Chapter 12

IMMUNIZATIONS FOR MILITARY TRAINEES

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INTRODUCTION

For thousands of years, infectious diseases have threatened military campaigns. Infections constitute one of the largest components of the morbidity category known as disease and nonbattle injury. Until 1990, loss of life from nontraumatic illness in military campaigns had decimated more US armies than bullets. Since the Persian Gulf War of 1990–1991, few American personnel have been lost to service because of vaccine-preventable infections,[1] but this results more from disease control than from disease eradication.

Among military forces, the preeminent forms of infectious disease control are sanitation and immunization.[2-8] This chapter reviews the effect of infectious diseases and immunization on military operations, and focuses on infection and immunization issues unique to military training settings. In addition, this chapter discusses the standards for high-quality immunization services, including evaluation of adverse events after immunization. These standards apply in any military setting, from austere field situations to problems at sea. Vaccination reflects a population-based intervention to reduce disease that might have rare, adverse consequences for individuals.

Immunizations administered before or during military training can provide both prompt and long-term protection. Prompt protection is needed against contagions that can spread rapidly through the relatively stressful and crowded conditions within training camps (eg, influenza, measles, varicella). Other immunizations are given during military training to protect against environmental exposures that can be reasonably expected to occur during military service (eg, tetanus, hepatitis A).[9]

Although most of the trainees at military training camps are junior enlisted personnel, the same general principles apply to congregations of officer candidates (eg, cadets, midshipmen) or junior officers (eg, basic officer courses). Entering and exiting training courses at any level of military service offer opportunities to screen the adequacy of immunizations of military personnel. Similarly, annual influenza immunization programs can be used as platforms for assessing other immunization needs.[10]

Tetanus provides a good example of the historical evolution of the immunologic means of keeping soldiers, marines, sailors, airmen, and coast guardsmen healthy. Traumatic injuries complicated by tetanus intoxication were a major cause of morbidity and mortality until World War I.[2] Using tetanus antitoxin to treat casualties was a major therapeutic advance. With the widespread introduction of tetanus toxoid by the start of World War II, medical interventions shifted from treatment to prophylaxis. Since the Vietnam War, service members who were first immunized against tetanus as children have received a booster dose of tetanus toxoid upon entering military service. This booster dose maintains their immunity from this disease and is followed by periodic supplemental booster doses throughout their service.

PREVENTABLE DISEASES AND VACCINES IN MILITARY SETTINGS

Prevention is the foundation of military medical readiness. The most effective weapons against the ravages of disease have been vaccines. Vaccines elicit antimicrobial shields within the bloodstreams of service members, thus offering protection for long periods (years or decades). Military trainees from each of the armed services, both active and reserve components, receive military immunizations from their first days of basic training. Vaccines that were widely used during various US military conflicts are summarized in Table 12-1.[2-8,11]

Active immunization (sometimes referred to as vaccination, particularly during the smallpox era) is the deliberate administration of antigens that stimulate the immune system. The long-term immune response (also known as immunologic memory) results in the production of antibodies and cells (specific immune response) that prevent illness (not necessarily infection) caused by microbes or their toxins. Generally, vaccines are whole or subunits of microbes prepared so that they do not cause the disease to be prevented. Vaccines are licensed for use in healthy populations if their efficacy and safety far outweigh the risk of adverse events in the setting of a disease threat with high morbidity and/or mortality. Immunization dates back a thousand years to early efforts to prevent smallpox.

Passive immunization is the administration of antibodies to prevent or reduce serious illness after an acute disease exposure or for short-term prophylaxis. The most common military application was the use of intramuscular immune globulin (or γ-globulin) to prevent hepatitis A. In the future, immune activators might be used to enhance a person's ability to fight infection or to modulate the infected person's response to reduce morbidity. The vaccine domain is rapidly expanding to include therapeutic vaccines not only for disease prevention but also for better disease treatment.

TABLE 12-1

WIDELY USED IMMUNIZATIONS DURING MAJOR US MILITARY CONFLICTS*

Conflict (Date)	Vaccines (Specific Type)	Antibodies
American Revolutionary War (1775–1783)	Smallpox (by variolation, inoculation with variola virus)	
War of 1812 (1812–1814)	Smallpox (vaccination with cowpox and later vaccinia virus)	
Mexican-American War (1846–1848)	Smallpox	
Civil War (1861–1865)	Smallpox	
Spanish-American War (1898)	Smallpox	
World War I (1917–1918)	Smallpox, typhoid (whole cell)	Tetanus antitoxin, diphtheria antitoxin
World War II (1941–1945)	Cholera (whole cell), diphtheria (toxoid) influenza (whole killed virus), plague (whole cell), scarlet fever (whole cell), smallpox (live), tetanus (toxoid), typhoid (whole cell), paratyphoid A and paratyphoid B (whole cell), typhus (whole cell), yellow fever (live)	Diphtheria antitoxin, gas gangrene antitoxin, tetanus antitoxin, polyclonal immune globulin
Korean War (1950–1953)	Cholera (whole cell), influenza (whole killed virus), plague (whole cell), smallpox (live), tetanus-diphtheria toxoids, typhoid (whole cell), typhus (whole cell), paratyphoid A and paratyphoid B (whole cell), yellow fever (live)	Diphtheria antitoxin, immune globulin (against hepatitis A, etc)
Vietnam War (1961–1975)	Cholera (whole cell), influenza (whole killed virus), measles (live), meningococcal (polysaccharide, A/C), plague (whole cell), poliovirus (live), smallpox (live), tetanus-diphtheria toxoids, typhoid (whole cell), typhus (whole cell), yellow fever (live)	Immune globulin (against hepatitis A, etc)
Persian Gulf War (1990–1991)	Adenovirus types 4 and 7 (live), anthrax (acellular), botulinum toxoid (very limited use), hepatitis B (subunit), influenza (split killed virus), measles-mumps-rubella (live), meningococcal (polysaccharide, A/C/Y/W-135), poliovirus (live), rabies (special operations), tetanus-diphtheria toxoids, typhoid (whole cell), yellow fever (live)	Immune globulin (against hepatitis A, etc)
Global War on Terror (notably Afghanistan and Iraq) (2001 to present)	Anthrax (acellular), hepatitis A (inactivated), hepatitis B (subunit), influenza (split-killed virus injection or live-attenuated virus intranasal), measles-mumps-rubella (live), meningococcal (polysaccharide or conjugate, A/C/Y/W-135), poliovirus (killed virus), rabies (special operations), smallpox (live), tetanus-diphtheria toxoids, typhoid (subunit or live-attenuated), varicella (live), yellow fever (live)	
On the horizon	Adenovirus type 4 and type 7 (live), papillomavirus	

*This list is not an exhaustive list of all licensed vaccines and antibodies for these time periods, nor an assertion that each service member in that conflict received each product. Rather, this is a list of widely used products for service members during these time intervals.
Data sources: (1) Blood CG, Jolly R. Comparisons of disease and nonbattle injury incidence across various military operations. *Mil Med*. 1995;160:258–263. (2) Parish HJ. *A History of Immunizations*. Edinburgh: E&S Livingstone Ltd; 1965. (3) Chase A. *Magic Shots*. New York: William Morrow; 1982. (4) Woodward TE. The public's debt to military medicine. *Mil Med*. 1981;146:168–173. (5) Benenson AS. Immunization and military medicine. *Rev Infect Dis*. 1984;6:1–12. (6) Takafuji ET, Russell PK. Military immunizations: Past, present, and future prospects. *Infect Dis Clin North Am*. 1990;4:143–158. (7) Woodward TE. *The Armed Forces Epidemiological Board: Its First 50 Years*. Falls Church, Va: Office of The Surgeon General, US Department of the Army; 1990. (8) Plotkin SL, Plotkin SA. A short history of vaccination. In: Plotkin SA, Orenstein WB, ed. *Vaccines*, 4th ed. Philadelphia: Elsevier; 2003:1–12. (9) US Department of Defense. US Army Regulation 40-562; Navy Bureau of Medicine and Surgery Instruction 6230.15; Air Force Joint Instruction 48-110; Coast Guard Commandant Instruction M6230.4E. *Immunizations & Chemoprophylaxis*. Washington, DC: DoD; 1995. Available at: http://www.e-publishing.af.mil/pubfiles/af/48/afji48-110/afji48-110.pdf. Accessed October 31, 2005.

In the 21st century, the quality of immunization delivery has assumed increased importance. Service members, like their civilian counterparts, have more knowledge and inquisitiveness about the safety of vaccines than in prior years, particularly because disease frequency and risk might be invisible or merely presumed (eg, bioterrorism threats). Military healthcare workers, perhaps more than civilian healthcare workers not tasked with implementing mandatory immunization programs, need to have a broad knowledge base to address questions surrounding risk, benefit, medical exemptions, adverse event diagnosis and management, and reproductive health concerns. Credible support services for quality immunization healthcare are essential to the success of immunization for the armed forces. The challenges and training requirements that support clinical education steadily increase, considering the expanding range of vaccines for children, adults, occupations, travel, and biodefense.

The Armed Forces Epidemiological Board (AFEB)—named in 1973, with a history dating back to 1941—is the civilian expert group of physicians and scientists who advise the Department of Defense and the Surgeons General on complex questions related to infectious disease prevention and control, health maintenance and promotion, and environmental and occupational health.[7] Recommendations from the AFEB help develop immunization policy requirements for trainees.

Tetanus and Diphtheria

Tetanus, commonly called lockjaw, is a bacterial disease (*Clostridium tetani*) that affects the nervous system when contracted through a cut or wound that becomes contaminated with the tetanus bacteria. In 1917, the only treatment for tetanus was tetanus antitoxin, a medication consisting of horse antibodies that neutralized tetanus toxin.[2] Tetanus antitoxins were relatively effective, but had a harsh side-effect profile (including serum sickness), and their benefit was transient. In 1933, tetanus toxoid was licensed in the United States. This protein vaccine prevented tetanus the disease before wound contamination could cause illness. This highly effective vaccine was initially not widely used by civilians.

In 1940 the US Army Surgeon General requested use of tetanus toxoid for all active-duty American troops.[2,5,12] Routine tetanus immunization was approved by the War Department on June 11, 1941. This decision featured adoption of a promising, but narrowly tested, new technology. A record of administered tetanus toxoid doses was stamped on troops' identification tags and in their paper records. Booster toxoid doses were routinely administered before troops entered an overseas theater and after they were wounded. Many duplicative immunizations (especially tetanus toxoid) resulted when records were not forwarded with the troops upon deployment to a new theater. The incidence of local reactions after immunization was greater than with less frequent dosage schedules.

Throughout World War II, from all theaters of operation, only 12 cases of tetanus were reported, despite more than 12 million Americans in uniform who incurred more than 2.7 million hospital admissions for wounds or injuries.[2,5,12] All 12 cases included incompletely immunized or unimmunized individuals.

The German Army (Wehrmacht) did not administer tetanus toxoid to its troops, continuing to rely on the obsolete tetanus antitoxin.[2] The Wehrmacht suffered high rates of morbidity and mortality from tetanus. In contrast, the German Air Force (Luftwaffe) immunized its men with tetanus toxoid and suffered lower rates of tetanus-related morbidity and mortality.

Diphtheria is an acute bacterial (*Corynebacterium diphtheriae*) infection that usually attacks the throat and nose. Toxigenic strains of diphtheria produce a toxin that disrupts protein synthesis in eukaryotic cells. The prevention of toxin-related morbidity and mortality followed a parallel course to tetanus disease control.[12,13] Diphtheria antitoxin was used to treat this leading cause of premature death in the early 20th century. Diphtheria toxoid was first licensed in the United States in 1926 and was later combined with tetanus toxoid to simplify the work of injecting the two protein products. Military clinicians noted the injection site swelling that followed diphtheria toxoid administration and developed a reduced dose formulation. In the 1950s, at the Great Lakes Naval Training Center (Illinois), the work of Edsall et al[14] demonstrated that this approach was comparably immunogenic, but with fewer injection site symptoms. The practice of administered DT (containing full strengths of each toxoid) to children up to the seventh birthday and Td (full-strength tetanus and reduced-strength diphtheria toxoid) to older children and adults continues to this day.[13] Concerns about recurring risks of pertussis in adolescents and adults might result in modified immunization recommendations in the near future for trainees and other military personnel.

Smallpox, Variolation, and Vaccination

Smallpox, the deadly viral infection caused by variola virus, plagued mankind for centuries.[8,15,16] It was a major threat to military forces worldwide. Smallpox

killed more than 30% of those infected, often scarring and blinding its survivors.

During the 1770s, smallpox outbreaks were common in the cities and towns of the North American colonies.[17-20] During the fall of 1775, British forces expelled the smallpox cases and the variolated people from Boston. They were sent across siege lines maintained by the fledgling Continental Army. In May and June 1776, approximately half of the Continental Army task force advancing on Quebec was ill with smallpox. The Americans suffered 5,500 smallpox casualties among their force of 10,000 colonial troops. Major General John Thomas, their commander, died of smallpox during the campaign, as did many other soldiers. Decimated, US forces lost the Battle of Quebec and retreated.

In response to the military defeat of Quebec, John Morgan, the director general of the Army Hospital, along with his successor William Shipper, recommended to General George Washington that the Continental Army be variolated. Variolation was an archaic and dangerous method of preventing smallpox, but it was the best method then available. Variolation involved applying smallpox-infected material (such as ground-up scabs) to an incision in the skin to induce immunity.[8,15,17-20]

Variolation had its roots in Africa and Asia.[15] First introduced in England in 1719, the mortality from intentional variolation was approximately 2%, but reached as high as 12%, particularly when traditional medical practices used immune-suppressing treatments such as starvation and bleeding to prepare for variolation. Furthermore, variolated individuals could spread smallpox for several weeks after the procedure. Washington was reluctant, however, to initiate such a drastic, unpredictable measure. Because variolation was attended by rumors of serious complications, respected leaders such as Benjamin Franklin opposed the practice; however, he later changed his opinion after his son died of smallpox. In January 1777, in Morristown, New Jersey, Washington finally ordered his troops to be inoculated because the risk of disease mortality was judged far greater than from variolation: "Should the disorder infect the Army in a natural way and rage with its usual virulence, we should have more to dread from it than from the sword of the enemy."[20]

Although some immunization was provided to the British Army, America's Continental Army was the first army to adopt immunization against smallpox as a force-wide policy, with measurable reductions in both morbidity and mortality rates (decreasing to less than 1%). To prevent smallpox from spreading via secondary contact with variolated troops, Washington's Army physicians performed the procedure in inoculation hospitals and isolated the troops in vaccination huts.[15,17,19]

The next major advance in vaccine safety was Edward Jenner's 1798 report that the intentional injection of the milder cowpox virus cross-protected against variola virus.[2,8,15] Despite some stubborn resistance to Jenner's discovery, the value of vaccination soon became apparent and made its way to America.

In the War of 1812, the US War Department ordered that, to prevent smallpox,[17] vaccination be substituted for variolation. In 1848, the US Navy did the same. Smallpox vaccination with a nonvirulent orthopox virus known as vaccinia was gradually but incompletely adopted among the civilian population. Smallpox remained an endemic and sometimes epidemic disease worldwide. During the American Civil War, use of smallpox vaccine expanded to include training camps. Nonetheless, an estimated 19,000 cases of smallpox occurred among the troops, with 7,000 deaths.[2,3,21]

In France in 1869, an estimated 200,000 people died of smallpox.[15] The 800,000-man Prussian Army revaccinated their personnel every 7 years at the time of the Franco-Prussian War (1870–1871). During the war, the Prussians contracted 8,463 cases of smallpox, with a case-fatality ratio of 5.4%. In contrast, the unvaccinated French Army was struck with 125,000 cases of smallpox, with a case-fatality ratio of 18.7%.

During the Spanish-American War of 1898, volunteer troops were vaccinated against smallpox as they entered military service. More smallpox cases occurred among these volunteers than among the regular Army, but most smallpox cases during that conflict occurred in the Philippine Islands.[2,3,15]

US military training camps continued to administer the smallpox vaccine during World War I.[22] The US military also conducted major smallpox vaccination programs during World War II for its own personnel, as well as for the local populations where American forces were deployed.[22] By the early 1970s, with smallpox no longer circulating within the United States, routine smallpox vaccination of civilians (especially children) was no longer practiced; complications like eczema vaccinatum and encephalitis were not considered justified risks with very little threat of disease.[15] By 1979, the World Health Organization's smallpox vaccination program succeeded in eradicating smallpox from the planet.

The US military routinely vaccinated all service members against smallpox from the 1940s[6,23] until 1984, when the vaccinations were limited to recruits entering basic training. Between 1984 and 1990 trainee smallpox vaccinations were intermittent because of a shortage of the vaccinia immune globulin used to treat certain adverse events after vaccination, as well as new

requirements to test for human immunodeficiency virus before vaccination. In 1990, the US Department of Defense discontinued smallpox vaccination of trainees. Military vaccination was limited to special circumstances (eg, laboratory workers exposed to other orthopox viruses). Not until December 2002, to counter threats of smallpox as a bioweapon, did the smallpox vaccination return specifically for troops deployed to high-threat areas and for US military medical personnel.

Typhoid Fever and Typhoid Vaccine

The next milestone in vaccinology was Louis Pasteur's development of the rabies vaccine in 1885.[2,3,8] This vaccine was administered to relatively few people as a form of postexposure treatment.

During the Spanish-American War, volunteer soldiers, officers, and physicians in trainee camps became sick from disease and died by the thousands.[1,6] Army Surgeon General George Miller Sternberg appointed Major Walter Reed to lead an investigative team that, using an epidemiological model of case clustering linked to local contamination of the water supply, found the cause to be typhoid. During the war, America experienced 280 battle fatalities and 20,738 cases of typhoid fever, many of them fatal.

At the start of the Spanish-American War, the new science of bacteriology was just taking root in Europe.[2,3,8] In 1896 Richard Pfeiffer demonstrated that cholera agglutinated in vivo. This finding guided Sir Almroth Wright to the hypothesis that dead bacilli could evoke an antibody response, thus resulting in the discovery of the typhoid vaccine. In 1898, Fernand Widal showed that serum from a recovered patient caused typhoid bacteria to clump. The Widal test was the first form of serodiagnosis. In 1899, during the Boer War in South Africa, the British Army used early forms of typhoid vaccine. Among the 14,000 immunized British troops in the siege of Ladysmith, approximately 2% contracted typhoid. In contrast, 14% of the unimmunized troops (58,000 troops) contracted typhoid fever, and 9,000 of them died. Lieutenant Colonel William Leishman continued typhoid research in the United Kingdom, standardizing production methods and performing studies that showed, by 1908, that two typhoid immunizations gave excellent protection.

In response to the American typhoid experience and British medical advances, Major Frederick F. Russell at the US Army Medical School manufactured and tested a new vaccine against typhoid fever.[2,3,6,8] This medical school was the first school of preventive medicine and public health in the United States and is known today as the Walter Reed Army Institute of Research (WRAIR).

In 1911 Army Chief of Staff Major General Leonard Wood (who began his Army career as a military physician) ordered the Army immunized against typhoid using Russell's vaccine. In addition, he ordered immunizations to be recorded in medical records.[2,3,6,8] The Navy also began typhoid immunizations in 1911. This made a critical difference in the health of military personnel. In 1914, this vaccine was licensed in the United States.

With a vaccine to shield troops from typhoid bacteria during World War I, a mere 1,529 cases of typhoid fever, with 227 deaths, were reported from among 4.1 million Americans in uniform.[2,3,8,24] The tragically high rates of typhoid morbidity and mortality during the Spanish-American War faded to nearly nothing by World War I.

Various vaccine combinations of typhoid, paratyphoid A, and paratyphoid B antigens were available in the 20th century.[2,3,24] The trivalent vaccine was commonly known as TAB vaccine, triple vaccine, or enteric vaccine. Inactivated by heat and phenol, the vaccine contained whole-cell preparations of *Salmonella typhi, Salmonella paratyphi* (A), and *Salmonella schottmuelleri* (B). The paratyphoid components were of questionable efficacy. Paratyphoid A and paratyphoid B bacilli were discovered in 1916 by the US Army Medical School, which soon developed a vaccine against them. In the following decade, TAB vaccine was withdrawn, reintroduced, and withdrawn again. In 1940, the triple TAB formulation was relicensed. Around 1945, paratyphoid A and paratyphoid B components were removed again from US formulation. Typhoid fever affected 0.42 cases per thousand soldiers in World War I; in World War II, thanks to immunization, it affected only 0.05 cases per thousand soldiers.

Today, clean water supplies prevent typhoid bacteria from entering military training camps (and cities) in the United States, but the risk of typhoid fever is still encountered overseas. Therefore, typhoid immunization is commonly performed before military deployments but not as a part of trainee immunization. New vaccine formulations—including an oral, live-attenuated vaccine and an injectable polysaccharide vaccine—are currently available if indicated by travel or occupational risk.

Yellow Fever

Yellow fever (a tropical disease spread to humans by infected mosquitoes) was a significant problem for US troops during the Spanish-American War, particularly in Cuba.[2,3,5,6,8] Army Surgeon General Sternberg appointed another board of investigation. Major Walter Reed and his colleagues proved Carlos Finlay's hypothesis of transmission of the disease by

the mosquito. Ultimately, follow-up research led to isolation of the yellow fever virus. Separately, in 1927, Max Thieler attenuated the virus by serial cell culture passage. The resulting vaccine strain 17D is still used today for travelers to yellow fever-endemic areas of the world, including deployed military personnel.

During World War II, yellow fever was considered a natural threat and a possible biological weapon. A yellow fever immunization program was set up for selected personnel in the US armed forces,[2-7,25] and by April 1942, 7 million doses of the vaccine had been administered. However, the program was complicated by reports of hepatitis.[2,3,5,7,26] In March 1942, 100 cases of hepatitis were noted at training camps in California, closely following yellow fever immunization. Health authorities quickly realized that the diluent for yellow fever vaccine contained human serum albumin contaminated with a previously unrecognized virus that caused hepatitis. Immunizations ceased, and the Rockefeller Foundation stopped producing the serum-derived product midway through 1942 until it could develop a serum-free formulation. By December 1942, more than 50,000 cases of hepatitis B and 84 deaths were noted to have followed approximately 2.5 million yellow fever immunizations from certain lots. This incident helped reveal differences between hepatitis A virus (then called infectious hepatitis) and the newly recognized hepatitis B virus (then called serum hepatitis). This finding highlighted the risks of using vaccines in large populations without preliminary safety testing, which is currently required for licensure of all drugs including vaccines.

Recent concerns about rare cases of neurotropic disease associated with yellow fever vaccine raise questions about whether military forces should use yellow fever vaccine narrowly[27,28] (focusing on those traveling in the near future) or broadly (minimizing the number of immunizations needed just before departure). Military policy makers balance the competing demands of risk and benefit as information about both components changes over time and in relation to target populations to be immunized.

Influenza

In 1918 and 1919, a worldwide outbreak of influenza killed over 25 million people, or 1% of the entire world population.[2,3,6,8,29] This pandemic caused a greater loss of life within a shorter period of time than any other catastrophe in history. At least 500,000 deaths occurred in the United States (400 deaths per 100,000). This worldwide pandemic killed more people than all combat deaths in the 20th century combined. Unfortunately, no influenza vaccine was available to quell the disaster.

The first indication of the developing American outbreak came in March 1918 at Camp Funston, Kansas, near Fort Riley. By April, influenza cases appeared in most American cities and followed American soldiers being deployed to Europe. The hospital commander at Camp Funston reported, "There are 1,440 minutes in a day. When I tell you there were 1,440 admissions in a day, you will realize the strain put on our Nursing and Medical force."[30]

During those first few months, the infection was incapacitating but not very lethal. By August, however, virulence increased, and people were dying in massive numbers. In response to the incapacitation and deaths, theaters, dance halls, bars, schools, churches, and other public places were closed. Football games were cancelled, and telephone booths were padlocked. The pandemic weakened German military forces, perhaps more than Allied troops. It might have also been a precipitating factor in Woodrow Wilson's physical and mental demise.[2,3,29]

By 1942, the science of virology had progressed enough that Army Surgeon Generals James C. MacGee and Norman T. Kirk commissioned research that resulted in the first effective influenza vaccines.[2-8] Field trials sponsored by the Army began with US service members, demonstrating an 80% efficacy. Efficacy of all such vaccines was dependent on correlation of the antigens in the vaccine formula with circulating viral types, but scientists did not yet fully appreciate the routine antigenic variation of the influenza virus. In fall 1945 and spring 1946, all troops were immunized against influenza. This disease prevention strategy was not repeated the following season, but by the early 1950s, military influenza immunizations were routine, a policy continuing today.

An example of the importance of preventing influenza in military communities comes from the USS *Arkansas*, sailing from its home port in February 1996.[31] After an influenza virus that did not match the strains used for immunization got into the ship, 42% of the ship's company became ill. The rate of incapacitating illness caused ship personnel to cancel training exercises and make an unscheduled return to port.

Over the decades, the benefits of influenza immunization have become more apparent for increasing sectors of the nation's population. Today, the most widely used vaccine in America is the influenza vaccine.

Adenoviruses

After World War II, adenovirus infections (particularly serotypes 4 and 7) attacked approximately 80% of military trainees and were linked with epidemic acute respiratory disease outbreaks in training camps.[6,32-35] Up to 60% of trainee acute respiratory

disease resulting in hospitalization was linked to adenovirus infections. Infections in seasoned military personnel were significantly lower. In the early 1960s, before widespread immunization of trainees, 600 to 800 acute respiratory disease hospitalizations per week occurred at military basic training sites in the northern United States, disabling 40% to 50% of these closed communities. Adenovirus infection, which resembles influenza in clinical manifestations, represented the leading cause of military hospitalizations in the United States at that time. Hospitalization rates of 6% to 8% per week typically occurred during basic training cycles.

In 1956 WRAIR developed formalin-inactivated vaccines against adenovirus types 4 and 7.[2,3,5,6,13,33,36] These vaccines were marketed from 1957 to 1965 by Parke-Davis (Morris Plains, New Jersey) as common cold vaccines, with viral types 3, 4, and 7 represented in the vaccine. In 1958 Maurice Hilleman of WRAIR demonstrated that attenuated adenovirus vaccine types 3, 4, and 7 reduced adenovirus disease incidence by 60% to 90% among US soldiers during the stressful and crowded conditions of basic training. A report estimated that the vaccine saved the Army about $5 million per year.

In 1959 inactivated adenovirus and influenza virus antigens were combined in a Parke-Davis product known as Resprogen. Several million doses were sold between 1959 and 1965. In retrospect, this was an irrational combination because the vaccine's strains remained unchanged while naturally circulating influenza strains change annually. However, the need to change influenza viral antigens annually was not recognized in clinical practice until the early- to mid-1960s.

In 1963 viral seed lots for this vaccine were found to contain the oncogenic SV40 virus and the SV40 genome in the adenovirus capsids. Safety concerns and, more directly, lack of efficacy resulted in the product being withdrawn from distribution. Questions regarding long-term sequelae to SV40 exposure arise periodically, but several studies have shown no elevated risk of cancer in vaccine recipients. Live adenovirus types 4 and 7 vaccine used in modern products have not been oncogenic.[37]

In 1964 clinical trials of live, attenuated type 4 vaccine began at WRAIR.[2,3,5,6,13,33,36] Trials of adenovirus type 7 began in 1969 and adenovirus type 21 in 1971. Adenovirus type 7 vaccine was added to the regimen given to American military trainees in 1970. Live adenovirus types 4 and 7 vaccines were developed in the 1970s and licensed in July 1980 as oral tablets. Vaccine tablets were given to trainees shortly after arrival at a basic training center, with a protective antibody response expected within 2 to 4 weeks after administration. Adenovirus vaccines achieved dramatic reductions in disease incidence: 95% in one study. A large trial of 8,238 soldiers reduced hospitalizations by 90%. Immunization induces specific protective serum and secretory intestinal antibodies, protecting against infection for at least 60 days and presumably longer.

By 1984, both vaccines were routinely administered in tablet form to trainees at all basic training camps. However, the manufacturer (Wyeth Laboratories, Madison, New Jersey) ceased production in 1996. The last lots of these vaccines expired in 1998. Since then, disease outbreaks among trainee populations have recurred, including several deaths.[38-40] A replacement manufacturing line for adenovirus types 4 and 7 vaccine will be submitted for regulatory review in the future.[41]

Meningococcal Disease

Meningococcal meningitis is a life-threatening bacterial infection that occurs with low frequency but with a high case-fatality ratio. In the 1960s the disease occurred with disturbing frequency in military trainees. Antibiotic prophylaxis was used initially, but the *Neisseria meningitidis* organisms became increasingly drug resistant.

In 1966 a meningococcal research unit was organized at WRAIR.[2-7,13,42,43] The first human tests of a meningococcal vaccine to protect against disease caused by group A meningococci began in July 1967. In 1968 scientists led by Goldschneider, Gotschlich, and Artenstein at WRAIR developed a serogroup C vaccine that prevented disease and also reduced the carrier rate. This was the first modern polysaccharide vaccine. Large clinical trials were conducted in thousands of military trainees. Their team defined the humoral responses to the meningococcal organism and the fact that the polysaccharide subunit vaccine could stimulate protective immunity. Later, they developed its serogroup A counterpart vaccine.

In 1972 scientists at the Institut Mérieux in France developed a serogroup A meningococcal vaccine using WRAIR's methods.[3,13] Work by both teams helped to manage meningococcal serogroup A epidemics that swept through Finland and Saõ Paulo, Brazil. In 1973 the entire Finnish population of, more than 4 million people was immunized against serogroup A to control an epidemic. The Brazilian epidemic of 1974 produced 150,000 cases of meningococcal disease and 11,000 deaths. During the Brazilian epidemic, 100 million doses of serogroup A vaccine were administered in one of the most dramatic mass immunization

efforts ever.

Widespread use of meningococcal vaccine among US military trainees began in 1971. The combined interventions of vaccination and reduced crowding (through smaller class size) reduced the risk of fatal meningococcal disease during basic training.[2-7,13,42,43] Since then, meningococcal immunization has been part of the core immunization requirement for new trainees.[44] The work of other researchers allowed the addition of meningococcal group Y and group W-135 polysaccharides to make a quadrivalent vaccine that could defend against four kinds of these bacteria. In April 1974, the US Food and Drug Administration licensed meningococcal group A vaccine, with group C vaccine and bivalent A + C vaccines following in July and October 1975. Sanofi Pasteur's (Lyon, France) tetravalent vaccine against serogroups A, C, Y, and W-135 (Menomune) received a US license on January 3, 1978.[13]

Meningococcal immunization marked another advance when the Food and Drug Administration licensed Sanofi Pasteur's protein-conjugated meningococcal vaccine, Menactra, in January 2005. Compared to polysaccharide immunization, the protein-conjugated characteristics are expected to offer prolonged duration of immunity. The military success with meningococcal immunization was cited when recognition of elevated rates of meningococcal disease among college freshman and dormitory residents led to calls for immunization in those populations.[45]

DEVELOPING POLICY FOR IMMUNIZATION REQUIREMENTS

Military trainees need immunologic protection against the infectious diseases that threaten them during training and after they enter into military service. As the number of available vaccines increases, prioritizing which vaccines to administer during training or later requires consideration of effectiveness, safety, and a cost-benefit equation from both the individual and the military service perspectives.

Senior preventive medicine officers develop vaccine recommendations for both military trainees and other military personnel, with decisions made by the Army, Navy, and Air Force Surgeon Generals and the US Coast Guard Director of Health and Safety. During policy development, advice can be sought from the AFEB.[7] This policy development process consists of public health recommendations published by the Centers for Disease Control and Prevention, in consultation with its Advisory Committee on Immunization Practices. Recommendations, guidelines, and disease surveillance information are also considered from other agencies and expert bodies, such as the National Vaccine Advisory Committee, the American Academy of Pediatrics, the American College of Physicians, the American College of Obstetricians and Gynecologists, and the World Health Organization. Risk assessment information on malicious infections and bioweapons is gathered from the Defense Intelligence Agency, the Armed Forces Medical Intelligence Center, the Department of Homeland Security, and similar organizations.

Vaccines are prescription drugs. Unlike clinical prescription decisions, in which medication use is customized to individual patients, vaccine policies typically involve a few decisions that lead to medication administration to large populations of people. Because they are administered primarily to healthy people to keep them well, vaccines are required to be among the safest of all categories of medications. No medication, however, is 100% safe. Therefore, the standard of practice with vaccines is to screen everyone eligible for immunization to identify the few individuals who should be exempted from that immunization or who require additional medical evaluation prior to vaccine administration.[46] Exemptions are granted based on medical contraindications or a history of serious adverse events after an earlier immunization. Some contraindications are absolute, but most are relative—clinicians need to weigh the individual risk-benefit ratio of immunization versus disease risk with no immunization.

Standard exemptions can be defined by policy, based on common medical contraindications or a history of an individual having a serious adverse event after an earlier immunization. Individuals can be screened for these exemptions by immunization clinic staff during preimmunization group education. Individual trainees can be privately interviewed by clinic staff to elicit further information and confirm the exemption. When a nonstandard exemption is suspected, a clinician can be consulted for clarification.

With the success of immunization in reducing the incidence of diseases like poliomyelitis, measles, and rubella,[47] the military health system faces the same challenges as the civilian public health sector—increasing concerns about vaccine safety and adverse events experienced after immunization. Even one adverse event among thousands of vaccine recipients, if serious or with prolonged health impact, can cause concerns about the safety of an immunization program.

The armed services and the AFEB are uniquely responsible for considering the special circumstances of military life. These circumstances include an enhanced emphasis on disease control at the community level.

Unlike civilian communities, in which individual choice for immunization is a key component, military teams rely on the health of each member. This interdependence has vital consequences in combat settings, where the loss of one service member from an infectious disease could degrade unit performance and cause the loss of other service members from enemy action. This interdependence is typically the reason for mandatory military immunization requirements. The unity of command, unique to military settings, allows individual public health decisions to be applied consistently across broad communities.

Immunization decisions are based on benefits expected from avoiding infections that have specific characteristics of incidence, prevalence (ie, endemic level), transmissibility, and incubation period, as well as disease characteristics reflected by the clinical spectrum and duration of morbidity, the case-fatality ratio, availability and effectiveness of treatments, and other factors. Risks from immunization similarly involve incidence, a clinical spectrum of severity, duration of impaired function, speed and probability of resolution, availability and effectiveness of treatments, and similar factors.

Vaccine Safety

Few conditions are uniquely caused by immunization.[48] One of the few examples is paralytic poliomyelitis that rarely follows use of the live-attenuated poliovirus vaccine. On the one hand, immunizations can be risk factors that increase the relative risk of an adverse event occurrence (eg, Guillain-Barré syndrome that was more likely with some annual formulations, but not others, of influenza vaccine). On the other hand, health conditions that occur in unimmunized people are fully expected to occur in immunized people, with the same background rates of incidence. Discerning when an adverse event that occurs after immunization is an adverse reaction that should be causally attributed to immunization can be a clinical challenge.

When vaccines are administered to groups, the physical responses of the recipients might be similar, causing a form of mass reaction. The mechanism is the same as that for mass reactions in other circumstances. These phenomena have been categorized as mass psychogenic illness.[49] It must be stressed, however, that this is a diagnosis of exclusion. Overuse of such a diagnosis can result in false classification of patient problems that undermine trust and interfere with a therapeutic relationship focused on healing and wellness, regardless of causality.

Mass psychogenic illness is defined as the collective occurrence of a constellation of symptoms suggesting organic illness, but without an identified cause, in a group with shared beliefs about the cause of the symptoms.[49] Such outbreaks have been reported in various cultural and environmental settings, including developing and industrialized countries, the workplace, public transport, schools, and military cohorts. Perceived threats have involved food, fire, toxic gases, and vaccines. Across the putative exposures, reported symptoms are often similar, including headache, dizziness, weakness, and loss of consciousness.

If vaccines are identified as a possible cause of illness in a population of immunized individuals, whether causality has been proven or not, a dismissive approach might not succeed in reassuring the group. The public might not be easily convinced that nothing was wrong with the vaccine until the situation has been thoroughly evaluated. Individual evaluations of rare adverse events might be complex and time-consuming, with causality not proven or disproven at the end of the process.

Clinic staff members often observe syncope among military trainees receiving immunizations. It is not uncommon for one or two individuals in a typical group of 50 to 200 trainees to develop syncope. An equal or greater number develop only presyncopal signs and symptoms. All cases require intervention to minimize the potential for injury, which can produce severe sequelae.

Because syncope can occur at any time despite adequate procedural modifications and close observation, the use of rubber padding on floors and the removal of fixed furniture around spaces where trainees are processed are recommended to minimize injuries. Where syncope occurs without these measures, vaccine recipients can sustain a variety of injuries (eg, simple contusions, dental trauma, or facial or skull fractures).

Where trainees assemble in lines in clear view of the immunization injection process, fear and anxiety can develop among those waiting. Syncope or presyncope in one trainee, visible to others, can increase the likelihood of a similar response in others as they approach the immunization point. Rather than long lines in view of an immunization station, the immunization process can be arranged so that waiting trainees view the immunization station for a shorter period of time. Careful observation of trainees around the time of injection can identify those in imminent danger of syncope, permit effective interventions that include removal of the trainee from the line, implement relaxation techniques, and adopt a seated or supine position for 5 to 15 minutes. Syncope can be confused with life-threatening hypotension related to anaphylaxis.

Precise medical evaluation is required to assure that life saving therapies (eg, epinephrine) are administered in a timely fashion when indicated.

A presyncopal trainee who verbalizes full recovery should be permitted to continue the immunization process. A trainee who experiences uncomplicated syncope generally can be evaluated and treated by clinic staff without the need for further medical workup. The affected trainee should be placed immediately in a supine or recovery position and be required to stay in that position for 5 to 15 minutes. Virtually all affected trainees will recover spontaneously after such interventions. Syncope by itself should not be considered a contraindication to future immunization. In all cases of syncope, clinic staff should ensure that the trainee receives the remainder of the immunizations as soon as possible after recovery.

It is not clear whether some individuals are at higher risk for syncope and presyncope than others. Putative individual risk factors include relative dehydration, sleep deprivation, anxiety, and nervous temperament. Formal research in this area among military trainees is lacking.

Providers care for individual patients with adverse events. The challenges of considering the risk-benefit ratio of continued immunization in the face of a more serious or prolonged adverse event cannot be underestimated. Rare immunologic adverse events, such as idiopathic thrombocytopenic purpura after measles-mumps-rubella immunization, were not recognized until many years after vaccine licensure and use. Although only described in childhood, it is currently unknown whether this rare adverse event also occurs in adult populations receiving booster doses of vaccine.[50,51] The study of vaccine safety—considering immunogenetic differences in vaccine responses and side effects—is a new specialty for 21st century immunization healthcare, and merits further examination of both new and old vaccines.

Specific Immunization Recommendations

Some diseases that service members need to be protected against are endemic in the United States (eg, tetanus, influenza, meningococcal, hepatitis B) or can spread rapidly in close living conditions (eg, influenza, measles, meningococcal, varicella). Other vaccines protect against occupational hazards (eg, rabies). Some vaccines guard against poor sanitary conditions that can affect prolonged field operations (eg, hepatitis A, typhoid) or the blood-borne exposures that can accompany traumatic injury (eg, hepatitis B). Other vaccine-preventable infections are unique to tropical or other areas outside the United States (eg, yellow fever, Japanese encephalitis, poliovirus). Some vaccines act as countermeasures to biological weapons (eg, anthrax, smallpox). Vaccine recommendations for various military cohorts appear in Table 12-2.[6,11]

The most acutely needed vaccines during military training protect against pathogens causing imminent risk of contagious disease in close-contact settings: adenovirus, influenza, meningococcal, measles- mumps-rubella, and varicella. Pneumococcal vaccine can be administered in training settings in which elevated incidence rates have been documented. Other vaccines are administered to prevent infections more likely to occur during international travel or during extended periods of military service, such as hepatitis A, hepatitis B, influenza, poliovirus, and tetanus-diphtheria. Marine Corps and Coast Guard trainees typically receive yellow fever immunization toward the end of training.

In their initial training courses, cadets, midshipmen, officer candidates, and officers typically do not encounter the same risk for adenovirus and meningococcal outbreaks as enlisted trainees. However, officer candidates and young officers receive immunizations for protection against preventable infectious diseases they might encounter or must avoid during military service (eg, influenza [seasonal], measles-mumps-rubella, varicella, tetanus, diphtheria, hepatitis A, and poliomyelitis). These individuals also receive travel vaccines based on a geographic risk analysis.

Although hundreds of trainees report to training centers within a short period of time, their immunization needs or contraindications can still be assessed individually.[46] Decades of experience show that customized immunization delivery with high throughput can be performed by dividing the tasks into several stations, performing education and screening for contraindications in groups, processing people with contraindications or special situations separately, setting up multiple lanes to overcome rate-limiting steps, and listening to individual service members. Maintaining compliance with the standards of quality immunization healthcare carries a high workload demand on the healthcare workers providing these services.

One of the more remarkable instances of mass customized immunization occurred in early 2003, when more than 400,000 service members deploying to southwest Asia were screened for smallpox vaccination.[23] The mission was to educate both providers and recipients thoroughly about the idiosyncrasies of smallpox vaccination, identify those with atopic dermatitis or other reasons not to be vaccinated, administer the vaccine safely, and care for the vaccination site appropriately while protecting others from secondary infection through contact with vaccinees.

TABLE 12-2

VACCINES TYPICALLY ADMINISTERED TO US MILITARY PERSONNEL, 2006[*]

Population Segment	Vaccine	Routine Schedule for Troops[†]
Trainees	Diphtheria	Single dose
	Hepatitis A	2 doses
	Hepatitis B	3 doses
	Influenza	Annual, seasonal
	Measles	Single dose
	Meningococcal disease	Single dose
	Mumps	Single dose
	Pertussis, acellular	Single dose (pending)
	Poliovirus	Single dose
	Rubella	Single dose
	Tetanus	Single dose
	Varicella[‡]	2 doses
	Yellow fever[‡]	Single
Routine during career (both active duty and reserve component)	Diphtheria	Every 10 years
	Hepatitis A	2 doses
	Influenza	Annual, seasonal
	Pertussis, acellular	With Td (pending)
	Tetanus	Every 10 years
Based on deployment or travel to high-risk areas (both active and reserve components), various alert forces	Anthrax	Multidose series
	Hepatitis B	3 doses
	Japanese encephalitis	3 doses
	Meningococcal disease	Single dose
	Smallpox	Single dose, every 10 years
	Typhoid	Dosage varies
	Yellow fever	Single dose, every 10 years
Individualized according to occupational or personal needs	*Haemophilus influenzae* type b	Single dose
	Hepatitis B	3 doses
	Meningococcal disease	Single dose
	Pneumococcal disease	Single dose
	Rabies	3 doses
	Varicella	2 doses

[*]Military personnel include US Army, Navy, Marine Corps, Air Force, and Coast Guard.
[†]Assumes basic immunizing series received earlier in life. Booster doses may be required at annual or other intervals to sustain immunity.
[‡]Vaccination policy varies among military services, based on individual needs.
Td: full-strength tetanus and reduced-strength diphtheria toxoid
Data sources: (1) Takafuji ET, Russell PK. Military immunizations: Past, present, and future prospects. *Infect Dis Clin North Am.* 1990;4:143–158. (2) US Department of Defense. US Army Regulation 40-562; Navy Bureau of Medicine and Surgery Instruction 6230.15; Air Force Joint Instruction 48-110; Coast Guard Commandant Instruction M6230.4E. *Immunizations & Chemoprophylaxis*. Washington, DC: DoD; 1995. Available at: http://www.e-publishing.af.mil/pubfiles/af/48/afji48-110/afji48-110.pdf. Accessed November 15, 2005.

This vaccination program was performed with standardized education materials, two- and three-page screening forms, bandages, and trained medical staff performing the vaccinations at each clinic. The design of this program was driven by lessons learned during the anthrax vaccine immunization program and the work of the Vaccine Healthcare Centers Network and the Military Vaccine Agency.

Typically, reserve personnel receive the same immunizations as active-duty personnel with similar occupational, travel, or other risk factors. Each military service preventive medicine authority maintains current health threat assessments based on disease prevalence in specific geographic regions using federal, Department of Defense, US Coast Guard, and other relevant sources of information. These assessments are disseminated to units within their respective jurisdictions by service or command messages. Installations and deployed units report disease occurrence through appropriate lines of communication. Combatant

commanders, in coordination with the appropriate surgeons general or Commandant of the Coast Guard, establish specific immunization requirements based on a disease threat assessment. For personnel entering specific areas for exercises or operational missions, these requirements can differ from standard military service immunization policies. Personnel on official deployment or travel orders are immunized by local medical support before departure in accordance with specific guidance established by the combatant commander.

The AFEB reviewed the scientific basis for the safety and effectiveness of simultaneous immunization in February 2004. In a March 2004 report,[52] the AFEB found that scientific panels have concluded consistently that available evidence has not documented any known serious health risk from receipt of concurrent immunizations. In most cases, concurrent immunization simply mimics simultaneous encounters with multiple viruses and bacteria in the natural environment. To minimize discomfort to immunized personnel, the AFEB recommended strategies to decrease concurrent immunizations without sacrificing individual and population benefits of widespread immunization. These strategies included spreading immunizations into clusters over a period of time, increasing the use of serologic screening to eliminate redundant immunization, presuming prior immunization when good evidence exists to support it, and minimizing just-in-time delivery of immunization—especially for reserve component personnel—by increasing the frequency of individual medical readiness reviews.

When military personnel travel on short notice to areas requiring multidose series vaccines, they should receive the first dose of the basic immunizing series and as many of the subsequent doses as time permits. If the series cannot be completed before departure, it should be done after arrival. However, to obtain optimal immunity, completing the series before departure remains the goal.

STANDARDS FOR QUALITY IMMUNIZATION SERVICES

To deliver immunization services properly, each military clinic must adhere to uniform standards. These standards apply even in austere field environments and at sea, and correspond to the National Vaccine Advisory Committee's quality standards for immunization programs in nontraditional settings.[46] A pragmatic checklist for organizing a large-scale immunization program appears in Exhibit 12-1.

Information and Education

Vaccine providers must be trained appropriately in all aspects of vaccine administration, including vaccine storage and handling, elicitation of preimmunization information from candidates, provision of general preimmunization information (eg, Vaccine Information Statements), vaccine administration and related techniques, and clinical handling of adverse reactions. A variety of training resources are available at the Web sites of the Military Vaccine Agency (http://www.vaccines.mil), the Vaccine Healthcare Centers Network (http://www.vhcinfo.org; including more than 50 hours of Internet-based training known as "Project Immune Readiness," which earns continuing education credit), and the Centers for Disease Control and Prevention (http://www.cdc.gov/nip).

Before immunization, the candidate must be informed about the associated risks and benefits. The Vaccine Information Statements developed by the Centers for Disease Control and Prevention or brochures distributed by the Military Vaccine Agency are succinct summaries of vaccine risks and benefits. Vaccine providers should be prepared to answer questions and concerns posed by the vaccinee, and point the way to more detailed information if needed.

During group education, trainees should be offered the opportunity to receive information and request private interviews. Because trainees might feel hesitant to ask questions or seek additional information around their peers, use of private interviews can facilitate education. Requiring the training cadre to remain outside while group education is conducted increases the trainees' willingness to obtain further information.

Vaccine Storage and Handling

Adhering to vaccine handling and storage recommendations is critical. Mishandling or inappropriate storage can render vaccines ineffective. Vaccines need to be either refrigerated or frozen in appliances in which storage temperature records are maintained. When vaccine supplies arrive, they need to be moved promptly to appropriate storage conditions. Training all personnel who might receive a vaccine shipment is essential. Large stocks of vaccine inventories should be connected to recording thermometers and alarm systems that can receive prompt attention 24 hours a day, 7 days a week.

Some trainee immunization clinics are located outside established medical facilities and lack the redundant power backup systems that exist in larger facilities. Even with proper alarms and notification, power failures or equipment malfunction can jeopardize vaccine integrity, if the volume of stored vaccines

EXHIBIT 12-1

PROTOTYPE SEQUENCE OF EVENTS FOR A TRAINEE IMMUNIZATION PROGRAM

1. **Identify session goals**. Which policies apply? Which diseases do individuals need protection from? What is the preexisting immunity of the individuals to be immunized? What other services will be provided during same session (eg, pregnancy testing, tuberculin skin testing, glucose-6-phosphate dehydrogenase or other blood testing, injecting long-acting penicillin for bacterial prophylaxis, dispensing malaria chemoprophylaxis)?
2. **Prepare facility and order supplies**. Arrange furniture for a common education area. Order vaccine and provide for cold-chain management at clinic site. Order other consumable supplies (eg, syringes, needles, bandages, sharps containers). Set up multiple lanes to process trainees efficiently. Arrange electricity and laptop computers or other electronic devices to record immunizations administered. Identify number of trainees to be educated, screened, immunized, and documented.
3. **Prepare staff**. Ensure staff are trained in indications and contraindications for vaccines to be administered. Training materials are available from http://www.vhcinfo.org, http://www.vaccines.mil, and http://www.cdc.gov/nip. Train staff in appropriate infection control procedures. Ensure a provider responsible for prescription vaccine administration is accessible and involved in program planning.
4. **Issue instructions to trainees**. Provide information on what kind of uniform to wear, especially regarding sleeve length, and tell them to bring official copies of prior immunization records.
5. **Customize procedures**. Obtain laboratory test results or documentation of prior immunizations that can reduce the immunization workload when trainees arrive.
6. **Educate vaccine candidates**. Provide copies of current Vaccine Information Statements and/or official Department of Defense vaccine education brochures for trainees to read before immunization. Provide any appropriate counseling on deferring pregnancy until after immunization. Create an environment that enables individuals to ask questions and to receive private counseling when needed.
7. **Screen for contraindications**. Identify relevant allergies, positive tuberculosis tests, or prior adverse events. For women, test for or ask about the possibility of pregnancy in a private, respectful way to elicit candid information and provide specialty referral when needed.
8. **Double-check safeguards**. Check preparations for fainting and anaphylaxis. Install rubber mats on the floor.
9. **Administer immunizations**. Vaccinees can assist with the procedure by swabbing their own arms with alcohol. For oral or nasal vaccines, they can be observed self-administering the immunization.
10. **Observe for anaphylaxis**. Observe vaccinees for at least 15 to 30 minutes, so that any acute allergic events can be properly treated. Some vaccines and/or vaccinees may require longer waiting periods.
11. **Document immunizations**. Document immunization data elements in the appropriate medical records and in the designated electronic immunization tracking system. Provide a record of the immunizations administered to the vaccinees whenever possible.
12. **Conduct quality improvement**. Include a quality improvement program to identify and respond to medication errors, accidents, or other incidents. Ensure proper storage and handling of vaccines, including cold chain and temperature tracking.

is too large to be transported quickly to alternative refrigeration. Decisions about the quantity of vaccine product to be kept on hand at local trainee immunization facilities require a balance between the clinic's operational requirements, the need to minimize frequent vaccine resupply, the risk of power failure, and risk aversion of involved personnel. Where possible, trainee immunization clinics should be retrofitted with redundant power supplies and freezer and refrigeration equipment to reduce product loss and ensure continuous delay-free operation. An understanding of vaccine storage and handling during the administration process is also critical to vaccine safety and efficacy. Some vaccines, such as live attenuated intranasal influenza vaccine, require special handling during administration.

Assessing Immunization Histories

Ideally, vaccine providers should read earlier immunization records and briefly interview each immunization candidate. The goals are to avoid duplicate or redundant immunization and to identify any contraindications. At a minimum, the following information

should be obtained from the vaccinee, either in person or through a review of available records: vaccines previously received, preexisting health conditions, allergies, and adverse events that occurred after previous immunizations. Consulting the vaccinee's paper and electronic medical records is the most reliable method of determining immunization status.

When determining individual immunization needs, trainees should receive credit for immunizations appropriately documented earlier in life. Trainees who did not complete basic immunizing series earlier in life should be identified and receive sufficient doses to complete those series. Serologic testing can minimize administration of vaccines to people who are already immune. Military trainees can be assumed to have similar proportions of preexisting immunity as the high school cohorts from which those trainees come. These proportions change over time as childhood immunization policies change.[52-59] When substantial proportions of immunization candidates are already immune, the cost of high-quality serologic testing for identification of true vaccine requirement will be recovered through savings gained by reduced vaccine supply utilization.[60,61] For example, in the face of expanded immunization with hepatitis B vaccine, serologic screening of military trainees for hepatitis B immunity is cost-effective.[62]

Cost-effectiveness analyses of serologic screening performed in civilian settings are not necessarily applicable in military settings, where improvements in economies of scale and lower direct and overhead costs can decrease the total cost of serologic screening. Missed immunizations caused by false-positive serologic screening results are rare because of the high specificity of modern screening tests. They do not result in clinically significant numbers of susceptible trainees, even in large cohorts.

Contraindications

Before administering an immunization, vaccine providers must identify any contraindications that would make an immunization unsafe or unwarranted. If a contraindication to immunization exists, this information should be provided to the clinic supervisor and the vaccine candidate, as well as documented in the medical record. Temporary and permanent contraindications should be annotated in electronic medical records to avoid recalling a service member for an immunization that should not be administered or that should be deferred.

Severe systemic hypersensitivity reactions (including anaphylaxis) to egg protein, gelatin, neomycin, or streptomycin are contraindications for vaccines that contain these products. Although they are important, these contraindications affect only a small number of adults. Live virus vaccines are generally contraindicated for adults who are immunocompromised and for women who are pregnant.

Vaccine providers should be aware of and avoid the most common misconceptions concerning contraindications. Initial and update training for vaccine providers at all levels (eg, medics, nurses, physicians) is important for quality immunization delivery.

Side effects vary among vaccinees in duration, severity, and reproducibility if more than one vaccine dose is required. In some individuals, when prior immunizations are disregarded, a high level of prior immunity can contribute to robust reactions and increased local and systemic side effects. The standard of care for adverse drug reaction management is that adverse events after drug administration must be evaluated carefully to avoid worsening problems with subsequent doses, unless the benefit of the drug outweighs the risk of the adverse event. This type of evaluation frequently requires a specialist, particularly if the concern is not easily categorized or has not been previously well defined.

An assumption that, because an immunization program is safe and effective, the individual's adverse event does not result from one or more vaccines, other medications, or environmental effects might not be valid. Such an assumption can undermine the long-term trust and therapeutic relationship between a healthcare provider and vaccinee. There is a well-documented difficulty associated with getting clinicians to report either medication errors or adverse drug events. In addition, prelicensure clinical trials may lack the size to detect rare adverse events.[63,64] There is a need for an increased commitment to postmarketing surveillance for detection of rare adverse events only detectable with wider drug use in larger and more diverse populations.

New approaches to postmarketing surveillance of adverse events in adults should consider age, gender, ethnicity, and other yet-to-be-identified risk factors, particularly as new vaccines are introduced.[65] There is a need for improved evaluation, management, and understanding of rare adverse events.[66,67] So that rare adverse events can be analyzed consistently at different locations, there is also a need for international concurrence on standardized case definitions. For example, the Brighton Collaboration demonstrates international interest and the need for centers of excellence in vaccine safety dedicated to studying rare events.[68-70] These efforts are a credible response to the rising concerns about safety.[71,72] Treatment of individuals with adverse events affects the troops' trust of military immunization programs and merits an ongoing commitment to

quality outcomes and performance improvements.

When the traditional smallpox vaccine was delivered to young adults, rather than children, a new epidemiologically linked adverse event—myopericarditis—was recognized.[73-75] Clinicians, healthcare workers involved in immunization delivery, program managers, and others need to be aware of unanswered questions and issues for future study and understanding. Each adverse event must be reported and evaluated in depth. Clinical detail related to adverse events supports efforts to understand newly recognized adverse events (eg, oculorespiratory syndrome identified with Canadian influenza vaccine).[76] The study of vaccine safety and efficacy is a dynamic and evolving area requiring more clinical involvement to complement epidemiological surveillance efforts.

An approach to adverse events and consideration of medical exemptions from further immunization are outlined in clinical guidelines (available at: http://www.vaccines.mil and www.vhcinfo.org). Table 12-3 outlines the categories of medical exemptions used in setting specific levels of safety concerns. Many exemptions are compatible with continuation of military service, but there might be service-specific variations for certain vaccines.

Record-keeping

Each time a person receives an immunization, the following information must be recorded: name, age, type of vaccine, dose, site and route of administration, name of the vaccine provider, name of person administering the vaccine, date vaccine was administered, manufacturer, and lot number. The date of the next dose should be communicated to the vaccinee. Electronic immunization tracking systems can calculate these dates automatically. Transferring electronic immunization records to central repositories reduces needless duplication of immunizations. The armed services use electronic communications methods (eg, information portals, e-mail) to inform service members of upcoming immunizations.

Vaccine Administration

Specific information regarding the recommended route of administration and appropriate dose is included in the package insert of each vaccine and summarized in other references. Most vaccines are administered intramuscularly or subcutaneously. The dose indicated in the insert should be the dose actually

TABLE 12-3

MEDICAL EXEMPTION CATEGORIES FOR IMMUNIZATION

Code	Meaning	Explanation	Duration*
MD	Medical, Declined	Declination of optional vaccines (not applicable to many military immunizations), religious waivers.	Indefinite
MI	Medical, Immune	Evidence of immunity (eg, by serologic antibody test, take after smallpox vaccination). Documented previous infection (eg, chickenpox infection). Natural infection presumed (eg, measles, if born before 1957).	Indefinite
MP	Medical, Permanent	HIV infection, prolonged or permanent immune suppression, other contraindication determined by physician. Can be reversed if the condition changes. For tuberculosis, positive tuberculosis test.	Indefinite
MR	Medical, Reactive	Permanent restriction from receiving additional doses of a specific vaccine. Use only after severe reaction after immunization (eg, anaphylaxis). Report such reactions to VAERS. Code can be reversed if an alternate form of prophylaxis is available. Do *not* code mild, transient reactions as MR. Code events referred for medical consultation as MT.	Indefinite
MT	Medical, Temporary	Pregnancy, hospitalization, events referred for medical consultation, temporary immune suppression, convalescent leave, pending medical evaluation board, any temporary contraindication to immunization.	Up to 365 days

* Indefinite status can be changed by a responsible provider at any time based on an individual medical evaluation assessing benefit-risk status and new information related to individual's risk management.
HIV: human immunodeficiency virus
VAERS: Vaccine Adverse Event Reporting System
Data source: Defense Eligibility Enrollment Reporting System. Available at: http://www.tricare.osd.mil/deers/default.cfm. Accessed December 27, 2005.

given. Administering partial doses to potentially reduce the risk for adverse reaction may not be an effective method and could result in inadequate protection against disease. Specialized individual vaccine safety and efficacy evaluations may result in modified vaccine dosing, route of vaccine administration, or timing of vaccine administration. Such modifications from standardized vaccine schedules require a credentialed provider order with documentation of the reasons for such customized orders.

Adverse Events

Vaccine providers must be trained to recognize and treat adverse reactions. The supplies and equipment needed to ensure this follow-through must be readily available onsite (eg, epinephrine).

Licensed vaccines are safe and effective, but adverse events can follow immunization. These adverse events can range from minor, injection-site reactions to severe systemic illness (eg, anaphylaxis). Although severe systemic reactions are rare, they can be life-threatening. Vaccine providers should be trained to use medications (eg, epinephrine, atropine, sodium bicarbonate) and conduct procedures necessary to maintain the airway and manage cardiovascular collapse (ie, basic and advanced cardiopulmonary resuscitation, and use of a self-reinflating ventilating bag to provide positive pressure ventilation during resuscitation). Vaccine providers must be in close proximity to a telephone or radio, so that emergency medical personnel can be summoned immediately, if necessary.

Vaccinees should be monitored for adverse events after immunization. If a severe adverse event occurs while the vaccinee is onsite or after receiving a vaccine—particularly during the first 30 to 45 days—a patient evaluation documenting the details of the events, any relevant clinical and laboratory testing, and recommendations for medical exemptions, if indicated, is needed. In an immediate reaction, the physician or provider supervising the immunization clinic should be notified. Education and written materials detailing how the vaccinee can receive medical assistance after leaving the immunization site are recommended for enhanced adverse events surveillance and reporting (eg, http://www.vaccines.mil/documents/642aefitrifoldpress2.pdf).

To improve knowledge about vaccines and vaccine-associated adverse events, all serious adverse events should be reported to the Vaccine Adverse Event Reporting System (VAERS). The Department of Defense requires VAERS reports for adverse events after immunization that involve hospitalization, a life-threatening event (eg, anaphylaxis), loss of more than 24 hours duty (more than 1 duty shift), or an event related to suspected contamination of a vaccine vial. These are minimum requirements. The Department of Defense encourages clinicians to report any other clinically relevant adverse events after administration of any vaccine or medication.

VAERS reporting forms and assistance can be obtained by telephone (1-800-822-7967) or through the VAERS Web site (http://www.vaers.org). The Vaccine Healthcare Centers Network was established in 2001 to support case management and in-depth reporting of adverse events with prolonged or more serious impact on health or quality of life. Support services can be accessed through http://www.VHCinfo.org or via a 24-hour, 7-day a week clinical call center (at 1-866-210-6469).

Quality care for service members—whether trainees or seasoned troops, active or reserve component—is a priority for the military health system. Rarely do adverse events have major impact, and these events can include medically unexplained physical symptoms that are disabling or limiting in some way, such as fatigue, poorly controlled pain syndromes, sleep disorders, headache, or prolonged myalgias and arthralgias. Focusing on contested causation when the vaccinee perceives a link with vaccines might interfere with the therapeutic relationship, creating an adversarial situation that interferes with the quality of evaluation and management, as well as access to care. It is important that clinical personnel involved in immunization healthcare recognize lessons learned from illnesses among Gulf War veterans and that medically unexplained physical symptoms can be evaluated as well as researched for improved outcomes.[77] Referrals to experts in vaccine safety and clinical immunology may support improved case management and outcomes.

IMMUNIZATION CHALLENGES IN THE 21ST CENTURY

In 1900, smallpox vaccine was widely used, rabies vaccine was available to treat animal bites, and typhoid vaccine was just coming to public attention. One hundred years later, 21 serious infections could be prevented with Food and Drug Administration-licensed vaccines. As vaccines increase in number and national focus on vaccine safety continues, the complexity of managing the challenges and trust of service members will undoubtedly increase.

Military trainee medicine and associated immunizations represent the entry point for service members into a career-long exposure to immunization programs. Military immunization programs maximize immunity to maintain the health of the military force, but need to

be customized based on individual contraindications as well as efficacy considerations. Some immunization needs are universal for everyone in military service (eg, tetanus), whereas other needs are derived from specific environmental or occupational risks (eg, rabies, Japanese encephalitis). These features challenge the military health system to conduct immunization programs ethically, with considerations of benefit versus risk and the need for detailed education of healthcare workers, service members, and other beneficiaries.

At the start of the 21st century, more than 30 vaccines were under various stages of development. Some of these vaccines could control diseases not currently preventable (eg, campylobacteriosis, parainfluenza) or that have a special relevance for military medical readiness (eg, botulism, plague).

The word immunization can be applied beyond the typical domain of infectious diseases. Today, immunization includes immunotherapy against inhalant allergens for allergic rhinitis and *Hymenoptera* venoms to prevent life-threatening anaphylaxis from insect stings. With improved understanding of immunology, it is possible that vaccines can be used to treat cancer after diagnosis. Whether vaccines can be developed to treat other immune-mediated diseases, such as multiple sclerosis, remains to be determined. Therapeutic vaccines can enable effective treatment and retention of military personnel with certain diseases that previously would have interfered with continued military service.

In the 21st century, with renewed threats from bioweapons such as anthrax and smallpox, discussions surrounding immunization programs and their validity have become more visible to the public. Extensive efforts have been made to evaluate and reevaluate specific vaccine safety questions, including comprehensive analyses by the National Academy of Sciences and the Institute of Medicine. These evaluations revisit the fundamental issues of risk versus benefit. For military cohorts, vaccine decisions pivot on the disease threat for military personnel and the potential benefit from a specific vaccine.

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