Chapter 13

RESPIRATORY INFECTIONS IN MILITARY RECRUITS

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INTRODUCTION

We have come to accept respiratory infections, from the common cold to more severe manifestations including fever and constitutional symptoms, as a part of life. It has long been recognized that military populations, especially recruits, are particularly susceptible to the ravages of these respiratory illnesses. Epidemiologically, the reasons why military populations are predisposed to the spread of pathogens with affinity for the respiratory tract are multifactorial. Clearly, the close living conditions, environmental challenges, and physical hardships all contribute. Additionally, the epidemiology of various pathogens is often different in the military than in civilian settings.

The terms used to discuss respiratory illnesses in civilian and military populations are as diverse as the many pathogens responsible. Historical terms such as "catarrhal fever" and "pharyngoconjunctival fever" are no longer used; in recent years, "acute respiratory disease" (ARD), "acute respiratory illness" (ARI), "influenza-like illness" (ILI), "upper respiratory illness" (URI), and "febrile respiratory illness" (FRI) are more commonly seen. Among working military populations, colorful phrases such as "recruit crud" or "plebe hack" are heard. The clinical presentations of the respiratory illnesses described by these terms are equally diverse and nonspecific, including nonfebrile common cold with congestion; febrile illness with malaise, sore throat, and cough; and increasing lower respiratory symptoms, such as severe pneumonia with radiographic consolidations. As respiratory illnesses are investigated, careful consideration should be given to the case definition that is being used, regardless of the term. No one term has maintained a clear, unique definition through time; to the contrary, different terms in separate populations or time periods often refer to the exact same case definition.

Recounting the role of respiratory infections throughout military history should serve two purposes: (1) to gain an appreciation of the ultimate destructive power of these infectious agents and (2) to learn from the generations of thoughtful, dedicated physicians and researchers who have preceded us. Only through consideration of these two goals can we hope to progress in our knowledge. To this end, this chapter will first explore the burden and epidemiology of respiratory illnesses in military forces throughout history, with emphasis on the recruit population. It will then consider individually the numerous pathogens of concern: group A streptococcus (GAS), adenovirus, influenza A, *Streptococcus pneumoniae*, rhinovirus, *Bordetella pertussis*, *Mycoplasma pneumoniae*, and atypical agents. Finally, preventive measures implemented both historically and currently will be discussed. The military medical community has given great effort to understanding and minimizing morbidity and mortality from respiratory illnesses during the past century. In many cases progress has been great; in other cases, successes were minimized and valuable ground gained has been lost.

HISTORY AND EPIDEMIOLOGY OF RESPIRATORY INFECTIONS IN MILITARY RECRUITS

History books often repeat the theme: death from infectious diseases far exceeds the loss of life from battle injuries. In the past, understanding that infectious organisms were responsible for the illnesses seen was nonexistent or in its infancy. Without this understanding, appropriate interventions could not be implemented and loss of life avoided. Even today, we struggle to enforce even basic handwashing recommendations. An 1873 US Navy hygiene report illustrates the ripe environment for transmission of infectious agents:

> If a man's cutlass is bright and his overshirt clean, the inspecting officer is satisfied, although his axillae, groins, and perinaeum may be abominably dirty and verminous, his under-garment unclean and unchanged for weeks, and his bedding disgustingly foul and offensive…every man should be required to possess one or more towels, which should appear among the paymaster's stores, and facilities should be afforded every day for drying them.[1(p66)]

Most common among the infectious diseases reported were those with respiratory symptoms, and recruits, inevitably, were disproportionately affected. An 1812–1813 pneumonia epidemic was thought to have originated among recruits: "…it appears most probable that this epidemic began in the camp of new levies, at Greenbush, opposite Albany, New York."[2(p49)]

Treatment modalities used in the early 1800s made some strides toward sensible "do no harm" palliative measures, as illustrated in the following: "A considerable war developed over the proper treatment; whether by the orthodox bleeding, purging, etc, or by milder methods. Dr Mann championed bleeding and advocated it in nearly all cases, claiming marked benefits. Dr Christopher C. Yates, of Albany, having treated a soldier with the usual bleeding, blister, calomel, jalap, and antimony, only to see him die more quickly, decided on milder measures. Two later cases he treated with an emetic, physic, laudanum for the pain and hot tea to promote sweating; as this plan was successful,

he repeated it in many other cases, with success, as he said."[2(p52)] Early public health officials tried to understand infectious disease and develop control measures. Indeed, the military setting was recognized not only as especially conducive to transmission of infectious agents, but also as a unique environment for medical research.[3]

Vital statistics from US Army medical records during World War I, from April 1917 to December 1919, document that 86% of the total force missed one or more days of duty because of illness. In contrast, 7% of missed days were from nonbattle injuries and 5.5% from battle trauma. Of all deaths during this period, 51% were from disease, 12% from wounds, and 32% from being killed in action. Of the total deaths from disease, respiratory causes accounted for 77.5%.[3]

Knowledge of the epidemiology of respiratory pathogens advanced greatly during World War II with the formation of the Commission on Acute Respiratory Diseases (CARD). Starting in 1942, the commission's studies at Fort Bragg, North Carolina, provided much of the foundation for later research. Because diseases with a known etiology were rare, CARD studies between 1942 and 1945 used cases of respiratory illness admitted to the wards as the basis for surveillance efforts. Researchers noted that approximately 10% of these respiratory illnesses were atypical pneumonias. Illnesses caused by known bacteria, such as hemolytic streptococcal pharyngitis and pneumococcal pneumonia, were uncommon. Influenza A and German measles were sporadic causes of respiratory illnesses, but no pathogen was discovered in the vast majority of respiratory illnesses.[4]

The commission's studies were repeated in ensuing years at other recruit training camps. Among the studies' significant contributions was the documentation that rates of respiratory disease among recruits were higher than other "seasoned" military groups. Figure 13-1 illustrates comparative respiratory illness rates for three different camps, performed by different investigators from 1942 through 1954.[4-6] Once this difference in infection rates was established, researchers could turn their attention to the unique features of the training environment that predisposed recruits to greater respiratory morbidity.

Another recurring theme in the CARD studies was the observation of seasonal patterns of respiratory illness. At Fort Bragg between 1942 and 1945, outbreaks occurred predictably in the winter and early spring but not in the summer or early fall. This pattern was

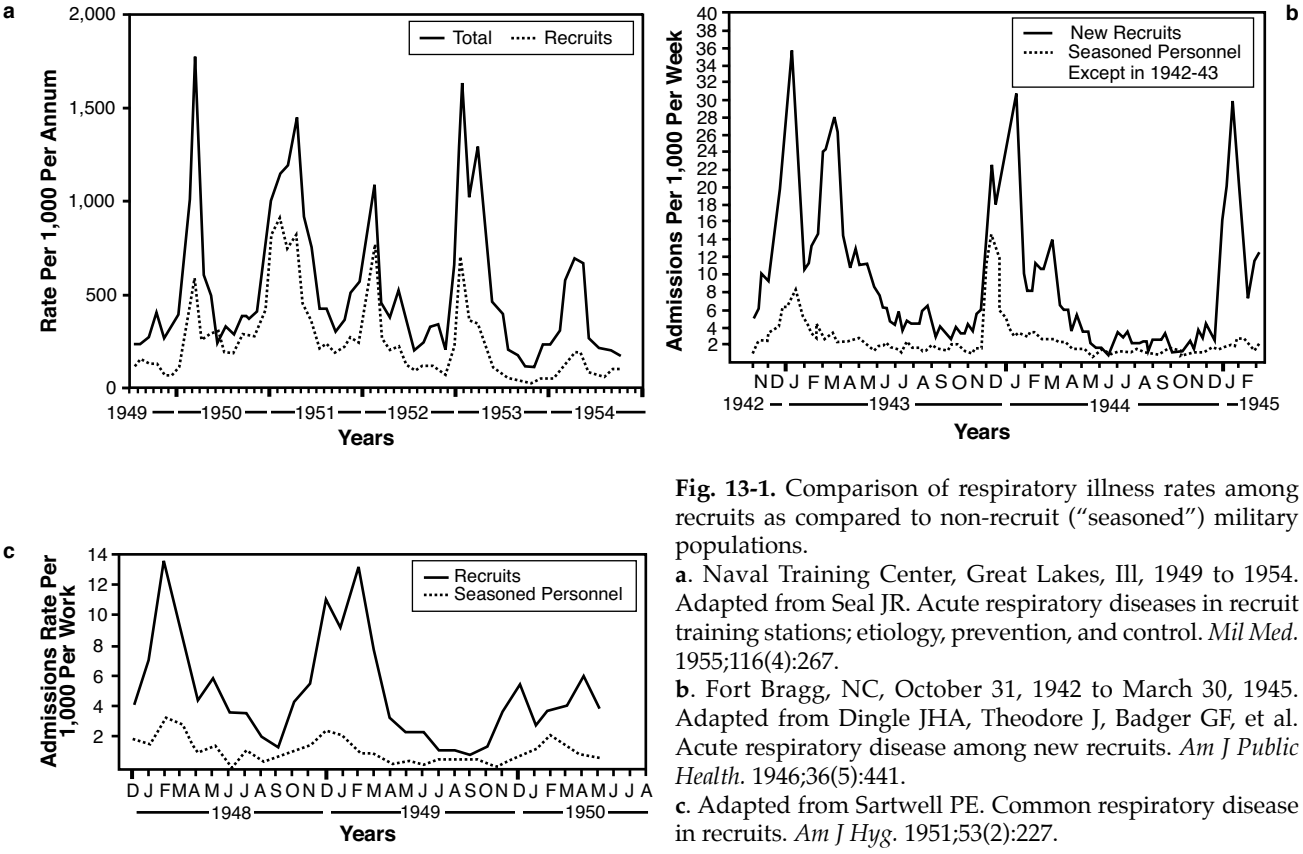

Fig. 13-1. Comparison of respiratory illness rates among recruits as compared to non-recruit ("seasoned") military populations.

a. Naval Training Center, Great Lakes, Ill, 1949 to 1954. Adapted from Seal JR. Acute respiratory diseases in recruit training stations; etiology, prevention, and control. *Mil Med.* 1955;116(4):267.

b. Fort Bragg, NC, October 31, 1942 to March 30, 1945. Adapted from Dingle JHA, Theodore J, Badger GF, et al. Acute respiratory disease among new recruits. *Am J Public Health.* 1946;36(5):441.

c. Adapted from Sartwell PE. Common respiratory disease in recruits. *Am J Hyg.* 1951;53(2):227.

less apparent at camps that received a constant influx of recruits, where a more dispersed pattern occurred.[7] Also, a considerable increase in the incidence of nonhospitalized cases of respiratory disease occurred in the late summer and fall, indicating that the pattern of less severe illness differed from the more severe, hospitalized cases. This suggested that different pathogens were responsible.[7-9] Studies by Sartwell and colleagues[5] at Fort Dix, New Jersey, from 1947 to 1950 showed much higher rates of respiratory disease among the recruits in the winter months as well, with steep reductions in the rates after 4 to 6 weeks of training.

Increased rates of respiratory disease in crowded populations were documented in several studies. Miller and colleagues[10] noted a direct correlation between changes in rates of pneumonias *and* respiratory illness with the number of recruits in training. The number of recruits proved to be an even stronger determinant of infection rates than seasonal factors.

Studies that examined the epidemiology and etiology of pneumonias, in addition to upper respiratory illness, were also performed. Outbreaks of pneumonia were often found to occur at times distinct from outbreaks of respiratory disease, suggesting different causative pathogens. This distinction was noted by Rosenbaum and associates[11] during their 10-year surveillance initiatives at Great Lakes Naval Training Center, Illinois.

Two early studies examined the relationship of vaccination to rates of respiratory illness to determine whether the different rates of respiratory illness in recruits and seasoned personnel resulted in any part from the large number of routine vaccinations administered to new recruits.[12,13] Studies by Pierce and colleagues[12] at Great Lakes in 1961 compared rates of respiratory illness in recruits who received their vaccinations in the traditional pattern (all at once upon arrival) with those whose vaccinations were spread over a 2-month period. The two arms of the study were conducted simultaneously, decreasing the confounding potential of seasonal variations. Receiving vaccinations over the 2-month period resulted in a 20% reduction of the more severe respiratory illnesses, including pneumonia.

Despite an incomplete understanding of the pathogens responsible for the majority of the respiratory illnesses, these early epidemiological studies revealed important characteristics and identified salient points. The importance of GAS was recognized early. Subsequently, the discovery of influenza and adenovirus as prominent causes of respiratory illness among recruits opened the door for targeted preventive measures. The remainder of this chapter will address causative pathogens independently, followed by a discussion of preventive modalities used through time.

MAJOR PATHOGENS IN RESPIRATORY INFECTIONS

Group A Streptococcus

GAS, also known as *Streptococcus pyogenes*, is a Gram-positive organism that causes a wide variety of clinical manifestations. With an incubation period of 2 to 4 days, symptom onset is characterized by sore throat with malaise, submandibular lymphadenopathy, fever, and headache. Characteristics that suggest a non-GAS etiology include rhinorrhea, cough, hoarseness, or conjunctivitis. Erythema and swelling of the posterior pharynx are common, with or without exudates. Signs and symptoms at clinical presentation are often indistinguishable from influenza or adenoviral illnesses. The spectrum of disease caused by GAS is broad, however, with asymptomatic infections and carriage common.

Various sequelae can result from GAS infection. These include scarlet fever—characterized by the common signs and symptoms of acute GAS infection—but with the addition of a characteristic scarlatinal rash. The diffuse red rash characteristically appears first on the upper trunk, extending to the neck and extremities; the palms of the hands and soles of the feet are usually spared. Suppurative complications such as peritonsillar abscesses, retropharyngeal abscesses, cervical lymphadenitis, or mastoiditis are of concern, with potential for extension into the surrounding bones. Other serious sequelae include toxic shock and necrotizing fasciitis. Nonsuppurative or sterile sequelae of GAS infection include rheumatic fever and acute glomerulonephritis. The exact cause of these disorders is unknown, but serious outcomes with long-term morbidity were common in the preantibiotic era.

The importance of GAS infections within the US military has long been recognized. It was among the first pathogens to be specifically identified as causing considerable morbidity in large numbers of troops. During World War II, scarlet fever alone was responsible for more than 1.3 million lost workdays.[14] More than 1,600 cases of *recognized* streptococcal illness were documented for every 108 cases of malaria and 1 case of polio. The highest incidence of streptococcal illness was among recruits. Unlike malaria and polio, in which symptomatic individuals would be unlikely to avoid medical care, it was clearly documented that a large percentage of streptococcal illness went unde-

tected, with only one third of individuals with acute respiratory illnesses seeking medical care.[6] Under such circumstances, control efforts seemed futile.

Given the toll of GAS infections among recruit populations, elegant studies of transmission and infection dynamics were performed in the 1940s. How infection was acquired was carefully investigated, from personal contact to various environmental sources such as bedding and shared equipment used in training. Although the potential contribution of numerous environmental sources could not be excluded, these early studies clearly demonstrated the predominance of person-to-person contact.[14,15] In particular, individuals with demonstrated nasal carriage were found to be more infectious than those with pharyngeal carriage.[16] Introducing streptococcal patients into new companies was associated with transmission to fellow recruits. Half of all patients discharged from scarlet fever wards were shown to be carriers in one study.[14] These studies suggested that if a recruit escaped GAS infection within his training group, he almost invariably contracted a "bad cold" and reported to sick call, where he would be exposed to the numerous streptococcal patients and become infected himself.[14]

Under such circumstances, it is easy to understand the difficulty of controlling GAS infections in the military, particularly in the recruit setting. Carriage states, prolonged shedding after symptomatic illness, and direct transmission in the very clinics that should have provided protection and healing created difficult odds for success. Fortunately, the antibiotic era was beginning at this time. Given the futility of other preventive efforts and the seriousness of the sequelae of GAS infections, mass chemoprophylaxis efforts using the first available sulfonamides were explored. Their demonstrated effectiveness was dramatic.[17] Unfortunately, so too was the speed that resistant organisms emerged. The first resistant isolates were identified in Farragut, Idaho, in the summer of 1944.[14] Additionally, toxic effects of the sulfa drugs—including agranulocytosis, exfoliative dermatitis, and hemolytic anemia—were common. The sulfa drugs also required continuous administration and were ineffective in eliminating the carrier state.[17]

The effectiveness of penicillin in not only controlling outbreaks of GAS, but also in decreasing the carrier state, was soon demonstrated.[16,18-20] Numerous studies performed by Wannamaker and colleagues[18,21] in the early 1950s, using controlled experimental designs, investigated different formulations and dosing regimens of the penicillins, from intramuscular to oral routes. Almost complete control of GAS infections, a dramatic reduction in sequelae, and a reduction in the carrier state were demonstrated. These studies were extended and validated by other investigators at the time.[6,20,22] Penicillins were also much safer than sulfonamides.[22,23]

Finally, safe, effective treatment regimens were becoming available. These regimens were futile, however, if asymptomatic infection occurred, continuing the spread of infection, or if symptomatic individuals failed to present for medical care and treatment. One study found that personnel with fevers higher than 103°F commonly avoided medical care.[6] The only potential solution, mass chemoprophylaxis, became widespread at recruit training centers by the 1950s.[24,25] Thomas and colleagues[25] recommended that streptococcal surveillance programs continue, and that the data generated should "influence prophylaxis decisions." The regimen adopted was 1.2 M units of benzathine penicillin G (BPG) administered intramuscularly.

During subsequent decades, GAS prophylaxis in recruit camps was discontinued and then reintroduced. Prophylaxis policies in the last 5 decades teach three recurring lessons:

1. Mass prophylaxis successfully controls GAS infections and their sequelae. When such efforts are stopped, recurrences often occur.
2. Individuals allergic to penicillin require an alternative chemoprophylactic antibiotic.
3. Lessons 1 and 2 must continually be relearned.

Illustrating point 1, Wallace and colleagues[24] reported an outbreak of acute rheumatic fever (ARF) among recruits at the Naval Training Center in San Diego, California. At this site, routine mass chemoprophylaxis was performed from the mid-1960s until 1980, when the practice was discontinued. Subsequently, in 1986–1987, 10 cases of ARF were described, including three cases of carditis. Six cases of GAS pneumonia were also recognized during this time period. Carriage rates were high: 328 of 1,298 recruits (25%) seen for respiratory tract infections tested positive by rapid test, and 66 of 149 recruits (44%) seen in the emergency room tested positive by culture.

Illustrating point 2, in early 1989 Gray and associates[26] investigated Marine recruits at a neighboring training center. Mass prophylaxis was done, but colonization and infections were still occurring. During 12 weeks of recruit training, 736 recruits were followed. Despite two intramuscular injections of 1.2 M units of BPG administered 30 to 39 days apart, 33% of the recruits were found to be colonized, and 42% had evidence of an infection. However, only 93% of the cohort had received the BPG injection. The remaining 7% were excused because of penicillin allergy histories. The results of the study showed not only that these 7%

were at an increased risk of colonization, but also that this small group appeared to put their BPG-covered comrades at risk. In platoons with a higher percentage of recruits who did not receive the penicillin injection because of allergies, there was an associated increase in colonization and infection among the recruits who *had* received the penicillin injection. This study clearly showed that to ensure effective GAS chemoprophylaxis programs, "prophylactic antibiotics must be administered to all members of the population."[26(p92)]

More recently, despite year-round chemoprophylaxis with BPG (twice during training, 28 to 35 days apart) *and* treatment of those with penicillin allergies with oral erythromycin, 127 radiographically confirmed pneumonias occurred among Marine recruits.[27,28] Approximately 44% of the cases were found to be associated with GAS infection. An investigation into this outbreak revealed that 30% of the recruits were not being given BPG because of allergy concerns; in addition, of those prescribed the regimen of 250 mg erythromycin by mouth twice daily, the compliance rate was less than 20%. Although adverse effects of the medication may have contributed to this poor compliance, the regimented environment of recruit training clearly does not lend itself well to self-administered treatment. As a result, more stringent screening criteria for determining penicillin-allergic recruits was implemented and azithromycin—500 mg each week for the first 4 weeks under directly observed therapy—replaced the erythromycin prophylaxis.[27,28]

Within the Army, mass chemoprophylaxis efforts with BPG at recruit training centers were discontinued in the 1970s because of the low incidence of ARF.[29] An outbreak of GAS-related illnesses was subsequently identified in the 1980s at Fort Leonard Wood, Missouri. Acute rheumatic fever, carditis, and polyarthritis were among the manifestations seen, and carriage rates in excess of 70% were observed.[30] BPG administration broke the transmission, and treatment of all new trainees was initiated again until the summer of 1989.

In 1992 a subsequent study by Gunzenhauser and colleagues[29] made an important distinction. In prior decades, BPG prophylaxis was indicated as a measure to decrease the incidence of *sequelae* of GAS infections, namely, ARF. For reasons as yet unclear, rates of sequelae decreased, and prophylaxis programs were thought to be unnecessary. Indeed, during World War II, rheumatic fever rates of 2% to 3% were documented among untreated streptococcal infections.[31] In the previously described work by Gray and colleagues, as well as other outlined studies, little or no rheumatic fever was seen. The question addressed by Gunzenhauser was whether BPG might be beneficial, and therefore indicated, for ARD alone. He demonstrated that with institution of BPG prophylaxis, admission rates for ARD fell 64%, but only 43% of these prevented hospitalizations could be explained by reduction in GAS infections.[29] Clearly, BPG is effective against pathogens other than GAS; the study demonstrated benefits beyond preventing the sequelae of GAS infections and reducing morbidity from GAS pharyngitis itself. Although at least one later study did not reveal this effect on non-GAS respiratory illness,[32] a paradigm shift had occurred. BPG was indicated to decrease rates of GAS pharyngitis, despite the rarity of additional sequelae.

A number of studies have evaluated appropriate antibiotics to treat recruits who are allergic to penicillin. Erythromycin was demonstrated effective at a twice-daily oral dose of 250 mg.[33] Although this self-administered regimen has had a low compliance rate,[27,34] it continues to be practiced at many recruit training centers. Azithromycin, although more expensive, has also been shown to be highly efficacious, and the dosing regimen of 500 mg orally every week is much more reasonable and better tolerated.[32,35]

In conclusion, a pathogen that at one time was responsible for considerable morbidity in recruits and deployed troops is now well-controlled. Outbreaks with considerable morbidity still occur, however. The military's long experience with GAS has shown that some sites require year-round chemoprophylaxis for adequate control; at other sites, seasonal administration suffices. All programs should include ongoing surveillance and be able to accommodate modification and chemoprophylactic intervention, if indicated.

Adenovirus

In the early 1950s, two groups independently reported discovery of a new respiratory pathogen nearly simultaneously. Publishing first in 1953, Rowe and colleagues[36] described an agent that was incidently identified during studies on human adenoid tissue growth. As researchers were attempting to grow the tissues, a large number, but not all, of them degenerated. Filtering the degenerating tissues, researchers noted that the filter effluent caused other cell cultures to degenerate as well. They called the filterable agent "Adenovirus Degeneration Agent" or "A.D. Agent."[36]

At the same time, Hilleman and colleagues[37] were performing an investigation of epidemic ARI among Army recruits at Fort Leonard Wood. Influenza was noted in a majority of patients during the peak of the epidemic but was absent at other periods. In addition, 20% of the noninfluenza patients had clinical and radiographic findings consistent with pneumonia. Throat washings collected from one of these patients (patient 67) demonstrated degenerative, or "cytopathic,"

effects in cultures of HeLa cells. The patient developed neutralizing and complement-fixing antibodies to the isolated agent, called "Respiratory Illness–67," or RI-67. A similar agent was isolated from four other recruits with respiratory illnesses during the same outbreak. Others in the epidemic developed neutralizing antibodies to the agent, but no such antibodies were detected in those diagnosed with an influenza A infection.[37] The term "adenovirus" was adopted for this agent, and many excellent studies of its epidemiology were conducted over the next decade.

Adenovirus was found in a large percentage of recruits during the annual winter–spring ARI epidemics that occurred regularly at many training camps. At Fort Dix in 1954–1955, only 12% to 26% of the illnesses seen were attributed to adenovirus from July through October. In contrast, during December through March, this percentage increased to between 56% and 77%. During the entire year, 10% of the total recruit population was hospitalized with an adenovirus-related respiratory illness. Recruit rates were up to 33 times higher than rates for enlisted soldiers who had completed training.[38]

Although adenovirus transmission was noted year-round, the contribution of adenovirus to the overall hospitalization rates was lower during the summer and fall.[38] This suggests that pathogens other than adenovirus were likely circulating during these periods. Attempts to determine the causative pathogens in undiagnosed cases continued.

A variety of sound epidemiological techniques were used during these years to establish a true cause-and-effect relationship between adenovirus and ARI. Perhaps the earliest (and most shocking by today's standards) were studies that took filtered throat washings from symptomatic patients and administered them to asymptomatic volunteers. The resulting clinical syndrome was found to include a range of illnesses from the common cold to ARI and primary atypical pneumonia.[39]

Recovery rates from adenovirus in individuals with different clinical presentations, as well as in asymptomatic individuals, were also extensively studied. In 1954 Hilleman and colleagues[38] demonstrated that among all recruits at Fort Dix, 20% became ill with adenovirus severe enough to require hospitalization, 20% were symptomatic but did not require hospitalization, 40% were infected but had either very mild or asymptomatic illnesses, and 20% escaped illness. Table 13-1 presents information from several studies of adenovirus isolation rates from different clinical syndromes. Although asymptomatic infection was not always clearly identified in these studies, the wide range of clinical presentation among those infected with adenovirus can be seen. Clearly, asymptomatic infections were not uncommon. Additional serological studies supported this observation. One study reported seroconversion in 24 of 33 recruits (73%) who had no sick call visits,[40] and another reported that 70% of adenovirus diseases did not come to the attention of the medical department.[41]

In studies looking at susceptibility to adenovirus disease in incoming recruits, one demonstrated that 88% of a total group of 1,092 lacked antibodies to adenovirus serotype 4 or 7. Lack of prior military service and younger age correlated with susceptibility.[42] A similar study demonstrated that 76% of incoming recruits were immunologically susceptible to either adenovirus serotype 4 or 7.[43]

Signs and symptoms of adenoviral illness were often compared with nonadenoviral illness. When comparisons were made, the clinical presentation of adenovirus was invariably more severe than that of most other identified pathogens. For example, surveillance conducted by Friedman and colleagues[44] at Great Lakes found a mean temperature among patients with a positive adenovirus culture (n = 50) of 101.6°F, with 95% having a sore throat and 91% a cough. In contrast, among those with no adenovirus isolated, the mean temperature was 100.2°F, with 77% complaining of a sore throat.

Adenovirus shedding studies, critical to the understanding of transmission dynamics, were performed by McNamara and associates[41] in two different recruit companies at Great Lakes. Adenoviruses were found in the oropharynx from 2 days before symptom onset until up to 8 days after symptom cessation. In several cases, shedding of homologous serotypes of adenovirus was found in the stools of recruits who had positive pharynx cultures. This rectal shedding was seen up to 15 days after symptom cessation.[41] Similar studies performed with marines in 1962 demonstrated a mean shedding period of 6 days, with a range of 1 to 26 days.[45]

The following salient points emerged from these early studies: (*a*) Adenovirus is clearly causative in up to 70% of the respiratory illness seen in recruits in the late fall to early spring. (*b*) Adenovirus appears to be endemic at most sites, with at least minimal transmission during the summer months. (*c*) Individuals manifest adenovirus illness in many ways, from asymptomatic infection to a severe, febrile, lower-respiratory illness. (*d*) Person-to-person transmission is clearly important in the spread of adenovirus. (*e*) Situations of crowding appear to accentuate person-to-person transmission. (*f*) Shedding of adenovirus begins before symptom onset and continues until more than a week after symptom cessation. (*g*) Season clearly impacts the transmission dynamics of adenovirus. Less

clear is whether this seasonal impact is a result of the change in total complement of recruits present at that time of year, or a manifestation of seasonal change in temperature or humidity. The variables of humidity and temperature have been inconsistently studied, and their impacts remain unclear. Likewise, the contributions of environmental sources of infection, although likely, remain obscure.

With much of the epidemiology understood, attempts to control the high rates of infection ensued.

TABLE 13-1

DISTRIBUTION OF ADENOVIRUS INFECTIONS AMONG DIFFERENT MILITARY POPULATIONS

Characteristics of Tested Group	Site, Year	Percentage Attributed to Adenovirus by Viral Isolation [% (No./Total)]
No respiratory complaint[1]	Great Lakes, Ill, 1954	0 (0/179)
Febrile respiratory infection (no evidence of streptococcus or influenza)[1]	Great Lakes, 1954	20.5 (23/114)
Afebrile respiratory infection (no evidence of streptococcus or influenza)[1]	Great Lakes, 1954	4.4 (6/137)
Hospitalized ARD[2]	Great Lakes, 1956	53 (50/95)
Nonhospitalized ARD[2]	Great Lakes, 1956	9 (17/185)
Febrile ARD, Jan–June[3]	Camp Lejeune, NC, 1959–1963	36–72
Afebrile ARD, Jan–June[3]	Camp Lejeune, 1959–1963	10–25
Non-ARD controls, Jan–June[3]	Camp Lejeune, 1959–1963	3–9
Seasoned troops, febrile ARD[3]	Camp Lejeune, 1959–1963	14–49
Seasoned troops, afebrile ARD[3]	Camp Lejeune, 1959–1963	5–12
Seasoned troops, non-ARD controls[3]	Camp Lejeune, 1959–1963	0.9–4
Afebrile ARD[4]	Ft Dix, NJ, 1965	29 (15/51)
Mild febrile ARD[4]	Ft Dix, 1965	54 (7/13)
Severe febrile ARD[4]	Ft Dix, 1965	79 (19/24)
Hospitalized ARD[5]	Ft Jackson, SC, 1997	66.1 (673/1,018)

ARD: acute respiratory disease

(1) Rowe WPS, John R, Huebner RJ, Whiteside JE, Woolridge RL, Turner HC. A study of the role of adenovirus in acute respiratory infections in a Navy recruit population. *Am J Hyg.* 1956;64:211–219. (2) Friedman M, Grayston JT, Loosli CG, Pierce WE, Whiteside JE, Woolridge RL. Studies on acute respiratory illness in naval recruits, with emphasis on the adenoviruses (APC-RI). *J Infect Dis.* 1956;99(2):182–187. (3) Bloom HH, Forsyth BR, Johnson KM, et al. Patterns of adenovirus infections in Marine Corps personnel. I. A 42-month survey in recruit and nonrecruit populations. *Am J Hyg.* 1964;80:328–342. (4) Top FH Jr. Control of adenovirus acute respiratory disease in US Army trainees. *Yale J Biol Med.* 1975;48(3):185–195. (5) Hendrix RM, Lindner JL, Benton FR, et al. Large, persistent epidemic of adenovirus type 4-associated acute respiratory disease in US Army trainees. *Emerg Infect Dis.* 1999;5(6):798–801.

Medical staff undertook a variety of methods, with minimal success. It became clear that primary prevention through vaccination would be a desirable intervention, and development of effective vaccines was explored. Many of the initial studies established the serotype of infection adenoviruses. The various serotypes encountered are shown in Table 13-2. Serotypes 3, 4, and 7 were most frequently encountered.

Researchers first investigated inactivated parenteral vaccines but encountered concerns about the neoplastic potential of the adenoviruses as well as contaminating agents in the cell lines used for growing the adenoviruses.[46,47] Next, intestinal infection with live adenovirus strains was attempted. With few adverse effects, high rates of seroconversion and very little transmission to closely associated unvaccinated individuals was observed.[46-52]

Interestingly, early introductions of the adenovirus serotype 4 vaccine alone resulted in increased prevalence of serotype 7 disease.[48] An "ecologic vacuum" appeared to have been created with use of the type 4 vaccine, which was subsequently filled with type 7 transmission. Additional studies showed that oral adenovirus vaccines directed against both serotypes 4 and 7 were not only safe but also highly effective in reducing disease in recruits, with no evidence of any other adenovirus serotype moving in to fill the niche.[43,51,53-56] Routine vaccination with the oral adenovirus type 4 and 7 vaccines began at US recruit training camps in 1971. At Great Lakes, rates of illness subsequently dropped to the lowest ever recorded in more than 15 years of observation.[55(p255)]

Several cost-benefit analyses were performed through the years demonstrating the benefits of the adenovirus vaccination program. The first, published in 1973, estimated cost savings for the Army during the years 1970 and 1971. It was estimated that the vaccines prevented 26,979 cases of ARD within the Army over the 2 years at a per illness cost of $279, and total savings over the expenses incurred by the vaccination program of $2.6 million.[57]

A second cost-benefit study also performed with Army data was published in 1998. This work estimated that 2.6 cases of ARD per 100 recruit-weeks of ARD were vaccine preventable. Direct and indirect costs were estimated at $2,134 per ARD case, saving a projected $15.5 million annually with vaccination.[58] A third study looked at cost savings if the adenovirus serotype 4 and 7 vaccines were reacquired and administered at the Navy recruit training facility at Great Lakes. Published in 2000, this study used the same estimates of vaccine-preventable ARD of 2.6 cases per 100 recruit-weeks, and estimated that 4,555 cases of illness could be avoided with year-round vaccination. Given that the Navy does not maintain ARD wards as does the Army, costs incurred per case took into consideration clinic visits and an ARD hospitalization rate of 7.6%, in addition to the indirect costs. Annual savings within the Navy were estimated at $860 per case, or $2.6 million annually.[59]

Unfortunately, few studies of the success of the adenovirus vaccination program respiratory illnesses among US military populations were conducted during the 1980s and early 1990s, and the sole manufacturer ceased production of the vaccines in 1996. Attempts to reach an agreement between the Department of Defense and the vaccine manufacturer were unsuccessful. Seasonal rationing of remaining vaccine stores occurred until the depletion of stocks in early 1999.

TABLE 13-2

SEROTYPES OF ADENOVIRUSES ENCOUNTERED IN EARLY STUDIES OF RECRUIT POPULATIONS

Site	Year	Serotypes Identified (No. of Cases)
Great Lakes, Ill[1]	1954–1955	4 7 3 5
Ft Leonard Wood, Mo; Ft Ord, Calif; Ft Dix, NJ[2]	1953–1955	4 (8) 7 (17) 3 (5)
Ft Ord[3]	1953–1954	4 (22) 7 (22) 3 (7)
Great Lakes[4]	1955–1966	4 (25) 2 (3)
Great Lakes[5]	1997	3 (132) 7 (378)

(1) Friedman M, Grayston JT, Loosli CG, Pierce WE, Whiteside JE, Woolridge RL. Studies on acute respiratory illness in naval recruits, with emphasis on the adenoviruses (APC-RI). *J Infect Dis.* 1956;99(2):182–187. (2) Hilleman MR. Epidemiology of adenovirus respiratory infections in military recruit populations. *Ann N Y Acad Sci.* 1957;67(8):262–272. (3) Berge TO, England B, Mauris C, Shuey HE, Lennette EH. Etiology of acute respiratory disease among service personnel at Fort Ord, California. *Am J Hyg.* 1955;62(3):283–294. (4) Grayston JT, Woolridge RL, Loosli CG, Gundelfinger BF, Johnston PB, Pierce WE. Adenovirus infections in naval recruits. *J Infect Dis.* 1959;104(1):61-70. (5) Ryan MA, Gray GC, Smith B, McKeehan JA, Hawksworth AW, Malasig MD. Large epidemic of respiratory illness due to adenovirus types 7 and 3 in healthy young adults. *Clin Infect Dis.* 2002;34(5):577–582.

During this transition period, the Naval Health Research Center in San Diego, California, instituted surveillance at five recruit training sites in 1996, expanding to eight centers in 1998. The resurgence of adenoviral illness in these now unvaccinated populations was documented in 2000.[60,61] Also during the transition period, Gray and colleagues[60] demonstrated that unvaccinated recruits were 28 times more likely than vaccinated recruits to be positive for adenovirus serotype 4 or 7. Respiratory illness outbreaks resulting from adenovirus, rare during the adenovirus vaccine era, again became common.[62,63] Deaths associated with adenovirus were also reported.[64]

This section outlined the impact adenovirus has had on military recruit populations. Although reported deaths have not been common, the burden of this pathogen in recruit training centers is great, affecting training more than any other infectious agent. Efforts to renew vaccine production are now under way, with availability anticipated by 2008. The Department of Defense research community is heavily engaged with these clinical trials. Few efforts will have greater direct impact on health and mission accomplishments than renewal and redistribution of the adenovirus vaccines.

Influenza A

Influenza has been known as a distinct disease entity since the 15th century, when an epidemic in Italy was attributed to "influence from the stars." The pathogen responsible was unknown for many centuries, however. As microbiological methods advanced, researchers recognized a filterable agent as causative in influenza. In 1933 Smith and colleagues first isolated the influenza A virus in ferrets. The ability to grow the virus in hen's eggs was introduced by Burnet in 1936. Three influenza viruses are now recognized: A, B, and C. Influenza A causes a moderate-to-severe illness that affects all age groups and can cause major epidemics or pandemics. In contrast, influenza B illness is usually milder, predominately affecting children, and associated with less severe outbreaks. Influenza C is rarely reported, with an infection that is usually subclinical and not associated with epidemics. This discussion will be limited to influenza A, which poses a unique threat not only to military populations, but also to global health. Public health professionals in the military *must* retain a healthy respect for this pathogen.

Influenza A is a single-stranded RNA virus of the Orthomyxoviridae family. The virus has eight separate ribonucleoprotein segments with an outer lipoprotein envelope containing distinct protruding spikes. These spikes, critical to an understanding of influenza, are involved in the pathogenicity of influenza as well as the induced immune response.

One of the two most critical surface proteins, or "spikes," is hemagglutinin (H), which is involved in the attachment of the virus particle to the cell membrane of the host cell it is invading. The other critical spike is neuraminidase (N), which enzymatically cleaves the terminal sialic acid residues that are the receptors for hemagglutinin. Neuraminidase prevents the viruses from clumping together on the surface of the infected cell, so they are free to migrate and infect other cells. Antibodies against neuraminidase, therefore, do not affect early infection, but can greatly attenuate the infection that results.

A segmented genome as seen in influenza is rare among viruses. This characteristic increases the potential for recombinants to form. Wild waterfowl have traditionally been believed to be the natural reservoir for pandemic influenza viruses, as they harbor a complete heterogeneous population, including all 16 known H types and all 9 known N types of influenza A. These are known as the "avian influenza viruses." Historically, humans were known to be susceptible to infection only with strains containing the hemagglutinin H1, H2, and H3 segments and the neuraminidase N1 and N2 segments. Intermediary mammals such as swine can become infected with both human and avian varieties simultaneously, providing an opportunity for recombination and formation of a new virus with increased potential for virulence in humans. An antigenic "shift" refers to a complete exchange of the H or N segment in the circulating strain, resulting in increased risk of epidemics, because antibodies in the population would not protect against the new strain. An antigenic "drift" refers to a minor change within the same circulating H or N types. Increased transmission or epidemics can also occur with a drift if the minor change results in an antigenic change.

It was once believed that the wholly avian influenza viruses could not infect humans. The 1997 discovery of H5 intermittently associated with human illness in Hong Kong, and the subsequent H9 and H7 human infections first identified in the Netherlands, proved this assumption wrong. More alarming, the first person-to-person spread of these avian influenza strains was documented in 2004, adding to concern about the potential for new virulent recombinants emerging.[65] When these wholly avian species of influenza are carried in humans simultaneously with human strains of influenza, the opportunity for humans themselves to play the traditional swine intermediary role for recombination arises, and the potential for a new strain forming with pandemic potential becomes real. Indeed, if genes contributing to efficient person-

to-person transmission recombined with the virulence attributes of the H5 strain in Hong Kong, which killed 6 of 18 people infected in 1997, the potential for an alarming pandemic exists.

Because of the close living conditions among people, avian species, and swine in the Far East, this region is often the focus of concerns for emergence of new pandemic strains of influenza. Ironically, however, one of the most devastating pandemics in history, the influenza pandemic of 1918–1919, did not originate in the Far East. The first documented influenza outbreak in the spring of 1918 was among recruits at Fort Riley, Kansas.

In the midst of World War I, this first wave spread quickly with the troops throughout Europe (Figure 13-2). The mortality of this wave was distinctly less than that of the second wave that began in the fall of 1918. For the first time in history, the potential for a true "pandemic" existed: the roads, railways, steamships, and all forms of transportation supporting global commerce and the global war provided efficient routes of spread never before seen. Before the second wave was over, between 22 and 50 million people were dead.[66]

The following letter was written by a US Army physician at Camp Devens, Massachusetts, in September 1918:

> Camp Devens is near Boston, and has about 50,000 men, or did have before this epidemic broke loose. This epidemic started about four weeks ago, and has developed so rapidly that the camp is demoralized and all ordinary work is held up till it has passed. These men start with what appears to be an ordinary attack of LaGrippe or influenza, and when brought to the hospital, they very rapidly develop the most viscous type of pneumonia that has ever been seen. Two hours after admission they have the mahogany spots over the cheek bones, and a few hours later you can begin to see the cyanosis extending from their ears and spreading all over the face, until it is hard to distinguish the coloured men from the white. It is only a matter of a few hours then until death comes, and it is simply a struggle for air until they suffocate. It is horrible. My total time is taken up hunting rales, rales dry or moist, sibilant or crepitant or any other of the hundred things that one may find in the chest, they all mean but one thing here…pneumonia…and that means in about all cases death.[67]

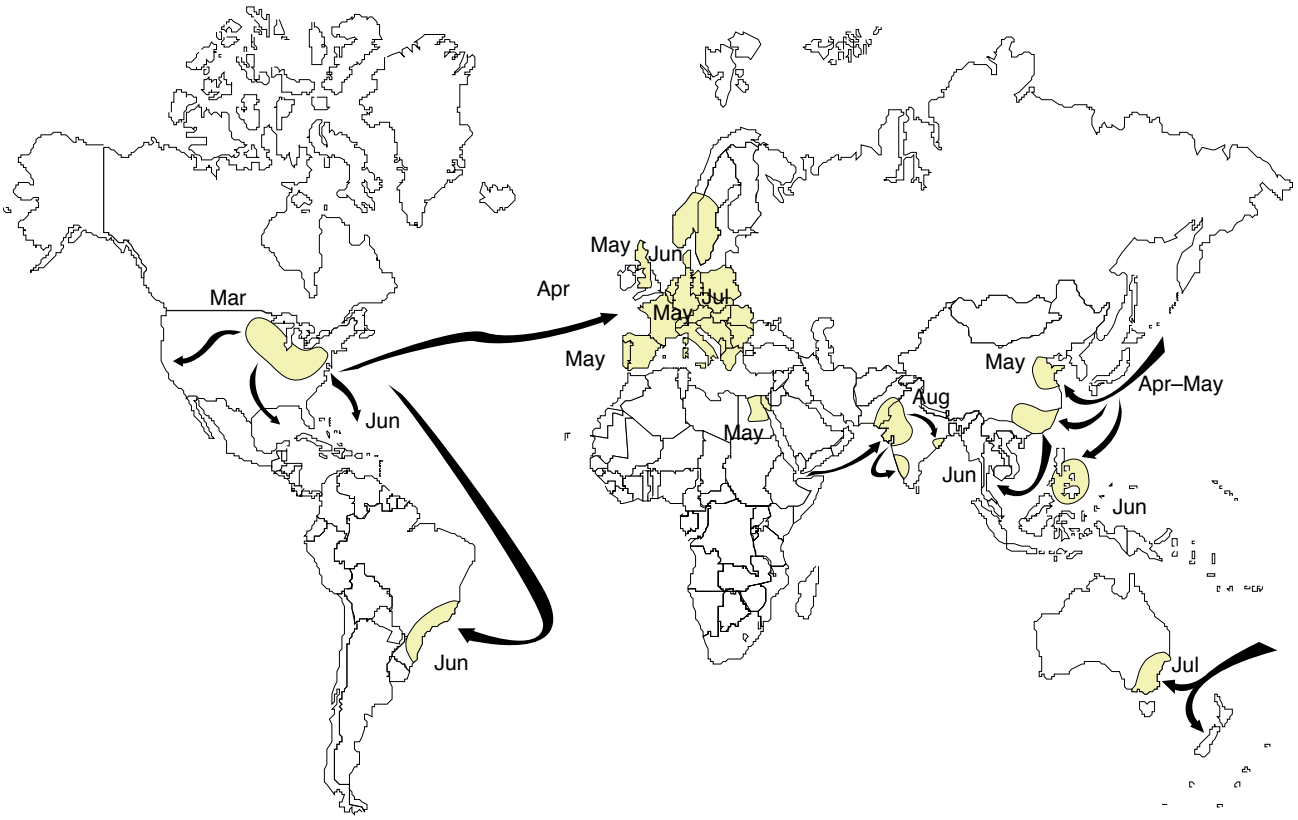

Fig. 13-2. Spread of the first wave of influenza in 1918.
Adapted from Patterson D, Pyle G. The geography and mortality of the 1918 influenza pandemic. *Bull Hist Med*. 1991;65:6.

This staggering pandemic was also significant in its unique mortality trends. Unlike typical seasonal influenza epidemics, in which the very old and very young are most susceptible to severe outcomes, the pandemic of 1918 killed many more of the young and middle-aged. Figure 13-3 demonstrates this unique pattern. Patterns such as this can provide clues to the pathogenesis of the disease.

During the pandemic, pneumonia played a major role in the mortality seen among members of the military. At Fort Riley, it was noted, "We have no evidence from this series that death occurred in influenza except from pneumonia or its complications."[68(p487)] Pneumonia mortality was 35.8%; necropsy cultures of the lungs showed pneumococcus alone or with other pathogens in 58.8% of the cases. *Streptococcus hemolyticus* was found in 41% of the necropsy cultures. The role of secondary bacterial infections was thus documented in the pandemic. This post-viral bacteria pathogen susceptibility has been well documented in the literature in the subsequent 9 decades.[69-71] Although researchers have suggested a variety of hypotheses explaining the propensity for acquiring these secondary infections, the effect of influenza's neuraminidase is implicated in many models. For example, the cleaving action of neuraminidase in the lungs exposes receptors for pneumoccocal adherence, making the affected individual more susceptible to bacterial invasion.[71]

High influenza vaccine coverage in recent years has been very successful in mitigating potential influenza outbreaks in recruit training camps throughout the military; however, outbreaks still occur. Given the high vaccine coverage rates, any influenza illness that occurs should be identified and tested for emergence of strains not covered by the current vaccine formulation. A prime example of this was transmission of a "swine influenza" H1N1 among soldiers at Fort Dix, New Jersey, in early 1976 (A/New Jersey/76) during a period of simultaneous H3N2 transmission (A/Victoria/75). There had been no documented transmission of H1N1 for nearly 20 years at that time, so recognizing this shift in the circulating strain was critically important. The potential for devastating transmission existed. For unknown reasons, however, the swine H1N1 transmission period was short-lived, with illness identified in 13 soldiers, including one death. The investigation of this outbreak by the Department of Defense was timely and very intense, utilizing extensive resources and leveraging laboratory capabilities both within military and civilian sectors. Perhaps this response was to credit for mitigating the spread of this unique swine H1N1 strain.[72,73]

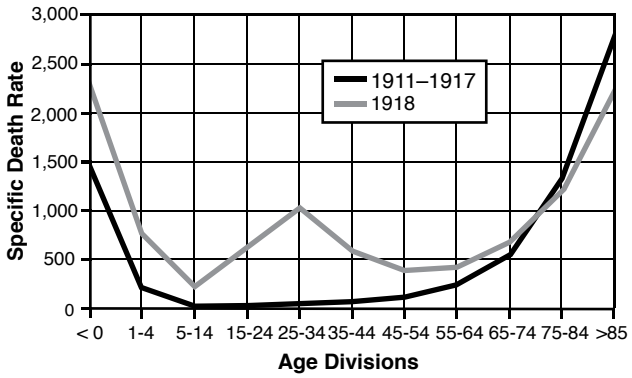

Fig. 13-3. Mortality trends by age in the 1918–1919 influenza pandemic. Adapted from Taubenberger JK, Reid AH, Janczewski TA, Fanning TG. Integrating historical, clinical and molecular genetic data in order to explain the origin and virulence of the 1918 Spanish influenza virus. *Philos Trans R Soc Lond B Biol Sci.* 2001;356(1416):1831.

Nonvaccine influenza strain circulation, off-season transmission, and vaccine supply shortages are important considerations for policy development of other intervention strategies, such as administration of antiviral prophylaxis. Currently, there are four influenza antiviral agents available in the United States: amantadine; rimantadine; zanamivir (Relenza, Glaxo Wellcome Inc, Research Triangle Park, NC); and oseltamivir (Tamiflu, Roche Laboratories, Nutley, NJ). Amantadine and rimantadine are related drugs that have activity only against influenza A, not influenza B. Zanamivir (inhalation) and oseltamivir (oral capsule) are neuraminidase inhibitors exhibiting activity against both influenza A and B.

In 1998 a case of influenza was documented in a recruit training group at Lackland Air Force Base, Texas. The exposed group had received the influenza vaccine only 6 days before, an insufficient amount of time for conferred protection. To mitigate morbidity, amantadine prophylaxis was initiated. Although only three additional cases were documented in this group, compliance with the prophylaxis was only 46.5%, emphasizing the need for directly observed therapy.[74] In 2000 a newer antiviral, zanamivir, was evaluated among military recruits in Finland, during a period of influenza transmission with a strain not represented in the vaccine. The treated arm had a significant reduction in viral load ($P = 0.003$), and a slight reduction in time to alleviation of symptoms (from 2.33 to 2.0 days, $P = 0.08$), compared with the placebo arm.[75] The researchers' swift identification and intervention, as well as available laboratory diagnoses, likely prevented more widespread outbreaks.

An important study used animal models to look at the effect of oseltamivir in improving the outcome

of secondary bacterial pneumonia infections. It was noted that use of antibiotics for the secondary bacterial infections is commonplace within the medical community; however, use of antiviral therapy against these infections is less commonly considered because the viral infection is often resolved. This study found that among mice with a secondary pneumococcal infection (100% mortality in the untreated model): (*a*) use of ampicillin cleared the bacterial infection, but did not improve survival; (*b*) treatment with oseltamivir, even up to 5 days postinfluenza infection, increased survival by 75%; and (*c*) treatment with oseltamivir *and* subsequently with ampicillin resulted in 100% survival.[76] Aggressive treatments might likewise decrease morbidity and stop the spread of an influenza epidemic. Current literature on such treatment modalities should be investigated if such a situation arises.

During the 2003–2004 influenza season, a drifted strain of H3N2 influenza A called the Fujian strain was in circulation. Although some protection from this strain was expected with the annual formulation, early reports indicated otherwise. Within the military recruit setting, however, the vaccine was shown to provide more than 90% protection against this drifted strain.[77] Vaccination proved very useful, and morbidity and probable mortality were averted.

Clearly, influenza vaccination is an important primary preventive measure in the recruit setting. Avoiding the morbidity from secondary bacterial infections is also a powerful reason to provide influenza vaccination to recruits. Heightened and continued surveillance for influenza, combined with proactive responses up to and including aggressive antiviral and antibiotic usage, is important for management of influenza within recruit and military populations as we strive to recognize and prevent global spread of newly virulent influenza strains.

Pneumococcus

S pneumoniae (also known as pneumococcus) is associated with a wide range of clinical illnesses, from sinusitis and otitis media to pneumonia and meningitis. Among adults, pneumococcus is the most frequent cause of meningitis and is responsible for approximately 25% of pneumonias. A Gram-positive coccus often seen in pairs (diplococci), pneumococcus was first isolated in the early 1930s and soon found to be a predominant cause of pneumonia, particularly among the elderly.

Within military populations, morbidity and mortality caused by pneumococcus has also been demonstrated. During the influenza pandemic of 1918–1919, 26% of those hospitalized at Camp Grant, Illinois, developed pneumonia. Of these, 43% died. Pneumococcus was the primary organism isolated from the lungs of these young men. In addition, 50% of their blood cultures were exclusively positive for pneumococcus. Very few asymptomatic individuals were found positive for pneumococcus at the time of this outbreak, providing further evidence that the bacteria was pathogenic in the patients from whom it was isolated.[78] During this pandemic, influenza was clearly the primary cause of the initial morbidity, but the subsequent role of bacteria in producing the lethal pneumonias is well documented.[78(p598)]

This pattern of pneumococcal or bacterial superinfection following a viral infection has been noted countless times through the years.[71] One of the earliest observations was an association with measles and influenza outbreaks and subsequent pneumonia during World War I.[79] Given the predominance of adenovirus in the recruit training environment, a particularly interesting association was made by Hakansson and associates[80] in the early 1990s. They found increased adherence of pneumococcus to *in vitro* human lung carcinoma cells previously infected with respiratory adenoviruses, including serotype 4. This work suggests that adenovirus infections might result in augmented expression of receptors for *S pneumoniae* and other bacteria, as is well documented for influenza infections, and an increased susceptibility to these infections.

A number of recent reports provide evidence of the burden of *S pneumoniae* among young military members. Pazzaglia and Pasternack[81] reviewed hospitalization records for the years 1970 to 1979. They demonstrated that among Navy and Marine Corps personnel under 25 years of age, *recruits* were 29 times more likely to be hospitalized for pneumonia than *nonrecruits* of the same age. The majority of these hospitalizations were coded without a specific cause (75.8%); among those with a pathogen implicated, however, *S pneumoniae* topped the list (19.7%). Another study by Amundson[82] examined pneumonia cases among Navy recruits in San Diego, California, from October 1987 to April 1989. Of 100 recruits with pneumonia studied, 75 provided convalescent sera. No etiology was identified in 47% of these cases. *M pneumoniae*, the most common pathogen identified, was found in 16 cases (21%). *S pneumoniae* was the fifth most common pathogen, identified in only four cases.

More recently, two additional outbreaks caused by pneumococcus were described. An outbreak of pneumococcal pneumonia among US Army Ranger candidates occurred in the winter of 1998–1999. An attack rate of 12.6% was described in a group of 239 students. Of the 18 hospitalized students, cultures were positive for *S pneumoniae* in 11.[83] Soon after, in a 2-week period

in November 2000, 52 cases of pneumonia occurred among Marine recruits. Half of these cases occurred in one company of 481 men, for an attack rate of 5.2%. *S pneumoniae* was the predominant organism identified in this outbreak. Administration of 1.0 g of oral azithromycin and the 23-valent pneumococcal polysaccharide vaccine resulted in a rapid cessation of the outbreak.[34]

The Naval Health Research Center in San Diego, California, recently completed a large, double-blind, placebo-controlled trial of the inactivated 23-valent pneumococcal polysaccharide vaccine at four recruit training facilities. The objective was to determine if administration of the vaccine would decrease the occurrence of all-cause pneumonias. More than 150,000 recruits were enrolled and followed for all-cause pneumonia outcomes both actively, during recruit training, and passively, using electronic databases after their departure from training. No demonstrable decrease in pneumonia was noted in the arm that received the vaccine, compared to the placebo arm,[84] and the trial demonstrated no evidence that use of the polysaccharide vaccine among recruits was warranted. Of note, however, was the lack of *S pneumoniae* transmission during the 3-year study period, perhaps secondary to the decreased community burden of pneumoccocus since implementation of the conjugate vaccine for infants.[85]

Studies of the antibiotic susceptibility of laboratory *S pneumoniae* isolates from military populations have mirrored similar work in the civilian sector. Isolates collected from military populations, including children, in Washington, DC, from 1990 to 1994 revealed increasing rates of penicillin resistance from 0% in 1990 to 36.2% in 1994.[86] Isolates collected from seven different military medical facilities from August 1997 to August 1999 included 31.9% resistant to penicillin and 15.9% multidrug resistant.[87] Such information is critical as healthcare providers consider appropriate treatment regimens for these infections. Despite such efforts, however, deaths from pneumococcal infections still occur. Recently a young recruit died from meningitis, despite pansensitivity of the infecting organism to all antibiotics tested.[88]

There is some preliminary evidence that the risk of outbreaks or morbidity from pneumococcus is decreasing, perhaps because of infant vaccination with the conjugate vaccine. Nevertheless, replacement serotypes may begin to increase in prevalence, and continued vigilance is warranted.

Rhinovirus

Interestingly, as with adenoviruses, recruit populations were instrumental in the discovery of rhinoviruses. First isolated from a Navy recruit in 1961,[89] rhinoviruses were soon shown to be responsible for up to 30% of the "common cold" in young adults. Infection usually results in illness, with a symptomatic to asymptomatic ratio of approximately 3:1 noted in some studies. Carriage is rare, with one study demonstrating 2% of asymptomatic adults culture positive. More than 100 serotypes of rhinoviruses have been recognized. Rarely implicated in epidemics, rhinoviruses have comparatively inefficient transmission and spread. Secondary infections are most commonly recognized within schools or families, where prolonged contact opportunities exist.[90,91]

Presentation and epidemiology of rhinovirus infections within military recruit populations are consistent with this description. Surveillance conducted with marines at Camp Lejeune, North Carolina, from December 1960 to January 1962 used extensive culture techniques that identified some rhinovirus infections. Although epidemic spread of adenovirus serotype 4 and coxsackievirus A was noted, only low levels of nonepidemic rhinovirus illness were detected. Total symptom scores were used to compare the clinical presentation of the rhinovirus illnesses with the adenovirus and coxsackievirus. Rhinovirus infections were found to cause a mild upper respiratory illness that was generally *less* severe than adenovirus infections, but similar in severity to other "common cold" or coxsackievirus illnesses.[92] The specific rhinoviruses isolated were noted to be diverse, with no one serotype predominating over time.[93]

George and Mogabgab[94] reported a series of 20 atypical pneumonias in young Air Force personnel, 17 to 21 years of age, that were attributed to rhinoviruses during a 5-year period from 1962 to 1966. Comprehensive viral and bacterial recovery attempts did not reveal any other pathogen. Surveillance implemented by Rosenbaum among Navy and Marine recruits in San Diego in 1965, conducted to monitor infections during an adenovirus vaccine trial, also identified rhinovirus infections. Nearly 90% of the recruits were found to be infected with a rhinovirus during the 4 weeks of surveillance. The majority had respiratory symptoms such as congestion, cough, sore throat, headache, and malaise, but fever was rare.[95]

Clearly, rhinoviruses find suitable hosts within military recruit populations, as they do in the civilian sector. Studies specifically for this pathogen are uncommon, however, and its burden in the military population is not fully understood. It is clear, however, that rhinoviruses are not a cause of significant morbidity on a scale of that caused by adenoviruses.

Bordetella Pertussis

Although published evidence of *B pertussis* infections in military recruits is scarce, there are important implications for this pathogen in young adults.

The causative agent of the disease commonly called "whooping cough," *B pertussis* is a Gram-negative bacteria with high affinity for the respiratory tract. Pertussis is highly infectious, easily spread by close contact, and has an incubation period of 7 to 10 days. Despite global vaccine coverage approaching 80% by some estimates, the World Health Organization reports that pertussis causes 200,000 to 400,000 deaths each year. Humans are the only reservoir of infection, and an asymptomatic carrier state does not appear to exist.[96]

Within the United States, immunization in the form of a whole-cell component of the diphtheria-tetanus-pertussis vaccine was widely implemented beginning in the late 1940s among infants 2, 4, and 6 months of age (protection was inadequate until three doses were received). This whole-cell formulation was not recommended for children older than 7 years of age because of increased risk of adverse events in this age group. Rates of pertussis dropped dramatically after the vaccination program began, leveling off at a 99% reduction.[97]

Considerable concern existed, however, regarding the reactogenicity of the whole-cell vaccines, especially whether the vaccine was directly responsible for outcomes such as seizures, encephalopathies, and autism. An acellular vaccine was first introduced in Japan in 1981 and became available on the US market in 1992. Initially approved only for use in children 18 months and 5 years of age, the indication extended to the entire vaccination schedule (2, 4, 6, and 18 months and 5 years) in 1996. From 1997 to 1999, both the whole-cell and acellular vaccines were available for use interchangeably, until the whole-cell product was removed from the US market entirely in late 2001. A review by Geier and Geier[98] of the US Department of Health and Human Services' Vaccine Adverse Event Reporting System examined reported outcomes during the years when both products were on the market and in use in the United States. They found that the whole-cell vaccine was significantly associated with increased risk of nearly every adverse outcome evaluated.

Vaccine- and natural infection-derived immunity for pertussis wanes in 5 to 12 years, leaving young adults susceptible to infection and symptomatic illness. The growing number of vaccinated adults reaching an age of waning immunity in the past 2 decades has resulted in a linear increase in the number of susceptible adults, as illustrated in Figure 13-4.[99-101]

The ramifications of the increased number of adults with waning immunity are greater than might first be recognized. Although the disease is invariably mild in adults, adults serve as the reservoir of infection for infants, for whom the illness can be life threatening. Although the currently available acellular pertussis vaccine is only approved for children under 7 years of age, recent work has investigated its effectiveness in adults. Decreasing the burden of illness in the young adult reservoir was the primary objective, with the hope of decreasing transmission to infants. A booster at 10 to 19 years of age was found to be the most economical recommendation, preventing 0.7 million to 1.8 million pertussis cases and saving $0.6 billion to $1.6 billion over 10 years.[102]

Some studies have been performed evaluating the burden of *B pertussis* infection in recruits and other military populations. Jansen and colleagues[103] studied Marine Corps trainees presenting with a prolonged cough of 7 days or greater from November 1993 to July 1994. Although the researchers did not identify any infected individuals through polymerase chain reaction or culture tests; of 120 recruits enrolled, 6% to 17% showed possible serological evidence of pertussis. They noted that recruits were "reticent to seek medical attention" and also that diagnostic detection methodologies for pertussis were imperfect. Evidence of pertussis was also found among American soldiers in Korea in 1997. Prolonged, nonproductive coughs were frequently seen, and a search for etiology ensued. Again, considering the challenges of diagnosis, 7% were considered to have had a recent *B pertussis* infection. Up to 76% had evidence of recent infection with a *Bordetella* species, *M pneumoniae*, or *Chlamydia pneumoniae*, however—all of which are treatable with macrolide antibiotics.[104] Studies of prolonged cough illness among recruit populations are currently underway at the Naval Health Research Center. Preliminary analysis suggests similarly low but persistent rates of mild *B pertussis* infection.

Because of the changing epidemiology of *B pertussis,* the demonstrated safety of the acellular pertussis vaccine among adults, cost savings, and the projected

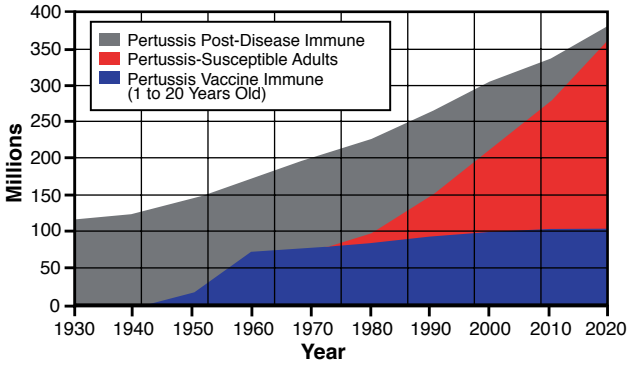

Fig. 13-4. Projected number of US adults (in millions) susceptible to pertussis by year. Adapted from Bass JW, Stephenson SR. The return of pertussis. *Pediatr Infect Dis J.* 1987;6(2):142.

decreased morbidity and mortality among infants, it is expected that the Department of Health and Human Services Advisory Committee on Immunization Practices (ACIP) will formally recommend boosting for young adults in the United States. Recruits are a prime population for targeting such public health intervention recommendations.

Mycoplasma Pneumoniae, Chlamydia Pneumoniae, and Atypical Agents (Respiratory Syncytial Virus and Coronaviruses)

Among the final agents that will be discussed in this chapter, *M pneumoniae* in military populations is the most frequently encountered in the literature. First isolated in 1942 by Eaton and colleagues[105] from a military recruit with pneumonia, *M pneumoniae* was originally called the "Eaton agent."[105,106] Because it was filterable, early researchers believed the pathogen was a virus. *M pneumoniae* is now known to have a genome of only 800 kbp, among the smallest of known bacteria, accounting for the filterability that confounded early researchers.

Because *M pneumoniae* lacks a cell wall, penicillin, which disrupts cell walls, was ineffective for treatment. Studies were performed to determine if a tetracycline antibiotic would be more useful. In a double-blind study, 290 nonbacterial atypical pneumonias were treated with either a placebo or dimethylchlortetracycline. The antibiotic significantly decreased symptomatology more rapidly than the placebo in individuals with *M pneumoniae* infection. No difference in outcome was seen in pneumonias caused by adenovirus or an unknown pathogen.[106]

Researching pneumonias in recruits, Miller and colleagues[10] noted that *M pneumoniae* caused approximately 10% of the pneumonias in an endemic, constant fashion, in contrast to the more epidemic nature of adenovirus. At Keesler Air Force Base, Mississippi, *M pneumoniae* was again recognized as a pathogen responsible for pneumonias during surveillance from 1959–1966.[107] Likewise at Keesler, a study of the etiology of 356 bacteria-negative atypical pneumonias among personnel recently out of basic training was performed between 1959 and 1965. Of these identified cases, 175 (49%) were diagnosed as *M pneumoniae* infections and 23 (6.4%) as adenovirus. The benefits of tetracycline or erythromycin administration were also measured, comparing outcomes in the *M pneumoniae* cases with the undetermined and adenovirus groups. Both antibiotics were equally effective in treating the *M pneumoniae* cases but showed no benefit with the adenovirus or undetermined group. Clinical or laboratory criteria unique to cases of *M pneumonia* were not found.[108]

In 1989 Gray and associates[109] investigated *M pneumoniae* burden among Marine recruits in San Diego, testing paired sera collected from 208 individuals. Evidence of prior infection with *M pneumoniae* was seen in 52.7%, and 5.8% demonstrated seroconversion as defined by a 4-fold increase in titer. The presence of preexisting antibodies was shown to decrease the odds of new infection during training. A follow-up study in 1993–1994 investigated 88 cases of radiographically confirmed pneumonias. The researchers found 36.4% to have laboratory testing consistent with a *M pneumoniae* etiology. Additionally, the study found that the attending clinician chose a different pathogen as the most likely offender 46.4% of the time, and 10% of the patients did not receive appropriate antibiotics.[110] As in the previously described study by George, clinical features could not predict the pathogen responsible for these pneumonias. Although atypical, *M pneumoniae* is not uncommon, and antibiotics often prescribed may not be appropriate. More accurate diagnoses are necessary.

C pneumoniae, also termed TWAR (after the first respiratory and conjunctival isolates, TW-183 and AR-39), has also been implicated in pneumonias of recruits and military members.[111] In 1989 Gray and colleagues[109] reported that among 208 marines with pneumonia, 3.8% had evidence of a recent *C pneumoniae* infection. At the Naval Academy, 41 of 85 midshipmen (52.5%) presenting with ARD during 11 months of surveillance in 1998 had evidence of *C pneumoniae* infection.[112] Ongoing surveillance of recruits at the Naval Health Research Center has demonstrated *C pneumoniae* as an etiology in 10% to 50% of identified pneumonias.

The published literature provides sparse information for other etiologies of febrile respiratory illness or pneumonias in the recruit setting. An article published in 1974 investigated coronaviruses (OC43 and 229E) among marines at the Parris Island, South Carolina, recruit training camp from 1970 to 1972. A cluster of cases was identified one winter, with 39 of 75 men studied infected with strain OC43. Thirty-seven of these men were hospitalized for a characteristic ARD.[113,114]

Johnson, Bloom, and colleagues[114,115] described coxsackievirus A21 infections in the early 1960s. They investigated an outbreak among Marine recruits in September through November 1960. Coxsackievirus A21 was isolated from 214 recruits, 10% of whom were found to be shedding virus in the stool. During this outbreak, infection rates as high as 75% were noted. There was no evidence, however, of sustained transmission, and no evidence of coxsackievirus transmission during the previous year.[114] These investigators also conducted surveillance among recent graduates of basic training at Camp Lejeune at the same time as the outbreak was occurring at Parris Island. Among

122 marines with respiratory symptoms, 26% were coxsackievirus-positive, whereas only 6% of those without a clinical respiratory disease were found to be harboring the virus. As is frequently seen in studies of different etiologies of respiratory disease, no difference in the "common cold syndrome" experienced by those virus-positive and those virus-negative was noted.[114]

A recent study investigated respiratory syncytial virus as a potential etiological agent among recruits at Fort Benning, Georgia, with a febrile respiratory illness. The epidemiology of respiratory syncytial virus is similar to pertussis. There is clear evidence that childhood infections do not provide life-long immunity, and young adults suffer repeat infections. Using culture, serology, and real-time polymerase chain reaction with a beacon probe, researchers found evidence of respiratory syncytial virus infection in 11% of 256 recruits enrolled.[116]

PREVENTION OF RESPIRATORY INFECTIONS

Sustained success in preventing respiratory illness in civilian and military populations has been elusive. Indeed, in the military alone, past decades have witnessed countless studies evaluating a wide variety of intervention strategies. Some proposals demonstrated promise, but none were sufficiently effective or practicable to solve the problem of respiratory illness in recruits and other military populations. Factors clearly contributing to the inability to effectively and continuously prevent and control infection include the vast number of causative pathogens, the different mechanisms through which they can be spread, operational concerns, and military requirements that can supersede any attempt at implementation of specific preventive measures. Despite these limitations, military medical personnel should have an understanding of efforts attempted by their predecessors to control infectious illnesses. With this understanding, together with knowledge of pathogen transmission, a medical officer should be able to evaluate infections and provide recommendations to reduce the morbidity suffered in a population.

Historical intervention strategies will be discussed first, followed by a review of current prophylaxis regimens and interventions that have shown promise in reducing the burden suffered from respiratory pathogens in the recruit setting. Antibiotic and chemotherapeutic treatment discussions can be found in the preceding sections on specific pathogens and will not be treated here.

Historical Interventions

In the 1930s and 1940s, viable bacteria were discovered in the bedding and on the floors of recruit training facilities. Researchers found that dust created in this environment also contained viable bacteria, and concern arose over the potential spread of respiratory infections via inhalation of dust.[117] Personnel oiled the wooden floors and cleaned the bedding in hopes of decreasing the dust created. These efforts consistently reduced actual counts of bacteria from air samples,[118,119] but the impact on respiratory illness was less clearly demonstrated. Some reports demonstrated little or no difference in respiratory illnesses between barracks with and without the dust suppression measures[120,121]; others showed modest decreases of up to 30%.[119]

Puzzled by these results, researchers performed additional studies to test the hypothesis that these infected surfaces were indeed vehicles of transmission. In the first study, 85 men were exposed to blankets heavily contaminated with GAS from nasal carriers (considered the most infective). As a control group, 177 soldiers in the same environment received fresh blankets essentially GAS free. At the end of 23 days, there was no evidence that GAS on the blankets resulted in respiratory infection in the users.[121] In another study, dust was taken from the floor of a heavily infected barracks. Viable organisms were demonstrated on culture media, and the dust was used to directly "inoculate" 17 volunteers through inhalation. No illness resulted. Infectious bacteria were then taken directly from symptomatic individuals and dried on dust; again, the number of streptococcus colonies that grew on artificial media from this dust did not decrease. This material was likewise used as an inhalation inoculum, and again no infections resulted. From these dust-suppression and transmission studies, researchers concluded that droplet nuclei, or dust contaminated with viable GAS, was not an important source of infection.[122]

Another early technique tested to decrease the environmental burden of respiratory pathogens included triethylene glycol vaporization in barracks. Studies of Navy recruit barracks in 1950 and 1951 note a 65% reduction in airborne bacteria.[123,124] However, no resulting difference in ARD rates was seen in recruits housed in treated and untreated barracks.[124] As with the earlier dust suppression methods, reducing viable organisms in the air did not consistently translate to decreased rates of ARD, and outbreaks of respiratory illness continued.

Ultraviolet Irradiation

Ultraviolet (UV) irradiation has been evaluated on many occasions throughout the last 5 decades. Studies in the mid-1940s among Navy recruits combined UV irradiation interventions with oil dust suppression. UV

irradiation appeared to be the more beneficial intervention. Reductions of 20% to 25% in overall respiratory disease were consistently noted among recruits in the irradiated barracks.[120,125,126] There were periods when this difference was less marked, leading the investigators to question whether the sterilization properties of the UV lights were more effective on some pathogens in circulation than on others. They concluded that the results, although promising, were not sufficient to recommend general use of irradiation.[120] In addition, concern arose over the potential harmful effects of UV light exposures, and subsequent studies were not performed. The attention of the medical community turned to the antimicrobial and vaccination efforts rapidly advancing during this period. Subsequently, with the loss of the adenovirus vaccines and rise in ARD rates in 1999,[60] effects of UV irradiation were again evaluated at Great Lakes from 1998 to 1999. Among 1,686 recruits under surveillance, a slight yet statistically significant reduction in respiratory illness was seen, with 59.5% of recruits in the UV-exposed barracks reporting to the outpatient clinic with respiratory illnesses as compared to 63.4% of recruits housed in the unexposed barracks (odds ratio [OR] = 1.3).[127]

Hygiene

All recruit training centers have one thing in common: little discretionary time is available. Providing sufficient time for adequate hygiene is a constant struggle, despite numerous publications that clearly describe the benefits of handwashing for control of infectious diseases.[128,129] The logistics of providing easy access to soap and water in the recruit setting are complex, such as supplying an adequate number of warm water stations and the huge requirement for paper towels and liquid soap.

A study performed by Ryan and colleagues[130] at the Great Lakes recruit training center from 1995 to 1998 demonstrated the effectiveness of handwashing. A requirement for washing hands five times per day was implemented, training was performed, and "Operation Stop Cough" was initiated. Although a control population was not available the same year as the handwashing intervention, respiratory illness rate comparisons were made between the 2 years of intervention and the previous year (without intervention). A 45% reduction in outpatient visits for respiratory illness was noted during the handwashing years. A subset of this recruit population was also asked to answer questions regarding respiratory illness and handwashing behavior. Infrequent handwashing was associated with an increased risk of self-reported respiratory complaints (OR = 10.9, 95% confidence interval [CI] = 2.7–46.2).[130]

Handwipes are an alternative to sink handwashing. A US Air Force study evaluated the effectiveness of antimicrobial handwipes as compared to placebo handwipes in reducing respiratory illness. Among individuals using the antimicrobial wipes, sick-call visits for ARD were reduced by 32.7% ($P = 0.02$), and sore throats were reduced by 40% ($P = 0.01$).[131] Recent years have also seen the introduction of alcohol-based hand cleaners, which have the potential of markedly improving access to adequate hand hygiene in the recruit setting. Effectiveness of these products in decreasing bacterial and viral counts on the hands has been demonstrated,[128] but their correct use is important. Current evidence suggests that these products should not be relied on when excessive dirt is present on the hands,[129] however, and studies evaluating the impact of these products on respiratory illness rates in the recruit setting are lacking.

Housing

The need for "adequate ventilation and avoidance of crowding to prevent disease in troops" was recognized centuries ago by Sir John Pringle in 1772 and Dr Richard Brocklesby in 1774,[132] long before the transmission of infectious diseases was clearly understood. Breese and colleagues[132] systematically investigated the influence of crowding among Navy recruits in 1943. Six different housing conditions were evaluated. The results suggested that the *number* of men in each room was related to the transmission of respiratory illnesses, *not* the amount of floor space per recruit or cubic feet per recruit. The results showed that rates of illness could be decreased, in times of acute need, by dividing rooms with partitions.

In the 1960s, Brodkey and colleagues[133] researched the history of space recommendations in the US Army. Studies leading to definitive recommendations were lacking, and the article concluded with the observation that "the benefits which might be derived from enforcing space standards are not impressive. This is due, at least in part, to success in controlling, by immunizations, meningococcal disease and acute respiratory disease due to adenoviruses."[133(p420)] This work was published in 1980, however, a period when respiratory illness was not considered a big problem among recruits; conclusions might have been different if the review had been conducted *after* the loss of the adenovirus vaccines in 1999 and the subsequent increase in ARD rates. Until the reintroduction of adenovirus vaccines, medical researchers are re-evaluating all potential factors that might influence and reduce rates of ARD.

Issues of ventilation and recirculation of air are often brought up when discussing engineering modi-

fications that might affect respiratory illness rates. Brundage and colleagues[134] conducted an important comparison of febrile respiratory illness rates in newer, energy-efficient barracks as compared to older barracks at four Army training facilities between October 1982 and September 1986. The results demonstrated an increased risk of respiratory infections among recruits housed in the *new* barracks as compared to the old (OR = 1.51, 95% CI = 1.46–1.56). This supported the hypothesis that newer buildings with closed ventilation systems resulted in increased exposure and enhanced respiratory pathogen transmission.

Vaccinations and Prophylaxis

A chapter in this textbook deals with the issue of vaccines in the recruit setting, so an exhaustive review will not be conducted here. Pertinent vaccines were mentioned in the respective pathogen sections; they will be briefly reviewed here.

Prophylaxis regimens for GAS are used, at least seasonally, at nearly all recruit training sites. Recruits at many facilities receive a penicillin G (Bicillin L-A,Wyeth-Ayerst Laboratories, Philadelphia, Pa) injection, 1.2 M units, on arrival. For individuals allergic to penicillin, most sites provide an alternative antibiotic such as erythromycin, 250 mg twice a day.[33] Erythromycin has emerging resistance and compliance problems, however, so despite its higher cost, azithromycin, 500 mg once a week, is an alternative used at one training site.[27]

The reader should clearly understand the enormous negative impact that adenovirus has on recruits in training. The cessation of the adenovirus vaccine production in 1996 was a huge step backward for recruit preventive medicine. As mentioned, another manufacturer of the vaccine was engaged in 2001, and efforts to renew the manufacturing and distribution are underway. Unique among vaccines, this enteric-coated formulation was enormously successful in producing respiratory protection. In an effort to expeditiously gain new US Food and Drug Administration approvals, the same formulation of this oral vaccine is now being used with minimal modifications. At the time of this printing, phase 1 trials have been complete, and discussions are under way for phase 2 and 3 studies in pertinent recruit training settings.

The changing epidemiology of pertussis has resulted in numerous recent studies examining the immunogenicity and effectiveness of the acellular pertussis vaccine in adult populations. New recommendations for a pertussis booster among the young adult population may be forthcoming, as we attempt to decrease the presence of this pathogen among military populations and thereby decrease the risk of serious *B pertussis* illness in infants.

Influenza vaccination is a high priority for recruits. As history shows, the recruit and military populations have the potential to inadvertently play an important role in the initiation and global distribution of new influenza strains.[66] Surveillance of recruits has been useful in monitoring the effectiveness of current-year vaccine formulations for the circulating strains.[77] Given the high rate of influenza vaccine coverage in this population, recruits serve as an excellent early-warning group for development and transmission of drifted or shifted strains. Shortages of influenza vaccines in recent years have created challenges in determining distribution priorities. Although deployed personnel are clearly at increased risk and should be protected, recruits should remain a very high priority. If sustained influenza transmission occurs among recruits, liberal use of influenza antivirals should be seriously considered.

The 23-valent polysaccharide pneumococcal vaccine is used in some advanced training groups and in at least one recruit training setting to decrease the risk of *S pneumoniae*-associated morbidity. However, a recent double-blind, placebo-controlled study—using pathogen-specific and all-cause pneumonia outcomes—failed to demonstrate effectiveness of this vaccine in the recruit setting or in the first 2 years of service (Russell KL, "Randomized Controlled Trial of the Polysaccharide Pneumococcal Vaccine in Young Healthy Adults," manuscript in prep). Clearly, since the initiation of the conjugate vaccine in infants, the epidemiology of this pathogen, and its burden in other age groups, is changing.[85] Monitoring *S pneumoniae* rates should continue, but currently, use of the polysaccharide vaccine does not appear warranted in an ongoing manner among recruits in training.

Although not discussed in this chapter, *Neisseria meningitidis* is another pathogen that can cause respiratory illness. Outbreaks of *N meningitidis* can have serious consequences, including mortality. A recent death of a recruit was described by Crum and colleagues[134] Given this risk, most training camps immunize incoming recruits with the trivalent (A, C, W-135) formulation.

A recent publication by Lee and colleagues[135] reviewed the literature for nonvaccine intervention strategies to distinguish which were most promising in preventing infectious ARD. Their conclusion was that practicing hand hygiene, reducing crowding, and reducing contact among training units (cohorting) "may offer benefits in respiratory disease control." The authors felt that UV lights and air ventilation issues among recruits needed more study.

SUMMARY

This chapter has covered the diverse topic of respiratory infections among US military recruit populations. Military medicine has a long history of dedicated researchers who have provided clarity to this complex field and ultimately improved the health of the young men and women who volunteer for recruit training. Several pathogens never before encountered, including adenovirus, *M pneumoniae*, and rhinovirus, were first described through work with military recruit populations. This chapter has discussed many factors that make the epidemiology of respiratory infections in recruit populations different from other definable groups; these unique factors can help explain why certain pathogens have found such a firmly established niche in recruits.

To understand respiratory infections in recruits, an understanding of the heavy burden, morbidity, and mortality of adenovirus is essential. GAS thrived before the antibiotic era, but it still remains a communicable disease threat. The history of influenza shows that we must maintain constant vigilance against new strains. Studies frequently demonstrate that signs and symptoms alone cannot predict the pathogen responsible for illness. Laboratory diagnostic support is needed.

The field of respiratory pathogens within US recruits and the rest of the military forces continues to require surveillance and thoughtful research. Although truly effective preventive measures have sometimes not been found, at other times great progress has been made. We should remain committed to maintaining the progress that has been made by our predecessors, avoid making hasty decisions to decrease existing interventions, and continue making every effort to keep the young men and women of the armed forces healthy and fit to fight.

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