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MAJOR ARTICLE

Large Epidemic of Respiratory Illness Due to Adenovirus Types 7 and 3 in Healthy Young Adults

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After 25 years of successful control through immunization, respiratory infections due to adenoviruses have reemerged to threaten the health of young adults in the military. Shortly after the loss of adenovirus vaccine supplies, a large outbreak of respiratory illness was observed at the United States Navy's sole basic training center. Laboratory testing confirmed 541 cases of adenovirus infection, including 378 cases due to serotype 7 and 132 cases due to serotype 3. This outbreak was remarkable because of its unique serotype distribution and the large amount of data available to describe demographic factors associated with infection. This was the largest outbreak of respiratory illness due to adenovirus types 7 and 3 documented in recent history, and it portends even greater challenges for young adults in the military in the postvaccine era.

The US military has long had concern about the impact of respiratory disease on the health and readiness of its service members [1, 2]. Military recruits appear to be especially vulnerable to respiratory infections, possibly because of the crowding and the physical and psychological stresses associated with the basic training environment.

Adenovirus infections have been a special threat to recruits, with outbreaks of adenovirus infection documented as interrupting training schedules as early as the 1950s [3–6]. The development of vaccines against adenovirus serotypes 4 and 7 essentially prevented adenovirus outbreaks in military basic training centers, beginning with their routine use in 1971 [7]. In 1995, the sole manufacturer of the adenovirus vaccines ceased production, and the US military limited the use of the remaining vaccine until supplies were completely depleted in 1999.

From 1996 through 1999, adenovirus vaccine was conserved by vaccinating recruits only during the winter months and during periods associated with high rates of respiratory illness. During these times, several outbreaks of adenovirus illness were well documented in military basic training centers [8–11]. All services were affected, and adenovirus illness was even identified in training centers beyond recruit camps [12, 13].

We report the first outbreak of non–serotype 4 adenovirus illness in a military training center in the postvaccine era. The controlled setting of the US Navy's only basic training command in Great Lakes, Illinois, afforded the opportunity to describe the clinical presentation of illness, the risk factors associated with adenovirus infections, and the value of vaccine in arresting disease transmission.

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METHODS

Surveillance established by the Naval Health Research Center allowed for the weekly tracking of respiratory illness rates at the Navy Recruit Training Command in Great Lakes, Illinois [14]. Preventive medicine professionals tracked new visits to the recruit medical clinic each week; total cases of respiratory illness and febrile (oral temperature, ⩾38°C) respiratory illness were counted. Patients with febrile respiratory illnesses were offered viral testing using throat swab specimens that were sent to the Naval Health Research Center Respiratory Disease Laboratory in San Diego, California.

At the Naval Health Research Center, each throat swab specimen was cultured for adenovirus by inoculation into a pair of A-549 seeded shell vials. The presence of adenovirus was confirmed by the observation of cytopathic effects and subsequent staining with fluorescein-labeled monoclonal antibody. Adenovirus specimens were serotyped, with use of type-specific hyperimmune rabbit serum samples, to the prototype adenoviruses 1–5, 7, and 21. Laboratory procedures and confirmation of serotyping are described in detail elsewhere [11, 15].

General demographic and medical history data were obtained from a questionnaire given to all navy recruits at the time of entrance into basic training [16]. Clinical medical records were reviewed for cases of confirmed adenovirus infection. Data on oral temperature, presence of respiratory symptoms, duration of symptoms, and time lost from training were extracted by a medical provider.

A multivariate polychotomous regression model was developed to describe factors associated with adenovirus infections. The outcome variable was categorized as serotype 7 adenovirus illness, serotype 3 adenovirus illness, or no illness. Independent variables in the model included age, sex, race/ethnicity, home state, history of prior medical problems (asthma, chronic cough, frequent colds, and ear, nose, or throat disorders), history of tobacco and alcohol use before enlistment, and receipt of adenovirus vaccine at the time of entrance into the service. Colinearity diagnostics were done to assess confounding between independent variables. Manual stepwise backward regressions were done to develop the final model that contained variables significantly associated with adenovirus infection ($\alpha < .05$). SAS software (SAS Institute) was used for the statistical analyses. The research, performed under institutional review board–approved protocol 31230, was conducted in compliance with all applicable Federal Regulations governing the protection of human subject in research.

RESULTS

More than 27,000 young adults began navy basic training between August and December 1997. An outbreak of respiratory illness was observed among recruits beginning in mid-September and peaking in late October. During the week of 27 October, the overall rate of respiratory illness reached 52 cases per 1000 recruits per week, with 575 new cases seen among 11,047 recruits in training. Febrile illness rates were lower but mirrored the rates of overall illness, reaching a peak of nearly 15 cases per 1000 recruits per week. Adenovirus vaccine, which was not in use at the site in the summer and early fall, was reintroduced in the recruit population beginning in the last week of October. Oral vaccines against serotypes 7 and 3 were given to all recruits on site and to new recruits immediately after arrival. There was a strong temporal association between vaccine use and declining rates of febrile respiratory illness and total respiratory illness (figure 1).

More than 800 patients with febrile respiratory illnesses had throat swab specimens sent to the Naval Health Research Center for adenovirus testing during the outbreak period. Of these patients, 541 were identified as positive for adenovirus by culture. The percentage of specimens that tested positive for adenovirus varied weekly, reaching a peak of 91% in mid-October. Serotyping of adenovirus specimens revealed 378 cases of serotype 7, there were 132 cases of serotype 3, and 31 cases that were other types or were not typed. The relative proportion of the rate of adenovirus illness represented by different serotypes is shown in figure 1. Serotype 3 illness appeared early during the outbreak, but the number of cases began to decline before serotype 7 illness rates peaked in late October. Rates of all illness declined sharply after reintroduction of the adenovirus vaccine.

Medical records of 116 patients with confirmed cases of illness due to adenoviruses documented the following symptoms at initial presentation: nasal congestion (96%), sore throat (71%), cough (68%), and nausea, vomiting, or diarrhea (46%). All case patients were febrile, as per the febrile respiratory illness case definition, and the average oral temperature was 38.9°C (range, 37.9–40.8°C). The clinical diagnoses given to case patients at presentation included viral syndrome (46%), sinusitis (21%), bronchitis (18%), and pharyngitis (14%). More than half of the patients received antibiotics at some point in their illness. No differences were seen in the clinical presentations of case patients with illnesses due to adenovirus serotype 7 and those with illnesses due to serotype 3.

On average, recruits experienced the onset of adenovirus illness after 40 days of training (range, 14–74 days). On the basis of review of case patients' medical records, the average duration of symptoms was 10 days (range, 7–21 days). Recruits lost an average of 3 training days because of fever and respiratory symptoms (range, 1–15 days lost). Two recruits were hospitalized for >7 days for supportive care. It was not possible to quantify the number of recruits set back in their training schedule, or "recycled," and unable to graduate on time. On the basis of training policies, however, it was estimated that

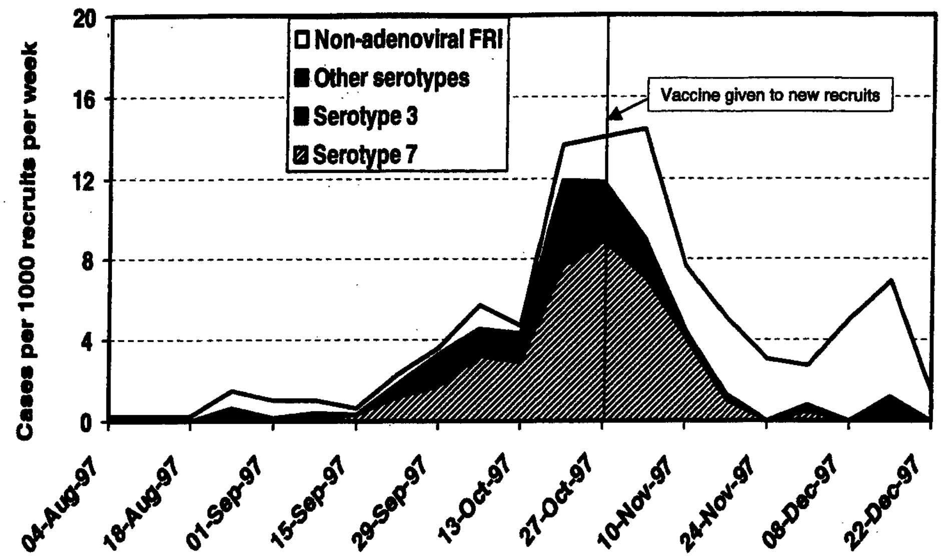

Figure 1. During the outbreak period, rates of febrile respiratory illness (FRI) and adenovirus respiratory illness with relative contributions of adenovirus serotypes, shown as the number of cases per 1000 recruits per week. Dates are given as day-month-year.

>200 recruits with adenovirus illness were recycled during this outbreak.

Factors associated with the development of adenovirus illness, as determined from multivariate regression analysis, are shown in table 1. Unvaccinated recruits were >17 times as likely as vaccinated recruits to have a verified case of adenovirus serotype 3 or serotype 7 infection. Recruits with a home state of New Mexico or Kansas were more likely to have serotype 3 infection. Recruits with a home state of Kansas, Tennessee, or Florida were more likely to have serotype 7 infection. A history of not smoking before enlistment was associated with serotype 3 illness but not with serotype 7 illness. The following factors were included in the model but were not significantly associated with illness in the regression analysis: age, sex, race/ethnicity, past medical history, and alcohol use before enlistment.

DISCUSSION

In the prevaccine era, adenovirus illness affected up to 10% of military recruits, causing as much as 70% of all cases of respiratory disease and 90% of pneumonia cases [3–6, 17, 18]. The development of live, enteric-coated oral vaccines against illnesses due to adenovirus serotypes 4 and 7 was associated with a 50%–60% reduction in overall respiratory illness and a 95%–99% reduction in adenovirus-specific illness rates in recruits [19–21]. Of importance, vaccination was also effective in interrupting adenovirus illness outbreaks [22]. After nearly 25 years of administering adenovirus vaccines to new recruits, the US military could no longer obtain vaccine after 1995 [7]. This report demonstrates the dramatic effect of adenovirus vaccine loss during a 6-month period at the Navy's only recruit training command. It also shows that adenovirus vaccine remained highly effective in interrupting a disease outbreak.

Adenovirus serotype 7 was the predominant pathogen identified in this outbreak. Illness due to type 7 has been extensively described in the medical literature, especially among pediatric populations [23–29]. This pathogen has sometimes been associated with severe morbidity and mortality, with subtypes 7b and 7h appearing to be especially challenging [30, 31]. A newly described genome type, 7d2 [32], has been associated with marked morbidity in recent outbreaks in the Chicago area [33], and it appears to be the same genetic variant responsible for this outbreak in military recruits [34]. Attenuated type 7 adenovirus was considered a valuable addition to the military vaccine regime during early vaccine development in the 1960s [35–38]. It is notable that the vaccine strain (7a) remained effective in arresting the outbreak described here.

Adenovirus serotype 3 illness appeared concomitantly with type 7 illness in this outbreak, albeit with much lower rates. Type 3 pathogens have been described less extensively in the medical literature but have also been associated with severe illness [39–41]. The co-occurrence of type 3 disease with type 7 disease has been reported in other populations [42]. In this outbreak, type 3 illness rates may have peaked and begun a natural decline before reintroduction of vaccines, but rates continued to decrease dramatically after vaccination was restarted. Although serotype 7 vaccine should not prevent serotype 3 illness, and although antiserum samples generally are not cross-reactive, some antigenic similarity between serotype 3 and serotype 7 pathogens has been suggested [43], and it could explain this observation.

The clinical presentation of adenovirus illness during this

Table 1. **Results of polychotomous logistic regression analysis comparing patients with illness due to adenovirus serotype 3 (n = 132) or serotype 7 (n = 378) with recruits without documented febrile respiratory illness (n = 26,799).**

		Adenovirus serotype 3 infection		Adenovirus serotype 7 infection[a]	
Risk factor	n	Patients, no. (%)	OR (95% CI)	Patients, no. (%)	OR (95% CI)
Vaccination status					
Unvaccinated	17,903	129 (0.7)	18.9 (6.0–59.5)	365 (2.0)	17.2 (9.4–31.5)
Vaccinated[b]	9404	3 (0.03)	1.0	11 (0.1)	1.0
Home state					
New Mexico	223	4 (1.8)	4.6 (1.7–12.6)	1 (0.5)	NS
Kansas	227	3 (1.3)	3.2 (1.0–10.2)	8 (3.5)	3.0 (1.5–6.2)
Tennessee	489	1 (0.2)	NS	13 (2.7)	2.0 (1.2–3.5)
Florida	1542	12 (0.8)	NS	31 (2.0)	1.6 (1.1–2.3)
All other states[b]	24,826	112 (0.5)	1.0	323 (1.3)	1.0
Smoking status					
Nonsmoker	22,549	128 (0.6)	3.4 (1.3–9.3)	345 (1.5)	NS
Smoker[b]	4758	4 (0.08)	1.0	31 (0.7)	1.0

NOTE. NS, not statistically significant: $P > .05$ and 95% CI includes 1.0.

[a] A total of 376 cases of serotype 7 illness are shown because 2 case patients had incomplete demographic data that excluded them from multivariate analysis.

[b] Referent group.

outbreak was similar to that described in reports from other military settings [8–10, 44, 45]. In contrast to adenovirus serotype 4 illnesses, however, nearly half of the patients with serotype 7 or serotype 3 illness in this outbreak experienced gastrointestinal symptoms, as has been seen in some pediatric populations [46]. Morbidity and lost time from training appeared to be related to the high fevers experienced by recruits. It was notable that patients with type 3 and type 7 illnesses were indistinguishable from each other in terms of their clinical presentations, as assessed by medical record review.

Risk factors associated with adenovirus illness could be very thoroughly explored in the controlled environment of military training, in which demographic and health histories were available for the entire cohort of recruits [16]. Multivariate regression modeling allowed for the examination of several variables that previously have not been described as being associated with adenovirus illness. Clearly, vaccine status was the factor most strongly associated with development of illness. Although this factor was controlled for in the multivariate model, it was also interesting to see the moderate associations with recruits' home states. Originating from Kansas was associated with illness due to both serotype 3 and serotype 7. These findings may imply fewer circulating serotype 3 or 7 adenoviruses among pediatric populations in some states. An alternative explanation is that recruits from certain states were clustered together in the basic training center, which exposed them to different risks of infection. Although recruits appeared to be randomly assigned to training units, and although all units mixed frequently, some clustering according to demographic variables cannot be ruled out as a reason for these findings.

The association seen between not smoking and type 3 adenovirus illness deserves some further consideration. This finding may appear counterintuitive, especially because past studies have shown that active smoking among military trainees and other young adults is a risk factor for viral illness [47–51]. Current military basic training commands are tobacco-free environments, so any risk associated with active smoking should be diminished. The observed "protective" effect of smoking might be the result of more frequent adenovirus infections—and the subsequent development of natural immunity—experienced by smokers before enlistment. Alternatively, smokers may be more likely to harbor latent adenovirus infections after exposure [52], diminishing the appearance of acute illness but predisposing them to chronic disease [53]. Finally, as with the geographic associations seen, undetected clustering of recruits on the basis of past smoking history might also confound interpretation of this finding.

In reviewing all risk factors for adenovirus illness, perhaps the most important finding in this large analysis was the lack of association between disease and most demographic factors. Recruits appeared to be equally vulnerable to infection, regardless of age, sex, or race/ethnicity. Past serological studies have also shown widespread susceptibility among new recruits, with >70% lacking antibodies to serotype 7 adenovirus at the time of enlistment [54]. Although some military vaccine programs had focused only on male recruits in the past [7], it would appear appropriate for future adenovirus control efforts to encompass the entire training community.

Above all, the outbreak described in the present study underscores the value of adenovirus vaccine in preventing respiratory illness in this population. Both the epidemic curve and the multivariate analysis demonstrated the significant beneficial effect of vaccination. Although the severe morbidity and mortality that are possible with adenovirus infection [55–57] were not observed, the outbreak challenged existing medical and training resources to a degree not commonly seen in the era of vaccine use. Previous cost-benefit and cost-effectiveness analyses have also supported the value of adenovirus vaccine, even in the absence of severe outcomes [58–60].

In the civilian sector, adenovirus is sometimes considered a problem only for very young, hospitalized, or immunocompromised populations [61–63]. However, adenovirus pathogens appear to be almost ubiquitous when testing for viruses is done on otherwise healthy children with respiratory illness [64–66]. Young adult populations outside of the military have also been severely affected by adenovirus [67–71]. Vaccination against adenovirus was proposed in the past as a public health intervention for civilians [66, 72, 73], and the military might be well advised to partner with the civilian sector in its attempts to reestablish the development and production of adenovirus vaccines. Until vaccine programs are reinstated, preventable disease outbreaks, such as this one, will continue to occur.

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This epidemic at the Naval Recruit Training Command in Great Lakes, IL in 1997, was the largest outbreak of adenovirus types 7 and 3 reported in recent history. Surveillance for disease, special laboratory testing, and linking of many large data sources allowed for clinical characterization and description of epidemiologic risk factors for adult adenovirus infections. The outbreak also portends challenges for the military until adenovirus vaccine production is reestablished.

14. SUBJECT TERMS
adenovirus infections, respiratory disease, military personnel, adenovirus types 7 and 3

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