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

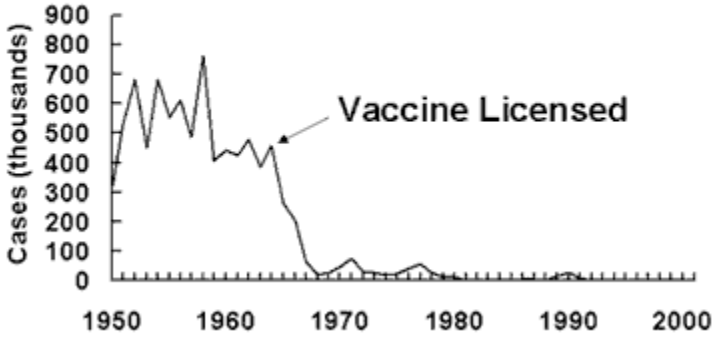
- Vaccination, or immunization, is the act of artificially inducing immunity from disease.
- Use dates back to 1796
  - milkmaids who had cowpox (vaccinia) were immune to smallpox
  - Jenners showed that inoculating fluid from cowpox lesions into the skin of smallpox susceptible people protected against smallpox infecetion
  - "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

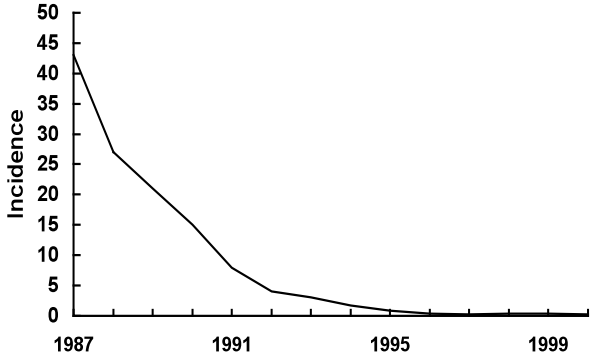
DISEASE	20th CENTURY MORBIDITY	U.S. TOTAL 2004 CASES	% DECREASE
Smallpox	48,164	0	100%
Diphtheria	175,885	1	100%
Pertussis	142,271	25,827	82.0%
Tetanus	1314	34	97.4%
Poliomyelitis	16,316	0	100%
Measles	503,282	11 indigenous 26 imported	99.9%
Mumps	152,209	258	99.9%
Congenital Rubella	47,745	10	99.4%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



*Rate per 100,000 children <5 years of age

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 agians hepatits 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 Tcell-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 vacination

- **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)*

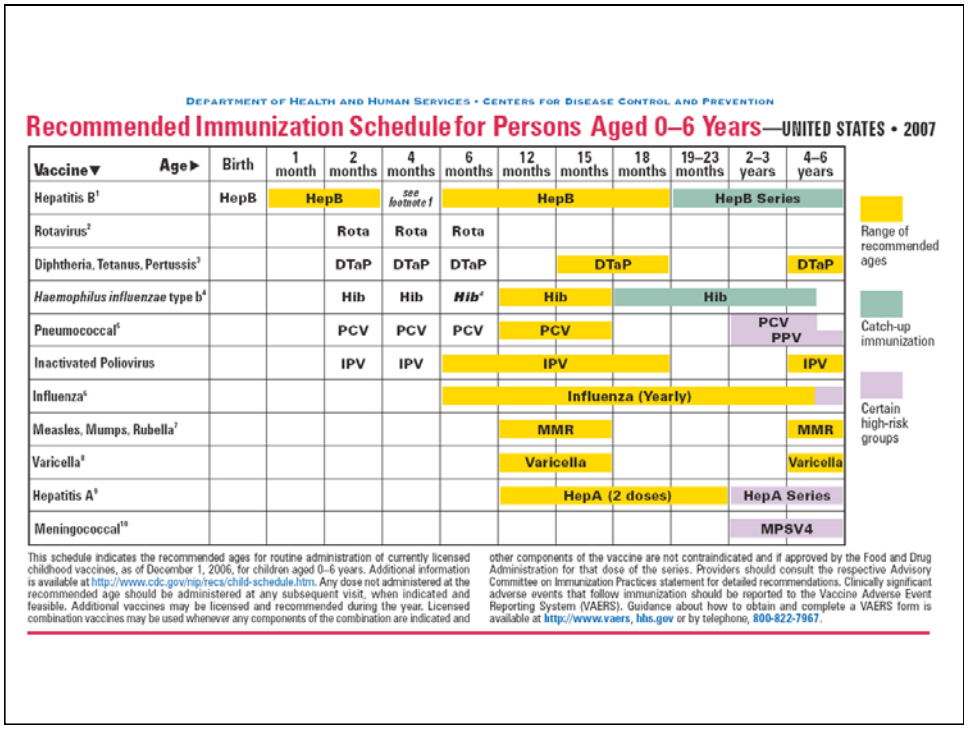
***except those administered orally**

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
  - Polyssaccharide: 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

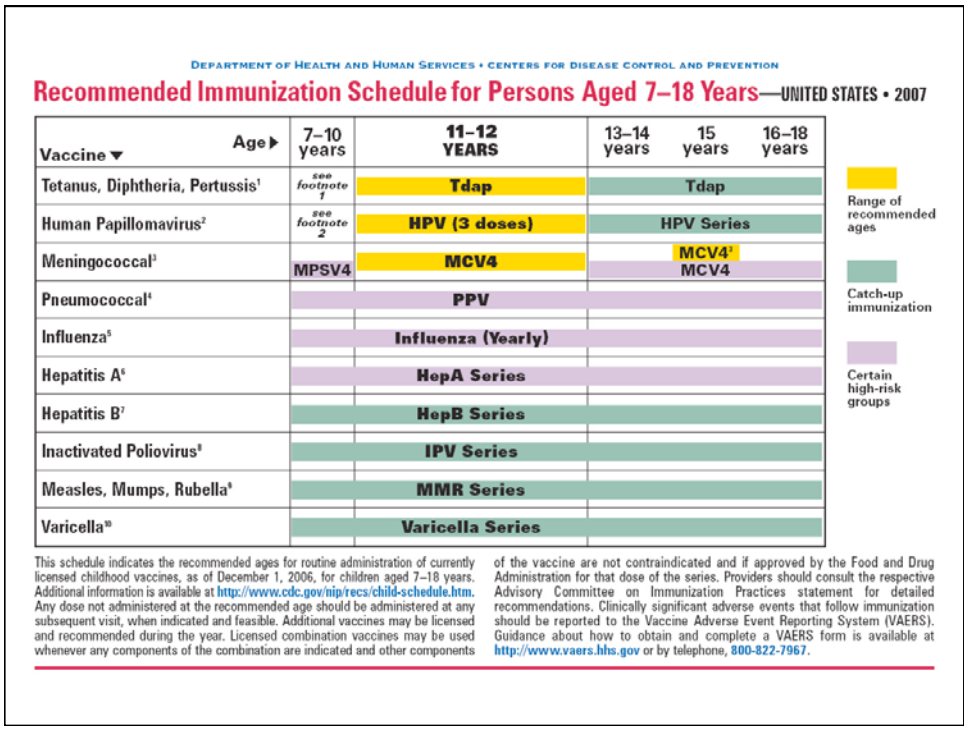
Vaccine ▼ Age ▶	Birth	1 month	2 months	4 months	6 months	12 months	15 months	18 months	19–23 months	2–3 years	4–6 years
Hepatitis B[1]	HepB	HepB		see footnote 1	HepB				HepB Series		
Rotavirus[2]			Rota	Rota	Rota						
Diphtheria, Tetanus, Pertussis[3]			DTaP	DTaP	DTaP		DTaP				DTaP
Haemophilus influenzae type b[4]			Hib	Hib	*Hib*[4]	Hib		Hib			
Pneumococcal[5]			PCV	PCV	PCV	PCV				PCV	PPV
Inactivated Poliovirus			IPV	IPV	IPV						IPV
Influenza[6]					Influenza (Yearly)						
Measles, Mumps, Rubella[7]						MMR					MMR
Varicella[8]						Varicella					Varicella
Hepatitis A[9]						HepA (2 doses)				HepA Series	
Meningococcal[10]										MPSV4	

Range of recommended ages

Catch-up immunization

Certain high-risk groups

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/nip/recs/child-schedule.htm. Any dose not administered at the recommended age should be administered at 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, 800-822-7967.



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[1]	see footnote 1	Tdap	Tdap		
Human Papillomavirus[2]	see footnote 2	HPV (3 doses)	HPV Series		
Meningococcal[3]	MPSV4	MCV4	MCV4[3]	MCV4	
Pneumococcal[4]	PPV				
Influenza[5]	Influenza (Yearly)				
Hepatitis A[6]	HepA Series				
Hepatitis B[7]	HepB Series				
Inactivated Poliovirus[8]	IPV Series				
Measles, Mumps, Rubella[9]	MMR Series				
Varicella[10]	Varicella Series				

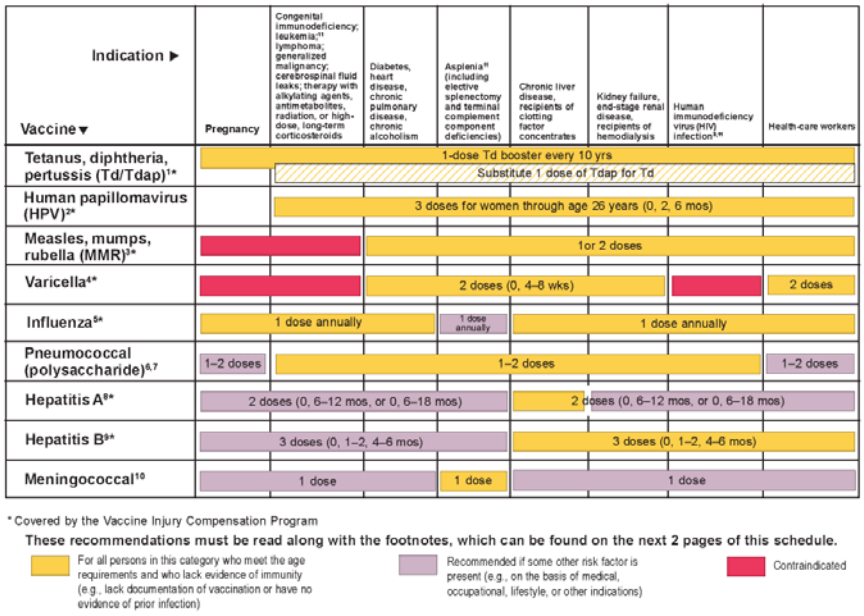
Range of recommended ages

Catch-up immunization

Certain high-risk groups

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/nip/recs/child-schedule.htm. Any dose not administered at the recommended age should be administered at 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, 800-822-7967.

Adult Immunization Schedule



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 polysaccaride (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-Barré 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