

Vaccines

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Outline

- Public health impact of vaccines
 - Historical perspective
- Active vs. Passive Immunization
- Immune system in active immunization
- Classification of vaccines
 - Discussion of two vaccines
- Safety considerations

What is a vaccine

- One of most effective means of preventing disease, disability, and death
- An attenuated live or killed antigen (e.g. bacteria, virus) administered to induce a strong and measurable immune response in the host
- 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



1827 lithograph by Louis Leopold Boilly depicts a smallpox vaccination

Vaccine - Definition

- An attenuated live or killed antigen (e.g. bacteria, virus) administered to induce a strong and measurable immune response in the host
- 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

Smallpox



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
 - Jenner 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

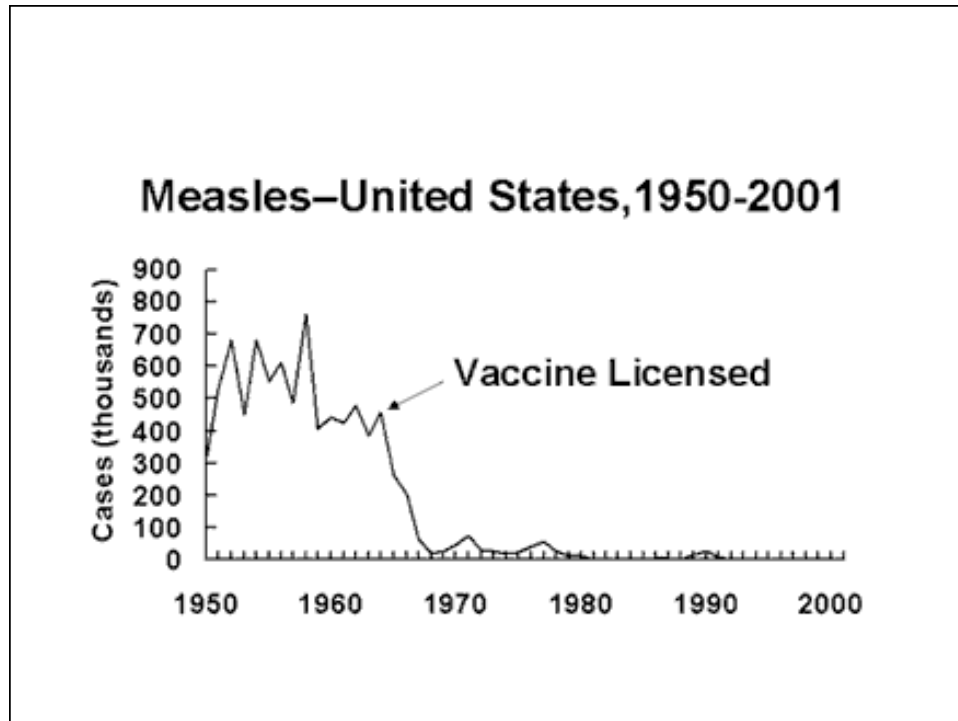
Vaccinia and eradication of Smallpox

- Modified cowpox virus (**vaccinia** virus) is currently used to protect against smallpox
 - (source of the term *vaccination*)
- 1977/1980 – smallpox eradicated worldwide
- Public health reasons
 - no non-human reservoir
 - intense WHO mounted public health effort and investment

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



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
 - RSV immune globulin (RSVIG) to protect premature infants and infants with lung disease from serious RSV infection
 - Tetanus immune globulin (TIG) to prevent tetanus infections in unimmunized, exposed individuals
- **Active immunization**
 - The act of stimulating the production of antibodies or inducing cell-mediated immunity, or both

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 \geq 2 wks after vaccination
 - 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 infection
 - Both humoral and T-cell mediated responses are generated
- Usually effective with one dose*
- Disadvantages
 - May cause disease in immunocompromised hosts
 - Passive maternal antibodies may interfere with efficacy – must delay vaccine until >1 yr of age for MMR and varicella

*except those administered orally

Live Attenuated Vaccines

- Examples:
 - Measles vaccine, Mumps vaccine, Rubella vaccine
 - Oral (Sabin) polio vaccine
 - Yellow fever
 - Live attenuated influenza vaccine (intranasal)
 - Rotavirus

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

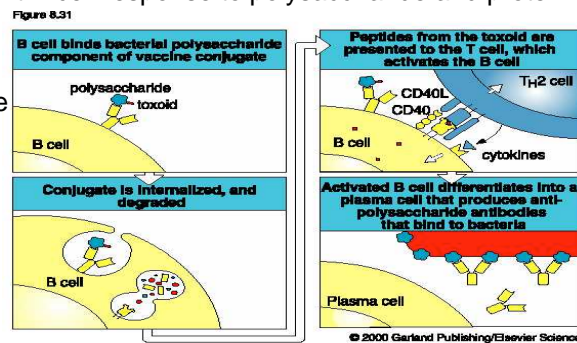
Inactivated vaccines

- **Whole killed vaccines:**
 - inactivated polio (Salk), 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 (polysaccharide-protein conjugate)
 - Examples: hepatitis B, Haemophilus influenzae type b, 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

Polysaccharide Conjugate Vaccines

- Overcoming limitations by rational vaccine engineering - *Haemophilus influenzae* type b and pneumococcal conjugate vaccines
 - Protective antigens are capsular polysaccharides
 - Pure polysaccharides = T cell independent antigen, little or no response <2 years age (highest risk age group), low affinity with no long term memory even in adults
 - Conjugate polysaccharide to protein (e.g., tetanus or diphtheria toxoid) → T dependent B cell response to polysaccharide and protein components

Essential elimination of *H. influenzae* meningitis since introduction of conjugate vaccine
Reduction in *S. pneumoniae* and *N. meningitidis* invasive disease



Vaccinations: Public Health issues

- Goals
 - Prevent carriage, infection, transmission → protect immunized individual and reduce risk for unimmunized = herd immunity usually requires >80-90% coverage
 - Prevent disease or slow disease progression but do not block transmission → protect immunized individual only
- Risk vs. benefit
 - Individual or society
 - relative and changes overtime
- Ethics and Vaccine utilization – universal-mandated vaccines compared to recommended/optional vaccines

Current Routine Childhood Vaccines (CDC)

Recommended Immunization Schedule for Persons Aged 0 Through 6 Years—United States • 2009 For those who fall behind or start late, see the catch-up schedule

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	<i>see footnote 1</i>		HepB						
Rotavirus ²				RV	RV	RV ²						
Diphtheria, Tetanus, Pertussis ³				DTaP	DTaP	DTaP	<i>see footnote 3</i>	DTaP				DTaP
<i>Haemophilus influenzae</i> type b ⁴				Hib	Hib	Hib ⁴		Hib				
Pneumococcal ⁵				PCV	PCV	PCV		PCV				PPSV
Inactivated Poliovirus				IPV	IPV			IPV				IPV
Influenza ⁶								Influenza (Yearly)				
Measles, Mumps, Rubella ⁷								MMR		<i>see footnote 7</i>		MMR
Varicella ⁸								Varicella		<i>see footnote 8</i>		Varicella
Hepatitis A ⁹								HepA (2 doses)				HepA Series
Meningococcal ¹⁰												MCV

Range of recommended ages
 Certain high-risk groups

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5751a5.htm?s_cid=mm5751a5_e

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

Examples of licensed vaccines

- Polio
 - Live attenuated and whole killed
- Measles
 - Live attenuated

Polio

- One of the most notorious disease of the 20th century until HIV appeared

"I have just figured out that during the coming summer, thirty or forty thousand children will get polio. About fifteen thousand of them will be paralyzed and more than a thousand will die. If we have the capacity to prevent this, we have a social responsibility ... we are supported by the people and it is our duty to save lives no matter how many difficulties may be involved."

—Basil O'Connor, president of March of Dimes, 1954

Polio Vaccine: Historical perspective

- From early 1900s, pursuit of two different kinds of polio vaccine.
- **Inactivated (killed) by Jonas Salk and live/ attenuated virus by Albert Sabin**
- Chief advantage of Salk's killed virus vaccine: safety
- Perceived disadvantage of Salk's vaccine: less immunogenic - shortened period of immunity?



Albert Sabin (left) and Jonas Salk (center) meeting with Basil O'Connor of the March of Dimes in 1961

Polio vaccine: historical perspective

- **1952-4:** encouraging results from small trials of Salk vaccine. Large scale trial launched
- **1955:** News of the success of the trials is announced
- **1955 – 57:** incidence of polio in the U.S. falls by 85 - 90%.
- **1957 – 59:** clinical trials of Sabin's oral attenuated vaccine in Russia
- **1979:** last case of polio caused by "wild" virus in U.S.
- **1988:** international campaign to stop worldwide transmission of polio (WHO, UNICEF, CDC)
- **1999:** inactivated polio vaccine (IPV) replaces oral polio vaccine (OPV) as recommended method of immunization in US

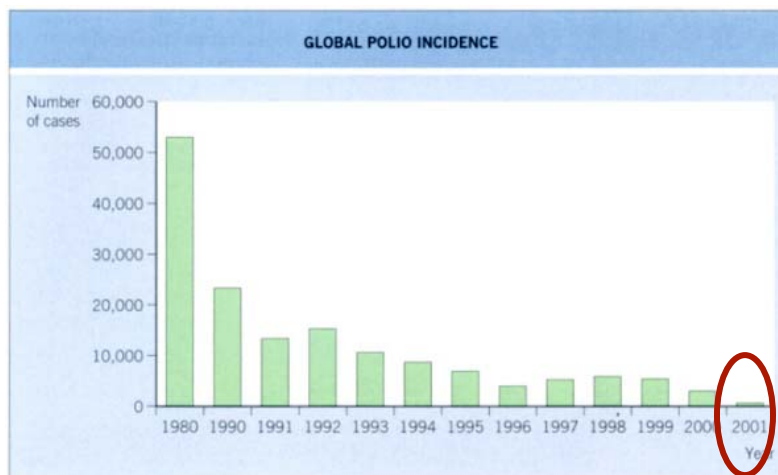


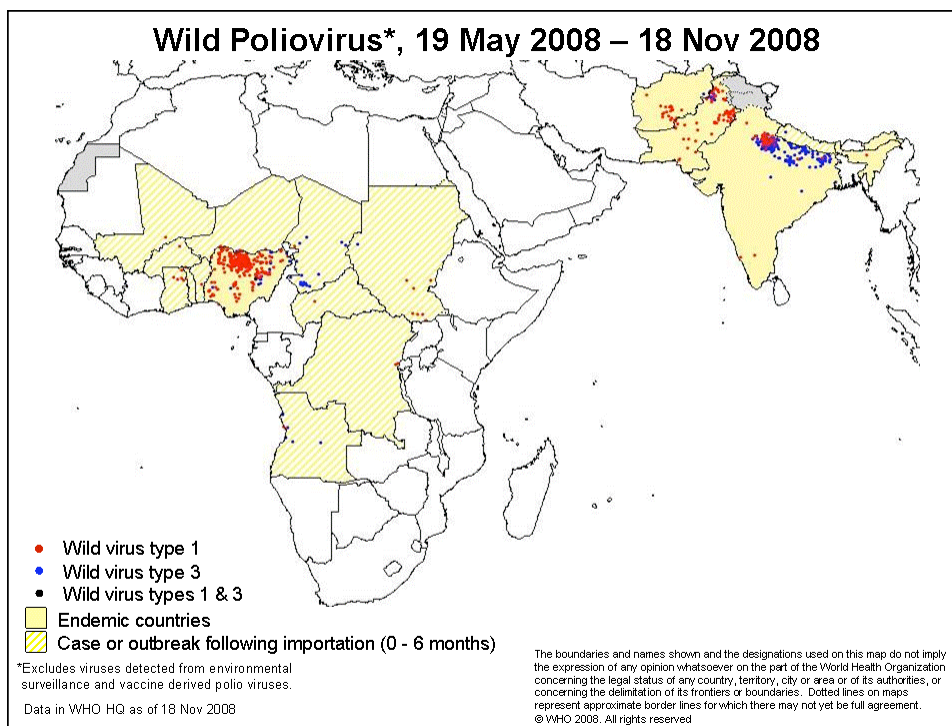
Some of the thousands of children who received free vaccine in the weeks following the announcement, waiting in segregated lines

Two formulations of polio vaccine

- **Live attenuated, oral vaccine**
- **Sabin vaccine**
 - Live virus secreted in feces of vaccinated individuals for short time after vaccination – spread of vaccine to unimmunized
 - Vaccine of choice of WHO's effort to eradicate polio from the world.
 - Can cause paralytic disease: no longer used in US
 - 3 Sabin strains of polioviruses, types 1, 2, and 3
 - Both vaccines are on a three-dose primary series
 - Booster doses of each vaccine are recommended at school entry
- **Inactivated polio vaccine, sc**
- **Salk vaccine**
 - Formulated to contain antigens recognized by 99% of the population (enhanced potency IPV).
 - Rarely cause paralytic polio: greatest risk after the first dose (1/ 750,000)
 - IPV given to a high proportion of individuals in developed countries eliminated disease without risk of serious side effects.
 - During control of an epidemic, OPV should be used for all age groups.

Global Polio Incidence Reported cases of poliomyelitis worldwide 1990-2001





Polio vaccine for adults

- Adults living in the U.S. who never received or completed a primary series of polio vaccine need not be vaccinated unless they intend to travel to areas where exposure to wild-type virus is likely.
- Available data do not indicate the need for more than one lifetime IPV booster dose
- Travelers who are unvaccinated, incompletely vaccinated, or whose vaccination status is unknown should receive 3 doses of IPV.

Polio vaccine: Contraindications and precautions

- IPV contraindicated in children who have experienced a severe allergic reaction to a previous dose of IPV or to streptomycin, polymyxin B, or neomycin.
- OPV contraindicated in children with immunosuppressive conditions
 - congenital immunodeficiency (agammaglobulinemia or hypogammaglobulinemia),
 - cancer (leukemia or lymphoma), immunosuppressive chemotherapy
 - HIV/AIDS
- OPV also contraindicated for family and other close contacts of immunocompromised people - potential risk of spread of OPV to the affected person

Measles vaccine

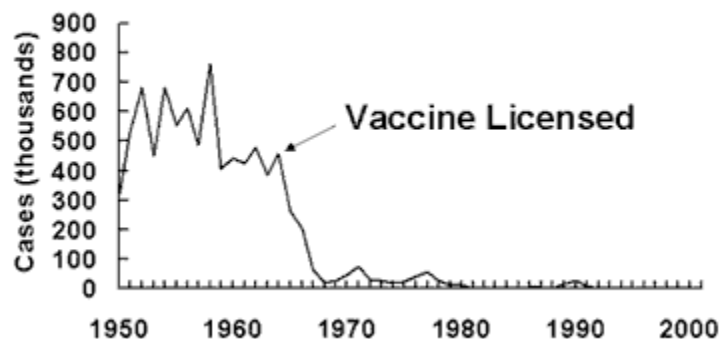
Live attenuated vaccine

- Measles: leading cause of childhood deaths in developing countries
- Measles accounts for nearly half of the 1.7 million annual deaths due to childhood vaccine-preventable diseases.
- Individuals are infectious before the appearance of the erythematous maculopapular rash, leading to 'silent spreaders'
- High levels of herd immunity and high vaccination coverage required to control the infection

Measles vaccine

- Recommended for use in all children 12-15 months of age who do not have contraindications (combined MMR)
- Only a single dose is needed to provide long lasting, probably lifelong, immunity in those who respond to the vaccine
- **Because measles is much more prevalent outside the United States, adequate vaccination is recommended for all travelers born after 1956.**
 - administer a second dose if not previously vaccinated and lack other evidence of measles immunity

Measles—United States, 1950-2001





THE CITY OF NEW YORK

DEPARTMENT OF HEALTH AND MENTAL HYGIENE

Michael R. Bloomberg
Mayor

Thomas R. Frieden, M.D., M.P.H.
Commissioner

nyc.gov/health

February 25, 2008

2008 DOHMH HEALTH ALERT # 5: Measles in Brooklyn

- 1) Two measles cases have been identified in a family in Brooklyn. The cases have not travelled outside of New York, indicating exposure to measles within the City.
- 2) All clinically suspect cases of measles (febrile illness accompanied by generalized maculopapular rash) must be reported immediately (prior to laboratory confirmation) to the New York City Department of Health and Mental Hygiene at (212) 676-2292 or 2313 (weekdays 9 am to 5 pm). For after hours and weekends, please call Poison Control 212-764-7667. Suspect cases of measles must be placed in respiratory isolation immediately.
- 3) Appropriate clinical specimens should be sent to the NYC DOHMH Public Health Laboratories for testing.

Please Distribute to All Primary Care Staff, Including Infectious Disease, Emergency Medicine, Internal Medicine, Pediatrics, Family Medicine, and Laboratory Medicine and All Infection Control Personnel

Dear Colleagues,

On February 13, 2008, the New York City Department of Health and Mental Hygiene (NYC DOHMH) was notified about a confirmed case of measles. The person had onset of rash on February 7, 2008 (contagious period 2/2-2/12/2008). Subsequently, an unvaccinated household contact developed measles on 2/17/2008. The index case denies international travel and had no known contacts with other measles cases. The Bureau is currently conducting an investigation to try to identify contacts, as well as the source of initial infection.

Measles vaccine contraindications

- Contraindicated for pregnant women
- Immunocompromised persons due to either congenital or acquired disorders (e.g., leukemia or immunosuppressive drugs)
- HIV positivity is NOT a contraindication except if $CD4 < 200$ cells/ μ L
 - MMR vaccination should be considered for all symptomatic HIV-infected persons who do not have evidence of severe immunosuppression or of measles immunity
- History of anaphylactic reactions to eggs not a contraindication
 - vaccinate and observe for at least 20 minutes

Measles vaccine

- Adverse events
 - fever (associated with febrile convulsions)
 - transient rashes in ~ 5% of vaccinees
 - reports of encephalopathy, onset ~ 10 days after vaccination has been reported in vaccine recipients(1 in 2 million vaccinations)
 - available evidence favors rejection of a causal role for MMR in autism

Measles vaccinations and safety

- Hypothesis -- 1998 -- measles component of MMR vaccine leads to inflammation in the gut and the release of neuroactive chemicals that promote developmental neuropathology
- Case control study*: Cohort of 25 children with both autism and severe GI disorders vs. 13 children with similar GI symptoms but not autism
 - No differences between children with autism and GI disorders and control children who had GI disorders, but not autism
 - There was no difference between the groups wrt presence of measles viral RNA in the intestine or with the timing of MMR and the onset of GI disorders
- Findings disprove the original hypothesis about measles vaccine and association with autism

**Horning M et al. PLoS ONE 2008*

Vaccines

- Safety concerns



Concern about thimerosal-containing vaccines and the neurodevelopmental disorders of ADHD, and speech or language delay

Safety Concerns

- Institute of Medicine review of reported serious adverse effects associated with 9 of the 12 vaccines universally recommended for children
- Concluded that available evidence did not support a relationship between MMR and autism
- Precautionary measure since 2001
 - thimerosal (mercury containing preservative) is not used as a preservative in routinely recommended childhood vaccines. exception: some influenza vaccines

Vaccine Safety – Real and Perceived

- Higher standard of safety needed for vaccines (especially universal) than therapeutic agents
- No vaccine is completely safe, therefore public acceptance may wane when the disease prevented is not common enough to remind of vaccine benefits
 - E.g. MMR lead to decrease rate measles → vaccine uptake fell in response to false assertion of role in risk for autism → rate of measles increased

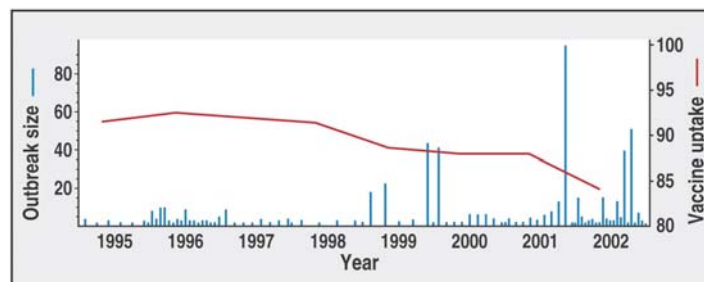


Figure 12-6 The Immune System, 2/e (© Garland Science 2005)

Vaccine research accomplishmentsand challenges

Vaccine	Discovery of cause	Vaccine developed	Years elapsed
Pertussis	1906	1926	20
Polio	1908	1955	47
Measles	1953	1983	30
Hepatitis A	1973	1995	22
Hepatitis B	1965	1981	16
HIV		???	
Malaria		???	
TB		???	

References

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