Immunization to Protect the US Armed Forces: Heritage, Current Practice, and Prospects

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Americans serving with the US Armed Forces need protection from the dangerous infections that they can contract during training, based on occupation, during overseas deployment, or because of underlying health status. For over 230 years, the military health-care system has immunized troops to protect them personally and to help them accomplish their missions. Military researchers have invented, developed, and improved vaccines and immunization delivery methods against more than 20 diseases. This article consolidates content from several previous historical reviews, adds additional sources, and cites primary literature regarding military contributions and accomplishments. Discussion emphasizes smallpox, typhoid fever, tetanus, influenza, meningococcal disease, adenovirus, yellow fever, pneumococcal disease, and anthrax. Delivery issues include documentation, simultaneous immunization, seroscreening, safety surveillance, jet injection, and cold-chain management. Immunization policies for each major US conflict are described. Military immunization programs need to be individualized on the basis of personal contraindications and prior immunity. The proper conduct of military immunization programs respects the need for detailed education of military personnel, maximizes quality in immunization delivery, and supports quality clinical care to prevent and treat adverse events after immunization. Military immunization programs maintain the health of soldiers, marines, sailors, airmen, and coast guardsmen, the resources most critical to military success.

biological warfare; endemic diseases; history; immunization; immunoglobulins; mass screening; military personnel; vaccines

Abbreviations: AFEB, Armed Forces Epidemiological Board; IGIM, immune globulin for intramuscular administration; WRAIR, Walter Reed Army Institute of Research.

Immunization protects the personal health of US military personnel and maintains their ability to accomplish missions. The immunization program of the US Department of Defense is broad ranging, protecting the forces from a variety of pathogenic threats. Over 12 percent of the US adult population has participated in the military immunization program, including over 2.6 million current members of the active and reserve components of the Department of Defense and 24.8 million living US veterans of military service (1).

This article updates and expounds on previous reviews of the US military immunization program (2–8). Military immunization requirements often exceed those for civilian adults, because of the travel and other occupational hazards confronted by soldiers, marines, sailors, airmen, and coast guardsmen. The requirements and recommendations are described in a joint immunization regulation (9), summarized in table 1.

Immunizations have both direct benefit to the recipient and indirect benefit to the people in the community in which the vaccinee resides or works (i.e., "herd immunity"). In military settings, the indirect benefit takes on an additional dimension, insofar as an immunized service member is less likely to succumb to a disease that threatens his or her team's mission. By staying healthy, the immunized service member helps other team members to accomplish their

TABLE 1. Vaccines typically administered to US military personnel, 2006

Population segment	Vaccine	Vaccine type	Routine schedule for troops*
Trainees	Diphtheria	Toxoid	Single dose
	Hepatitis A	Inactivated	Two doses
	Hepatitis B	Subunit	Three doses
	Influenza	Live or subunit	Annual, seasonal
	Measles	Live	Single dose
	Meningococcal disease	Subunit, conjugate	Single dose
	Mumps	Live	Single dose
	Pertussis, acellular	Subunit	Single dose
	Poliovirus	Inactivated	Single dose
	Rubella	Live	Single dose
	Tetanus	Toxoid	Single dose
	Varicella†	Live	Two doses
	Yellow fever†	Live	Single dose
Routine during career (both active-duty and reserve components)	Diphtheria	Toxoid	Every 10 years
	Hepatitis A	Inactivated	Two doses
	Influenza	Live or subunit	Annual, seasonal
	Pertussis, acellular	Subunit	With Td‡
	Tetanus	Toxoid	Every 10 years
Individualized on the basis of deployment or travel to high-risk areas (both active and reserve components), various alert forces	Anthrax	Subunit	Multidose series
	Hepatitis B	Subunit	Three doses
	Japanese encephalitis	Inactivated	Three doses, boosters
	Meningococcal disease	Subunit, conjugate	Single dose, boosters
	Smallpox	Live	Single, every 10 years
	Typhoid	Subunit or live	Dosage varies
	Yellow fever	Live	Single, every 10 years
Individualized on the basis of occupational or personal needs	*Haemophilus influenzae* type b	Subunit, conjugate	Single dose
	Hepatitis B	Subunit	Three doses
	Meningococcal disease	Subunit, conjugate	Single dose
	Pneumococcal disease	Subunit	Single dose
	Rabies	Inactivated	Three doses, boosters
	Varicella	Live	Two doses

  * Assumes that the basic immunizing series was received earlier in life. Booster doses may be required at appropriate intervals to sustain immunity. Derived primarily from references 8 and 9.

  † Immunization policy varies among military services on the basis of specific needs.

  ‡ Td, tetanus-diphtheria toxoids (adult strength).

mission and return home safely. Because of both direct and indirect benefits, most US military immunizations are required, rather than voluntary. Figures 1, 2, and 3 illustrate the records used to document immunizations of troops during World War II. Figure 4 shows a contemporary electronic immunization record.

Senior preventive-medicine officers from the five Armed Services develop vaccine recommendations for military trainees and other military personnel, with decisions made by the Army, Navy, and Air Force Surgeons General and the Coast Guard Director of Health and Safety. During policy development, advice may be sought from the Armed Forces Epidemiological Board (AFEB), an expert advisory board of civilian physicians and scientists (10, 11). Before the US Food and Drug Administration took its present dominant role in vaccine regulation in the mid-1970s, the AFEB's cutting-edge expertise was pivotal in deciding immunization dosing schedules and vaccine composition.

Modern immunization policy development takes into account the public-health recommendations published by the Centers for Disease Control and Prevention, in consultation with its Advisory Committee on Immunization Practices.

A synopsis of the vaccines commonly administered at various historical points to US military personnel appears in table 2 (2–19). The US military contributions to vaccine development are summarized in table 3.

IMMUNIZATION REGISTER
AND OTHER MEDICAL DATA
(SEE AR 40-210)

NAME (LAST, FIRST, MID, INITIAL)			ASN
Grabenstein, Herman J			Jr0863988

DATE OF BIRTH	RACE	BLOOD GROUP	MED. OFF.
22Apr21	W	O	*W/ld*

SMALLPOX VACCINE

DATE	TYPE OF REACTION	MED. OFF.
19Nov43	Immune	*W/ld*
19Oct44	Immune	*W/ld*

TRIPLE TYPHOID VACCINE		TYPHUS VACCINE	
DATES EACH DOSE	MED. OFF.	DATES EACH DOSE	MED OFF.
		Comp	
Comp		14Apr44	*W/ld*
Nov42	*W/ld*	7Oct44	*W/ld*
19Nov43	*W/ld*		
19Oct44	*W/ld*		
8Sep45	*W/ld*		

TETANUS TOXOID		CHOLERA VACCINE	
DATES EACH DOSE	MED. OFF.	DATES EACH DOSE	MED. OFF.
		Comp	
Comp		3Apr44	*W/ld*
Dec42	*W/ld*	7Oct44	*W/ld*
19Nov43	*W/ld*		
15Aug44	*W/ld*		

YELLOW FEVER VACCINE

DATE	LOT NO.	MED. OFF.
15Dec43		*W/ld*

W. D., A. G. O.
FORM 8-117
15 AUGUST 1944

THIS FORM SUPERSEDES M. D. FORM 81, 23 SEPTEMBER 1942, WHICH WILL NOT BE USED AFTER RECEIPT OF THIS REVISION.

FIGURE 1. Immunization record of First Lieutenant Herman J. Grabenstein, Jr., US Army Air Corps, 1940s. ASN, Army service number; MED. OFF., medical officer; Comp, compilation; W. D., War Department; A. G. O., Adjutant General's Office; M. D., Medical Department. (The authors seek additional examples of individual military immunization records from other eras.)

SMALLPOX

The first immunization program implemented for the US military was variolation (i.e., variola inoculation) of trainees entering the Continental Army in 1777 (4, 12, 14, 17, 20–24). Impetus for this program began in the fall of 1775, as British forces expelled smallpox cases and recently variolated people from Boston and sent them across the siege lines maintained by the fledgling Continental Army. In the winter of 1775–1776, up to half of the Continental Army task force advancing on Québec, Canada, was ill with smallpox. The Americans suffered 5,500 smallpox casualties among their force of 10,000 colonial troops. Decimated, the US forces lost the Battle of Québec and were obliged to retreat in May 1776.

In response to the military defeat outside Québec, the Director General of the Army Hospital recommended to George Washington that the Continental Army be variolated (12, 17, 21, 24). Variolation was an archaic and dangerous method of preventing smallpox with a mortality risk as high as 2 percent, but the best method then available.

At Morristown, New Jersey, in January 1777, Washington finally ordered a mandatory inoculation program for his troops if they had not survived smallpox infection earlier in life, because the lethal risk from infection (~16 percent) was judged far greater than that from variolation (1 in 300) (12, 17, 21, 24).

Variolation was later replaced by vaccination with cowpox virus. For the War of 1812, the US War Department ordered that vaccination be substituted for variolation to prevent smallpox (12, 17). In 1848, the US Navy did the same.

During the American Civil War, use of smallpox vaccine expanded on both sides of the conflict, including in training camps. Nonetheless, an estimated 19,000 cases of smallpox occurred among the troops, with approximately 7,000 deaths (5, 13, 17, 25, 26).

In the Spanish-American War of 1898, volunteer troops were vaccinated against smallpox as they mustered into service. More smallpox cases occurred among these new volunteers than among the Regular Army. Most of the 825 smallpox admissions (258 fatal) occurred in the Philippine Islands during that conflict (5, 13, 17, 20, 26).

Military training camps continued to administer smallpox vaccine during World War I (27). Despite the large mobilization, there were only 853 smallpox admissions (780 within the United States) and 14 deaths. In 1919, an American citizen named Charles Higgins sent an angry and lengthy manuscript to President Woodrow Wilson, pleading that he stop smallpox vaccination for Armed Forces, listing both true and erroneous risks of smallpox vaccination (28), but vaccination continued through the decades (20).

The US military conducted major smallpox vaccination programs during World War II (16, 17, 27). Among US troops, there were 115 smallpox cases (105 overseas). Cases were attributed to three main causes: failure to vaccinate properly, an inadequate cold chain to keep the vaccine potent, and failure to read and interpret vaccination reactions properly. Perhaps the last Americans to contract smallpox were five soldiers, one of whom died, during the 1953 smallpox outbreak amid the Korean War.

FIGURE 2. Immunization record of Staff Sergeant Eric W. Sandquist, US Army Air Corps, 1940s. REGT., regiment; STIM or Stim, stimulant; MED. OFF., medical officer; cc, cubic centimeter; MFR'S., manufacturer's; M. C., Medical Corps.

FIGURE 3. Military identification tag of Thornton T. Perry, who received tetanus toxoid in 1942 and 1944 ("T42 44"). O, type O blood; P, Protestant.

(20). US service members were routinely vaccinated against smallpox until 1984 (2, 29).

In 1984, routine military smallpox vaccinations were limited to new troops entering basic training (10). In March 1990, the Department of Defense "temporarily discontinued" smallpox vaccination of basic trainees (30).

This "temporary" policy seemed to be a permanent state of affairs, until the anthrax attacks along the eastern seaboard in the fall of 2001 heightened concerns about bioterrorism generally. President Bush announced a national smallpox vaccination program on December 13, 2002 (29). In this plan, smallpox vaccinations resumed for medical and epidemic response teams and for troops deployed to high-threat areas. The current program is described below.

PROPHYLAXIS OF DISEASES RELATED TO POOR HYGIENE OR SANITATION

During actual conflict, sanitation is often compromised, and wound and blood-borne infections become a greater hazard to military forces.

The science of vaccinology advanced slowly in the 1800s, so smallpox vaccine was the only vaccine available for nearly the whole century. A few troops may have received postexposure prophylaxis against rabies using Pasteur's 1885 vaccine (31).

Preventive medicine gained new prominence as a contributor to the war effort during World War I, but the lack of antibiotics or specific vaccines forced a reliance on passive immunization via antitoxins. Diphtheria antitoxin was an important form of therapy (5). Antitoxins to treat gas gangrene provided some therapeutic value (5, 8, 16). Antibiotics largely replaced these products by the end of World War II.

Typhoid fever

In the Spanish-American War, volunteer soldiers, their officers, and physicians marched to the trainee camps, where some began to get sick and die as a result of

By the early 1970s, with smallpox not circulating within the United States, routine smallpox vaccination of civilians (especially children) was no longer practiced, because complications like eczema vaccinatum and encephalitis were not considered justified risks in the face of no disease threat
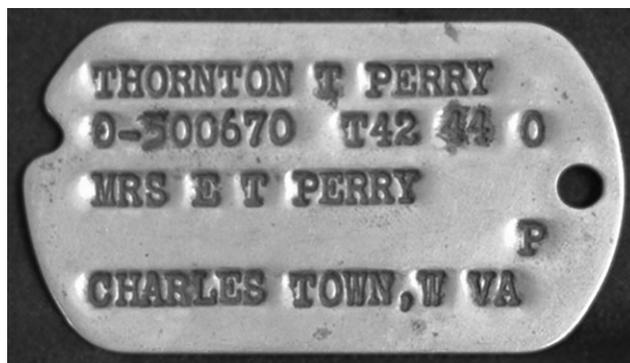
IMMUNIZATION HISTORY: 99999999920   TEST PATIENT

Immunization	Date	Series	Result	Mfg	Lot Nbr	Exempt	Expires	Last Edit	AFCHIPS	MTF Code	Route	Site	Dosage
Hep A (Adult)	19 May 1997	2						4 Aug 2003	5 Jun 2005	TRAN		Left Arm	
Hep B - Adult	10 Apr 1998	1		OTH		Pos Titer		18 Jul 2003	4 Aug 2003	TRAN		Left Arm	
Influenza	31 Oct 1997	1		WA	4978176			18 Jul 2003	4 Aug 2003	TRAN			0.5cc
Influenza	8 Jan 1998	2		CON	7J81910			18 Jul 2003	4 Aug 2003	TRAN			
Influenza	27 Oct 1998	3		WAL	4988247			18 Jul 2003	4 Aug 2003	TRAN			
Influenza	20 Jan 2000	4						18 Jul 2003	4 Aug 2003	TRAN			
Influenza	4 Jan 2001	5		SKB	4008200			18 Jul 2003	4 Aug 2003	TRAN	IM	Left Arm	1.0 mL
Influenza	30 Oct 2001	6		PMC	U0674AA			18 Jul 2003	4 Aug 2003	TRAN	IM	Left Arm	.5 mL
Influenza	9 Oct 2002	7		PMC	U0880AA			18 Jul 2003	4 Aug 2003	TRAN	IM	Left Arm	.5 mL
Influenza	8 Dec 2003	8		PMC	U1270AA			14 Sep 2004	14 Sep 2004	LANG	IM	Left Arm	0.5 mL
Influenza	8 Nov 2004	1		PMC	U1457AA			8 Nov 2004	8 Nov 2004	LANG	IM	Left Arm	0.5 mL
Influenza Split Virus	21 Nov 2005	1		PMC	U1839AA			21 Nov 2005	4 Dec 2005	MAXW	IM	Left Arm	0.5 mL
Influenza Split Virus	30 Nov 2005	1		PMC	U1911AA			30 Nov 2005	4 Dec 2005	MAXW	IM	Left Arm	0.5 mL
Influenza Split Virus	1 Dec 2005	1		PMC	u1935aa			1 Dec 2005	4 Dec 2005	MAXW	IM	Left Arm	0.5 mL
Meningococcal	1 May 1993	1						18 Jul 2003	4 Aug 2003	TRAN			
Meningococcal	30 Oct 2001	2		PMC	UB058AA			18 Jul 2003	4 Aug 2003	TRAN	SC	Left Arm	.5 mL
Meningococcal	13 Sep 2004	3		PMC	UE301AA			14 Sep 2004	14 Sep 2004	LANG	SC	Left Arm	0.5 mL
MMR	20 Jun 1995	1						18 Jul 2003	4 Aug 2003	TRAN			
MMR	9 Jun 2004					Pos Titer		9 Jun 2004	9 Jun 2004	LANG			
OPV	1 May 1993	1						18 Jul 2003	4 Aug 2003	TRAN			
PPD	10 Apr 1998	1	N	CON	244111			18 Jul 2003	4 Aug 2003	TRAN			
PPD	18 Apr 2001	4	N					18 Jul 2003	4 Aug 2003	TRAN		Left Arm	
PPD	13 May 2002	5	N					18 Jul 2003	4 Aug 2003	TRAN		Right Arm	
PPD	12 May 2003	6	N	TRS				18 Jul 2003	4 Aug 2003	TRAN		Left Arm	
PPD	19 May 2004		N	PMC	C1422AA			27 Jan 2006	24 Feb 2006	MAXW	ID	Left Arm	.1 mL
PPD	6 Mar 2006		N					9 Mar 2006		MAXW	ID	Left Arm	.1 mL
Td	1 May 1993	1						18 Jul 2003	4 Aug 2003	TRAN			
Td	30 Apr 2003	2		PMC	U0818AA			18 Jul 2003	4 Aug 2003	TRAN	IM	Left Arm	.5 mL
Typhoid - Parenteral-M	20 Jun 1995	1						18 Jul 2003	4 Aug 2003	TRAN			
Typhoid, Vi	20 Jan 2000	1		CON	P1346-50			18 Jul 2003	4 Aug 2003	TRAN			0.5CC
Typhoid, ViCPs	1 Nov 2001	1						18 Jul 2003	4 Aug 2003	TRAN		Left Arm	
Varicella	6 Dec 2000	1				Not Suscep		18 Jul 2003	4 Aug 2003	TRAN		Left Arm	
Yellow Fever	16 Nov 1995	1						18 Jul 2003	4 Aug 2003	TRAN			

Add Vax | Add Exemption | Add Ped | Edit | Delete | Excel | AFCHIPS Inquire | DEERS Inquire | Close

FIGURE 4. Notional electronic immunization record, Air Force Complete Immunization Tracking Application, 2006. Mfg, manufacturer's abbreviation following the Vaccine Identification Standards Initiative system (refer to www.cdc.gov/nip/visi/ for the complete list); Nbr, number; AFCHIPS, Air Force Corporate Health Information Processing Service; MTF, military treatment facility; Hep, hepatitis; Pos, positive; cc, cubic centimeter; IM, intramuscular; SC, subcutaneous; MMR, measles-mumps-rubella; OPV, oral poliovirus; PPD, tuberculin-purified protein derivative; N, negative; ID, intradermal; Td, tetanus-diphtheria toxoids; ViCPs, Vi capsular polysaccharide; Suscep, susceptible; Vax, vaccine; DEERS, Defense Enrollment Eligibility Reporting System.

TABLE 2.   Immunizations used widely during major conflicts*

Conflict, era	Vaccines (specific type)	Antibodies
American Revolutionary War, 1775–1783	Smallpox (by variolation)	
War of 1812, 1812–1815	Smallpox (vaccination with live cowpox or later vaccinia virus)	
Mexican-American War, 1846–1848	Smallpox (live)	
Civil War, 1861–1865	Smallpox (live)	
Spanish-American War, 1898	Smallpox (live)	
World War I, 1917–1918	Smallpox (live), typhoid (whole cell)	Therapeutic tetanus antitoxin, diphtheria antitoxin
World War II, 1941–1945	Routine: influenza (whole virus inactivated), smallpox (live), tetanus (toxoid), typhoid (whole cell), paratyphoid A and B (whole cell)	Therapeutic diphtheria antitoxin, gas gangrene antitoxin, tetanus antitoxin. Immune globulin (measles prophylaxis)
	Situational: cholera (whole cell), diphtheria (toxoid), plague (whole cell), scarlet fever (whole cell), typhus (whole cell), yellow fever (live)	
Korean War, 1950–1953	Cholera (whole cell), influenza (whole virus inactivated), plague (whole cell), smallpox (live), tetanus-diphtheria (toxoid), typhoid (whole cell), paratyphoid A and B (whole cell), typhus (whole cell), yellow fever (live)	Therapeutic diphtheria antitoxin. Immune globulin (hepatitis A, hepatitis B, and measles prophylaxis)
Vietnam War, 1964–1973	Cholera (whole cell), influenza (whole virus inactivated), measles (live), meningococcal A/C (polysaccharide), plague (whole cell), poliovirus (live), smallpox (live), tetanus-diphtheria (toxoid), typhoid (whole cell; acetone killed, dried; or heat and phenol inactivated), typhus (whole cell), yellow fever (live)	Immune globulin (hepatitis A and hepatitis B prophylaxis)
Persian Gulf War, 1990–1991 (i.e., Operation Desert Shield/Desert Storm)	Common: adenovirus type 4 and type 7 (live), hepatitis B (subunit), influenza (subunit), measles-rubella or measles-mumps-rubella (live), meningococcal A/C/Y/W-135 (polysaccharide), poliovirus (live), tetanus-diphtheria (toxoid), typhoid (whole cell; acetone killed, dried; or heat and phenol inactivated), yellow fever (live)	Immune globulin (hepatitis A prophylaxis)
	Limited use: anthrax (subunit), botulinum (toxoid), rabies (whole virus inactivated)	
Global War on Terror, 2001 to present (i.e., Operation Enduring Freedom (Afghanistan) and Operation Iraqi Freedom)	Common: hepatitis A (whole virus inactivated), hepatitis B (subunit), influenza (live or subunit), measles-mumps-rubella (live), meningococcal A/C/Y/W-135 (polysaccharide), poliovirus (whole virus inactivated), tetanus-diphtheria-pertussis (toxoid-subunit), typhoid (subunit or live), varicella (live), yellow fever (live)	
	Situational: anthrax (subunit), rabies (whole virus inactivated), smallpox (live)	

* This list is neither an exhaustive list of all licensed vaccines and antibodies for these eras nor an assertion that each service member in a conflict received each product. Rather, this is a list of widely used products for service members during these time intervals. Derived primarily from references 2–19.

contamination of the water supply. Overseas, America experienced 280 battle fatalities. However, at the five main US training camps, before getting anywhere near a battlefield, there were 20,738 cases of typhoid fever, 1,590 of them fatal. In the Army overall, there were an estimated 2,620 typhoid fever deaths (2–4, 17, 26, 32–36).

Almroth Wright developed a heat- and phenol-treated typhoid vaccine in Britain (37, 38). The British Army used

early forms of typhoid vaccine during the Anglo-Boer War in southern Africa in 1899. Among 14,626 immunized British soldiers, there were 1,417 cases of typhoid fever and 163 deaths (11 of 1,000 soldiers). In contrast, among 313,618 unimmunized soldiers, there were 48,754 cases and 6,991 deaths (32 of 1,000) (39).

Major Frederick Russell of the US Army Medical School adapted British and German production methods to produce

TABLE 3.   Major contributions of US military medicine to human immunization*

Date	Disease	US military contribution to immunization	Key people
1775–1783	Smallpox	Variolation of Continental Army	General George Washington, John Morgan, Benjamin Rush
1880	Pneumococcal disease	Discovery of *Streptococcus pneumoniae*, the pneumococcus	Major (later Brigadier General) George M. Sternberg
1898	Typhoid fever	Typhoid Board improves camp sanitation and shows cause of outbreak and carrier state	Major Walter Reed, Major Victor C. Vaughan, Major Edwin O. Shakespeare
1900	Yellow fever	Virus carried by *Aedes aegypti* mosquitoes shown to transmit yellow fever	Major Walter Reed, Major James Carroll, Major Aristide Agramonte, Major Jesse W. Lazear, Major (later Brigadier General) William Gorgas
1909	Typhoid fever	First American typhoid vaccine produced at US Army Medical School	Captain (later Brigadier General) Frederick F. Russell
1942	Tetanus	First large-scale use of tetanus toxoid	
1940s	Influenza A and B	Inactivated vaccines developed	Thomas J. Francis, Jr.; Jonas E. Salk
1940s	Typhus	Sonic vibration of infected yolk sacs used for vaccine manufacture	Captain Joseph E. Smadel, Colonel (later Brigadier General) Stanhope Bayne-Jones, Theodore E. Woodward
1940s, 1950s	Japanese encephalitis	Asian Japanese encephalitis vaccines adapted for American use and given to 250,000 military personnel; discoveries in epidemiology and ecology	Captain Joseph E. Smadel, Major Albert B. Sabin, Colonel Edward L. Buescher, William F. Scherer
1944–1950	Hepatitis B	Investigation of jaundice outbreak among yellow fever vaccinees	
1945	Hepatitis A, measles, mumps	Immune globulin fractionated from plasma; passive immunization with intramuscular immune globulin prevents or attenuates disease.	Edwin J. Cohn, John L. Oncley, Joseph Stokes, Jr., Captain John R. Neefe, Jr., John F. Enders
1945	Pneumococcal disease	Multivalent polysaccharide vaccine tested at Army Air Corps Technical School, Sioux Falls, South Dakota	Colin M. MacLeod, Michael Heidelberger
1950s	Diphtheria	Advantages of low-dose diphtheria toxoid for adults demonstrated	Geoffrey Edsall
1950s	Anthrax	Culture filtrate developed as effective vaccine	George G. Wright, Milton Puziss
1950s	Immune deficiency	Immune globulin intramuscular used to treat child with agammaglobulinemia	Colonel Ogden C. Bruton
1957	Influenza	Antigenic shift and drift of influenza described	Thomas Francis, Jr., Maurice R. Hilleman
1950s–1970s	Adenovirus	Adenoviruses isolated at Fort Leonard Wood (1952); burden of adenovirus infection on hospitalizations measured; inactivated vaccines developed (1956); live vaccines developed in 1960s–1970s	Maurice R. Hilleman, Colonel Edward L. Buescher, Colonel Franklin H. Top, Jr., Colonel (later Major General) Phillip K. Russell
1961	Rubella	Rubella virus isolated from trainee hospitalized at Fort Dix, New Jersey	Captain Paul D. Parkman, Malcom S. Artenstein, Colonel Edward L. Buescher
1960s–1970s	Meningococcal disease	Immune responses to bacteria described; first meningococcal polysaccharide A (1970) and C (1978) vaccines developed	Malcolm S. Artenstein, Captain Irving Goldschneider, Captain Emil C. Gotschlich, Major Ronald Gold
1960s, 1970s	Hepatitis B	Advances in viral subtyping; protective effect of antibodies demonstrated	Colonel William H. Bancroft; Colonel Marcel E. Conrad
1980s	Japanese encephalitis	Efficacy of two Japanese encephalitis vaccines compared in Thailand	Colonel Charles H. Hoke, Jr.
1980s	Gonorrhea	Gonococcal pilus vaccine produces measurable genital mucosal antibody but not effective in field trial	Colonel Edmund C. Tramont, Colonel John W. Boslego
1980s	Respiratory syncytial virus	Polyvalent, high-titer, anti-respiratory syncytial virus immune globulin effective prophylaxis in infants	Major Gerald W. Fischer, Val G. Hemming, Greg A. Prince
1980s–present	Human immunodeficiency virus	gp160† vaccine immunogenic but did not affect disease progression	Colonel Edmund C. Tramont, Lieutenant Colonel Robert R. Redfield
1985–1995	Hepatitis A	Prototype hepatitis A vaccine developed. Army conducts pivotal efficacy trial in Thailand.	Leonard N. Binn, Colonel Charles H. Hoke, Jr., Lieutenant Colonel Bruce L. Innis, Major Stanley M. Lemon
1980s–1990s	Tick-borne encephalitis	American experience with European-licensed vaccines	
1990s	Plague	Recognition of F1 and V antigens on virulence and immunity	Colonel Arthur M. Friedlander
1990s	Cholera	Oral whole-cell plus recombinant B subunit cholera vaccine tested with Peruvian Army and Navy	Colonel Jose L. Sanchez, Colonel David N. Taylor
1990s–present	Anthrax	Animal challenge studies of vaccine efficacy; cohort studies of anthrax vaccine safety	Colonel Arthur M. Friedlander, Colonel John F. Brundage, others

* Derived primarily from references 2–19 and other references cited in the text.

† gp160, glycoprotein 160 (a precursor of human immunodeficiency virus envelope proteins glycoprotein 41 and glycoprotein 120).

the inactivated, whole-cell, typhoid vaccine supply used by the entire United States. Voluntary immunization of some American soldiers against typhoid fever began in 1909 (5, 13, 14, 17, 40–42). In 1911, Army Chief of Staff Major General Leonard Wood ordered mandatory typhoid immunization for a 15,000-man division, using Russell's vaccine. Wood also required that immunizations be recorded in medical records. Only two cases of typhoid fever occurred. A few months later, immunization became mandatory for all soldiers. The Navy adopted typhoid immunization as well.

With a vaccine to shield troops from typhoid bacteria during the unsanitary conditions of World War I, a mere approximately 2,000 cases of typhoid fever, with 227 deaths, were reported among 4.1 million Americans in uniform (5, 13, 14, 16, 33, 43, 44).

Various vaccine combinations of typhoid, paratyphoid A, and paratyphoid B antigens were used during the 20th century (5, 13, 43, 44); the trivalent vaccine was commonly known as "TAB vaccine," triple vaccine, or enteric vaccine. Typhoid fever affected 0.42 cases per thousand soldiers in World War I but only 0.05 cases per thousand in World War II, because of expanded immunization.

Various typhoid vaccines were developed at the Walter Reed Army Institute of Research (WRAIR), notably the acetone-killed and dried and the heat-phenol treated formulations (4, 8, 45). Development of the typhoid Vi polysaccharide-injectable vaccine and live attenuated typhoid vaccine capsules rendered obsolete the whole-cell typhoid vaccines, renowned for high degrees of injection-site pain and swelling, fever, and systemic reactions (8, 46).

Tetanus

Wound tetanus was a major cause of morbidity and mortality until World War I. Passive immunization with tetanus antitoxin was relatively effective. However, it had a harsh side-effect profile, notably serum sickness, due to its equine protein content. In 1933, tetanus toxoid was licensed in the United States, but this vaccine was adopted slowly for the civilian populace (5, 8, 13, 14, 44, 47).

In May 1940, the Army Surgeon General requested that tetanus toxoid be given to all active-duty troops (4, 5, 15, 16, 48, 49). Routine tetanus immunization was approved by the War Department in June 1941. A record of the tetanus toxoid doses administered was stamped on soldiers' identification tags (e.g., "T42 44") and also recorded in paper records (15). The example in figure 3 reflects tetanus immunizations given in 1942 and 1944. Booster toxoid doses were routinely given before entering an overseas theater and after a wound. The incidence of local reactions after immunization increased when booster doses were administered at short intervals. The US Navy tended to use alum-precipitated toxoid, which induced more persistent antibody concentrations, compared with the fluid toxoid used by the US Army at that time (50).

Only 12 cases of tetanus were reported throughout World War II, from all theaters of operations, despite more than 12 million Americans in uniform who incurred more than 2.7 million hospital admissions for wounds or injuries (4, 5, 48).

All 12 cases were in unimmunized or incompletely immunized troops.

Until recently, tetanus-diphtheria toxoids were administered to all trainees upon entry into military service. This left military cohorts vulnerable to intermittent pertussis outbreaks (51, 52). Now, the recently licensed tetanus-diphtheria-acellular pertussis vaccines are being adopted (8), with the added benefit of preventing prolonged cough illness among service members. This approach provides indirect benefit to service members' children. Adult-strength tetanus-diphtheria toxoids or tetanus-diphtheria-acellular pertussis booster immunizations are given at intervals consistent with recommendations from the Advisory Committee on Immunization Practices. People who may not have received a basic immunizing series earlier in life receive a basic immunizing series.

Hepatitis A

During the second year of the Civil War, an estimated 5 percent of Union troops were jaundiced. During World War II, 180,000 troops developed infectious hepatitis (i.e., hepatitis A), principally in North Africa, Italy, the South Pacific, and postwar Germany. Within the Pusan perimeter during the Korean War, 4,000 American troops were hospitalized with hepatitis (5, 15, 18, 53, 54).

Edwin Cohn, John Oncley, and colleagues at Harvard University isolated the gamma-globulin fraction of serum in 1944, under contract to the US Navy. Their methods yielded immune globulin for intramuscular administration (IGIM, "gamma globulin"). Joseph Stokes, Jr., and John Neefe reported the utility of IGIM in reducing the incidence of hepatitis A in 1945. Clinicians used this drug primarily to prevent or mitigate measles, mumps, hepatitis A, and hepatitis B (2–4, 7, 8, 10, 11, 47, 53–58). IGIM prevented posttransfusion hepatitis in battle casualties, if given promptly (59). IGIM was routinely given in the 1960s to troops assigned to Korea or Vietnam (10, 58, 60–63).

In 1985, Leonard Binn and colleagues tested a formalin-inactivated hepatitis A vaccine at WRAIR. In 1991, Lieutenant Colonel Bruce Innis and a team of WRAIR scientists began an efficacy trial in Thai schoolchildren that found a protective efficacy effect of 94 percent (8, 54, 64, 65).

Hepatitis A prophylaxis was transformed in 1995 with the US licensing of inactivated hepatitis A vaccines, rendering obsolete serial painful injections of IGIM into the buttocks. With hepatitis A infection the most common vaccine-preventable infection among international travelers (8, 11, 66, 67), the 1995 universal immunization policy for US military personnel was a logical step.

Hepatitis B

In 1942, infectious hepatitis and serum hepatitis were first clearly differentiated. This came about when some lots of yellow-fever vaccine were unknowingly manufactured with tainted serum albumin, added as a protein stabilizer (10, 53, 54, 68–70).

No immunologic means of preventing hepatitis B were available until the Food and Drug Administration licensed

the first hepatitis B vaccine in 1981. IGIM was found to provide temporary prophylaxis against both hepatitis A and hepatitis B infections in troops assigned to Korea (54, 58, 62).

Today, hepatitis B immunization policy for US military personnel focuses on several cohorts at occupational risk (e.g., medical and mortuary affairs). Personnel assigned to the Korea peninsula since 1986 have been immunized, as have accessions since 2001 (10, 54, 71). Increasingly, basic trainees immunized as children or adolescents are joining the military, which favors preimmunization seroscreening, discussed below. Because of the vaccine's relatively high cost, hepatitis B vaccine initially was administered intradermally, but this route of administration fell out of favor nationally, because of inconsistent injection technique and antibody response (8, 72, 73).

Cholera

The first injectable cholera vaccines date back to the 1890s. The bacterial strains used in the United States were selected at the Army Medical School during World War II (4). From the 1940s to the 1980s, injectable whole-cell cholera vaccine was given to alert units. However, the vaccine fell into disfavor as cholera immunization ceased being a condition for passage of international borders, as well as the vaccine's tendency to evoke substantial injection-site and systemic reactions, modest efficacy, and short duration of protection.

The AFEB recommended cessation of routine cholera immunization in 1973 (10). Emphasis on sanitation is now considered more important in a healthy adult military population than reliance on a vaccine with limited efficacy. At present, the oral cholera vaccines developed under US Army contract by the University of Maryland and licensed in Europe and Canada are unlicensed in the United States (8, 34, 74, 75).

PROPHYLAXIS OF CONTAGION AND EPIDEMICS

Until 1990, loss of life due to nontraumatic causes had decimated more armies than bullets had in American military campaigns (17, 76). During basic training, military accessions come from disparate locations with varying degrees of innate or naturally acquired immunity, are placed in relatively confined living quarters, and subjected to a high degree of physical stress (77). As with college freshmen in dormitories, respiratory pathogens, in particular, can spread easily in this setting.

Influenza

During 1918–1919, a worldwide outbreak of viral influenza killed over 50 million people (4, 5, 7, 13, 14, 17, 44, 78–82). More than 500,000 deaths occurred in the United States. The worldwide pandemic killed more Americans than the military death tolls of all of America's wars in the 20th century combined. Scientists tried a vaccine against Pfeiffer's bacillus (*Bacillus influenzae*, now called *Haemophilus influenzae*) in the belief that the epidemic had a bac-

terial cause. This vaccine was manufactured at the Army Medical School and elsewhere (82–85).

US Army statistics for the pandemic showed that 791,907 soldiers were admitted to hospitals in the United States or France for influenza, and 24,664 of them died (86). Overall, one in 67 American soldiers died of influenza or pneumonia in 1918 (5, 13, 44, 80, 81).

Remembering how the outbreak quickly sapped the fighting strength of American troops, the US Army Surgeon General commissioned research to develop influenza vaccines in the 1940s, the first iterations of the vaccines we still use today (2–5, 8, 10, 13, 14, 87, 88). Double-blinded field trials began among US service members, demonstrating as much as 80 percent efficacy. In 1943, the first influenza vaccine against types A and B infection was used widely. In the fall of 1945 and the spring of 1946, all 7 million troops were immunized against influenza. The efficacy of all such vaccines was dependent on correlation of the vaccine's antigens with circulating viral types, but scientists did not yet fully appreciate the unceasing antigenic variation of influenza virus. Medical officials were surprised that the influenza vaccine was not effective in the fall-winter season of 1947. We now realize that the virus had shifted antigenically, making the vaccine mismatched to the circulating viral strain. By the early 1950s, annual immunization for all military personnel was routine, a policy continued ever since (4, 8, 10, 89–92).

Assessments of influenza vaccine containing various mineral-oil adjuvants in the late 1940s and 1950s were promising but not pursued. Despite concerns about the safety of the adjuvant vaccine, no prolonged morbidity or mortality effects were evident two decades after immunization (4, 10, 93, 94).

Memories of the 1918–1919 influenza pandemic arose again when an outbreak of severe respiratory illness occurred in a basic training camp at Fort Dix, New Jersey. Among 230 infected soldiers, 13 were severely ill, with one fatality in February 1976 (95–100). Scientifically designated A/New Jersey/76 (H1N1), this viral strain was called "swine flu" by the public. This finding set in motion a process that led to the National Influenza Immunization Program, in which the Department of Defense participated (99, 100). In November 1976, several cases of Guillain-Barré syndrome, a demyelinating neuromuscular disorder, were reported from Minnesota. Nationwide, 532 cases (32 fatal) were reported among vaccinees, mostly civilians. Epidemiologic investigation suggested an increased risk among civilian influenza vaccine recipients that year (101–104) but not among military vaccine recipients (105).

One of the starkest modern examples of the importance of preventing influenza in military communities comes from the USS *Arkansas* in February 1996 (106). After influenza virus that did not match the strains used for immunization entered the ship's spaces, 42 percent of the ship's company became ill. The rate of incapacitating illness was sufficient to cause the ship to cancel its training exercise and make an unscheduled return to the nearest port.

Today, all active-duty members and most personnel in the National Guard or military reserves are immunized annually, usually by the end of December. Basic trainees receive

influenza vaccine through its empirical June 30 expiration date each year. Antiviral medications are not widely used for prophylaxis, because of the superior protection provided by immunization. The Department of Defense sponsors an extensive, global, laboratory-based influenza surveillance program (107). This surveillance system contributed the clinical isolate used to develop the A/Panama/2007/99 (H3N2) influenza vaccine strain in influenza vaccines used from the fall of 2000 to early 2004 (108).

With contemporary concern about influenza A/H5N1 mutating into a pandemic form, the lessons from 1918 and 1976 are being relearned around the world. The Department of Defense is actively engaged in surveillance and planning. It purchased stockpiles of neuraminidase inhibitors to protect the nation's capabilities until a pandemic-strain influenza vaccine could be manufactured and provide durable immunity.

Meningococcal disease

Meningococcal meningitis is a life-threatening bacterial infection that can spread rapidly in dense populations, as in military training camps, colleges, and religious pilgrimages (4). The disease occurred with disturbing frequency in military trainees in the 1960s. Antibiotic prophylaxis was used initially, but the *Neisseria meningitidis* organisms became increasingly drug resistant.

In 1966, a meningococcal research unit was organized at WRAIR (3–5, 7, 8, 13, 14, 109–111). In 1968, scientists led by Goldschneider, Gotschlich, and Artenstein at WRAIR developed a serogroup C vaccine that prevented disease and also reduced the bacterial carrier rate. This was the first modern polysaccharide vaccine. Clinical trials were conducted in thousands of military trainees. Later, they developed its serogroup A counterpart vaccine.

Widespread use of meningococcal A/C vaccine among US military trainees began in 1971. A combination of immunization and smaller class sizes reduced the risk for fatal meningococcal disease during basic training (3–5, 13, 112). A tetravalent vaccine against serogroups A, C, and Y and W-135 combined (Menomune; Sanofi Pasteur, Swiftwater, Pennsylvania) received a US license in January 1978 (113).

Meningococcal immunization marked another advance in January 2005 when the Food and Drug Administration licensed a protein-conjugated meningococcal vaccine (Menactra; Sanofi Pasteur). Its protein-conjugated characteristics promise prolonged duration of immunity compared with polysaccharide immunization (8). The Department of Defense is currently transitioning from Menomune to Menactra for military personnel and has adopted national immunization recommendations for adolescent beneficiaries. Unfortunately, attempts to develop a serogroup B meningococcal vaccine have not yet been fruitful.

Adenoviruses

After World War II, adenovirus infections (particularly serotypes 4 and 7) were linked with epidemic acute respiratory disease outbreaks in training camps and noted to infect up to 80 percent of military trainees (4, 114–123).

Before widespread immunization of trainees, 600–800 acute respiratory-disease hospitalizations per week occurred at military basic-training sites in the northern United States in the early 1960s, disabling 40–50 percent of these closed communities.

In 1956, WRAIR developed formalin-inactivated vaccines against adenovirus types 4 and 7 (3–5, 7, 8, 13, 91, 92, 114–116, 124). Maurice Hilleman's team at WRAIR demonstrated in 1958 that inactivated adenovirus vaccine types 4 and 7 reduced adenovirus disease incidence by 60–90 percent among US soldiers under the stressful and crowded conditions of basic training, with cross-protection against type 3.

In 1963, viral seed lots for this vaccine were found to contain the oncogenic simian virus 40 as well as the simian virus 40 genome in the adenovirus capsids (32, 125–127). Safety concerns and lack of efficacy caused the product to be withdrawn from distribution. Several studies have shown no elevated risk of cancer in these vaccine recipients. The live types 4 and 7 adenoviruses used in the modern products have been shown not to be oncogenic (128).

In 1964, clinical trials of live, attenuated type 4 vaccine began at WRAIR (3–5, 7, 8, 13, 117–119, 121–123, 129). Trials of type 7 began in 1969 and of type 21 in 1971. Type 7 adenovirus vaccine was added to the regimen given American military trainees in 1970. These vaccines were developed as oral tablets in the 1970s, using viruses serially passaged but not attenuated (130), and licensed in July 1980. A report estimated that the vaccine saved the Army about $5 million a year in 1973 dollars (120). The tablets were given shortly after trainees' arrival at a basic training center, triggering no respiratory manifestations (90, 130). Adenovirus vaccines produced dramatic reductions in disease incidence.

By 1984, both vaccines were routinely administered as tablets to trainees at all basic-training camps the year round. Unfortunately, the manufacturer (Wyeth Laboratories, Madison, New Jersey) and the Department of Defense did not make capital improvements to the manufacturing facilities for these vaccines, and production ceased in 1996 (11). The last lots of these vaccines expired in 1998. Since then, disease outbreaks among trainee populations have recurred, including several deaths (128, 131–134). A replacement manufacturing line for adenovirus type 4 and type 7 vaccines will be subjected to regulatory review (11, 135, 136).

Measles, mumps, rubella, and varicella

During the Revolutionary War and the Civil War, measles was one of the principal causes of death among troops. Measles and secondary pneumonias in 1917 led to 48,000 hospitalizations and 1 million lost work days and represented 30 percent of all Army deaths, including combat deaths (44, 137, 138). During 1917 and early 1918, measles and mumps were leading causes of hospitalization and days lost from active service by members of the American Expeditionary Force in Europe (17, 44, 137, 139). During World War II, measles, mumps, rubella, and varicella accounted for over 300,000 hospital admissions or restrictions

to quarters (140, 141). Even into the 1970s, measles and rubella caused a substantial number of hospitalizations and lost training time at basic training centers (90).

In 1961, Paul Parkman and his colleagues at WRAIR were codiscoverers of the rubella virus, isolating the virus among trainees at Fort Dix (4, 141). Vaccines to prevent measles, mumps, and rubella were licensed in the United States between 1963 and 1969. The AFEB helped to fund development of an attenuated measles vaccine (142). Indeed, the AFEB represented a major national source of grant funding for military and civilian biomedical researchers from the 1940s to the 1970s (10, 11, 53).

For military trainees, rubella vaccine was adopted first, in 1972, with measles vaccine added in 1980 to immunize those who evaded infection as children (10, 143, 144). Mumps outbreaks were less common than were the other two diseases, so mumps immunization was not uniformly adopted until 1991 (11, 145). A varicella policy of screening and as-needed immunization was also adopted in 1991 (11). The Food and Drug Administration licensed varicella vaccine in 1995. Now that a large proportion of basic trainees enter military service immune to these infections because of childhood immunization, the Services are increasingly testing for antibody and exempting those already immune (11, 146–152).

Diphtheria

Diphtheria toxoid was first licensed in the United States in 1926 and was later combined with tetanus toxoid to simplify the task of injecting the two products. Diphtheria toxoid, however, was known to cause substantial injection-site swelling if injected into someone already immune to diphtheria. So diphtheria immunization policy was complicated by whether or not to perform the Schick skin test to determine if an individual was immune (induration after injecting diphtheria toxin is considered a positive test, implying susceptibility) (8, 15, 153, 154).

Military clinicians noted the injection-site swelling that followed diphtheria toxoid administration in adults and developed a reduced-dose formulation. The work of Geoffrey Edsall and colleagues at the Great Lakes Naval Training Center in the 1950s demonstrated that this approach was comparably immunogenic, but with fewer injection-site symptoms (4, 8, 155, 156).

PROPHYLAXIS OF DISEASES WITH ECOLOGIC NICHES

Deployment vaccines include those vaccines administered to personnel sent to regions where the risk of contracting a specific endemic vaccine-preventable disease is increased. Deployment vaccines include typhoid, hepatitis B, meningococcal, yellow fever, Japanese encephalitis, and rabies. The first few were discussed above. Beyond its use in military basic training, meningococcal immunization may be required for specific assignments (e.g., personnel traveling to sub-Saharan Africa during the dry season) (67).

Yellow fever

Yellow fever was a significant problem for US troops throughout the southern United States in the 19th century. This infection was especially troublesome during the Spanish-American War of 1898, particularly in Cuba (3–5, 7, 13, 14, 17, 32, 157, 158). To investigate, Army Surgeon General Sternberg appointed another board of investigation. Walter Reed and his colleagues proved Carlos Finlay's hypothesis of transmission of the disease by mosquito (159–163). The follow-up research ultimately led to isolation of the virus. Separately, Max Thieler attenuated yellow-fever virus by serial cell culture passage in 1927.

During World War II, yellow fever was considered as a natural threat, with speculation about its potential as a biologic weapon if adversaries could release infected mosquitoes (164). As a result, a yellow-fever immunization program was instituted for selected personnel in the US Armed Forces.

By April 1942, 7 million doses of the vaccine had been given. The program was complicated by reports of hepatitis in recipients (3–5, 13, 55, 57, 69, 70). In March 1942, 100 cases of jaundice and hepatitis were noted at training camps in California soon after yellow-fever immunization. Health authorities quickly realized that the diluent for yellow-fever vaccine contained human serum albumin that had not been heat treated. The albumin was contaminated with a previously unrecognized virus that caused hepatitis (i.e., hepatitis B virus). Immunizations ceased, and the Rockefeller Foundation stopped producing the serum-containing product midway through 1942, until it could develop a serum-free formulation. By December 1942, over 50,000 cases of hepatitis B and 84 deaths followed some 2.5 million yellow-fever immunizations from certain lots. This accident helped to reveal the differences between hepatitis A (then called "infectious hepatitis") and the newly recognized hepatitis B virus ("serum hepatitis").

In 1985, follow-up studies interviewed and seroscreened 597 Army veterans from 1942. The authors concluded that hepatitis B virus caused the outbreak, that about 330,000 persons may have been infected, that the hepatitis B virus carrier state was a rare consequence, and that the outbreak induced hepatitis B-specific antibodies that appear to persist for life (165). The small excess liver cancer mortality seen in a related cohort study and the results of a case-control study are consistent, nevertheless, with the now well-established etiologic role of hepatitis B virus in liver cancer (166).

In addition to the hepatitis B issue, the yellow-fever vaccine of the 1940s was grown in eggs of chickens infected with avian leucosis virus. Evaluation identified no related harm in vaccine recipients (167).

From the 1950s onward, yellow-fever immunization for adults proceeded with few problems, until recently. Yellow-fever vaccine is a live, attenuated product given to personnel with assignments to yellow fever-endemic areas. As a general rule, personnel assigned to Latin America or sub-Saharan Africa or with missions that may take them to these regions are immunized. However, recent concerns about

rare cases of yellow-fever vaccine-associated viscerotropic disease, including a female airman (168), raise questions about how best to balance the risks and benefits of immunization. Should military forces use yellow-fever vaccine narrowly (i.e., focused on those traveling soon) or broadly (i.e., focused on those who may travel eventually) to minimize the number of immunizations given just before departure? Military policy makers, in concert with medical consultants, work to balance the two competing objectives (11, 169). The goal is to optimize benefit and to minimize risk for service members.

Japanese encephalitis

A Japanese encephalitis vaccine based on a Russian vaccine was produced in 1943 through the efforts of Albert Sabin and colleagues in the Far Eastern theater. Japanese encephalitis vaccine was administered to a limited number of personnel in Japan (primarily Okinawa) in 1945 during an outbreak in the civilian population (5, 13, 17, 170, 171). This vaccine was derived from virus-infected mouse brain.

By the 1980s, military, diplomatic, and travelers' need for a Japanese encephalitis vaccine led to studies by military scientists that permitted US licensure of Department of Defense vaccine (8, 172–175). The Food and Drug Administration licensed Department of Defense vaccine in 1992. Because of an uncommon risk of delayed-onset urticaria and angioedema, the vaccine's labeling recommends deferring travel for 7–10 days after immunization. Current military policy provides this vaccine to military members on assignments to areas with a high endemicity of disease, primarily on Okinawa, with extended field exposure and rural areas of Thailand. The manufacturer intends to cease production in mouse brains and transition to a cell-culture production process.

Rabies

Today, rabies vaccine is provided before exposure to selected troops who have missions to areas endemic for rabies and who may have an elevated risk of being bitten by a rabid animal. The rationale for immunization focuses on troops who lack ready access to definitive medical care if bitten (e.g., special operations personnel). In addition, veterinarians, veterinary technicians, and those with animal-control responsibilities receive standard occupational immunization before exposure (8, 31, 175, 176).

PROPHYLAXIS AGAINST BIOWEAPONS

Smallpox

The historical use of smallpox vaccine was addressed above. In December 2002, a national program of smallpox vaccination resumed, to counter the consequences of a malicious release of variola virus (29).

In a remarkable example of mass individualized immunization, more than 400,000 service members deploying to southwest Asia were screened for smallpox immunization (29). After a trial run at Walter Reed Army Medical Center,

military clinics used standardized education materials, concise screening forms, bandages, and staff training to educate recipients about the idiosyncrasies of smallpox vaccination, to identify contraindications (e.g., atopic dermatitis), to safely administer the vaccine, and to care for the vaccination site appropriately.

The accompanying prospective surveillance system identified an elevated risk of myopericarditis in the second week after primary smallpox vaccination, disproportionately among young adult Caucasian men (177–179). The military smallpox vaccination program continues in order to preserve critical military capabilities in case of an attack, with over 1,100,000 people screened and over 1,000,000 people vaccinated between December 2002 and April 2006.

Anthrax

The intelligence community and civilian experts consistently rank anthrax spores as the number one threat from bioweapons. This ranking is due to the stability of spores, which can persist for decades despite environmental extremes. Anthrax spores can be easily dispersed, as seen in the multiple releases via mailed letters or packages on the US eastern seaboard in the fall of 2001 (180, 181).

Early anthrax vaccines were developed at Fort Detrick, Maryland, by George G. Wright and colleagues (182–187). An aluminum-adsorbed anthrax vaccine was tested in a human field trial in the 1950s, demonstrating 92.5 percent reduction in disease incidence (cutaneous and inhalation cases combined) (188), and was licensed in 1970 (8, 189, 190). Subsequent inhalation challenges in nonhuman primates and rabbits showed greater than 95 percent protection against lethal challenge. A comprehensive review by the National Academy of Sciences affirmed the efficacy of anthrax vaccine adsorbed (186).

An estimated 150,000 American troops received one or two anthrax immunizations during the Persian Gulf War in 1991, but individual records were either not kept (in an attempt not to identify those unimmunized and hence vulnerable to enemy bioweapons) or were marked with terms such as "Vaccine A" (186, 191–195). In March 1998, a much larger immunization program began that has now administered over 5.6 million anthrax immunizations to over 1.5 million troops. Anthrax immunizations are primarily intended for people serving in areas judged to be at higher risk (e.g., southwest Asia, Korea), as well as military personnel with homeland biodefense roles.

Anthrax vaccine was the target of prolonged skepticism, evoking review by the National Academy of Sciences and an extraordinary array of postmarketing safety studies. These studies involved cohort studies of acute symptoms (196–204), hospitalizations (186, 205, 206), disability evaluations (207), and reproductive outcomes (208–210), as well as secondary review of the spontaneous reports to the Vaccine Adverse Event Reporting System (211, 212).

Public concerns about health problems against anthrax immunization encompassed so many divergent diagnoses (e.g., lupus erythematosus, hypothyroidism, diabetes, cancers, Guillain-Barré syndrome, multiple sclerosis) that epidemiologists conducted objective comparisons of

anthrax-immunized and -unimmunized personnel for each major diagnostic group. The objective comparisons showed that the immunized and unimmunized cohorts had comparable rates of illness and health. Several of the cohort studies span observation for multiple years after immunization (186, 205–207, 209, 213, 214). Many of the individual concerns can now be understood as instances of the post hoc ergo propter hoc fallacy.

After the National Academy of Sciences heard from vaccinees and comprehensively reviewed the accumulated scientific data, it concluded that anthrax vaccine has an adverse-reaction profile similar to that of other adult vaccines (186). The AFEB concurred (11). However, an elevated rate of injection-site pain and swelling, occasionally with peripheral neuropathy due to pinching of the ulnar nerve, is associated with administering a vaccine adjuvanted with aluminum hydroxide by subcutaneous injection. Studies underway are evaluating rare adverse events (e.g., prolonged myalgia or arthralgia) and the relative effectiveness of intramuscular injection on immunogenicity and safety. The anthrax immunization program also pointed out needed improvements in the way the Department of Defense exchanges information with military personnel and their families and provides clinical immunization services in general.

Plague

A formalin-inactivated plague vaccine saw limited use during World War II (4, 16, 187). American soldiers deploying to Vietnam during the 1960s received a similar inactivated plague vaccine. Conversely, the South Vietnamese government gave the live EV or EV76 strain of plague vaccine to its soldiers (3, 4, 19, 187, 215–219). American use of plague vaccine declined substantially after the 1960s, given a relatively high degree of injection-site reactions and limited exposure to the bacteria. Today, no plague vaccine is licensed by the Food and Drug Administration (8, 11, 136, 220).

A plague vaccine is potentially of interest in countering bioweapon threats (221), but the previous whole-cell plague vaccine did not adequately protect mice against inhalation challenge with *Yersinia pestis* bacteria (222). Modern technology may provide an improved plague vaccine containing F1 and V proteins as the principal antigens (218, 219, 223).

PROPHYLAXIS OF OTHER INFECTIOUS HAZARDS

Pneumococcal disease

Army Major George Sternberg discovered *Streptococcus pneumoniae*, the pneumococcus, in New Orleans, Louisiana, in 1880, shortly before Louis Pasteur did. Early successful tests of pneumococcal polysaccharide vaccines occurred at Camp Upton, New York, and Camp Wheeler, Georgia, in 1918–1919. The Army Medical School made 2 million doses of pneumococcal types I, II, and III vaccine in a few weeks toward the end of 1918.

During the 1930s, polyvalent pneumococcal polysaccharide vaccine was tested in five trials in 120,000 men at Civilian Conservation Corps camps (5, 8, 13, 14, 17, 82,

224–227). In 1937, Frank Horsfall prepared a therapeutic rabbit pneumococcal antiserum. Equine or rabbit pneumococcal antiserum was available from several sources as late as 1965 (5, 8).

Successful clinical trials of pneumococcal vaccine were conducted in military trainees in 1944–1945 at the Sioux Falls Army Air Force Technical School, where a high incidence rate of pneumococcal infections was found (3–5, 13, 226, 227). Pneumococcal vaccines were not widely prescribed because of greater confidence in another newly introduced drug, penicillin. The vaccines were voluntarily withdrawn by the manufacturer in 1954, because of lack of acceptance and low sales.

Today, 23-valent pneumococcal polysaccharide vaccine is given to asplenic military personnel. On the basis of episodic outbreaks, the vaccine has also been given to selected Marine Corps and special operations trainees; its value in training settings is being evaluated (11, 228, 229).

Poliovirus

In 1955, the US government licensed Jonas Salk's inactivated poliovirus vaccine. In 1961, the first of several formulations of Albert Sabin's oral attenuated vaccine was licensed. One year later, the oral polio vaccine largely replaced the Salk vaccine in the United States (8, 19).

Initially, military poliovirus immunization was a "catch-up" program for adults who had not been immunized as children. Basic training centers switched from injectable vaccine to oral vaccine once the trivalent oral product became available in the early 1960s (10, 11, 230).

Historical notes

Several immunizations given to earlier generations of American troops, but no longer used, are worthy of brief mention. The military immunization experience includes long-term follow-up of laboratory personnel who received multiple common and exotic vaccines (213, 231–236).

A formalin-inactivated typhus vaccine was provided primarily to troops serving in Europe during World War II and then in the Korean and Vietnam wars. Plotz and colleagues at WRAIR helped purify the specific antigen. The vaccine prevented louse-borne (epidemic) typhus but not murine or scrub typhus. The microbes, cultured in chicken-embryo yolk sacs and inactivated with formaldehyde, were first licensed for general use in 1941 (3–5, 8, 10, 237–240). However, subsequent attempts to purify this vaccine resulted in inadequate potency, so immunization eventually gave way to insecticides and antibiotics. Production ceased voluntarily in 1980, and the last batch expired in 1981.

During the late 1980s, an inactivated tick-borne encephalitis vaccine produced in Austria was administered as an investigational vaccine to certain inspectors enforcing the Intermediate-Range Nuclear Forces Treaty (11, 136). These inspectors regularly visited rural and forested areas of the Soviet Union that are highly endemic for tick-borne encephalitis. A similar product was used in 1996 during the US military deployment to Bosnia (8, 11, 136, 175, 241, 242).

In the 1950s, IGIM was used to treat patients deficient in the antibody-rich, gamma-globulin fraction of serum, first described by Colonel Ogden C. Bruton, an Army pediatrician at Walter Reed Army Hospital (243–245). His discovery opened new approaches in passive immunization and the diagnosis and treatment of humoral (antibody) immune deficiencies. Human hyperimmune globulins largely replaced corresponding equine antisera and antitoxins in the 1960s (8, 10, 47).

In the 1980s, Major Mark Fischer, Val Hemming, and their colleagues showed that a polyvalent, high-titer, respiratory syncytial virus immune globulin was effective prophylaxis in infants. Their work at the Uniformed Services University of Health Sciences established the cotton-rat model of respiratory syncytial virus disease (8, 139, 246, 247).

VACCINE-SAFETY SURVEILLANCE PROGRAMS

Even with the success of immunization in reducing the incidence of the diseases discussed above, the military health system faces the same challenges that the civilian public-health sector does—increasing concerns about vaccine safety and adverse events experienced after immunization. Vocal objection to military immunization programs occurred with variolation in the 1770s (7, 17), smallpox and typhoid vaccines in the 1910s (28, 38), various vaccines in World War II (15), and anthrax vaccine in the 1990s (186).

The military health system that implements immunization programs also has a responsibility to implement safety surveillance programs (11). In recent times, these surveillance programs may be best exemplified by assessments of anthrax vaccine safety and smallpox vaccine safety, where the Department of Defense has been the primary user of these vaccines (29, 177–179, 186, 196–214). A Navy allergist was among the first to recognize the role of gelatin in vaccine-associated anaphylaxis (248).

PRACTICAL ISSUES IN PROGRAM IMPLEMENTATION

Most vaccines require continuous refrigeration. A few require storage in a freezer. Maintaining the "cold chain" to ensure injection of potent vaccines appears simple but requires considerable effort (8, 15–18). In World War II, smallpox vaccine was transported by propeller-driven aircraft over long distances, using kerosene-powered refrigerators or packed in dry ice. Improper vaccine storage was one of the principal factors in breakthrough infections. In January 1946, a special shipment of smallpox vaccine was ordered from the US mainland, after doubts arose about the potency of vaccine on the Korean peninsula (27, 249). Today, monitoring devices can record the temperature of vaccine shipments, allowing improperly handled product to be replaced rather than injected.

Documentation of immunizations is important to record a health-care encounter and to avoid redundant immunization at future health-care visits. During World War II, tetanus immunizations were marked on troops' identification tags ("dog tags"; figure 3) and on paper records (figures 1

and 2). Increasingly since the 1990s, the Department of Defense uses electronic immunization tracking systems (i.e., registries) to permanently record immunizations, even if paper records are lost (11, 250).

The administration of immunizations to new military personnel is based on several assumptions. First, accession physical examinations establish that trainees comprise a healthy population without underlying conditions known to predispose people to serious adverse effects from immunization (e.g., immune deficiencies). Second, most trainees are assumed to have been exposed to childhood vaccine antigens through natural infection or childhood immunization programs. Vaccines with highest priority are those to prevent infections most transmissible in closed settings (e.g., meningococcal disease, influenza, measles, varicella) (9).

During training, accessions must acquire immunity to multiple infections within a short period of time. Thus, simultaneous immunizations have been provided to tens of millions of trainees since World War II (10, 11, 213, 225, 232, 234, 236, 250). The AFEB considered the issue in 2004 and concluded that available data "do not demonstrate serious or long-term adverse health effects causally related to multiple, concurrent immunizations, and there is no reason to deviate from current consensus guidelines for adult immunization" (251, p. 3). Similarly, an Institute of Medicine committee (252) and others (253) found that the evidence favors rejecting a conclusion that simultaneous immunization causes heterologous infection, type-1 diabetes, or other patterns of adverse events. Additional work is needed to identify risk factors that might predispose to rare problems.

Because American adolescents today have a high degree of preexisting immunity, the Department of Defense increasingly uses seroscreening to individualize immunizations according to personal vulnerabilities (11, 146–152, 254–257). Training sites are planning to separate immunizations into clusters based on acute versus long-range need. The first cluster would protect against pathogens posing an imminent risk in closed communities (e.g., influenza; meningococcal; measles, mumps, rubella; varicella). The second cluster would protect against pathogens posing a threat later in military service (e.g., hepatitis A, hepatitis B, poliovirus, tetanus-diphtheria-pertussis).

Additional vaccines can be given later during training. The Marine Corps, for example, administers yellow fever vaccine to trainees late in the training cycle. Typhoid or rabies immunization can be started during advanced or specialty training, on the basis of the first assignment or occupational specialty, respectively (9).

Jet-injection devices were first developed in the private sector in the 1940s. Military scientists adapted the early devices to create needle-free, multiuse-nozzle jet injectors capable of 600 or more subcutaneous injections per hour from 1949 onward, primarily for basic training camps. The Army's Aaron Ismach and Abram Benenson developed a nozzle for intradermal vaccination, used in civilian mass smallpox immunization campaigns in the 1960s (4, 10, 20, 258–262). Unfortunately, the device's use of the same unsterile nozzle and fluid pathway to provide injections to consecutive patients allowed transmission of blood-borne pathogens (e.g., hepatitis B, human immunodeficiency virus)

in civilian settings, and the devices have fallen into disfavor (263, 264). In contrast, a new generation of disposable-cartridge jet injectors is being developed to avoid these safety concerns by using a disposable, sterile fluid pathway for each patient.

RESEARCH PORTFOLIO

Military personnel confront infectious hazards for which there are not yet licensed vaccines. Over the past few decades, the US military medical research community, working with civilian partners, developed several investigational vaccines, toxoids, and immune globulins to counter specific military threats associated with high morbidity. These threats included both natural, endemic diseases and microbes that could be deployed as bioweapons (136, 175). Such vaccines have been studied to prevent Argentine hemorrhagic fever (Junín virus) (158, 265, 266), botulism (267), chikungunya (158, 268, 269), dengue fever (265, 270), eastern equine encephalitis (271), Ebola fever (158, 265, 272, 273), *Escherichia coli* (34, 274), hepatitis E (275), human immunodeficiency virus disease (276–279), Lassa fever (158, 265, 272), malaria (280–283), *Mycoplasma pneumoniae* (284), *N. meningitidis* serogroup B (285, 286), Q fever (187, 287, 288), Rift Valley fever (158, 265, 289–293), shigellosis (34, 294), tularemia (187, 236, 295–298), Venezuelan equine encephalitis (3, 175, 236, 299–301), and western equine encephaltitis (302). A gonococcal vaccine produced neutralizing antibodies but was not sufficiently protective in a field trial (279, 303).

New versions of some of the older vaccines are in early clinical trials, including recombinant botulinum bivalent AB vaccine and live attenuated Venezuelan equine encephalitis V3526 vaccine (304). Next-generation anthrax vaccines in clinical trials include recombinant protective antigen vaccine and a vaccine adjuvanted with CpG oligodeoxynucleotides (305–307) (in genetics, "CpG" is a site where cytosine (C) lies next to guanine (G) in the DNA sequence; the "p" indicates that C and G are connected by a phosphodiester bond). The role of anthrax capsule/exosporium and toxin proteins and spores is being evaluated in animal models. A F1-V plague vaccine should enter clinical trials soon (223). Vaccines advancing toward clinical trials include staphylococcal enterotoxin B/A vaccine (308), hantavirus vaccine (158, 309, 310), and next-generation eastern equine encephalitis and western equine encephaltitis vaccines (175, 300, 311). Novel approaches being pursued include RNA replicons as vaccines against Marburg and other filoviruses (312, 313) and DNA vaccines against hantavirus (314). The candidate malaria vaccine known as "RTS,S" reduced the rate of parasitemia by 37 percent and severe malaria by 58 percent over a 6-month period in Mozambiquean children (281, 282).

Venezuelan equine encephalitis vaccines were given to 2 million horses in Texas to control an equine outbreak there that had contributed to 84 human deaths (3, 175). During an outbreak in the Sinai peninsula, until 1979, the formalin-inactivated Rift Valley vaccine was given to 963 Swedish soldiers under the United Nations' peace-keeping flag (291,

292, 315, 316). More than 175,000 doses of the Argentine hemorrhagic fever vaccine have been administered in Argentina, dramatically reducing disease incidence (158). About 8,000 troops received the investigational botulinum pentavalent (ABCDE) toxoid during the Persian Gulf War (191–195). Successful vaccine research may not be carried through to commercial development and licensure, such as improved vaccines against Rocky Mountain spotted fever developed at WRAIR (240, 317, 318).

Similar to the movement toward more combination vaccines for children, multiagent vaccines for military personnel are also a priority. A panfilovirus vaccine protecting against Marburg and Ebola variants may be possible within a decade. Novel delivery systems being pursued include aerosols, microneedle or adjuvanted patches, and oral dosage forms.

Military personnel need vaccines that are 1) safe (associated with few adverse reactions); 2) effective (substantial reduction in disease incidence); 3) easy to administer; 4) robust (long-lasting immunity, prolonged shelf life, tolerant of shipping conditions); and 5) affordable (offering good value for the price paid). The ideal vaccine formulation would produce prolonged immunity against several diseases through a single dose. Genetically engineered products may lend themselves to this ideal. Adjuvant research will help (319). Yet even with 20 years' experience in biotechnology, the development and licensing process is no shorter or simpler than it was in the 1980s.

If infection cannot be prevented outright, passively acquired immunity may be clinically useful. The Department of Defense has investigated the use of human immune globulin preparations (e.g., hyperimmune globulins, antitoxins) to treat or protect against *Klebsiella* and *Pseudomonas* infections in burned or severely wounded patients (320) and to provide passive protection against Lassa fever (158, 265), Ebola fever (265, 321), Bolivian hemorrhagic fever (caused by Machupo virus) (158, 322), and botulism (323). The Department of Defense has assisted in the development and evaluation of polyclonal and monoclonal antibodies for the treatment of anthrax infection (324).

The Department of Defense invests in research and development of countermeasures to natural infectious diseases and bioweapons that might harm military personnel, as described above. In addition, the Department of Defense will take advantage of the fruits of private-sector research and development, such as vaccines to prevent papillomavirus-related cervical cancer and herpes zoster.

SUMMARY

In 1900, smallpox vaccine was generally available, rabies vaccine found limited use as postexposure prophylaxis after animal bites, and typhoid vaccine was just coming to public attention. A century later, 22 serious infections can be prevented with Food and Drug Administration-licensed vaccines (7–9). As vaccines increase in number and national focus on vaccine safety continues, the complexity of managing clinical immunization challenges will undoubtedly increase. Information technologies are increasingly used to disseminate

immunization information (e.g., www.vaccines.mil) and to conduct long-distance, on-demand training (e.g., https://www.projectimmunereadiness.amedd.army.mil/).

Military immunization programs maintain the health of soldiers, marines, sailors, airmen, and coast guardsmen, the most important resources within the Department of Defense, the resources most critical to military success. These people deserve the best available protective measures.

Some immunization needs are universal for all in military service (e.g., tetanus), while others derive from specific environmental or occupational risks (e.g., Japanese encephalitis, rabies). Military immunization programs, however, need to be individualized on the basis of personal contraindications and prior immunity. The proper conduct of military immunization programs respects the need for detailed education of military personnel about the immunizations they get, maximizes quality in immunization delivery, and supports quality clinical care to prevent and treat adverse events after immunization.

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