IMMUNOLOGY

THE IMMUNE SYSTEM	ONTOGENTY OF IMMUNE SYSTEM	LYMPHOCYTE DEVLOPMENT AND SELECTION	PHERIPHERY : INNATE IMMUNE RESPONSE	SECONDARY LYMPHOID TISSUE : INNATE IMMUNE RESPONSE MEETS ADAPTIVE
SOCONDARY LYMPHOID TISSUE: T AND B CELL ACTIVATION	HUMORAL IMMUNITY	CELL MEDIATEDD IMMUNITY	IMMUNODIAGNOSIS	IMMUNIZATIONS
	PRIMARY IMMUNE DEFICIENCY	HYPERSENSITIVITY	TRANSPLANTATION	

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Learning Objectives

- Explain information related to vaccinations and secondary/subsequent responses
- Differentiate between killed, live, and component of vaccines
- Differentiate between bacterial and viral vaccines
- Answer questions about acquisition of immunoglobulins in the foetus and neonate
- Explain information related to childhood vaccine schedule

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VACCINATION

Vaccination is a true milestone of medicine and has saved countless lives from preventable diseases. The concept dates back into the 1100s when the Chinese practiced the art of variolation. However, the practice is credited to Edward Jenner in 1798, when he used a strain of cowpox virus to protect a child from smallpox.

This chapter will discuss the science behind vaccination as well as a summary of the types of vaccine currently used in medicine.

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SECONDARY AND SUBSEQUENT RESPONSES

When an antigen is introduced into the system a second time, the response of lymphocytes is accelerated and the result amplifi d over that of the primary immune response. The increased speed of this response is due to the presence of the memory-cell progeny of the primary response throughout the body. The increased amplitude of effector production is due to the fact that activation and cloning begin from a much larger pool of respondents.

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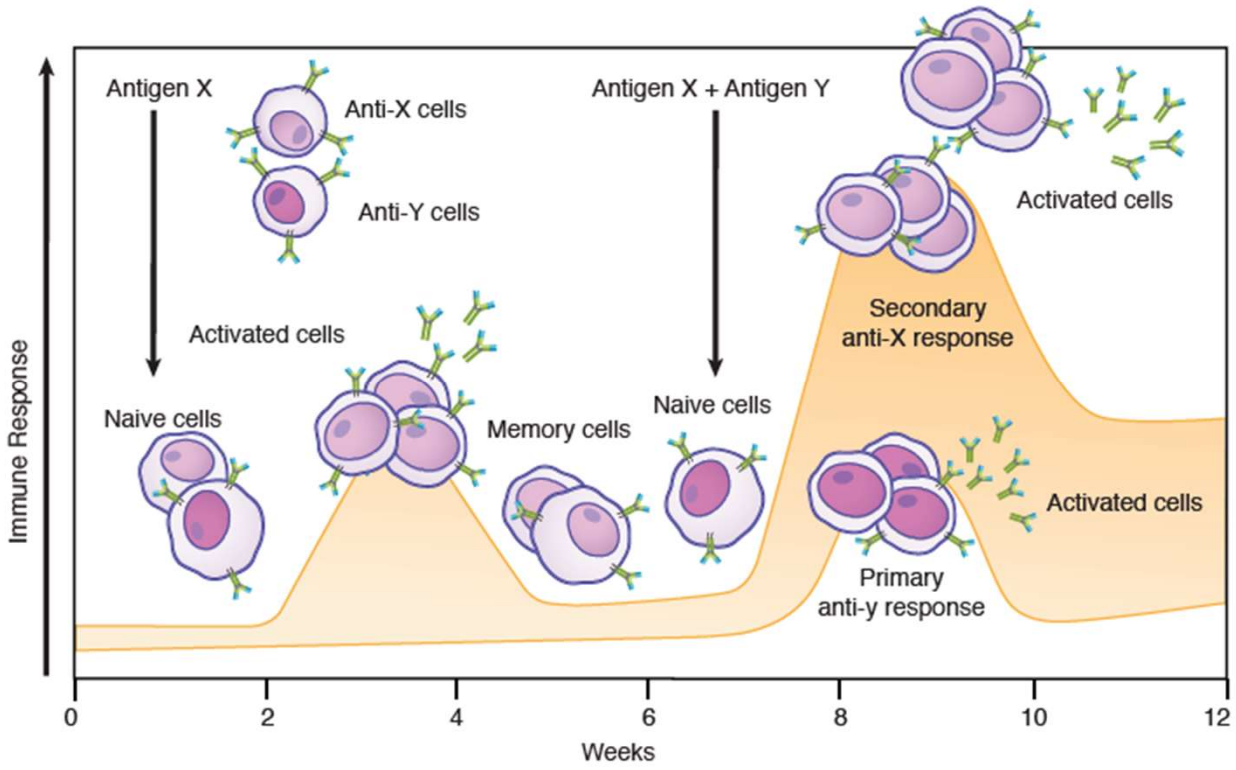
PRIMARY AND SECONDARY RESPONSE



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Primary versus Secondary Immune Response

Feature	Primary Response	Secondary Response
Time lag after immuniza-tion	5–10 days	1–3 days
Peak response	Small	Large
Antibody isotype	IgM, then IgG	Increasing IgG, IgA, or IgE
Antibody affinit	Variable to low	High (affinit maturation)
Inducing agent	All immunogens	**Protein** antigens
Immunization protocol	High dose of antigen (often with adjuvant)	Low dose of antigen (of-ten without adjuvant)

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TYPES OF IMMUNITY

Immunity to infectious organisms can be achieved by ACTIVE or PASSIVE immunization.

The goal of passive immunization is transient protection or alleviation of an existing condition, whereas the goal of active immunization is the elicitation of protective immunity and immunologic memory.

Active and passive immunization can be achieved by both natural and artificial means.

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Natural
- Active
- Passive

Artificial
- Active
- Passive

Active
- Natural
- Artificial

Passive
- Natural
- Artificial

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Active and Passive Immunizations

Type of Immunity	Acquired Through	Examples
Natural	Passive means	Placental IgG transport, colostrum
Natural	Active means	Recovery from infection
Artifi ial	Passive means	Horse antivenin against black widow spider bite, snake bite Horse antitoxin against botulism, diphtheria Pooled human immune globulin versus hepatitis A and B, measles, rabies, varicella zoster or tetanus "Humanized" monoclonal antibodies versus RSV*
Artifi ial	Active means	Hepatitis B component vaccine Diphtheria, tetanus, pertussis toxoid vaccine *Haemophilus* capsular vaccine Polio live or inactivated vaccine Measles, mumps, rubella attenuated vaccine Varicella attenuated vaccine

*Monoclonal antibodies prepared in mice but spliced to the constant regions of human IgG

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Passive Immunotherapy

Passive immunotherapy may be associated with several risks:

• Introduction of antibodies from other species can generate IgE antibodies, which may cause systemic anaphylaxis. The generation of IgE after infusion with even human gamma globulins is particularly an issue in persons with selective IgA deficiency (1:700 in population) as IgA is a molecule they have not encountered before. These patients can, however, be given IgA depleted globulins.

• Introduction of antibodies from other species can generate IgG or IgM anti-isotype antibodies, which form complement-activating immune complexes, leading to possible type III hypersensitivity reactions.

• Introduction of antibodies from humans can elicit responses against minor immunoglobulin polymorphisms or allotypes.

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LIVE VACCINE

- Attenuated
- Non- attenuated

Killed Vaccine

Toxoid vaccine

Polysaccharide vaccine

Conjugate Vaccine

Component Vaccine

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Live Vaccines

Attenuated (attenuated = weak)

- Comprised of **live** organisms which lose capacity to cause disease but still replicate in the host Best at stimulating both a humoral and cell mediated immune response, as they mimic the natural infection and typically elicit lifelong immunity
- Typically, 1 dose provides immunity but 2 doses are used to ensure seroconversion in most individuals
- Dangerous for immunocompromised patients because even attenuated viruses can cause them significant disease; since attenuated vaccines are comprised of live organisms, there is slight potential to revert back to a virulent form.

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Live viral vaccines:

Recommended in the United States:

- Measles, mumps and rubella (MMR)
- Varicella zoster (VZV) (for both chicken pox and zoster [shingles])
- Rotavirus
- Influenza (flu-mist)
- Available in the United States but recommended only underspecial circumstances:
- Polio (sabin)
- Smallpox
- Yellow fever

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Live Viral Vaccine

Non-attenuated

- Used by U.S. military against adenovirus types 4 and 7
- Enteric coated, live, non-attenuated virus preparation
- Produces an asymptomatic intestinal infection, thereby inducing mucosal IgA memory cells; these cells then populate the mucosal immune system throughout the body
- Vaccine recipients are thus protected against adenovirus acquired by aerosol, which could otherwise produce pneumonia (this is the **only example** of a live non-attenuated vaccine that is used)

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Killed Vaccines

- Utilize organisms that are killed so they can **no longer** replicate in the host
- Inactivated by chemicals rather than heat, as heat will often denature the immunogenic epitopes
- Typically require several doses to achieve desired response
- Predominantly produce humoral immunity
- Killed (inactivated) vaccines:

Rabies

Influenza

Polio (Salk)

Hepatitis A

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Toxoid Vaccines

- Made from inactivated exotoxins from toxigenic bacteria
- Prevent disease but not infection
- Toxoid vaccines:
- Diphtheria, tetanus, and Acellular pertussis (DTaP)*
- The DTaP vaccine prep is composed of toxoids from both diphtheria and tetanus, while the pertussis is comprised of whole inactivated pertussis. The DTaP vaccine is considered safe with few side effects, and is the vaccine currently used in the United States.

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Polysaccharide Vaccines

- Comprised of the capsular polysaccharide found in many bacteria
- Are only capable of producing IgM because of the inability of polysaccharide to activate Th cells (which require protein to become activated)
- Have largely been replaced with conjugate vaccines (see below)
- Polysaccharide vaccine(s):
- *Streptococcus pneumoniae*, pneumococcal polysaccharide (PPSV23)
- Comprised of 23 capsular serotypes of the most invasive and common strains of *S. pneumoniae*
- Indicated for use in adults age >65 or special circumstances, i.e., splenectomy, COPD

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Conjugate Vaccines

• Comprised of capsular polysaccharide conjugated to protein (usually a toxoid (see figure I-10-3); this creates a T cell-dependent immune response with class switching

• Creates a booster response to multiple doses

• Conjugate vaccines:

Haemophilus influenzae type b (Hib)

Streptococcus pneumoniae, Pneumococcal conjugate (PCV13)

Comprised of 13 capsular serotypes

Indicated for use in infants

Neisseria meningitidis

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Component Vaccines

• Comprised of an immunodominant protein from the virus that is grown in yeast cells

• For example, in the hepatitis B vaccine, the gene coding for the

HBsAg is inserted into yeast cells, which then releases this molecule into the culture medium; the molecule is then purified and used as the immunogen in the vaccine

• Component vaccines: HBV Hepatitis B surface antigen HPV Quadrivalent vaccine with serotypes 6, 11, 16 and 18 9-valent vaccine (Gardasil 9) to prevent >90% of cancers, as opposed to the quadrivalent vaccine which can protect up to 70% of cancers; contains serotypes 6, 11, 16, 18, 31, 33, 45, 52 and 58

• Released in February 2015

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ACQUISITION OF IMMUNOGLOBULINS IN THE FETUS AND NEONATE

Persistence of maternal Ab affects vaccinations.

- Live attenuated virus vaccines are given only age >12 months because residual maternal antibodies would inhibit replication and the vaccine would fail.
- When children are at exceptionally high risk for exposure to a pathogen, this rule is sometimes broken, but administration of vaccine at age <6–9 months is almost always associated with the need for repeated booster inoculations.
- IgM is the only isotype useful in diagnosing infections in neonates.
- Normal infants have few infections during first few months because of maternal IgG.
- Children with immune deficiencies don't become ill until maternal IgG is low.
- Infants have 20% of adult IgA at age 12 months, so colostrum is important.

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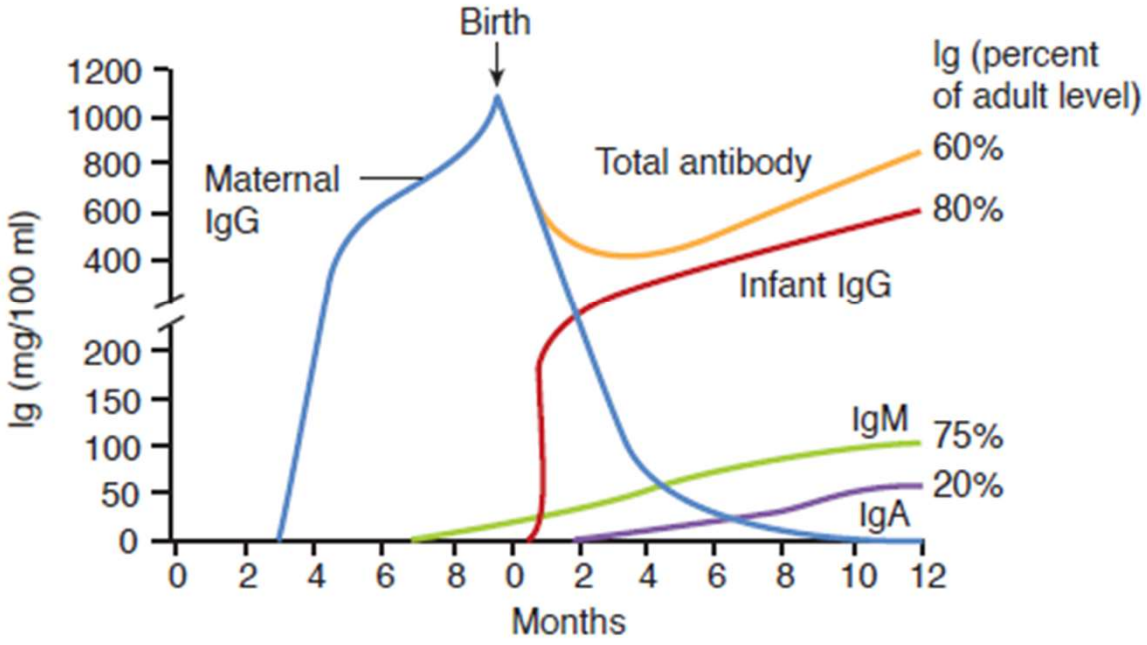
Immunoglobulin and Fetus and Neonate



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Bacterial Vaccine

Organism	Vaccine	Vaccine Type
C. diphtheriae	**D**TaP	Toxoid
B. pertussis	DT**a**P	Toxoid plus fi amentous hemagglutinin
C. tetani	DT**a**P	Toxoid
H. influen ae	Hib	Capsular polysaccharide and protein
S. pneumoniae	PCV Pediatric	13 capsular serotypes and protein
	PPV Adult	23 capsular serotypes
N. meningitidis	MCV-4	4 capsular serotypes (Y, W-135, C, A) and protein

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Viral Vaccine

Virus	Vaccine	Vaccine Type
Rotavirus	RV	Live
Polio	IPV	Killed (Salk)
	OPV	Live (Sabin)
Influe za	IIV	Inactivated (killed)
	LAIV	Live
Varicella zoster virus	VAR	Live
Hepatitis A	HepA	Inactivated (killed)
Human papilloma virus	HPV	Component
Hepatitis B virus	HepB	Component
Measles	MMR	Live
Mumps	MMR	Live
Rubella	MMR	Live

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Chapter Summary

Active immunization occurs when an individual is exposed (naturally or artificially) to a pathogen; **passive immunization** occurs when an individual receives preformed immune products (antibodies, cells) against a pathogen (naturally or artificially).

• Passive immunotherapy is useful in postexposure prophylaxis but runs the risk of eliciting adverse immune responses (hypersensitivity).

• Childhood vaccination protocols must take into account risk of exposure, presence of maternal antibodies, and the type of protective immune response needed.

• Live vaccines are not safe for use in immunocompromised patients.

• Live viral vaccines elicit both cellular and humoral responses, whereas killed viral vaccines elicit primarily antibody responses.

• The hepatitis B and human papilloma virus vaccines are component vaccines produced by recombinant DNA technology.