Appendix: Vaccines, Immune Globulins, & Other Complex Biologic Products

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Vaccines and related biologic products constitute an important group of agents that bridge the disciplines of microbiology, infectious diseases, immunology, and immunopharmacology. A list of the most important preparations is provided here. The reader who requires more complete information is referred to the sources listed at the end of this appendix.

ACTIVE IMMUNIZATION

Active immunization consists of the administration of antigen to the host to induce formation of antibodies and cell-mediated immunity. Immunization is practiced to induce protection against many infectious agents and may utilize either inactivated (killed) materials or live attenuated agents (Table A–1). Desirable features of the ideal immunogen include complete prevention of disease, prevention of the carrier state, production of prolonged immunity with a minimum of immunizations, absence of toxicity, and suitability for mass immunization (eg, cheap and easy to administer). Active immunization is generally preferable to passive immunization—in most cases because higher antibody levels are sustained for longer periods of time, requiring less frequent immunization, and in some cases because of the development of concurrent cell-mediated immunity. However, active immunization requires time to develop and is therefore generally inactive at the time of a specific exposure (eg, for parenteral exposure to hepatitis B, concurrent hepatitis B IgG [passive antibodies] and active immunization are given to prevent illness).

Current recommendations for routine active immunization of children are given in Table A–2.

PASSIVE IMMUNIZATION

Passive immunization consists of transfer of immunity to a host using preformed immunologic products. From a practical standpoint, only immunoglobulins have been used for passive immunization, because passive administration of cellular components of the immune system has been technically difficult and associated with graft-versus-host reactions. Products of the cellular immune system (eg, interferons) have also been used in the therapy of a wide variety of hematologic and infectious diseases (see Chapter 55).

Passive immunization with antibodies may be accomplished with either animal or human immunoglobulins in varying degrees of purity. These may contain relatively high titers of antibodies directed against a specific antigen or, as is true for pooled immune globulin, may simply contain antibodies found in most of the population. Passive immunization is useful for (1) individuals unable to form antibodies (eg, congenital agammaglobulinemia); (2) prevention of disease when time does not permit active immunization (eg, postexposure); (3) for treatment of certain diseases normally prevented by immunization (eg, tetanus); and (4) for treatment of conditions for which active immunization is unavailable or impractical (eg, snakebite).

Complications from administration of *human* immunoglobulins are rare. The injections may be moderately painful and rarely a sterile abscess may occur at the injection site. Transient hypotension and pruritus occasionally occur with the administration of intravenous immune globulin (IVIG) products, but generally are mild. Individuals with certain immunoglobulin deficiency states (IgA deficiency, etc) may occasionally develop hypersensitivity reactions to immune globulin that may limit therapy.

TABLE A–1 Materials commonly used for active immunization in the United States.[1]

Vaccine	Type of Agent	Route of Administration	Primary Immunization	Booster[2]	Indications
Diphtheria tetanus acellular pertussis (DTaP)	Toxoids and inactivated bacterial components	Intramuscular	See Table A–2	None	For all children
Haemophilus influenzae type b conjugate (Hib)[3]	Bacterial polysaccharide conjugated to protein	Intramuscular	One dose (see Table A–2 for childhood schedule)	Not recommended	1. For all children 2. Asplenia and other at-risk conditions
Hepatitis A	Inactivated virus	Intramuscular	One dose (see Table A–2 for childhood schedule) (administer at least 2–4 weeks before travel to endemic areas)	At 6–12 months for long-term immunity	1. Travelers to hepatitis A endemic areas 2. Homosexual and bisexual men 3. Injection drug users 4. Chronic liver disease or clotting factor disorders 5. Persons with occupational risk for infection 6. Persons living in, or relocating to, endemic areas 7. Household and sexual contacts of individuals with acute hepatitis A (with additional gamma globulin in select patients) 8. For all children
Hepatitis B	Inactive viral antigen, recombinant	Intramuscular (subcutaneous injection is acceptable in individuals with bleeding disorders)	Three doses at 0, 1, and 6 months (see Table A–2 for childhood schedule)	Not routinely recommended	1. For all infants 2. Preadolescents, adolescents, and young adults 3. Persons with occupational, lifestyle, or environmental risk 4. Hemophiliacs 5. Persons with end-stage renal disease, HIV, or chronic liver disease 6. Postexposure prophylaxis 7. Household and sexual contacts of individuals with acute and chronic hepatitis B
Human papillomavirus (HPV)[4]	Virus-like particles of the major capsid protein	Intramuscular	Three doses at 0, 2, and 6 months (HPV4) or 0, 1, and 6 months (HPV2)[4]	None	HPV2 or HPV4 for females between 9 and 26 years of age; HPV4 for males aged 9–26 years
Influenza, inactivated	Inactivated virus or viral components	Intramuscular	One dose (Children < 9 years who are receiving influenza vaccine for the first time should receive two doses administered at least 1 month apart.)	Yearly with current vaccine	1. Adults > 18 years 2. Persons with high-risk conditions (eg, asthma) 3. Health care workers and others in contact with high-risk groups 4. Residents of nursing homes and other residential chronic care facilities 5. All children aged 6 months to 18 years 6. Women who will be pregnant during the influenza season

Influenza, live attenuated	Live virus	Intranasal	Split dose in each nostril. Children age 5–8 who are receiving influenza vaccine for the first time should receive two doses administered 6–10 weeks apart	Yearly with current vaccine	Healthy persons aged 19–49 years who desire protection against influenza. May be substituted for inactivated vaccine in healthy children 2–18 years
Measles-mumps-rubella (MMR)	Live virus	Subcutaneous	See Table A–2	None	1. For all children 2. Adults born after 1956
Meningococcal conjugate vaccine	Bacterial polysaccharides conjugated to diphtheria toxoid	Intramuscular	One dose	Unknown	1. All adolescents 2. Preferred over polysaccharide vaccine in persons aged 11–55 years
Meningococcal polysaccharide vaccine	Bacterial polysaccharides of serotypes A/C/Y/W-135	Subcutaneous	One dose	Every 5 years if there is continuing high risk of exposure	1. Military recruits 2. Travelers to areas with hyperendemic or epidemic meningococcal disease 3. Individuals with asplenia, complement deficiency, or properdin deficiency 4. Control of outbreaks in closed or semiclosed populations 5. College freshmen who live in dormitories 6. Microbiologists who are routinely exposed to isolates of *Neisseria meningitidis*
Pneumococcal conjugate vaccine	Bacterial polysaccharides conjugated to protein	Intramuscular or subcutaneous	See Table A–2	None	For all children
Pneumococcal polysaccharide vaccine	Bacterial polysaccharides of 23 serotypes	Intramuscular or subcutaneous	One dose	Repeat after 5 years in patients at high risk	1. Adults ≥ 65 years 2. Persons at increased risk for pneumococcal disease or its complications
Poliovirus vaccine, inactivated (IPV)	Inactivated viruses of all three serotypes	Subcutaneous	See Table A–2 for childhood schedule. Adults: Two doses 4–8 weeks apart, and a third dose 6–12 months after the second	One-time booster dose for adults at increased risk of exposure	1. For all children 2. Previously unvaccinated adults at increased risk for occupational or travel exposure to polioviruses
Rabies	Inactivated virus	Intramuscular	**Preexposure:** Three doses at days 0, 7, and 21 or 28 **Postexposure:** Four doses at days 0, 3, 7, and 14	Serologic testing every 6 months to 2 years in persons at high risk	1. **Preexposure** prophylaxis in persons at risk for contact with rabies virus 2. **Postexposure** prophylaxis (administer with rabies immune globulin)
Rotavirus	Live virus	Oral	See Table A–2	None	For all infants. The series of 3 doses should be initiated by age 14 weeks and completed by age 32 weeks
				None	
Tetanus-diphtheria (Td or DT)[5]	Toxoids	Intramuscular	Two doses 4–8 weeks apart, and a third dose 6–12 months after the second	Every 10 years or a single booster at age 50	1. All adults 2. Postexposure prophylaxis if > 5 years has passed since last dose

(*continued*)

TABLE A–1 Materials commonly used for active immunization in the United States.[1] (Continued)

Vaccine	Type of Agent	Route of Administration	Primary Immunization	Booster[2]	Indications
Tetanus, diphtheria, pertussis (Tdap)	Toxoids and inactivated bacterial components	Intramuscular	Substitute 1 dose of Tdap for Td in patients 19–64 years of age	None	All adults < 65 years
Typhoid, Ty21a oral	Live bacteria	Oral	Four doses administered every other day	Four doses every 5 years	Risk of exposure to typhoid fever
Typhoid, Vi capsular polysaccharide	Bacterial polysaccharide	Intramuscular	One dose	Every 2 years	Risk of exposure to typhoid fever
Varicella	Live virus	Subcutaneous	Two doses 4–8 weeks apart in persons past their 13th birthday (see Table A–2 for childhood schedule)	Unknown	1. For all children 2. Persons past their 13th birthday without a history of varicella infection or immunization 3. Postexposure prophylaxis in susceptible persons
Yellow fever	Live virus	Subcutaneous	One dose 10 years to 10 days before travel	Every 10 years	1. Laboratory personnel who may be exposed to yellow fever virus 2. Travelers to areas where yellow fever occurs
Zoster	Live virus	Subcutaneous	One dose	None	All adults ≥ 60 years of age

[1]Dosages for the specific product, including variations for age, are best obtained from the manufacturer's package insert.

[2]One dose unless otherwise indicated.

[3]Three Hib conjugate vaccines are available for use: (1) oligosaccharide conjugate Hib vaccine (HbOC), (2) polyribosylribitol phosphate-tetanus toxoid conjugate (PRP-T), and (3) *Haemophilus influenzae* type b conjugate vaccine (meningococcal protein conjugate) (PRP-OMP).

[4]Two HPV vaccines are available for use: (1) quadrivalent vaccine (HPV4) for the prevention of cervical, vaginal, and vulvar cancers (in females) and genital warts (in males and females), and (2) bivalent vaccine (HPV2) for the prevention of cervical cancers in females.

[5]Td is tetanus and diphtheria toxoids for use in persons ≥ 7 years of age (contains less diphtheria toxoid than DPT and DT). DT is tetanus and diphtheria toxoids for use in persons < 7 years of age (contains the same amount of diphtheria toxoid as DPT).

TABLE A–2 Recommended routine childhood immunization schedule.

Age	Immunization	Comments
Birth to 2 months	Hepatitis B vaccine (HBV)	**Infants born to seronegative mothers:** Administration should begin at birth, with the second dose administered at least 4 weeks after the first dose. **Infants born to seropositive mothers:** Should receive the first dose within 12 hours after birth (with hepatitis B immune globulin), the second dose at 1–2 months of age, and the third dose at 6–18 months of age.
2 months	Diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP), inactivated poliovirus vaccine (IPV), *Haemophilus influenzae* type b conjugate vaccine (Hib),[1] pneumococcal conjugate vaccine (PCV), rotavirus vaccine (RV)	
1–2 months	HBV	The second dose should be given at least 4 weeks after the first dose.
4 months	DTaP, Hib,[1] IPV, PCV, RV	
6 months	DTaP, Hib,[1] PCV, RV	
6–18 months	HBV, IPV, influenza	The third dose of HBV should be given at least 16 weeks after the first dose and at least 8 weeks after the second dose, but not before age 6 months. Influenza vaccine should be administered annually to children aged 6 months to 18 years.
12–15 months	Measles-mumps-rubella vaccine (MMR), Hib,[1] PCV, varicella vaccine	The second dose of varicella vaccine should be administered at age 4–6 years
12–18 months	DTaP at 15–18 months	DTaP may be given as early as age 12 months.
12–23 months	Hepatitis A vaccine	Two doses ≥ 6 months apart.
4–6 years	DTaP IPV, MMR, varicella vaccine	The second dose of MMR should be routinely administered at age 4–6 years but may be given during any visit if at least 4 weeks have elapsed since administration of the first dose. The second dose should be given no later than age 11–12 years.
11–12 years	Tetanus, diphtheria, pertussis (Tdap) vaccine, human papillomavirus vaccine (HPV),[2] meningococcal conjugate vaccine	Three doses of HPV should be administered to females at 0, 1–2, and 6 months. HPV4 may be administered to males aged 9–18 years to reduce the likelihood of developing genital warts.

[1]Three Hib conjugate vaccines are available for use: (1) oligosaccharide conjugate Hib vaccine (HbOC), (2) polyribosylribitol phosphate-tetanus toxoid conjugate (PRP-T), and (3) *Haemophilus influenzae* type b conjugate vaccine (meningococcal protein conjugate) (PRP-OMP). Children immunized with PRP-OMP at 2 and 4 months of age do not require a dose at 6 months of age.

[2]Two HPV vaccines are available for use: (1) quadrivalent vaccine (HPV4) for the prevention of cervical, vaginal, and vulvar cancers (in females) and genital warts (in males and females), and (2) bivalent vaccine (HPV2) for the prevention of cervical cancers in females.

Adapted from MMWR Morb Mortal Wkly Rep 2010;58:(51&52).

Conventional immune globulin contains aggregates of IgG; it will cause severe reactions if given intravenously. However, if the passively administered antibodies are derived from *animal* sera, hypersensitivity reactions ranging from anaphylaxis to serum sickness may occur. Highly purified immunoglobulins, especially from rodents or lagomorphs, are the least likely to cause reactions. To avoid anaphylactic reactions, tests for hypersensitivity to the animal serum must be performed. If an alternative preparation is not available and administration of the specific antibody is deemed essential, desensitization can be carried out.

Antibodies derived from human serum not only avoid the risk of hypersensitivity reactions but also have a much longer half-life in humans (about 23 days for IgG antibodies) than those from animal sources (5–7 days or less). Consequently, much smaller doses of human antibody can be administered to provide therapeutic concentrations for several weeks. These advantages point to the desirability of using human antibodies for passive protection whenever possible. Materials available for passive immunization are summarized in Table A–3.

LEGAL LIABILITY FOR UNTOWARD REACTIONS

It is the physician's responsibility to inform the patient of the risk of immunization and to use vaccines and antisera in an appropriate manner. This may require skin testing to assess the risk of an untoward reaction. Some of the risks previously described are,

TABLE A–3 Materials available for passive immunization.[1]

Indication	Product	Dosage	Comments
Black widow spider bite	Aontivenin (*Latrodectus mactans*), equine	One vial (6000 units) IV or IM.	For persons with hypertensive cardiovascular disease or age < 16 or > 60 years.
Bone marrow transplantation	Immune globulin (intravenous [IV])[2]	500 mg/kg IV on days 7 and 2 prior to transplantation and then once weekly through day 90 after transplantation.	Prophylaxis to decrease the risk of infection, interstitial pneumonia, and acute graft-versus-host disease in adults undergoing bone marrow transplantation.
Botulism	Botulism antitoxin, equine	Consult the CDC.[3]	Treatment and prophylaxis of botulism. Available from the CDC.[3] Incidence of serum reactions is 10–20%.
	Botulism immune globulin (IV)	50 mg/kg IV.	For the treatment of patients < 1 year of age with infant botulism caused by toxin type A or B.
Chronic lymphocytic leukemia (CLL)	Immune globulin (IV)[2]	400 mg/kg IV every 3–4 weeks. Dosage should be adjusted upward if bacterial infections occur.	CLL patients with hypogammaglobulinemia and a history of at least one serious bacterial infection.
Cytomegalovirus (CMV)	Cytomegalovirus immune globulin (IV)	Consult the manufacturer's dosing recommendations.	Prophylaxis of CMV infection in bone marrow, kidney, liver, lung, pancreas, and heart transplant recipients.
Diphtheria	Diphtheria antitoxin, equine	20,000–120,000 units IV or IM depending on the severity and duration of illness.	Early treatment of respiratory diphtheria. Available from the CDC.[3] Anaphylactic reactions in ≥ 7% of adults and serum reactions in ≥ 5–10% of adults.
Hepatitis A	Immune globulin (intramuscular [IM])	**Preexposure prophylaxis:** 0.02 mL/kg IM for anticipated risk of ≤ 3 months, 0.06 mL/kg for anticipated risk of > 3 months, repeated every 4–6 months for continued exposure. **Postexposure:** 0.02 mL/kg IM as soon as possible after exposure up to 2 weeks.	Preexposure and postexposure hepatitis A prophylaxis. The availability of hepatitis A vaccine has greatly reduced the need for preexposure prophylaxis. Patients > 40 years should receive hepatitis A vaccine in addition to immune globulin for postexposure prophylaxis
Hepatitis B	Hepatitis B immune globulin (HBIG)	0.06 mL/kg IM as soon as possible after exposure up to 1 week for percutaneous exposure or 2 weeks for sexual exposure. 0.5 mL IM within 12 hours after birth for perinatal exposure.	Postexposure prophylaxis in nonimmune persons following percutaneous, mucosal, sexual, or perinatal exposure. Hepatitis B vaccine should also be administered.
HIV-infected children	Immune globulin (IV)[2]	400 mg/kg IV every 28 days.	HIV-infected children with recurrent serious bacterial infections or hypogammaglobulinemia.
Idiopathic thrombocytopenic purpura (ITP)	Immune globulin (IV)[2]	Consult the manufacturer's dosing recommendations for the specific product being used.	Response in children with ITP is greater than in adults. Corticosteroids are the treatment of choice in adults, except for severe pregnancy-associated ITP.
Kawasaki disease	Immune globulin (IV)[2]	400 mg/kg IV daily for 4 consecutive days within 4 days after the onset of illness. A single dose of 2 g/kg IV over 10 hours is also effective.	Effective in the prevention of coronary aneurysms. For use in patients who meet strict criteria for Kawasaki disease.
Measles	Immune globulin (IM)	**Normal hosts:** 0.25 mL/kg IM. **Immunocompromised hosts:** 0.5 mL/kg IM (maximum 15 mL for all patients).	Postexposure prophylaxis (within 6 days after exposure) in nonimmune contacts of acute cases.
Primary immunodeficiency disorders	Immune globulin (IV)[2]	Consult the manufacturer's dosing recommendations for the specific product being used.	Primary immunodeficiency disorders include specific antibody deficiencies (eg, X-linked agammaglobulinemia) and combined deficiencies (eg, severe combined immunodeficiencies).

(*continued*)

TABLE A–3 Materials available for passive immunization.[1] (Continued)

Indication	Product	Dosage	Comments
Rabies	Rabies immune globulin	20 IU/kg. The full dose should be infiltrated around the wound and any remaining volume should be given IM at an anatomic site distant from vaccine administration.	Postexposure rabies prophylaxis in persons not previously immunized with rabies vaccine. Must be combined with rabies vaccine.
Respiratory syncytial virus (RSV)	Palivizumab	15 mg/kg IM once prior to the beginning of the RSV season and once monthly until the end of the season.	For use in infants and children < 24 months with chronic lung disease or a history of premature birth (≤ 35 weeks' gestation).
Rubella	Immune globulin (IM)	0.55 mL/kg IM.	Nonimmune pregnant women exposed to rubella who will not consider therapeutic abortion. Administration does not prevent rubella in the fetus of an exposed mother.
Snake bite (coral snake)	Antivenom (*Micrurus fulvius*), equine	At least 3–5 vials (30–50 mL) IV initially within 4 hours after the bite. Additional doses may be required.	Neutralizes venom of eastern coral snake and Texas coral snake. Serum sickness occurs in almost all patients who receive > 7 vials.
Snake bite (pit vipers)	Antivenom (Crotalidae) polyvalent immune Fab, ovine	An initial dose of 4–6 vials should be infused intravenously over 1 hour. The dose should be repeated if initial control is not achieved. After initial control, 2 vials should be given every 6 hours for up to 3 doses.	For the management of minimal to moderate North American crotalid envenomation.
Tetanus	Tetanus immune globulin	**Postexposure prophylaxis:** 250 units IM. For severe wounds or when there has been a delay in administration, 500 units is recommended. **Treatment:** 3000–6000 units IM.	Treatment of tetanus and postexposure prophylaxis of nonclean, nonminor wounds in inadequately immunized persons (less than two doses of tetanus toxoid or less than three doses if wound is > 24 hours old).
Vaccinia	Vaccinia immune globulin	Consult the CDC.[3]	Treatment of severe reactions to vaccinia vaccination, including eczema vaccinatum, vaccinia necrosum, and ocular vaccinia. Available from the CDC.[3]
Varicella	Varicella-zoster immune globulin	**Weight (kg) / Dose (units)** ≤ 10 — 125 IM 10.1–20 — 250 IM 20.1–30 — 375 IM 30.1–40 — 500 IM ≥ 40 — 625 IM	**Postexposure prophylaxis** (preferably within 48 hours but no later than within 96 hours after exposure) in susceptible immunocompromised hosts, selected pregnant women, and perinatally exposed newborns.

[1]Passive immunotherapy or immunoprophylaxis should always be administered as soon as possible after exposure. Prior to the administration of animal sera, patients should be questioned and tested for hypersensitivity.

[2]See the following references for an analysis of additional uses of intravenously administered immune globulin: Ratko TA et al: Recommendations for off-label use of intravenously administered immunoglobulin preparations. JAMA 1995;273:1865; and Feasby T et al: Guidelines on the use of intravenous immune globulin for neurologic conditions. Transfus Med Rev 2007;21(2 Suppl 1)S57.

[3]Centers for Disease Control and Prevention, 404-639-3670 during weekday business hours; 770-488-7100 during nights, weekends, and holidays (emergency requests only).

however, currently unavoidable; on balance, the patient and society are clearly better off accepting the risks for routinely administered immunogens (eg, influenza and tetanus vaccines).

Manufacturers should be held legally accountable for failure to adhere to existing standards for production of biologicals. However, in the present litigious atmosphere of the USA, the filing of large liability claims by the statistically inevitable victims of good public health practice has caused many manufacturers to abandon efforts to develop and produce low-profit but medically valuable therapeutic agents such as vaccines. Since the use and sale of these products are subject to careful review and approval by government bodies such as the Surgeon General's Advisory Committee on Immunization Practices and the Food and Drug Administration, "strict product liability" (liability without fault) may be an inappropriate legal standard to apply when rare reactions to biologicals, produced and administered according to government guidelines, are involved.

RECOMMENDED IMMUNIZATION OF ADULTS FOR TRAVEL

Every adult, whether traveling or not, should be immunized with tetanus toxoid and should also be fully immunized against poliomyelitis, measles (for those born after 1956), and diphtheria. In addition, every traveler must fulfill the immunization requirements of the health authorities of the countries to be visited. These are listed in *Health Information for International Travel*, available from the Superintendent of Documents, United States Government Printing Office, Washington, DC 20402. A useful website is http://wwwnc.cdc.gov/travel/page/vaccinations.aspx. *The Medical Letter on Drugs and Therapeutics* also offers periodically updated recommendations for international travelers (see *Treatment Guidelines from The Medical Letter,* 2006;4:25). Immunizations received in preparation for travel should be recorded on the International Certificate of Immunization. ***Note:*** Smallpox vaccination is not recommended or required for travel in any country.

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