

CHAPTER 9 Principles of Immunization

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KEYPOINTS

- Both live attenuated and killed vaccines are in current use. Each category has advantages in terms of potential for induction of long-term memory cells, adverse effects, duration of response, and amount of antigen needed
- Intramuscular vaccinations are used for adjuvant-containing, potentially irritating antigens, subcutaneous injection is preferred for live viral vaccines, and intradermal injection can reduce the amount of antigen needed
- The oral route of administration is used for certain vaccines where the stimulation of intestinal IgA and other mucosal immune mechanisms defend against the pathogenesis of infection (e.g. oral polio vaccine, oral typhoid vaccine, oral cholera vaccine)
- Live and inactivated vaccines can be safely and effectively (in terms of seroconversion rates) administered at the same time. Vaccines can be administered at any time before or after a different vaccine with the exception of some live vaccines, if not given simultaneously, should be separated by at least 4 weeks
- Strict guidelines for body site, route of administration, and length of needle are in place for each vaccine and should be adhered to regardless of desire to maximize convenience or patient comfort. Separate recommendations are in place for children

INTRODUCTION

Recent decades have provided the indisputable insight that the control of major infectious diseases is less effective by therapeutic than preventive means of intervention, in particular by well targeted use of vaccines. The global eradication of smallpox in 1977 serves as the primary example for effective disease control through immunizations. Application of modern biotechnological tools has resulted in an array of vaccine candidates arising from various sources, creating the promise of effective prevention (and treatment) of many more diseases that are associated with high mortality and morbidity.

IMMUNOLOGY OF VACCINATION

Active immunization

Generally, active immunization represents a harmless, yet highly effective active interaction between the host's immune system and specific pathogens. The main requirement of a successful vaccine is the induction of a sufficiently high titer of protective antibody including immunological memory, both memory T- and memory B-cells (seroprotection), enabling the organism to respond to a

recurring confrontation with the same pathogen in an effective manner by enhanced and accelerated recruitment of protective antibodies (Table 9.1).

Three main categories of vaccines can be defined:

- Live vaccines
- Killed vaccines
- Genetically engineered vaccines (DNA-, RNA-vaccines, transgenic plants).

Active immunization involves administration of either killed (inactivated) or live (attenuated) whole pathogens, parts of inactivated microorganisms, or modified pathogen's product (e.g., tetanus toxin) by either oral or parenteral route. The induction of antibodies of antitoxin, anti-invasive, or neutralizing activity usually represent an indirect measure of protection (immunogenicity).¹ However, in some cases, such as pertussis vaccine, serum antibody titers are not necessarily predictive of protection (Table 9.1). If so, reliance can only be placed on quantifying the protection rate against natural infection in the field (efficacy, Table 9.2).

Live vaccines

Live vaccines contain live attenuated microorganisms, which are still capable of replicating within the host (vaccinee). The microorganisms are attenuated, meaning that they have lost most of their disease causing capacity but still need to be in possession of their immunogenic property. In most cases, live vaccines show a significantly higher immunogenicity (Table 9.2) than inactivated vaccines since natural infection is imitated almost perfectly by eliciting a wider range of immunologic responses both, humoral (B cells) as well as cellular immunity (CD8⁺ and CD4⁺ T cells). A single vaccine administration is usually sufficient to induce long-term sometimes even lifelong protection.

However, the main disadvantage of this vaccine category is the potential of reversion to natural virulence via back mutations of the attenuated vaccine-organism and the possibility of causing a symptomatic affection similar to wild-virus infection in the recipient or in unprotected contacts (e.g., vaccine-associated-paralytic-poliomyelitis after oral poliovirus vaccine, OPV).

Killed vaccines

The vaccines for some viruses and most bacteria are inactivated (killed) whole cell or subunit preparations (Table 9.2), which are incapable of replicating within the vaccinee. These types of vaccines need to contain a higher antigenic quantum than live vaccines to induce an adequate immunologic response usually including B cell and CD4⁺ T cell response. Therefore, most of the killed pathogens or their products need immunomodulators, so called adjuvants, mostly aluminium-hydroxide or -phosphate, to improve antigen presentation and prolong the stimulatory effect by an antigen depot formation.² More recently, various other potent adjuvant

Table 9.1 Degree of correlation^a between different immune mechanisms and clinical protection induced by vaccines

Vaccine type	Humoral immune response	Cell mediated immunity	Comments
Diphtheria	++		Protective titer ELISA >0.01 IU/mL. Serology indicated in the case of unclear vaccination status and lack of documentation
Hib	++	+	Precise minimal protective Ab titer not known; possibly 0.15–1.0 µg anti-PRP Ab. Test not routinely used
Hepatitis A	++		Pre-vaccination serology might be cost-effective for persons with likely prior natural infection. (ELISA >10 mIU: protective titer)
Hepatitis B	++		Post-vaccination serology indicated in high-risk persons (protective ELISA titer >10 mIU/mL, except UK: ≥100 mIU/mL)
Influenza (inact.)	++	+	Protective anti-hemagglutinin titer: 1/40. Immunity rarely exceeds 1 year. Concomitant CTL induction? Testing recommended in the immunocompromised
JEV (mouse brain)	++		No international standard for protective Ab titer established. Cave: Cross-reactive antibodies (flavivirus).
Measles	++	+	Protective titer: NT >1:4; induction of important cellular immune response?
Meningococcus	++		Correlation between post-vaccination ELISA titers and vaccine efficacy suggest that >2 µg of antibody to be protective
Mumps	++		Post-vaccination serology (ELISA) correlates with protection. Precise minimal protective Ab titer not known
Pertussis (acellular)	+	+	Precise minimal protective Ab titer not known. Routine tests not available. Efficacy tested in controlled field trials
Pneumococcus	++		23 subtypes, determination of Ab titer not feasible for routine use
Polio ^b	++		IPV: protective Ab titer NT >1:8. Correlated with immunity OPV: serum+ mucosal Ab response. NT does not necessarily correlate with immunity
Rabies	++	+	Protective Ab titer: RFFIT: >0.5 IU/mL or NT: 1:25
Rubella	++		Protective Ab titer: >1:32 (hemagglutination-inhibition-test) or ELISA. Tests correlate with protection. Mucosal Ab involved in protection
Tick-born-encephalitis	++		ELISA tests give surrogate markers for immunity. Cave: cross-reactivity of antibodies (flavivirus) – NT required!
Tetanus	++		Protective Ab titer: ELISA >0.01 IU/mL but usually >0.1 IU/mL (more reliable). See also under diphtheria
Tuberculosis (BCG)	–	++	No easily measurable correlate of immunity to tuberculosis
Typhoid ^b	+		Testing almost impossible. Mucosal antibodies following live typhoid vaccine (oral)
Varicella	+	+	Regular antibody testing indicated for leukemia patients
Yellow fever	++		Cave: cross-reactive antibodies (flavivirus). Neutralization-test only available at the CDC

^a–, no correlation; +, low correlation; ++, high correlation.

^bDepending on vaccine type.

Table 9.2 Major terms to aid perusal of clinical vaccine literature

Acellular vaccines	Purified component vaccines
ACIP	Advisory Committee on Immunization Practices
Adjuvant	Constituent particularly of killed vaccines to increase immunogenicity and prolong the stimulatory effect (e.g., aluminium salt)
Adverse reaction	Very rarely unpredictable events which may result in permanent sequelae or be life-threatening. Occurrence does not necessarily prove causality
Antigenicity	(Syn: Immunogenicity) The ability of an agent(s) to elicit systemic or local immunologic response
Booster	Repeated immunizations in defined intervals to generate further antibody secreting cells and memory B cells to provide long-term immunity
CMI	Cell mediated immunity (T-cell response)
Conjugate vaccine	Chemical linking of polysaccharide antigen to a carrier protein which converts the polysaccharide from a T-cell independent into a T-cell dependent antigen
Efficacy of vaccines	(Syn: Protective efficacy). Proportion of subjects in the placebo group of a vaccine trial who would have not become ill if they had received the vaccine
GMT	Geometric Mean Titer
Immunity	Resistance developed in response to a stimulus by an antigen (infecting agent or vaccine) and usually characterized by the presence of antibodies
Immunogenicity	The ability of an infectious agent or vaccine antigen to induce specific immunity
Immunologic memory	Ability of the immune system (B-cell and T-cell memory) to recognize antigens and response in an reinforced manner after reinfection or booster
Inactivated vaccines	Vaccines containing killed whole cell, subunit, or toxoid preparations of the pathogen which are incapable of replicating within the vaccinee
Live attenuated vaccines	Vaccines containing live attenuated microorganisms, which are still capable of replicating within the vaccinee
Priming	Stimulation of adequate humoral immune response including immunologic memory to be accelerated by follow-up booster inoculations
Recombinant vaccine	Vaccine containing antigens (e.g., HBs Antigen) attained by expression of a gene encoding for a specific protein in a heterologous host
Seroconversion	Detectable humoral immune response after natural infection or vaccination
Seroprotection	Specific serum antibody titer predictive of protection
Side-effect	Unavoidable reactions intrinsic to the antigen or other vaccine components are mild to moderate in severity without permanent sequelae
Subunit vaccine	Active vaccines merely containing purified protective epitopes and their corresponding polypeptides
Toxoid	Active vaccines containing detoxified bacterial toxins (e.g. tetanus, diphtheria) as immunogenic agent
Vaccination	Procedure for immunization against infectious diseases
Vaccine	Immunobiological substance used for active immunization
Vaccine coverage	Proportion of vaccinated individuals within a group or population
Whole cell vaccine	Vaccines containing inactivated whole bacteria or whole viruses

systems, such as virosomes, biodegradable microspheres or novel adjuvant substances like MF59 or MPLA are undergoing clinical evaluation.

The maintenance of long-term immunity of some vaccines, including toxoids, recombinant subunit and polysaccharide conjugate vaccines (Table 9.2) require multidose immunization courses consisting of 2–3 inoculations, followed by periodic administration of booster (Table 9.2) doses. Doses administered at intervals less than the minimum interval can lead to a suboptimal immune response. In clinical practice, however, it is recommended that vaccine doses administered ≤ 4 days before the minimum interval may be counted as valid (except rabies vaccine).

Unconjugated polysaccharide vaccines, however, do not require multiple doses. In general, bacterial antigens do not induce long-term immunity irrespective of the route of vaccination. Because of immunological memory, delays of recommended booster intervals or interruption of primary immunization courses are usually neglectable and do never require re-institution of the complete vaccination series.

However, some inactivated vaccines are incapable of eliciting immunological memory, thus being booster-incompetent. These vaccines include all preparations using capsular polysaccharides as vaccine antigens. Yet another shortcoming of carbohydrate vaccines is that capsular polysaccharides, being T-cell-independent immunogens,

are poorly immunogenic in vaccinees younger than 2 years of age owing to the immature status of their immune systems. However, coupling of those antigens with protein carriers renders the polysaccharides visible to T cells, which provide help for antibody response including stimulation of B cell memory, also induced in the young (e.g., conjugated Hib and pneumococcus vaccines).

The main advantage, regardless of the type, of inactivated vaccines lies in their superior safety profile due to the incapacity of antigen multiplication and reversion to pathogenicity within the host.

DNA-vaccines

A recent new technology has been the injection (via gene guns) of naked DNA encoding for a specific vaccine antigen. The aim of DNA vaccines is to be taken-up by host cells in which it generates the synthesis and secretion of the vaccine antigen, thus triggering a humoral or cellular immune response. Prior to clinical use of DNA-based vaccines in humans, detailed safety issues need to be investigated and there is unlikely to be any commercial products available in the near future.

Passive immunization

In some circumstances, immediate protection against a specific infection proves to be necessary. Since active immunization does not elicit protective antibodies until 1–2 weeks following inoculation, administration of specific preformed antibodies, such as hepatitis B immunoglobulin (HBIG), rabies IG, tetanus IG, varicella-zoster IG and hepatitis A IG, seems to be indicated if potential disease exposure is given in recent past or near future. These specific hyperimmunoglobulins, derived from adult donors with high titers of the desired antibodies (95% IgG, trace amounts of IgA and IgM), stimulated by immunization or recent natural infection, are not known to transmit viruses such as HIV-1, or any other infectious agent. Hyperimmunoglobulins are usually recommended for i.m. administration followed by peak serum antibody levels about 48–72 h after administration.

Vaccine handling and administration

Personnel administering vaccines should take necessary precautions to minimize risk for spreading of disease. Hands should be washed before and after each patient contact. Gloves are not required unless the person vaccinating has a lesion on their hands; is likely to come into contact with potentially infectious body fluids; or as long as hand contact with blood or other potentially infectious materials is not reasonably anticipated. To prevent contamination, syringes and needles must be sterile and a separate needle and syringe should be used for each injection. Changing the needle between drawing the vaccine into the syringe and injecting it is not necessary. Unless specifically licensed, different vaccines should never be mixed in the same syringe.

To prevent needle-stick injury, needles should never be re-capped after use and should be discarded promptly in puncture-proofed, specifically labeled containers. In the USA, federal regulations require safer injection devices (needle-free injectors) to be used if such technology is commercially available and medically appropriate. Additional information concerning this regulation may be obtained at: <http://www.immunize.org/genr.d/needle.htm>

Anesthetic techniques

Anxiety about vaccinations is widespread. Some local anesthetic agents such as 5% lidocaine-prilocaine emulsion (EMLA[®] manufactured by AstraZeneca), applied 30–60 min before injection, may relieve discomfort during vaccination without interfering with the

immune response. Because of the risk of methemoglobinemia, such lidocaine-prilocaine treatment should not be used in infants younger than 12 months old under treatment with methemoglobin-inducing agents. A topical refrigerant spray may be administered shortly before vaccination to reduce short-term pain. Moreover, in newborn infants, sucrose placed on the tongue immediately before injection may have a calming effect.

Techniques of vaccine administration

Route of immunization

The route of vaccination is generally determined in pre-licensure studies. Intramuscular vaccinations are used for adjuvant-containing, potentially irritating antigens (e.g. tetanus/diphtheria vaccine). Administration by subcutaneous injection is preferred for live viral vaccines, to lessen the discomfort due to local inflammation (e.g. yellow fever vaccine). Intradermal injection, such as for BCG vaccine requires careful technique to avoid inadvertent subcutaneous antigen injection and consequent diminished immunologic response. The oral route of administration is used for certain vaccines where the stimulation of intestinal IgA and other mucosal immune mechanisms defend against the pathogenesis of infection (e.g. oral polio vaccine, oral typhoid vaccine, oral cholera vaccine). Vaccines for administration by nasal, rectal and vaginal routes are under investigation.

Local pain and swelling at the site of injection are the most common side-effects of all vaccines given by injection. The severity of the symptoms and number of patients experiencing them may vary from vaccine to vaccine, depending on the components of the vaccine. However, it is advisable to use only the administration technique and site of injection recommended by the manufacturer, unless data are available to support using alternative sites. Using unapproved alternate sites could reduce the immune response to the vaccine.

Intramuscular route

The choice of site for i.m. administration (Table 9.3) is based on the volume of injected material and the size of the muscle. For infants younger than 18 months of age the preferred site for i.m. injections is the musculus vastus lateralis in the anterolateral aspect of the thigh (Fig. 9.1). In older children and adults, the deltoid muscle provides the ideal site of i.m. injections (Fig. 9.2). The needle length used for i.m. injections depends on age for infants and children and weight in adults (Table 9.3). A 22–25-gauge needle is appropriate for administration of most i.m. vaccinations (Fig. 9.3).

Due to the thickness of overlying subcutaneous fat and the consequentially decreased immune response, moreover, because of the possibility of damaging the nearby sciatic nerve, the gluteal region should be avoided for active i.m. vaccinations. However, the gluteal site is often used for i.m. administration of large volumes of immunoglobulin preparations. At this site of injection, caution should be taken to avoid nerve injury, which is most perfectly done by injecting in the center of a triangle bordered by the anterior superior iliac spine, the tubercle of the iliac crest, and the upper border of the greater trochanter of the femur.

Many experts recommend ‘aspiration’ by pulling back the syringe plunger before injection, although there exists no data to document the necessity for this procedure and in the USA, CDC guidelines do not require it. However, if blood appears after aspiration, the needles should be withdrawn and a new site selected.

In patients with bleeding disorders, the risk of bleeding after i.m. injection can be reduced by application of firm pressure to the site of inoculation, vaccinating shortly after application of clotting factor replacement, or using smaller needles (23-gauge or smaller). Moreover, some vaccines recommended for i.m. application may

Table 9.3 How to administer vaccines via the intramuscular route. Needle length and injection site of intramuscular injections¹⁰

Age	Needle length	Injection site
≤18 years		
Newborn ^a	{5/8}" (16 mm) ^b	Anterolateral thigh
Infant 1–12 months	1" (25 mm)	Anterolateral thigh
Toddler 1–2 years	{5/8}" ^b –1" (16–25 mm)	Anterolateral thigh ^c
	1"–1{1/4}" (25–32 mm)	Deltoid muscle of the arm
Child/adolescent 3–18 years	{5/8}" ^b –1" (16–25 mm)	Deltoid muscle of the arm ^c
	1"–1{1/4}" (25–32 mm)	Anterolateral thigh
≥19 years		
Sex/weight		
Male and female <60 kg (130 lbs)	1" (25 mm)	Deltoid muscle of the arm
Female 60–90 kg (130–200)	1–1{1/2}" (25–38 mm)	
Male 60–118 (130–260 lbs)		
Female >90 kg (200 lbs)	1{1/2}" (38 mm)	
Male >118 (260 lbs)		

^aFirst 28 days of life.

^bIf skin stretched tight, subcutaneous tissues not bunched.

^cPreferred site.

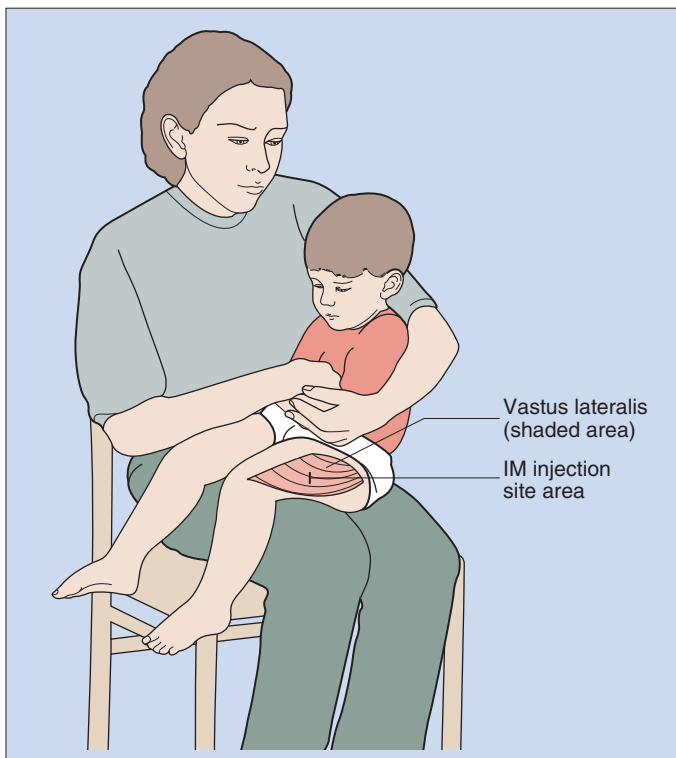


Figure 9.1: Intramuscular injection site for infants and toddlers (birth to 36 months of age). Insert needle at an 80–90° angle into vastus lateralis muscle in anterolateral aspect of middle or upper thigh.

exceptionally be given subcutaneously (s.c.) to persons at risk for bleeding. If a patient with bleeding diathesis must receive an i.m. injection, using a smaller gauge needle, placing steady pressure over the injection site for at least 2 min and limiting the movement of the extremity for a few hours may decrease the development of bleeding complications.

Subcutaneous route

Subcutaneous injections (Table 9.4)³ can be administered in the anterolateral aspect of the thigh or the upper arm by inserting the needle at about 45° angle in a pinched-up skinfold. A {5/8}" , 23–25 gauge needle is recommended (Figs 9.4–9.6).

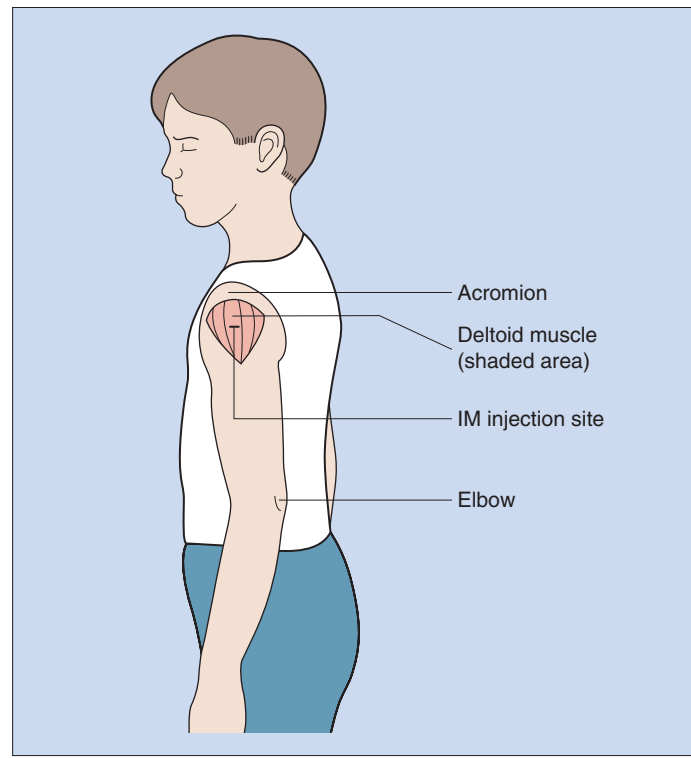


Figure 9.2: Intramuscular injection site for older toddlers, children and adults. Insert needle at an 80–90° angle into the densest portion of deltoid muscle – above armpit and below acromion.

Intradermal route

Intradermal injections are usually administered on the volar surface of the forearm or the deltoid region by inserting the needle parallel to the long axis of the arm and raising a small bleb by the injection material. A {3/8}–{3/4}" , 25 or 27-gauge needle is optimal (Figs 9.7, Figs 9.8).

Oral application

Vaccines given orally such as OPV or live typhoid vaccine should be swallowed and retained. The dose should be repeated if the person fails to retain the vaccine longer than 10 min following the first application.

Simultaneous administration of different vaccines

Simultaneous administration of different vaccines is of particular importance when preparing for international travel. Moreover, simultaneous administration of vaccines is critical for childhood immunization programs.⁴ Since combination vaccines increase the probability that a child will be fully immunized at the appropriate age, immunization rates are raised significantly. Usually, most widely used live and inactivated vaccines can be safely and effectively (in terms of seroconversion rates) administered at the same time (Table 9.5).^{5,6}

With the exception of live vaccines administered within an interval of 4 weeks of each other, vaccines can be administered at any time before or after a different vaccine. Due to the potential immunological interference, some live vaccines, if not given simultaneously, should be separated by at least 4 weeks. No evidence, however, exists indicating that OPV and Ty21a interfere with other parenterally administered live vaccines when administered concurrently or within 4 weeks.

The administration of immunoglobulin (IG)-containing preparations shortly before or simultaneously with certain vaccines may also adversely affect the immune response of the active immunizations (e.g. measles and rubella vaccine), depending on the dose of IG. The immune response following yellow fever and oral polio vaccine

seems not to be influenced by co-administration of immunoglobulin.⁷ Similarly, Ty21a can be administered at any time with respect to IG. The interference with inactivated vaccines is far less pronounced than with attenuated vaccines. For example, concurrent administration of HBIG, or tetanus IG and the corresponding vaccine or toxoid in the course of pre- or post-exposure prophylaxis has not been demonstrated to cause inhibition of the immune response, yet providing immediate and long-term protection. The combined administration of hepatitis A vaccine and IG has been observed to negligibly decrease serum antibody titers, but not impairing seroconversion rates.

Interchangeability of vaccine products

Although precise data concerning safety, immunogenicity, and efficacy is lacking, vaccines against the same diseases with similar antigens from different manufactures are usually considered interchangeable when used according to their licensed indication. Available data indicate that all brands of diphtheria, tetanus toxoids, live and inactivated polio, hepatitis A, hepatitis B, tick-borne encephalitis, and rabies vaccines can be used interchangeably within a vaccine series. Due to a lacking correlate for *Bordetella pertussis* infection, the interchangeability of acellular pertussis vaccines is difficult to assess. Therefore, whenever feasible, the same brand of DTaP should be used. Vaccination series should never be interrupted if the same brand is not available.

Special caution is indicated, when using vaccines of the same brand and vaccine name obtained in different countries, since differences in vaccine formulation might exist.

Serologic testing before and after immunizations

In any case, except BCG, vaccination may be undertaken regardless of prior knowledge of the immunity status of the vaccinee. This is particularly true for low-priced vaccines such as polio, diphtheria or tetanus vaccines. Whereas in the case of high-priced vaccines (e.g. Hepatitis A or B vaccine), it may be more cost-effective to test immunity status prior to vaccination, particularly if acquisition of immunity via natural infection in the past is very likely. Moreover, serologic testing may be reasonable in the case of unclear immunization status due to incomplete or lack of documentation of vaccination courses.

Checking post-vaccination antibody titer for healthy vaccinees is medically merely indicated after hepatitis B and rubella vaccine. Unresponsiveness to the hepatitis B vaccine poses a serious problem since more than 10% of healthy immunocompetent adults fail to develop protective antibody levels after the recommended three-dose i.m. vaccination course (non-responders).⁸ In the chronic dialysis population, current hepatitis B vaccination regimens result in a disappointing 50–75% rate of development of anti-HBs.⁹ In addition, all women of child-bearing age need to be protected adequately against rubella infection. Due to likewise potential unresponsiveness to rubella vaccine, it appears most reasonable to check antibody titer post-vaccinally.

- Use a needle long enough to reach deep into the muscle. Insert the needle at an 80°–90° angle to the skin with a quick thrust.
- Retain pressure on the skin around injection site with thumb and index finger while needle is inserted.
- There are no data to document the necessity of aspiration, however, if performed and blood appears after negative pressure, the needle should be withdrawn and a new site selected.
- Multiple injections given in the same extremity should be separated as far as possible (preferably 1" to 1½" with minimum of 1" apart).

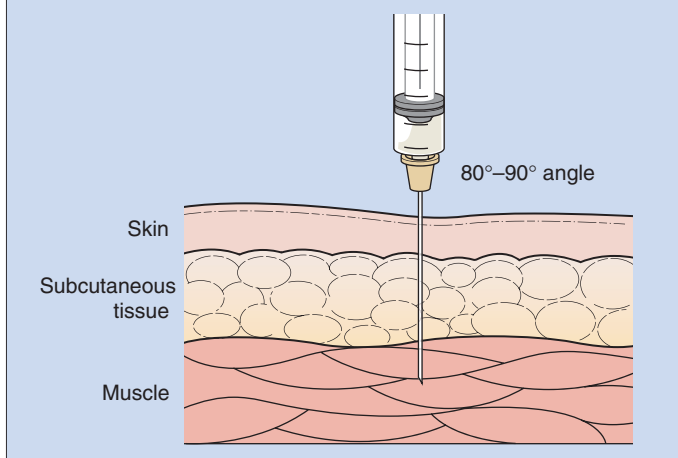


Figure 9.3: Angle of needle insertion for intramuscular injection.

Table 9.4 How to administer vaccines via the subcutaneous route

Age	Needle size	Injection site
Infants (≤12 months)	{7/8}–1", 23–25 gauge	Vastus lateralis muscle in anterolateral
Toddlers (1–3 years)	{5/8}–{3/4}", 23–25 gauge	Fatty area of the thigh or outer aspect of upper arm
Children and adults	{5/8}–{3/4}", 23–25 gauge	Outer aspect of arm

Adapted from: American Academy of Pediatrics, Red Book, 2006.3

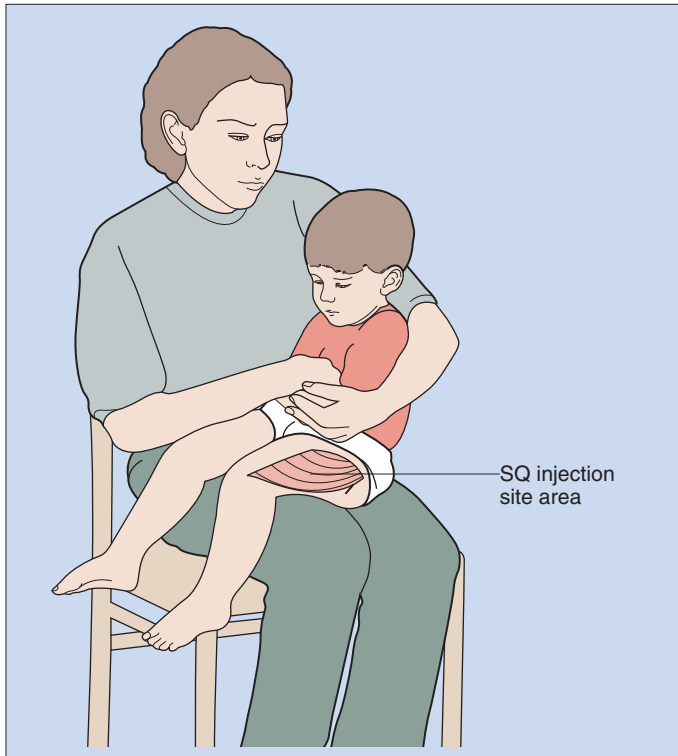


Figure 9.4: Subcutaneous injection site for infants and toddlers (birth to 36 months of age). Insert needle at a 45° angle into the fatty area of anterolateral thigh. Make sure subcutaneous tissue is pinched, to prevent injection into muscle.

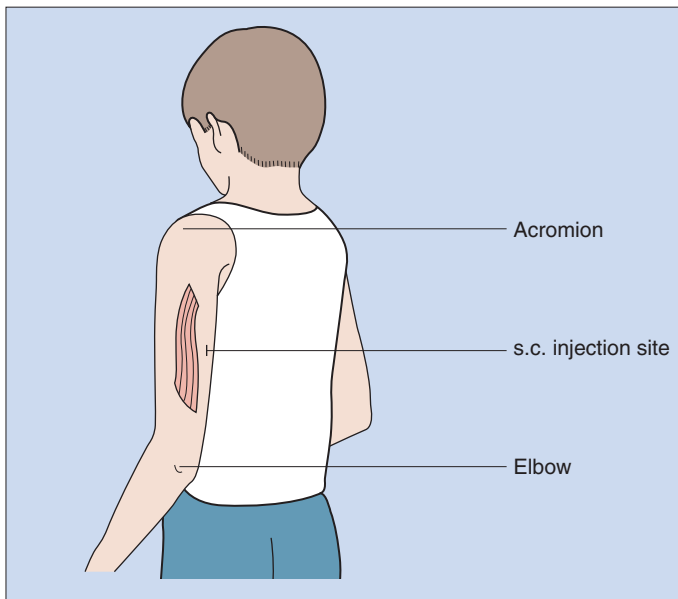


Figure 9.5: Subcutaneous injection site for injection of toddlers, children and adults. Insert needle at a 45° angle into the outer aspect of upper arm. Make sure subcutaneous tissue is pinched, to prevent injection into muscle.

Moreover, seroconversion rates and antibody levels after vaccines may be reduced in immunocompromised subjects who should be considered for post-vaccination serologic testing.

However, when interpreting serological results by employing specific antibody titers as surrogate markers for level of protection, we have to bear in mind that assessed serum antibodies, such as

- Insert the needle at 45° angle to the skin.
- Pinch up on s.c. tissue to prevent injection into muscle.
- There are no data to document the necessity of aspiration, however, if performed and blood appears after negative pressure, the needle should be withdrawn and a new site selected.
- Multiple injections given in the same extremity should be separated as far as possible (preferably 1" to 1½" with minimum of 1" apart).

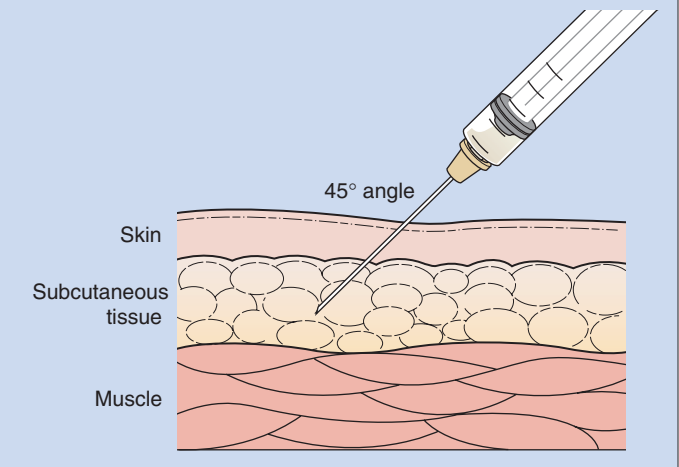


Figure 9.6: Angle of needle insertion for subcutaneous injection.

antibodies after pertussis vaccination, are not reliably of neutralizing activity and therefore may not be necessarily predictive of protection. Thus, we may not always rely on serology as the standard means of measurement of post-vaccination clinical protection (Table 9.1).¹ Though specific methods to measure cellular immunity exist, they are unsuitable for routine application.

Vaccination in those with impaired immunity

In the case of impaired immunocompetence, including congenital immune deficiencies, HIV infection, malignant neoplasm, or recipients of immunosuppressive therapy, cautious considerations about risks and benefits of vaccinations need to be made.¹⁰ In general, patients with uncertain or severely impaired immune status should not receive live vaccines because of the risk of disease from the vaccines strains after administration of attenuated viral or bacterial vaccines. One exception, however, is delivery of the combined measles-mumps-rubella (MMR) vaccine to individuals with asymptomatic HIV infection or symptomatic HIV infection without severe immunosuppression.

Since decreased immunity results in reduced immunogenicity of vaccines reflected by significantly diminished seroconversion rates and antibody levels these patients should be considered for post-vaccination serologic testing.

Detailed management of specific risk groups will be covered elsewhere.

MANAGEMENT OF ADVERSE REACTIONS

It is beyond doubt, that currently licensed modern vaccines are safe and effective and have to undergo extensive and strictly controlled pre-clinical and clinical safety trials before licensed for routine use by public health authorities. However, despite all sorts of safety precautions one can not absolutely exclude sporadic cases of undesirable vaccine-associated adverse reactions (Table 9.6). Therefore, vaccine

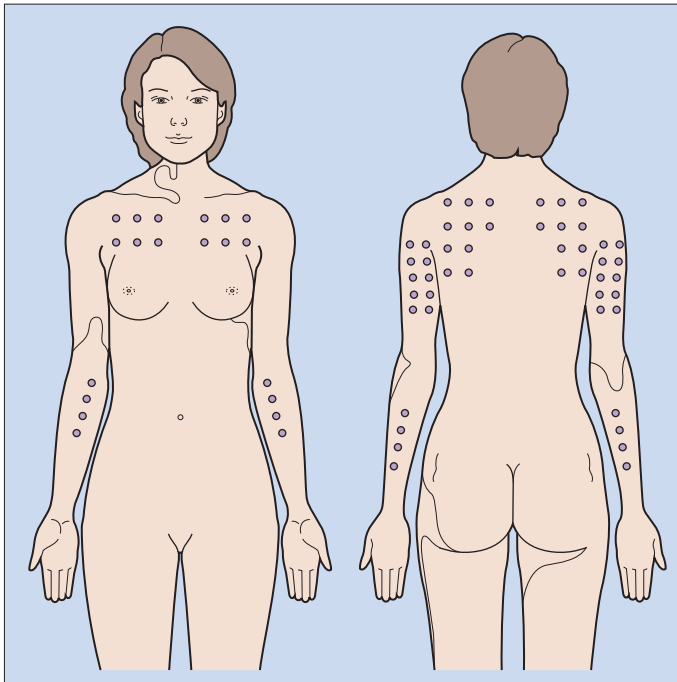


Figure 9.7: Intradermal injection sites. The most common intradermal injection site is the ventral forearm. Other sites (indicated by dotted areas) include the upper chest, upper arm, and shoulder blades. Skin in these areas is usually lightly pigmented, thinly keratinized, and relatively hairless, facilitating detection of adverse reactions.

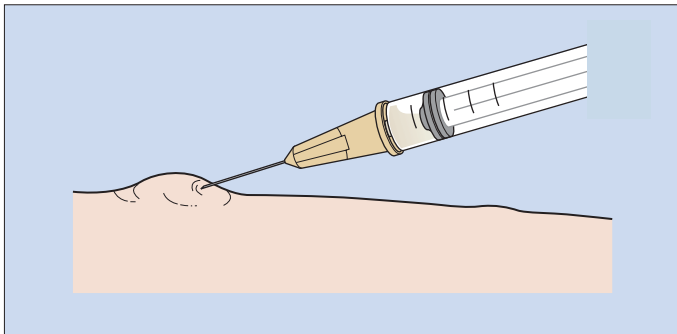


Figure 9.8: Angle of insertion for intradermal injection. Insert the needle at a 10–15° angle, so it punctures the skin's surface. When injected, the drug should raise a small wheal.

recommendations should always be orientated on the basis of careful evaluation of vaccine benefits and safety weighed against the risk of vaccine preventable disease.

Vaccine-associated side-effects (Table 9.2) are usually mild and harmless. On average, about 5–10% of all vaccinees complain about post-vaccination problems of mostly moderate local (redness, swelling and pain of the limb), or systemic (fever, headache) nature, occurring shortly after vaccination (6–48 h).

Vaccine-associated anaphylactic reaction resulting in cutaneous, respiratory, cardiovascular, and/or gastrointestinal signs and symptoms is an extremely rare event. Vaccine components that may cause allergic reactions include the vaccine antigen (e.g., tetanus toxoid), animal protein (e.g., gelatin), and antibiotics (e.g., neomycin). A report of anaphylaxis after hepatitis B vaccination suggests that latex used in vial stoppers and syringe plungers may also be a cause of vaccine-associated anaphylaxis. A history of anaphylaxis to a vaccine component is a contraindication to receipt of that vaccine. A recent study, however, suggests that the frequency of anaphylaxis after vaccination is very low, estimating a risk of 1.5 cases/million doses.¹¹ Nonetheless, immediate facilities (epinephrine and equipment for maintaining an airway) and personnel should always be available for treating such allergy emergencies.

Very rarely, unpredictable serious life-threatening adverse reactions may occur. However, occurrence does not necessarily prove causality. Association of such an event is only considered if there is timely and symptomatic correlation between vaccination and adverse reaction and, if other diseases with similar symptomatic appearance can be excluded. For most attenuated virus-vaccines, definite causative association is established by isolation of the vaccine strain from the vaccinee or vaccinee's contacts.

If there is strong suspicion of such a serious adverse reaction, official reporting of this event to the national health authority is of utmost importance, since in the context with other similar reports, further clues about this incidence may be detected.

CONTRAINDICATIONS TO VACCINATIONS

Absolute contraindications against administration of vaccines are most uncommon. Except for severe hypersensitivity to vaccine constituents, no further contraindications exist against killed vaccines. Administration of live vaccines however, may be contraindicated in specific situations such as pregnancy and impaired immunity.

Hypersensitivity reactions can vary in severity from mild local symptoms to severe anaphylaxis (Table 9.6). However, allergic reactions occurring immediately after vaccination are very suggestive of an anaphylactic reaction and act as a contraindication for

Table 9.5 Recommended spacing of different vaccines

Combination of different vaccine antigens	Minimum interval
Killed – Killed	None
Live – Killed	None
Killed – Live	None
Live – Live	≈4 weeks, if not given simultaneously (except OPV – MMR – oral typhoid vaccines: no interval required)
Killed – Immunoglobulin	None
Immunoglobulin – Killed	None; if simultaneously: at different sites
Live – Immunoglobulin	≈2–3 weeks (except OPV, yellow fever, oral typhoid: no interval required)
Immunoglobulin – Live	≈3–5 ^a months (except OPV, yellow fever, oral typhoid: no interval required)

^aDose-dependent.

Table 9.6 Potential hypersensitivity reactions to common vaccine components

Vaccine component	Contained in the vaccine against	Hypersensitivity reaction
Egg protein	Yellow fever ^c Influenza ^b Measles ^a Mumps ^a Rabies ^a TBE ^a	On rare occasions, anaphylaxis or immediate hypersensitivity reaction; dose-dependent risk
Antibiotics (gentamicin, neomycin etc.)	Measles Mumps Rubella TBE Rabies	Mostly delayed-type (cell-mediated) local contact dermatitis; no contraindication to vaccinations
Mercury compounds (Merthiolate)	Almost eliminated from modern vaccines	Mostly delayed-type local contact dermatitis, no contraindication to vaccinations
Phenol	Cholera (old killed vaccine) Pneumococcus	Delayed-type local contact dermatitis, no contraindication
Gelatin	Measles Mumps Rubella Yellow fever	Very rarely anaphylaxis or immediate hypersensitivity reaction

^aVery low risk.^bModerate risk.^cHigh risk.

follow-up vaccinations. However, persons with a history of systemic anaphylactic-like symptoms after egg ingestion needing yellow fever vaccine may be skin tested before vaccination and desensitized. Local delayed-type hypersensitivity reactions, such as allergic response to neomycin, are no contraindication for vaccinations. If a person reports an anaphylactic reaction to latex, vaccines supplied in vials containing natural rubber should be avoided unless the benefit of the vaccination outweighs the risk of an allergic reaction.

No evidence indicates any influence on vaccine-associated reactivity or efficacy, if vaccine is administered during minor illness ($\leq 38^{\circ}\text{C}$, $\leq 100^{\circ}\text{F}$). However, if fever ($\geq 38^{\circ}\text{C}$, $\geq 100^{\circ}\text{F}$) or clinical symptoms suggest serious illness, immunizations should be delayed after disease recovery.

Vaccinations during pregnancy are not recommended unless specifically indicated. Live vaccines, particularly rubella and varicella vaccine, are contraindicated 3 months before and during pregnancy. However, in non-immune women at imminent risk for yellow fever exposure, vaccination is indicated. Breast-feeding poses no contraindication for either vaccine.

LEGAL ISSUES

Documentation and risk counseling

Vaccinees or parents of under-aged children need to be counseled by the person responsible for vaccine administration about benefits of disease prevention as well as risk of preventive and therapeutic options, including vaccinations. In the USA, the National Childhood Vaccine Injury Act of 1986 requires that the person administering a vaccine covered by this act must provide a copy of the relevant, current edition of the vaccine information material provided by the Centers for Disease Control and Prevention (CDC). It is recommended to document consent, but vaccinees do not need to sign a consent form.

In addition, the liable physician is obligated to keep a record about the exact date of vaccination; occurrence of adverse reactions; vaccine manufacturer; lot number; the site and route of administration; the date of risk-benefit counseling, and vaccine type and date,

in case of rejection of a recommended vaccination by the patient. Moreover, mentioned vaccination details need to be documented in an official vaccination document. Such data are essential for surveillance and studies of vaccine safety, efficacy, and coverage.

Vaccinations currently regulated by the World Health Organization (WHO), such as yellow vaccine, need to be documented in an international valid immunization certificate.

MERCURY PRESERVATIVES IN VACCINES

Thimerosal, which contains 49% ethylmercury, has been used as a preservative in vaccines since the 1930s. Preservatives are not required for single-dose vials. Thimerosal is added at the end of the production process to prevent contamination of multi-dose vials after they are opened. Thimerosal may also be used in the early stages of manufacturing for a few vaccines but is removed during processing, with only trace (insignificant) amounts remaining. Vaccines can be classified into 3 groups: (1) Thimerosal-free; (2) containing a trace ($< 0.3\ \mu\text{g}$) of mercury (considered by the US FDA to be equivalent to thimerosal-free products); (3) containing thimerosal as a preservative ($25\ \mu\text{g}$ of mercury/ $0.5\ \text{mL}$ dose).

Recently, concerns about the use of thimerosal in vaccines and other products have been raised even though both the US FDA and the US Institute of medicine have found no harm from the use of thimerosal other than local hypersensitivity reactions. Nevertheless, since the late 1990s, most countries have mandated the removal of thimerosal from all pediatric vaccines as a precautionary measure and very few vaccines are currently produced in multi-dose vials. For travelers, the vaccines that still contain $25\ \mu\text{g}$ of thimerosal are Biken Japanese encephalitis vaccine, quadrivalent polysaccharide meningococcal vaccine in multidose vials, and many brands of influenza vaccine. A few vaccines in a few countries still contain trace amounts of thimerosal, JE-VAX and Menomune (multi-dose vial only). An updated list of the thimerosal content of all vaccines available in the USA can be found at: <http://www.fda.gov/cber/vaccine/thimerosal.htm>. Many of these vaccines are the same preparations that are available internationally.

VACCINE STOCKING AND STORING

Vaccines need to be suitably stored and handled to avoid vaccine failure. Once opened, the remaining doses from a multi-dose vial that does not require any reconstitution may be used until the expiration date printed on the vial, providing that the vial has been stored correctly. For vaccines requiring reconstitution, the manufacturer's guidelines need to be followed.

Regular temperature monitoring and control (by 'minimum-maximum' thermometer) is essential to guarantee stable temperature. It may be advisable to designate a single person as a vaccine coordinator responsible for vaccine accounting, purchasing, and safe and careful handling.

Recommendations for handling regulations are usually given in the manufacturers' product information and in publications by the Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention.¹²

IMMUNIZATIONS IN TRAVELERS

Besides eradication of disease, immunizations can reduce the risk of vaccine-preventable diseases in individuals including travelers. The risk for travelers of contracting infections abroad is variable depending mostly on well-known risk factors such as destination, travel season, duration of stay, and individual travel conditions.

Since most travelers seeking pre-travel health advice often just refer to vaccinations officially required for entry, it appears most reasonable to point out the differentiation between official vaccination regulations and individual vaccination recommendations for the travelers' safety:

- The only vaccination currently regulated by the WHO, yellow fever vaccination, is required for all travelers going to certain endemic countries that have established this requirement under the International Health Regulations. In addition, many countries outside the endemic zone require proof of immunization from travelers arriving from or via an infected country (see Ch. 10)
- Saudi Arabia requires proof of vaccination against meningococcal meningitis in order to procure a *Hajj* or *Umrah* visa. This is a frequently encountered situation in travel medicine practice, although not recognized under the International Health Regulations.

To compile an individually tailored immunization schedule, selection of travel vaccinations are based on various critical factors including:

- *The epidemiological trends in the country of destination:* which vaccine-preventable diseases stand for risk to the traveler? What is the disease incidence? Detailed updated information about disease epidemiology and immunization requirements can be obtained from the Centers for Disease Control and Prevention (CDC) and the WHO.^{13,14} In addition, many countries regularly publish national guidelines regarding travel vaccinations and health requirements
- *Style of travel:* detailed itinerary, duration of travel, timing of departure, type of accommodation, adventure travel or luxury tour
- *Purpose of travel:* tourism, work, visiting relatives, etc.
- *Vaccinations officially required for entry* (e.g. yellow fever vaccination)
- *Cost/benefit of vaccinations:* prioritization of certain immunizations by ability to pay and frequency of traveling
- *Individual contraindications to vaccinations:* hypersensitivity, concomitant disease, medication, pregnancy, medical history
- *Personal history of immunizations:* including primary and booster doses of routine and travel vaccinations.

CONCLUSION

By assisting health professionals in obtaining a deeper understanding of major immunologic as well as practical issues of vaccination, this chapter contributes to the elimination of potential malevolent prejudices concerning vaccine-associated harmfulness. It is beyond doubt that the benefit of immunization, if utilized correctly, outweighs, by far, vaccine associated risk. Immunization prevents disease. However, the best vaccine will have little impact unless promoted and delivered by motivated health professionals and taken up by individuals.

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