VACCINATION

GOALS:

1. Understand passive and active immunization
2. Understand the role of humoral and cell-mediated immunity in vaccination
3. Review the types of vaccines currently available

INTRODUCTION AND DEFINITIONS

Immunization and sanitation are the most effective medical interventions aimed at reducing the incidence of infections and related deaths worldwide. The act of immunization (or vaccination) implies artificially inducing immunity or providing protection from disease or infection; it can be active or passive. Immunizing agents include vaccines, toxoids, and antibody-containing preparations from human or animal donors.

The use of vaccines dates back to 1796 when Jenners demonstrated that milk maids who had contracted cowpox (vaccinia) were immune to smallpox. He showed that inoculating the vesicular fluid from cowpox lesions into the skin of susceptible individuals could protect them against smallpox infection. The term vaccination is derived from this practice. Current vaccine against smallpox uses the modified cowpox virus (i.e. vaccinia virus).

Antigens: Molecules that elicit an immune response in the body. Antigens can be protein, polysaccharides, or lipids attached (conjugated) to proteins (lipoproteins) and polysaccharides (glycolipids).

Antibodies react with antigens in the blood stream, extracellular fluid and at mucosal surfaces. They cannot readily reach intracellular sites of infection. They are part of **humoral immunity**.

Cell mediated immunity is directed against intracellular antigens and thus is most effective against organisms that spend at least part of their lifecycle inside cells. T-lymphocytes (e.g. cytotoxic T cells, T helper cells) are an integral part of this arm of the immune system. Cytotoxic T cells (CTL), for example, recognize small fragments of antigens presented on the surface of infected cells in combination with HLA class I molecules (MHC class 1 complex) and kill the infected cell.

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). The purpose of vaccination is to provide protection by priming the recipient's immune system to recognize and attack the disease-causing organism when and if it is ever presented again. ***Live-attenuated vaccines*** are developed either by (1) serial passage of an initially pathogenic bacteria/virus and selection of less pathogenic strains that still induce protective immunity (e.g. MMRV and see below); or (2)combining attenuated animal or human virus strains with viral

antigens, usually from the viral coat, from pathogenic strains (rotavirux vaccine). ***Inactivated vaccines*** or ***whole killed vaccines***, on the other hand, can be composed of (1) whole organism inactivated by heat, formalin etc (polio, hepatitis A, rabies); (2) purified protein (influenza) or polysaccharide antigens (pneumococcal, meningococcal) derived from whole organisms; (3) purified antigens produced by a genetically altered organism (hepatitis B and HPV vaccine produced by yeast); or (4) chemically modified antigens, such as polysaccharides conjugated to a carrier protein to increase their immune response (*Haemophilus influenzae* type b conjugate vaccines, pneumococcal and meningococcal vaccines). Whole killed vaccines are incapable of infecting or multiplying within the vaccinated host. Live, attenuated vaccines are believed to induce an immunologic response more similar to that resulting from natural infection than do killed vaccines.

Toxoids: are modified bacterial toxins that have been rendered non-toxic but retain the ability to stimulate the formation of antibodies (antitoxins). Toxoids are generally safe and well-tolerated but most do not produce life-long immunity and require booster doses. Examples of toxoids include diphtheria toxoid and tetanus toxoid and are discussed below.

Immunoglobulin (Ig): A sterile solution for intramuscular administration containing antibody from human donor pools with high levels of antibodies specific to certain infectious agents. It is primarily indicated for routine protection of certain immunodeficient persons and for passive immunization against measles and hepatitis A. Used to prevent infection in individuals with immune deficiencies such as X-linked agammaglobulinema. .

Adjuvants: Substances (e.g. aluminum salt) used in some vaccines to enhance the immune response to inactivated vaccines or toxoids.

TYPES OF IMMUNIZATION

Passive immunization

Passive immunization consists of administration of exogenously produced antibody to provide temporary protection from disease. Antibodies provided by this route are usually short-lived and protection is temporary compared to active immunization. Examples of passive immunization include: (1) transplacental transfer of antibodies to the fetus whereby the child is protected against certain disease for the first 3 to 6 months of life.
(2) administration of pooled human IgG, immunoglobulins, used for passive immunization against hepatitis A and measles used after a non-immune person has been exposed to the disease and before they develop the disease.
(3) Hepatitis B immune globulin is used to protect babies born to hepatitis B carrying mothers and to protect non-immune exposed persons.
(4) Varicella zoster immune globulin is used to prevent serious varicella (chickenpox) infection in non-immune, exposed individuals at high risk of severe infection (e.g. immunocompromised patients)
(5) Rabies immune globulin is used to protect people exposed to rabies before immunity builds up following active immunization.
(6) other examples include; tetanus immune globulin, RSV immunoglobulin; the latter is used to protect premature infants with lung disease

Active immunization
Active immunization consists of inducing the body to develop defenses against an infectious agent. This is accomplished by stimulating the production of antibodies or inducing cell-mediated immunity, or both (see below). **The rest of the material will focus on active immunization.**

Active immunization employs either live-attenuated vaccines or inactivated vaccines described above. The advantage of a live-attenuated vaccines is that because replication of the organism and processing of antigens mimics natural infection, both humoral (antibody based) and cell-mediated (T-cell mediated) responses are generated to a wide range of antigens. Furthermore, conferred immunity may be long-lasting, perhaps life-long; the magnitude of response (particularly antibody response) may wane with time, however.
Inactivated vaccines (whole killed vaccines), on the other hand, do not replicate in the vaccinee and thus provide less antigenic stimulus than live attenuated vaccines; commonly, multiple doses of vaccine are required to induce sufficient antibody response that persists for a long period of time. The nature of the reponse (humoral or cell-mediated) depends on the type of antigen: e.g. polysaccharide (induce only humoral response) vs. protein antigens (induce both types of responses).

The next sections will review how an immune response is generated after a vaccination, and the determinants of immunogenicity. Lastly, common types of vaccines will be described.

IMMUNE RESPONSE TO ACTIVE IMMUNIZATION
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. The steps described below are part of a continuum and it is important to recognize that both the humoral and cell-mediated responses to a vaccine may occur simultaneously.

Step one: After an antigen, in this case a vaccine component, enters the body, it is recognized and processed by antigen processing cells (mononucelar phagocytes or dendritic cells) and subsequently presented on their surface, in association with major histocompatibility complex (MHC) molecule, to helper T lymphocytes.
The type of MHC molecule with which the antigen is depends on the source and processing of the polypeptide. For example, inactivated antigens, are processed and presented with MHC class 2 complex (HLA class 2); antigens from live-attenuated vaccines are presented with MHC class 1 complex (HLA class 1).

Step two: Presentation of an antigen to helper T-lymphocyte triggers the secretion of a cascade of cytokines (α-, β-, γ-interferons), that stimulate the maturation of naïve T-helper cells and communication between leukocytes to regulate the immune response (via interleukins). Depending on the antigen and its MHC presentation (see above), T lymphocytes differentiate into either:

- Type 1 T-helper lymphocytes (T_H1) stimulated by MHC class 1-associated antigen, which mediate cellular immune response. T_H1 cells release cytokines that cause the maturation of naïve cytotoxic T cells (CTL)

which can then recognize intracellular antigens using their T cell receptors. When the T cell receptor of the mature CTL recognizes its antigen combined with its HLA class I molecule (MHC) on the surface of an infected cell, it releases substances that kill the infected cell. Like antibody producing B cells, CTL can become resting memory cells ready to become activated as soon as the host is exposed to the antigen again.

OR

- Type 2 T-helper lymphocytes (T_H2), stimulated by MHC class 2-associated antigen. T_H2 cells in turn produce cytokines that lead to maturation of naïve B lymphocytes and thereby result in specific antibody production.

Step three: Antibodies are produced in response to the immunization; it is important to recognize that their production requires activation of T helper cells to stimulate B cell activation and proliferation. Antibodies interact with antigens in the blood stream, extracellular fluid, or at mucosal surfaces. Following the initial immune response induced by activation, activated B lymphocytes turn into resting memory cells ready to be deployed rapidly when the antigen is encountered again.
Protective antibodies may function either by: (1) opsonization (neutralization) of organisms; (2) initiation of or combination with the complement pathway to lyse organisms or promote phagocytosis of bacteria (e.g. pneumococcal vaccine); (3) reaction with lymphocytes to promote phagocytosis; or (4) sensitization of macrophages to promote phagocytosis. Of note, protective antibodies against viral infections can act only when the virus is extracellular. They may (1) bind to viruses and prevent entry into the cell; or may (2) interfere with uncoating of virus particles thereby prevent locally replicating virus from disseminating from the site of entry to an important target organ, as in the spread of poliovirus from the gut to the central nervous system or of rabies from a puncture wound to peripheral neural tissue.

TEMPORAL COURSE OF THE RESPONSE TO ACTIVE IMMUNIZATION

The primary response after first exposure to a vaccine antigen occurs after a latent period of several days; afterwards humoral (antibody) and cell-mediate immunity can be detected. Circulating antibodies do not usually appear for 7 to 10 days. The first antibodies to appear are usually IgM class; two or more weeks after vaccination the IgG antibody titers rise. As the titer of IgG rises, the IgM titer falls. IgG antibodies are produced in large amounts and function in the neutralization, precipitation, and fixation of complement. The antibody titer usually peaks in approximately 2 to 6 weeks and then falls gradually.

After a second exposure to the same antigen, a heightened humoral or cell-mediated response (an anamnestic response) is observed. This response occurs sooner than the primary response, usually within 4 to 5 days, and depends on a marked proliferation of antibody-producing cells or T cells.

The response to a vaccine is usually measured by the antibody titer (easier to measure) in the host; however, because cell mediated immune responses are known to be induced by vaccines, the lack of measurable antibody does not imply that the individual is necessarily not protected by the vaccine.

DETERMINANTS OF RESPONSE TO ACTIVE IMMUNIZATION

The complex process of antigen composition and presentation are critical for evoking the desired immune response. The ability of a vaccine to produce this response is determined by several factors which are discussed below:

Genetic characteristics of the host (vaccinated individual): The extensive polymorphism of the MHC in human populations (i.e. variation in the HLA types) contributes to the recognition by different individuals of different parts of a complex protein antigen. To vaccinate a population effectively, a vaccine must contain antigenic molecules that can be recognized and presented by at least one HLA molecule (MHC molecule) in every vaccinated individual. This variability in HLA types is particularly important for vaccines that aim to elicit primarily cell mediated immunity, for example in HIV vaccines. Differences in HLA types among individuals may explain why certain individuals never respond to vaccines such as hepatitis B vaccine.

Age and immune status of the host: Young infants often do not respond to vaccines because the presence of high levels of passively acquired maternal antibody in the first few months of life impairs the initial immune response to some killed vaccines (hepatitis A vaccine) and many live vaccines (measles). In the elderly, the response to antigenic stimulation may be diminished (e.g., influenza, hepatitis B vaccines) because of waning cellular immunity. Similarly, individuals with immune deficiencies (e.g. HIV-1 infection) may be unable to respond to many vaccines.

Live attenuated vs. Killed or subunit vaccines: The type of vaccine may have an effect on immunogenicity. The live attenuated vaccines (e.g., measles, mumps, rubella) multiply in the host until checked by the immune response it is intended to induce; because large amounts of antigen are presented to the immune system, they are generally are believed to confer lifelong protection with one dose in those who respond. In contrast, killed or subunit vaccines (vaccines containing only part of the infecting organism) generally do not induce permanent immunity with one dose, thereby necessitating repeated vaccination and booster shots to develop and maintain high levels of antibody (e.g., diphtheria, tetanus, rabies, typhoid).

Dose of the vaccine is important because presentation of an insufficient amount of antigen may result in an absence of immune response. There is usually a dose response curve relationship between antigen dose and peak response obtained beyond a threshold; however, this response often plateaus.

Route of administration. The routes of administration (e.g., intradermal, subcutaneous, intramuscular, and mucosal) may determine the magnitude and nature of the immune response. For example, mucosal administration (intranasal or oral) stimulates higher levels of local IgA antibodies that may inhibit disease transmission with greater effectiveness than parenteral administration, which induces limited or no mucosal response. The immunogenicity of some vaccines is reduced when not given by the

recommended route, for example, administration of hepatitis B vaccine subcutaneously into the fatty tissue of the buttock was associated with lower seroconversion rates (antibody response) than intramuscular administration into the deltoid.

Adjuvants are added to vaccines to augment the immune response to antigens. They are particularly useful with inactivated products such as diphtheria and tetanus toxoids, acellular pertussis vaccines (DTaP) and hepatitis B vaccine. The mechanism of immune enhancement by adjuvants is not completely understood but may involve mobilization of phagocytes to the site of antigen deposition, and delayed release of antigen.

LICENSED VACCINES RECOMMENDED FOR GENERAL USE (TABLE 1-4)

As discussed above, currently available vaccines are composed of either whole killed organisms, live attenuated organisms fractions of organisms, or toxoids. Please refer to appendices 1-5 for summary of currently recommended vaccinations for infants, children and adults and for review of contraindications to specific vaccine products.

Table 1. Whole Killed Vaccines (see also pages 1, 3 and 5)

Require multiple doses and for the most part can be used in immunocompromised individuals. Adverse reactions to whole killed vaccines are often seen in children.

Vaccine Name	Target Population	Efficacy and Safety Data	Comments
Hepatitis A derived from formalin inactivation of hepatitis A virus	Recommended for individuals traveling to endemic areas and for children in communities with high rates of hepatitis A	Very effective at least in the short term. Two doses given 6-12 months apart appear to be protective for at least 10 years. Longer term protection may require further boosting	
Influenza virus	Recommended for:	Revaccination is recommended	A live attenuated nasal

composed of whole or disrupted (split) influenza viruses	•children 6 through 59 months of age •Persons ≥65y.o. •Nursing Home residents. •Individuals with chronic medical conditions regardless of age (e.g asthma). •Pregnant women in 2nd or 3rd trimester during the influenza season. •Physicians and other health care workers caring for high risk individuals. Refer to updated recommendations on www.cdc.gov	yearly as strains change and antibody levels decline over a 6-9 month period after vaccination. Efficacy of this vaccine is 60-80% in healthy adults. It is less in elderly and immunocompromised individuals; however, the vaccine is still effective in this group at preventing serious illness, hospitalization and death.	influenza vaccine (Flumist) recently received FDA approval for healthy individuals aged 5-49. Not recommended for immunocompromised individuals.
Inactivated polio (IPV) formalin inactivated poliovirus strains	•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. •Children at ages 2m, 4m, 6–18m, 4–6yrs.	Currently the polio vaccine of choice in the US. Contains antigens recognized by 99% of the population. It is more immunogenic than OPV (oral) but must be administered subcutaneously. Administered on the same schedule as OPV (2, 4, 6-18 months) and has an excellent safety safety record.	Vaccination against polio has resulted in the eradication of wild-type polio infection from the Western hemisphere and from Europe.
Pertussis Two preparations in US (see comments)	Usually combined with diphtheria and tetanus vaccines to produce the DTP (now DTaP as the acellular preparation is used) given to infants at 2, 4, 6, and 15-18 months with a booster at school entry age.	Whole cell pertussis vaccines are associated with a higher rate of adverse events after vaccination than are most other vaccines in common use. In a large prospective study more than 60% of vaccinees had local reactions or fever after receiving the vaccine. Febrile convulsions (without sequelae) were noted in 1/1750 vaccinees. Acellular pertussis vaccine causes fewer local and systemic reactions than the whole virus vaccine, it is thus the favored form of vaccination.	1. Whole cell vaccine consists of whole killed *Bordetella pertussis*. 2. More recent *acellular* preparation consists of combinations of purified components of the organism and detoxified pertussis toxin.

Table 2. Subunit vaccines

Immunogenic parts of whole organisms and are used when attenuation of the organism is difficult and whole killed vaccines are either not immunogenic enough or too toxic. Often are attached to protein carriers to enhance their immunogenicity. Cannot cause disease. Generally, adverse events are rare.

Vaccine Name	Target Population	Efficacy and Safety Data	Comments
Hepatitis B purified, inactivated hepatitis B surface antigen particles derived from recombinant DNA technology.	Recommended for all adults with potential blood/ body fluid exposure (medical students and health care workers) and is given to all infants in the United States (usually in combination with a Hib vaccine).	The vaccine is safe, well-tolerated and generally highly effective although a small number of vaccinated individuals never seroconvert.	In some other countries HBV vaccine is still made from HBsAg particles derived from the plasma of chronic carriers of HBV.
Haemophilus b Purified high molecular weight haemophilus b polysaccharide (PRP) which is covalently linked to a carrier protein. The linkage of the polysaccharide to the carrier protein enhances vaccine immunogenicity and allows for its use in young infants (the group most at risk of serious Hib infection). Hib vaccine is	Indicated for young infants who are at greatest risk of serious Hib infection Administered at 2 and 4 mo of age with a boost at 12-15 months if using the PRP-OMC preparation. If using PRP-T or HbOC a third dose at 6 months followed by a boost at 12-15 months is recommended (see comments).	All preparations of the vaccine are quite safe and have resulted in a dramatic decrease in serious Hib infections in vaccinated populations.	There are currently 4 licensed formulations of the vaccine which differ in their carrier protein. PRP-D, which consists of the PRP linked to diphtheria toxoid, is the least immunogenic of the 4 and is not recommended for use in infants. PRP-OMC, which consists of the PRP linked to the outer membrane protein complex derived from N. meningitidis, is the most immunogenic formulation. PRP-T (PRP linked to tetanus toxoid) and HbOC (oligosaccharide linked to mutant diphtheria toxin protein) are as effective as PRP-OMC but require an extra dose of vaccine at 6 months.
Meningococccal polysaccharide (MPSV4) purified meningococcal polysaccharides of groups A, C, Y, and W135.	Recommended for high risk groups including those with complement deficiency, asplenia, and travelers to countries with endemic disease. It is recommended by some for college students, esp. freshmen living in dormitory accommodation (esp MCV4 vaccine).	A single IM dose induces protective antibody levels in over 90% of vaccinees over the age of 2. Adverse events are rare. Duration of protection is short (1-3 yrs in children < 5 years of age and 3-5 yrs in adolescents and adults).	Recently approved **quadrivalent meningococcal conjugate vaccine** (MCV4) contains the same antigens as MPSV4; may provide more durable protection, reduce nasopharyngeal carriage of N.meningitides, thereby reducing tranasmission. There is no vaccine against group B meningococcus infection -- an important cause of meningitis.
Pneumococcal polysaccharide	The unconjugated polysaccharide vaccine is	Unconjugated polysaccharide vaccine is	The unconjugated polysaccharidevaccine

and ***Conjugated pneumococcal polysaccharide***	recommended for people over the age of 65 and in adults and children over the age of 2 with high risk for pneumococcal disease. The conjugated vaccine is recommended for all children aged 2-23 months and is generally given at 2,4,6, and 12-15 months.	not effective in children younger than 2 years of age. The polysaccharide vaccine is effective against pneumococcal bacteremia but not against nonbacteremic pneumococcal pneumonia in adults.	consists of 23 different serotypes of pneumococcal capsular polysaccharide covering the strains responsible for 85% of all bacteremic pneumococcal disease in the US. The conjugated pneumococcal polysaccharide vaccine consists of polysaccharide from 7 serotypes of pneumococcus linked to protein carriers.

Table 3. Live Attenuated Vaccines (see also pages 1, 3 and 5)

Live organisms modified to make them considerably less virulent than wild type pathogens. Generally the most effective vaccines available; however, because they do contain live organisms their use may be problematic in certain populations (e.g. pregnant women, people with AIDS, transplant recipients).

Vaccine Name	Target Population	Efficacy and Safety Data	Comments
Measles Formulated with mumps and rubella as MMR	Children >15 mo old with a second dose at school entry. International travelers and individuals born after 1957 without documented evidence of immunity.	Efficacy of over 95% when administered in a single dose to children over the age of 15 mo; measles can continue to circulate in the 2-5% of the population who do not respond, thus 2 doses of vaccine are recommended. Contraindications: Pregnancy, cancer, leukemia, lymphoma, immunosuppressive drugs. HIV positivity is NOT a contraindication except if CD4<200 cells/μL	The introduction of the measles vaccine in the US has resulted in 99.75% decrease in measles cases. Vaccination rates may be quite low in developing countries. Travelers should be adequately vaccinated (recent outbreak of measles in Queens in US born infants who had traveled to India before being vaccinated illustrates).
Mumps component of the MMR vaccine	Recommended for all children over the age of one who do not have specific contraindications (immunocompromise).	Protection is life-long after a single dose although most people receive two doses as part of the MMR vaccine. The mumps vaccine has led to a 98.3% decline in mumps cases in the US since 1968. Contraindications: see the measles section	Most persons born before 1957 are likely to have been infected naturally by mumps virus and can generally be considered immune; otherwise, consider susceptible unless documented receipt of live mumps vaccine on or after the first birthday, laboratory evidence of mumps immunity, or physician-diagnosed mumps disease.
Rubella component of the MMR vaccine	Aims to prevent the congenital rubella syndrome by ensuring that all women of childbearing age are protected against infection. Most persons born before 1957 can be considered immune.	A single dose confers lifelong protection in 95% of vaccinees. Because the live attenuated rubella virus can cross the placenta it is contraindicated in all pregnant women and within 3 months of a planned conception.	Data on 226 women who received rubella vaccine during pregnancy or within three months of conception showed no evidence of congenital rubella syndrome.
Oral polio	Administered in three doses to children at 2, 4, and 6 months	It is highly effective and easy to administer;	Oral polio vaccine is still the vaccine of choice of the

	of age.	however, because live polio virus is secreted from the intestines of vaccinated individuals for a short time after vaccination and because vaccine polio virus can cause paralytic disease this form is no longer used in US where polio has been eradicated.	WHO's effort to eradicate polio from the world.
Varicella zoster	Administered at 12-15 months and second dose 4-6 yrs. Also recommended for adults who may be exposed to VZV and who are not immune (health care workers, daycare attendants, etc).	It is > 95% effective in protecting against severe disease and 70% to 90% effective against mild to moderate illness for children 1 to 2 y.o. for at least 7 to 9 years after vaccination. Contraindicated in pregnant women because of the theoretical risk of birth defects. Upon completion/ termination of pregnancy, women witout evidence of varicella immunity should be vaccinated.	Can cause chickenpox-like symptoms (5-10%) and thus it is contraindicated in individuals with severe immunodeficiency. In immunocompetent host shown to go latent in dorsal ganglion cells with subsequent reactivation zoster; however, this risk of zoster in vaccinated individuals is less than that in naturally infected ones.

Table 4. Toxoids

Modified bacterial toxins capable of stimulating the formation of antibodies (antitoxins). Most do not produce life-long immunity and require booster doses.

Name	Target Population	Efficacy and Safety Data	Comments
Diphtheria toxoid purified preparation of inactivated diphtheria toxin	Recommended for children and adults (the latter if no documentation of primary series)	Highly effective in inducing antibodies that will prevent disease; little effect on acquisition or carriage of the actual organism, *Corynebacterium diphtheriae*, that makes the toxin. Frequent local reactions esp. with boosting. After the initial 3 doses of toxoid, booster doses need to be given every 10 years to ensure continued protection against diphtheria.	A high dose of toxoid is given in combination with pertussis vaccine and tetanus toxoid to young children (DTaP) and in a lower dose in combination with tetanus toxoid (Td) to older children and adults. The use of the diphtheria toxoid has resulted in a 99.99% decrease in cases of diphtheria in the United States from 1921 to 1992.
Tetanus toxoid purified preparation of inactivated tetanus toxin precipitated with alum	Recommended for young children as part of the DTaP vaccine and to older children and adults as the Td vaccine.	One of the most effective immunizing agents. Three doses induces protective antibodies in over 95% of recipients. After the initial series, boosters recommended every 10 years (given as Td to ensure both tetanus and diphtheria protection is given).	The most common side effects are fever and local reactions. As the local reactions can be quite severe, boosters are recommended only every 10 years unless a particularly tetanus-prone wound has occurred in which case a booster should be given if it is more than 5 years since the last booster. Tetanus cases have decreased over 97% since the introduction of tetanus toxoid.

OTHER VACCINES

A number of other vaccines are available and recommended for use under certain special circumstances. It is worth knowing about these vaccines especially if you work with travelers and immigrants, plan to travel yourself, or have an interest in potential agents of bioterrorism.

Anthrax vaccine is a cell-free filtrate prepared from microaerophilic cultures of an avirulent strain of *Bacillus anthracis*. The vaccine is indicated only for those at high risk of anthrax infection (this definition may change over time but currently consists of people coming into contact with animal hides from endemic areas, laboratory personnel working with anthrax, and military personnel). Its efficacy is not known but it does induce antibodies in over 90% of individuals who receive the primary course of 6 subcutaneous injections. Annual boosting is required to sustain antibody levels. Mild local reactions are quite common however system reactions are very rare. It is not commercially available in the United States, all anthrax vaccine lots are owned by the US Department of Defense.

BCG vaccine contains living Calmette-Guerin bacillus, an attenuated strain of *Mycobacterium bovis*. Although widely used throughout the world (especially in areas where TB is very prevalent), it is not recommended for general use in the United States because it can affect the PPD test and is of controversial efficacy. Most individuals who received the BCG vaccine will have a PPD reaction of 3 to 19 mm in size at two to three months following vaccination; this reaction wanes with time, and generally does not persist more than ten years after vaccination. BCG vaccine appears to be most effective in preventing complications of disseminated TB in young children and it is therefore recommended primarily for infants and young children at high risk of exposure to TB in the US. Reviews of published literature reveal that the vaccine provides an estimated 75-86% protective effect against milliary and meningeal tuberculosis among vaccinated children; and may be 50% protective against tuberculosis. The duration of immunity following BCG vaccination has not been established.
Because BCG vaccine contains live organisms, it can disseminate in immunocompromised individuals and therefore it should not be used in this population. BCG produces a vigorous local immune response and has been instilled into the bladder to produce an immune response in people with bladder cancer.

Rabies vaccine is an inactivated virus vaccine prepared in human or fetal rhesus lung diploid cell culture. The human diploid cell preparation (HDCV) can be used either intramuscularly or intradermally, while the rhesus lung preparation (RVA) can only be used IM. Rabies vaccine is used in people likely to be exposed to rabies (veterinarians, certain travelers, etc) or in people who have been exposed to potentially rabid animals. Preexposure prophylaxis is given as three doses either IM or intradermally at 0, 7, 21-28 days with follow-up boosting every 2 years or when a potential exposure has occurred. Postexposure prophylaxis is given as 5 IM shots on days 0, 3, 7, 14, and 28 along with rabies immune globulin on day 0. Rabies immune globulin is not needed in persons who have received pre-exposure prophylaxis. Local reactions are common (30-74% of vaccinees) and systemic complaints are also frequently seen with rabies vaccine but no contraindication exists for its administration to at risk or exposed individuals (remember the alternative is certain death).

Yellow fever vaccine is composed of a live attenuated virus.. It is highly effective and very well tolerated and excellent immunity is achieved after a single dose of vaccine. It is recommended for travelers to areas of endemnicity and is required by some countries for entry. Because the vaccine is a live attenuated virus, its use is contraindicated in immunocompromised individuals; although pregnancy is not an absolute contraindication for its use.

Smallpox vaccine has resulted in the eradication of naturally occurring smallpox infection on earth. Smallpox vaccines are derivatives of cowpox (vaccinia) virus and are the derivatives of one of three strains: Elstree (Lister, France) strain, EM63 (Moscow) strain, and the New York City Board of Health strain. Smallpox vaccines are produced from a seed virus propagated on the skin of calves and then processed to eliminate bacterial contamination. Vaccinations are given over the deltoid region of the upper arm using a bifurcated needle dipped in the vaccine. The needle is held perpendicular to the skin and pressed in and out 5 times in unvaccinated individuals, 15 times in previously vaccinated individuals. A successful vaccination is defined as a pustular lesion or an area of definite induration or congestion surrounding a central lesion 6-8 days after vaccination. Although smallpox vaccine is highly effective, it does have a number of serious adverse consequences which preclude its general use at the current time. The most frequent complications include:

- *vaccinia necrosum*: an often lethal complication of inadvertent vaccination of an immunocompromised host which consists of the insidious progression of an initially normal appearing vaccination with the development of metastatic lesions throughout the body
- *eczema vaccinatum*: the consequence of local spread and/or dissemination of vaccinia virus infection in individuals with atopic dermatitis
- *generalized vaccinia*: a nonspecific term used to describe a vesicular rash that develops after vaccination. Unlike actual generalized infection such as is seen in vaccinia necrosum or eczema vaccinatum, these reactions can be seen in normal hosts, are generally not accompanied by systemic symptoms, and do not yield virus on culture of the lesions
- *erythematous urticarial eruptions*: erythematous rashes observed in otherwise healthy individuals 7-12 days after vaccination.
- *Postinfectious encephalitis* is one of the most serious complications of vaccination in normal hosts with a mortality of 10-30%. It occurs in 1/100,000 primary vaccinees.
- *Myocarditis*: since the reactivation of smallpox vaccination in military personnel and selected civilian populations, myocarditis, pericarditis and myopericarditis have been reported. Persons with preexisting heart disease are currently advised not to be vaccinated.

Other Resources and Further Reading

1. Vaccine Administration Guidelines. This document can be found on the website listed below; it contains vaccine schedules and pictures of where to administer vaccines. **http://www.cdc.gov/vaccines/recs/vac-admin/default.htm#guide**

2. Another resource that includes updated schedules as well as information on how to administer vaccines (where to administer, which ones can be given together), adverse events, and information on individual vaccines.
   http://www.cdc.gov/nip/ACIP/default.htm

3. The CDC's web pageincludes information on vaccination for travelers. **www.cdc.gov**

4. The WHO lists travel advice and world-wide vaccination effort updates.
   http://www.who.int/en/

5. Gardner, P. Prevention of Meningococcal Disease. New England J Medicine. 2006; 355:1466-73.

6. Wright, P. Vaccine Preparedness — Are We Ready for the Next Influenza Pandemic? New England J Medicine. 2008; 358: 2540-43

7. Ada, G. Vaccines and Vaccination. New England J Medicine. 2001; 345: 1042-53.

Appendices 1-5

1. Immunization schedule for ages 0 to 6 years. Updated 2008
2. Immunization Schedule for ages 7-18 years. Updated 2008
3. Adult Immunization Schedule. Updated 2008
4. Summary of Recommendations for Adult Immunizations. Updated 2008
5. Summary of Recommendations for Childhood and Adolescent Immunizations. Updated 2008