health. They available on line free of charge:

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National Institute of Health. (2007). *Understanding vaccines*. The U.S. Department of Health and Human Services. Available at: http://www.niaid.nih.gov/topics/vaccines/understanding/Pages/Default.aspx