

Vaccines

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What's a vaccine

- An attenuated live or killed antigen (e.g. bacteria, virus) administered for the purpose of inducing a strong and measurable immune response in the host (i.e. an effective vaccine must be immunogenic).
- Provides protection by priming the recipient's immune system to recognize and attack the disease-causing organism when and if it is ever presented again

Vaccines – Historical perspective

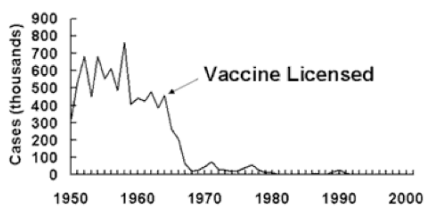
- Vaccination, or immunization, is the act of artificially inducing immunity from disease.
- Use dates back to 1796
 - milkmaids who had cowpox (vaccinia) were immune to smallpox
 - Jenners showed that inoculating fluid from cowpox lesions into the skin of smallpox susceptible people protected against smallpox infection
 - “1st” documented use of a less virulent related species to protect against an exclusively human pathogen
- Modified cowpox virus (**vaccinia virus**) is currently used to protect against smallpox (source of the term *vaccination*)

Morbidity from Nine Diseases with Vaccines Recommended before 1990 for Universal Use in Children- United States

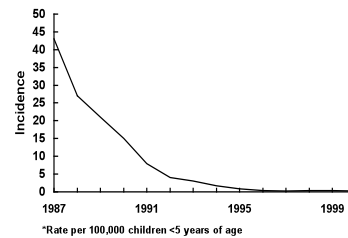
DISEASE	20 th CENTURY MORBIDITY	U.S. TOTAL 2004 CASES	% DECREASE
Smallpox	48,164	0	100%
Diphtheria	175,885	1	100%
Pertussis	142,271	25,827	82.0%
Tetanus	1314	34	97.4%
Poliomyelitis	16,316	0	100%
Measles	503,282	11 indigenous 26 imported	99.9%
Mumps	152,209	258	99.9%
Congenital Rubella	47,745	10	99.4%
H. influ type b	20,000	331	99.0%

Adapted from MMWR, 2005, www.cdc.gov

Measles–United States, 1950-2001



Estimated Incidence* of Invasive Hib Disease, 1987-2000



Active vs. Passive Immunization

- **Passive Immunization**
 - Temporary protection from disease through the administration of exogenously produced antibody.
 - Examples: Transplacental transfer of maternal antibodies, pooled human IgG to protect non-immune persons against hepatitis A, measles
- **Active immunization**
 - The act of stimulating the production of antibodies or inducing cell-mediated immunity, or both

How is an immune response induced after vaccination?

- The interaction of T lymphocytes with antigen-processing and antigen-presenting cells (dendritic cells or macrophages) is generally required to develop an immune response.
- Responses are part of a continuum and both the humoral (Ab-mediated) and T cell-mediated responses to a vaccine may occur simultaneously

The immune system in active immunization

- **Role of Antibodies**
 - React with antigens in the blood stream and extracellular fluid and at mucosal surfaces
 - Most antibodies produced by vaccines are thymus-dependent and require activation of T helper cells to initiate B cell proliferation and antibody production.
- **Antigen (vaccine component) enters the body: cascade of events**
 - presentation by mononuclear phagocytes or dendritic cells triggers a cascade of cytokines
 - maturation of naïve T helper cells into T helper type 2 cells (TH2).
 - TH2 cells in turn produce cytokines that lead to maturation of naïve B cells and release of specific antibody.
 - After the initial immune response activated B cells become resting memory cells ready to respond rapidly when the antigen is encountered again

The immune system in active immunization Role of antibodies cont'd

- **Protective antibodies against bacterial infections:**
 - Inactivate soluble toxic products (anti-toxins, e.g. diphtheria vaccine)
 - Facilitate phagocytosis of bacteria (e.g. pneumococcal vaccine)
 - Interact with serum complement to damage bacterial membranes and facilitate bacteriolysis (typhoid vaccine) and/or
 - Interfere with the bacterium's ability to adhere to mucosal surfaces. Protective antibodies against viral infections can only work when the virus is in extracellular spaces. These antibodies may bind to viruses preventing their entry into cells or may interfere with uncoating of virus particles or other steps in the viral lifecycle.

The immune system in active immunization

- The role of cell mediated immunity
- Directed against intracellular antigens
- Cytotoxic T cells (CTL) recognize small fragments of antigens presented on the surface of infected cells in combination with HLA class I molecules.
- Induction of cellular immunity is dependent upon the activation of T helper cells
 - TH1 cells release cytokines → maturation of naïve cytotoxic T cells
 - Recognition of intracellular antigens using T cell receptors
- CTL can become resting memory cells ready to become activated as soon as the host is exposed to the antigen again

Temporal course of immune response to vaccination

- **Primary response**
 - 1st exposure to the antigen
 - 7-10 day lag time between exposure and production of antibody and cell-mediated responses
 - Initial antibody response is IgM, later switch to IgG
 - Establish populations of memory T & B cells
 - Antibody titer peaks in ~ 2 to 6 weeks and then falls
- **Secondary response: repeat exposure to the antigen (or to the pathogen)**
 - Heightened humoral or cell-mediated response (an anamnestic response)
 - Shortened lag time between exposure and production of antibody and cell-mediated responses
 - Antibody response is almost all IgG
 - Rapid expansion/ Memory T & B cell populations

Classification of Vaccines

- Live attenuated
- Inactivated

Live Attenuated Vaccines

- Attenuated (weakened) form of the "wild" virus or bacterium
 - Must replicate to be effective
 - Immune response similar to natural
 - Both humoral and T-cell mediated responses are generated
 - Usually effective with one dose*
 - Examples:
 - Measles vaccine
 - Mumps vaccine
 - Rubella vaccine
 - Oral polio vaccine
 - Live attenuated influenza vaccine (intranasal)
- *except those administered orally**

Inactivated Vaccines

- Cannot replicate
- Less antigenic stimulus than live attenuated vaccines
- Generally require 3-5 doses to induce sufficiently durable antibody response
- Antibody titer may diminish with time
- Immune response mostly humoral but may depend on type of antigen
 - Polysaccharide: induce humoral response
 - Protein antigen: induce both types of responses

Inactivated vaccines

- **Whole killed vaccines:**
 - inactivated polio, hepatitis A, influenza, rabies
- **Subunit vaccines:** immunogenic parts of whole organisms, used when attenuation of the organism is difficult and whole killed vaccines are either not immunogenic enough or too toxic; many are *conjugated* to enhance immunogenicity
 - Examples: hepatitis B, influenza, pneumococcal polysaccharide vaccine and conjugated pneumococcal polysaccharide vaccine
- **Toxoid:** modified bacterial toxins that have been rendered non-toxic but retain the ability to stimulate the formation of antibodies; most do not produce life-long immunity and require booster doses
 - Examples: diphtheria, tetanus

DEPARTMENT OF HEALTH AND HUMAN SERVICES • CENTERS FOR DISEASE CONTROL AND PREVENTION

Recommended Immunization Schedule for Persons Aged 0–6 Years—UNITED STATES • 2007

Vaccine	Age	Birth	1 month	2 months	4 months	6 months	12 months	15 months	18 months	19–23 months	2–3 years	4–6 years
Hepatitis B ^a		HepB	HepB	HepB	HepB	HepB	HepB			HepB Series		
Rotavirus ^b			Rota	Rota	Rota							
Diphtheria, Tetanus, Pertussis ^c			DTaP	DTaP	DTaP		DTaP					DTaP
Haemophilus influenzae type b ^d			Hib	Hib	Hib	Hib				Hib		
Pneumococcal ^e			PCV	PCV	PCV							PCV PPV
Inactivated Poliovirus			IPV	IPV			IPV					IPV
Influenza ^f							Influenza (Yearly)					
Measles, Mumps, Rubella ^g							MMR					MMR
Varicella ^h							Varicella					Varicella
Hepatitis A ⁱ							HepA (2 doses)					HepA Series
Meningococcal ^j												MPSV4

This schedule indicates the recommended ages for routine administration of currently licensed childhood vaccines, as of December 1, 2006, for children aged 0–6 years. Additional information is available at <http://www.cdc.gov/vaccines/imz/childhood.htm>. Age does not refer to the recommended age for administration of any subsequent visit, when indicated and feasible. Additional vaccines may be licensed and recommended during the year. Licensed combination vaccines may be used whenever any components of the combination are indicated and other components of the vaccine are not contraindicated and if approved by the Food and Drug Administration for that dose of the series. Providers should consult the respective Advisory Committee on Immunization Practices statement for detailed recommendations. Clinically significant adverse events that follow immunization should be reported to the Vaccine Adverse Event Reporting System (VAERS). Guidance about how to obtain and complete a VAERS form is available at <http://www.vaers.hhs.gov> or by telephone, 800-422-7967.

DEPARTMENT OF HEALTH AND HUMAN SERVICES • CENTERS FOR DISEASE CONTROL AND PREVENTION

Recommended Immunization Schedule for Persons Aged 7–18 Years—UNITED STATES • 2007

Vaccine	Age	7–10 Years	11–12 YEARS	13–14 Years	15 Years	16–18 Years
Tetanus, Diphtheria, Pertussis ^a		Tdap	Tdap			Tdap
Human Papillomavirus ^b		HPV (3 doses)				HPV Series
Meningococcal ^c		MPSV4	MCV4		MCV4 ^d	MCV4
Pneumococcal ^e			PPV			
Influenza ^f			Influenza (Yearly)			
Hepatitis A ^g			HepA Series			
Hepatitis B ^h			HepB Series			
Inactivated Poliovirus ⁱ			IPV Series			
Measles, Mumps, Rubella ^j			MMR Series			
Varicella ^k			Varicella Series			

This schedule indicates the recommended ages for routine administration of currently licensed childhood vaccines, as of December 1, 2006, for children aged 7–18 years. Additional information is available at <http://www.cdc.gov/vaccines/imz/childhood.htm>. Age does not refer to the recommended age for administration of any subsequent visit, when indicated and feasible. Additional vaccines may be licensed and recommended during the year. Licensed combination vaccines may be used whenever any components of the combination are indicated and other components of the vaccine are not contraindicated and if approved by the Food and Drug Administration for that dose of the series. Providers should consult the respective Advisory Committee on Immunization Practices statement for detailed recommendations. Clinically significant adverse events that follow immunization should be reported to the Vaccine Adverse Event Reporting System (VAERS). Guidance about how to obtain and complete a VAERS form is available at <http://www.vaers.hhs.gov> or by telephone, 800-422-7967.

Adult Immunization Schedule

Indication ▶	Contraindications: Severe allergic reaction to vaccine component or previous dose Pregnancy Febrile illness Acute illness with fever Moderate or severe acute illness with ongoing treatment	Diabetes: Type 1 or 2 Insulin therapy with ongoing treatment Diabetic neuropathy, retinopathy, or nephropathy Diabetic foot ulcers or infections	Asplenia: Splenectomy Hypoplasia or aplasia of spleen Splenectomy with chemotherapy or radiation therapy	Chronic liver disease: Alcoholism Chronic liver disease with abnormal liver function tests	Kidney failure: End-stage renal disease Dialysis or transplantation	Human immunodeficiency virus (HIV) infection ¹	Health-care workers
Tetanus, diphtheria, pertussis (Td/Tdap) ¹							
Human papillomavirus (HPV) ²							
Measles, mumps, rubella (MMR) ³							
Varicella ⁴							
Influenza ⁵							
Pneumococcal polysaccharide ⁶							
Hepatitis A ⁷							
Hepatitis B ⁸							
Meningococcal ⁹							

* Covered by the Vaccine Injury Compensation Program
 These recommendations must be read along with the footnotes, which can be found on the next 2 pages of this schedule.
 1 For all persons in the category who meet the age requirements and who lack evidence of immunity (e.g., lack documentation of vaccination or have no evidence of prior infection)
 2 Recommended if some other risk factor is present (e.g., on the basis of medical, occupational, lifestyle, or other indications)
 3 Contraindicated

- ### Routine Adult Immunizations
- **Diphtheria & Tetanus boosters every 10 years**
 - Pertussis added to the adolescent & adult schedule
 - Tdap vaccines containing a reduced amount of diphtheria antigen
 - **Influenza A/B**
 - Yearly regardless of age
 - **Pneumococcal polysaccharide (23-valent)**
 - High risk adults <65 years
 - All adults ≥ 65 years
 - **Hepatitis A & B:**
 - if susceptible, & have liver disease, or at occupational risk (Hep B)
 - **If not immune:**
 - Varicella, Rubella
 - Measles & Mumps: if born after 1956
 - **Zoster vaccine for adults ≥ 60 years of age**
 - Boost prior immune response to prevent reactivation of latent varicella virus

Vaccines

- Safety concerns

Causality Conclusion	Hypothesis	Biological Mechanisms or Plausibility Conclusions
Evidence is inadequate to accept or reject a causal relationship	Thimerosal-containing vaccines and the neurodevelopmental disorders of ADHD, and speech or language delay	Biologically plausible
	Hepatitis B vaccine and first episode CNS demyelinating disorder, ADEM, optic neuritis, transverse myelitis, Guillain-Barre syndrome, and brachial neuritis	Weak
Evidence favors rejection of a causal relationship	MMR vaccine and autism spectrum disorder	Biologic model incomplete and fragmentary
	Multiple immunizations and heterologous infections	Strong
	Thimerosal-containing vaccines and autism	Theoretical
	Relapse of multiple sclerosis and influenza vaccines	Weak
	Hepatitis B vaccine in adults and incident or relapse of multiple sclerosis	Weak