Vaccines and Vaccination

- Chapter 21
- Components of a vaccine
- Selection of antigens to be used in a vaccine
- Immune effector mechanisms activated by vaccines
- Practical consideration for vaccine development and use
- Examples of successful vaccines
- Factors that prevent development of vaccines against certain microorganisms

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Vaccination

- US Centers for Disease Control declarations
- #1 public health achievement of the 20th century
- Elimination of smallpox in 1977
- Impending elimination of paralytic polio

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What is a Vaccine?

- A preparation that stimulates a an immune response to protect against foreign substances
- A successful vaccine will induce a memory response

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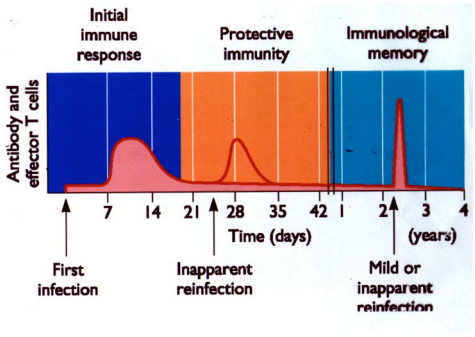
Goal of Vaccination



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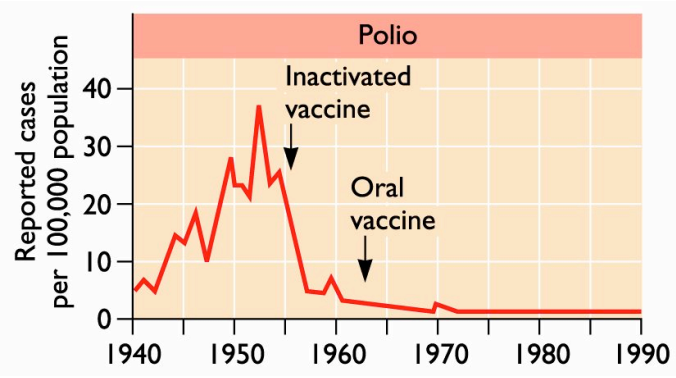
Vaccines can control viral epidemics



from, Principles of Virology, 2nd edition

Vaccination

Table 21.1 Decrease in cases of vaccine-preventable diseases in the United States through 1998 as reported by the U.S. Centers for Disease Control and Prevention[a]

Disease	No. of cases		Reduction (%)
	Baseline[b]	1998	
Smallpox	48,164	0	100
Diphtheria	175,885	0	100
Pertussis	147,271	7,405	95
Tetanus	1,314	41	97.9
Paralytic polio	16,316	0	100
Measles	503,282	100	100
Mumps	152,209	666	99.6
Rubella	47,745	364	99.3
H. influenzae type b	20,000	63	99.7

[a]Reported in *Morb. Mortal. Wkly. Rep.* **48:**243–248, 1999.
[b]Baseline = 20th-century annual prevaccine infection rate.

Vaccine Development

- Edward Jenner first vaccine in 1796
- Infected an 8 year old boy with cowpox
- Then challenged with infection with smallpox
- Boy did not get smallpox

- 1774 Benjamin Jesty innoculated wife and daughters with cowpox hoping to protect from smallpox
  - Did not challenge with smallpox
  - But family did not get smallpox

  - Jenner got his idea from Jesty

Vaccine Development

- Louis Pasteur found that he could prevent disease by using a weakened microorganism infection
  - Used anthrax in cattle and rabies in humans

- Emil Adolf von Behring and Shibasaburo Kitasato
  - Developed a serum therapy for diphtheria
  - Antibodies in immune serum

- Maxwell Finland used specific antisera against strep pneumoniae to treat patients at Boston City Hospital
  - Before antibiotics were developed

What are the phases for vaccine development?

- The Phases of Clinical Trials

- Preclinical
- Phase 1
- Phase 2
- Phase 3

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What are the phases for vaccine development?

Preclinical

- Design and production of the vaccine product
- In vitro assays
- Small animal models
- Non-human primate models

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What are the phases for vaccine development?

Phase I

- Under 50 participants per dose or approach
- Low-risk population
- Measures safety and how the drug/vaccine is tolerated
- (Measures immune response)
- 8-12 months to complete

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What are the phases for vaccine development?

Phase II

- Hundreds of participants
- Low and higher risk
- Expanded safety
- Measures immune response
- 18-24 months

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What are the phases for vaccine development?

Phase III

- Thousands of participants
- Moderate to high risk
- Expanded safety
- Determines efficacy and immune response
- Approximately 3 years

Vaccination

- Types of protection
- Active Immunization
  - Develop an immune response after immunization or infection
  - T and B cell responses elicited
  - Cell mediated and antibody mediated immune responses
- Passive Immunization
  - Given antibodies from another individual or organism or from the lab
- Serum sickness
  - Recipient makes antibodies against antigens in Horse serum
  - Human serum better, but expensive and not widely available
- Purified IgG from human serum
  - Bloodborne pathogen scare (HIV, hepatitis)
- Monoclonal antibodies produced in the lab
  - Testing and marketing currently

Active Immunization

Table 21.7 Bacterial vaccines developed to date

Disease	Causative organism	Efficacy
Diphtheria	*Corynebacterium diphtheriae*	>95%
Tetanus	*Clostridium tetani*	>95%
Meningitis and sepsis	*Haemophilus influenzae* type b	>90%
	Neisseria meningitidis	90% for 2- to 3-yr-olds
		In development
Pneumonia and sepsis	*Streptococcus pneumoniae*	60% for >2-yr-olds
		>95% for sepsis
Whooping cough	*Bordetella pertussis*	80–90%
Typhoid fever	*Salmonella enterica* serovar Typl	50–70% (short-lived)
		50–70%
		>70%
		>75%
Plague	*Yersinia pestis*	Uncertain
Anthrax	*Bacillus anthracis*	Uncertain
Tuberculosis	*M. tuberculosis*	Controversial; best protection against disseminated disease
Cholera	*Vibrio cholerae*	50% (short-lived)

Active Immunization

Table 21.8 Viral vaccines developed to

Disease	Type of virus	Vaccine constituents	Vaccine constituents
Smallpox	Variola virus	Vaccinia virus	Vaccinia virus
Polio	Picornavirus	Oral: live, attenuated virus	Oral: live, attenuated virus
		Inactivated virus particles	Inactivated virus particles
Hepatitis A	Picornavirus	Killed virus	Killed virus
Hepatitis B	Hepadnavirus	Recombinant antigen	Recombinant antigen
Influenza	Orthomyxovirus	Inactivated virus	Inactivated virus
Measles (rubeola)	Paramyxovirus	Live, attenuated virus	Live, attenuated virus
Mumps	Paramyxovirus	Live, attenuated virus	Live, attenuated virus
Rubella (German measl	Togavirus	Live, attenuated virus	Live, attenuated virus
Chicken pox (varicella)	Varicella-zoster vi	Live, attenuated virus	Live, attenuated virus
Rabies	Lyssavirus	Inactivated virus	Inactivated virus
Yellow fever	Flavivirus	Live, attenuated virus	Live, attenuated virus
Japanese encephalitis	Flavivirus	Inactivated virus	Inactivated virus

Active Immunization

Table 21.9 Fungal vaccines under development

Disease	Etiologic agent	Immune effectors	Vaccines in development
Histoplasmosis	*Histoplasma capsulatum*	Cell mediated	H glycoprotein (β-glucosidase), HIS-62 (heat shock protein), cell wall and cell membranes
Coccidioidomycosis	*Coccidioides immitis*	Cell mediated	Enzyme, spherule outer wall extract, alkali-soluble antigen, water-soluble antigen, urease
Blastomycosis	*Blastomyces dermatitidis*	Cell mediated	WI-1 surface adhesin
Cryptococcosis	*Cryptococcus neoformans*	Humoral	Capsular polysaccharide, melanin
Candidiasis	*Candida albicans*	Humoral Cell mediated	Mannan, mannoprotein Enolase
PCP	*Pneumocystis carinii*	Humoral Cell mediated	Major surface glycoproteins

Passive Immunization

Table 21.11 Passive immunotherapeutic reagents available for postexposure prophylaxis

Disease(s)	Reagent
Botulism	Equine botulism antitoxin
Measles	Standard human immune globulin (high titers of antibody in most individuals)
Rubella	Standard human immune globulin (high titers of antibody in most individuals) but only for pregnant women in first trimester of pregnancy; efficacy unreliable
Tetanus	Human tetanus immune globulin
Rabies	Human rabies immune globulin
Hepatitis A; non-A, non-B hepatitis	Normal human immune globulin
Hepatitis B	Human hepatitis B immune globulin, usually for neonates born to infected mothers to prevent neonatal transmission
Spider toxins	Horse antivenin
Snake toxins	Antivenins developed to be specific to the particular snake toxin

Vaccination

- Usually killed bacterial or fungal cells do not generate protective immunity
- Only some killed viral particles generate protective immunity
  - Inactivated polio vaccine
- Only a small minority of antigenic targets actually provide protective immunity
  - Certain classes of antigens are associated with protective immunity

Certain classes of antigens are associated with protective immunity

- Antibody mediated immunity protective antigens
  - Toxins
  - Microbial surface antigens
  - Prominent viral surface capsid proteins
  - Surface capsular polysaccharides of some bacteria and fungus
- Cell mediated immunity protective antigens
  - Harder to define
  - Can be anywhere in microbe
  - Only effective if they can be presented by APCs to T cells

Certain classes of antigens are associated with protective immunity

Table 21.3 Microbial antigens that can be targeted for vaccine development

Type of organisms	Antigenic target	Mechanisms of immunity
Bacteria	Toxins	Neutralization of toxin
	Capsular polysaccharides	Opsonophagocytic killing Bacteriocidal killing
	Surface proteins	Opsonophagocytic killing Transmission blocking
Viruses	Capsid coat protein Internal core antigens	Neutralization of infectivity CMI
Fungi	Capsular polysaccharide Surface proteins	Opsonophagocytic killing Unknown
Protozoan parasites	Surface proteins	Antibody-mediated neutralization CMI

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Certain antigens are associated with protective immunity

Table 21.10 A selection of *P. falciparum* antigens as targets for parasite-neutralizing immune response[a]

Antigen	Mol wt (10^3)	Antigenic diversity	Potential targets for[b]	Location[b]	gets for[b]	Location[b]
PfEMP1	250–300	Extensive	Cytoadherence Ab	RBC surface	Ab	RBC surface
Pf332	280	No	ADCI, inhibitory Ab	RBC surface	γ Ab	RBC surface
RIFINS	27–45	Yes	NK cell	RBC surface		RBC surface
MSP-1	230	Extensive	Inhibitory Ab	MS		MS
MSP-2	45–55	Extensive	Inhibitory Ab	MS		MS
MSP-3	50	Yes	ADCI	PV, MS-associated		PV, MS-associated
GLURP	220	No	ADCI	PV, MS-associated		PV, MS-associated
Pf155/RESA	155	No	Inhibitory Ab	Dense granules		Dense granules
AMA-1	80	Yes	Inhibitory Ab	Rhoptries		Rhoptries
EBA-175	175	Yes	Inhibitory Ab	Microneme		Microneme

[a]Reprinted from A. Bolad and K. Berzins, *Scand. J. Immunol.* 52:223–239, 2000, with permission.
[b]Ab, antibody; ADCI, antibody-dependent immunity; RBC, red blood cell; MS, merozoite surface; PV, parasitophorous vacuole.

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Requirements for a Safe vaccine

- Safe, minimal side effects
- Effective duration -depends on use
- Immunogenic - needs adjuvant or protein carrier
- Nonimmunosupressive - measles vaccine FcR binding
- Host responds with proper type of immunity - CMI vs Ab
- Cost vs benefits
  - Monetary to produce and deliver and any health risk associated with its use
  - Benefit to individual and population
- Relative risk of vaccine vs infection

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Table 21.5 Types of effector mechanisms known to be involved in immunity to microbial pathogens that would need to be elicited by a vaccine

Effector mechanisms	Type of pathogen targeted	Mediators of immunity
Opsonophagocytic killing	Bacteria Fungi Some viruses	IgG and IgM antibody Complement Phagocytes
Microbicidal killing	Bacteria Viruses?	IgM and IgG antibody Complement
Mucosal immunity	Bacteria	IgA, IgG, and IgM antibody
	Viruses	Complement for IgG and IgM
	Fungi Protozoan parasites Helminthic parasites	Mucosal phagocytes IgE antibody Eosinophils
DTH	Bacteria Fungi Some viruses Protozoan parasites Helminthic parasites	$CD4^+$ T cells Activated macrophages Cytokines
Cytotoxic cells	Some bacteria Viruses Fungi Protozoan parasites Helminthic parasites	$CD8^+$ T cells NK cells Eosinophils Cytokines Antibody for antibody-dependent cell-mediated cytotoxicity

Need to know what effector mechanisms need to be provoked by vaccine for protective immunity

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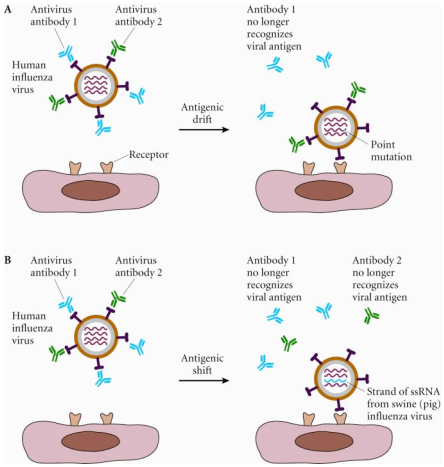
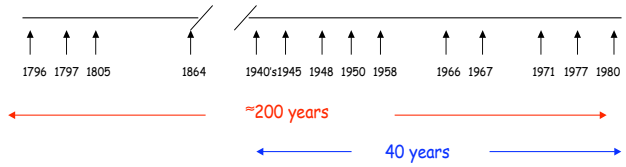
Vaccine Duration

- Antigenic variation is the most common microbial mechanism for evading the host defenses
  - Microbe may produce up to hundreds or thousands of distinct surface antigens
  - Effective immunity is needed against many if not all these
- Antigenic drift
  - Influenza virus
  - Mutations in HA and NA
- Antigenic shift
  - Influenza virus
  - Reassortment of genes for HA and NA between 2 different viruses



Vaccine Duration

Smallpox Eradication



What was it about smallpox?

- No secondary hosts
- Long incubation
- Low communicability
- No persistent infection
- Easily diagnosed
- Infection confers long term immunity
- One stable serotype
- Vaccine existed
- Vaccine is stable and inexpensive

What was it about smallpox?

- Severe disease with high morbidity and mortality
- Much cheaper to eradicate than treat
- Eradication from developed countries demonstrated feasibility
- Few cultural or social barriers to case-tracing

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What if we stopped vaccinations?

- Before immunization nearly everyone in US got measles
- ≈ 450 deaths/yr 1953-1963
- 3/1000 deaths in US
- 1/100 deaths in developing world
- >90% not immune will get measles if exposed to the virus
- If measles vaccination were stopped we would see:
- 2.7 million measles deaths worldwide

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