

Outbreak of Severe Respiratory Disease Associated with Emergent Human Adenovirus Serotype 14 at a US Air Force Training Facility in 2007

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(See the editorial commentary by Gray and Chorazy and the article by Lewis et al., on pages XXX–XX and XXX–XX, respectively.)

Background. In 2007, a US Air Force training facility reported a cluster of severe respiratory illnesses associated with a rare human adenovirus (Ad) serotype, Ad14. We investigated this outbreak to better understand its epidemiology, clinical spectrum, and associated risk factors.

Methods. Data were collected from ongoing febrile respiratory illness (FRI) surveillance and from a retrospective cohort investigation. Because an Ad7 vaccine is in development, Ad7 antibody titers in pretraining serum samples from trainees with mild and those with severe Ad14 illness were compared.

Results. During 2007, an estimated 551 (48%) of 1147 trainees with FRI were infected with Ad14; 23 were hospitalized with pneumonia, 4 required admission to an intensive care unit, and 1 died. Among cohort members ($n = 173$), the Ad14 infection rate was high (50%). Of those infected, 40% experienced FRI. No cohort members were hospitalized. Male sex (risk ratio [RR], 4.7 [95% confidence interval {CI}, 2.2–10.1]) and an ill close contact (RR, 1.6 [95% CI, 1.2–2.2]) were associated with infection. Preexisting Ad7 neutralizing antibodies were found in 7 (37%) of 19 Ad14-positive trainees with mild illness but in 0 of 16 trainees with Ad14 pneumonia ($P = .007$).

Conclusions. Emergence of Ad14, a rare Ad serotype, caused a protracted outbreak of respiratory illness among military recruits. Most infected recruits experienced FRI or milder illnesses. Some required hospitalization, and 1 died. Natural Ad7 infection may protect against severe Ad14 illness.

Human adenoviruses (Ads) are associated with a broad spectrum of clinical illnesses, including febrile upper respiratory disease, pneumonia, gastrointestinal disease, and conjunctivitis. Mild or inapparent Ad illness is common; by the age of 10 years, most children have serological evidence of exposure to 1 or more serotypes [1].

Different Ad serotypes are associated with different disease syndromes, and severe disease and death are rare in otherwise healthy persons [2, 3]. Species B Ads other than serotype 14, including 3, 7, and 21, have caused outbreaks of febrile respiratory disease among older children and adults, and serotype 4, a species E Ad, has caused outbreaks of acute respiratory disease among new recruits during basic military training [4–9]. Until 1996, vaccines against Ad4 and Ad7 were routinely administered to new recruits [10].

In 2006, sporadic cases of infection with an uncommon Ad serotype, Ad14, were identified among military recruits with febrile respiratory illness (FRI) [11]. In 2007, clusters of civilian and military patients with severe Ad14 respiratory illness, along with several deaths, were reported in 3 different states in the United States [12]. Sequence studies of isolates from all clusters

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showed that the isolates were the same strain of Ad14 and that this strain was distinct from the prototype strain, suggesting that a new Ad14 variant was emerging and spreading in the United States [12]. The largest cluster occurred among basic military trainees (BMTs) at a US Air Force training base in Texas.

In April 2007, medical staff of the military medical center supporting the basic training facility noted an increase in the rate of severe pneumonia among BMTs [13]. This observation was supported by an increase in rates of FRI associated with Ad14 infection detected through ongoing surveillance among BMTs at this facility. We investigated this cluster of Ad14 cases to better understand the epidemiology and transmission of this emergent Ad, to characterize the full spectrum of Ad14 disease, and to identify risk factors for infection, with the intent of clarifying the public health risk and implementing control measures. Moreover, because a new vaccine against Ad7—a serotype antigenetically related to Ad14 [14]—is under development, we sought to determine whether naturally acquired neutralizing antibodies to Ad7 would also provide some protection against severe Ad14 disease.

METHODS

Setting. All new US Air Force recruits complete a 6.5-week basic training course at this facility. Approximately 3500–4500 BMTs are in training at any time, and 600–900 new recruits arrive weekly. BMTs are assigned to 50–60-member sex-specific units called “flights,” and members train and live together, sharing dormitories and bathrooms. There is little interaction between members of different flights.

Data sources. We used 3 data sources to analyze the outbreak: (1) weekly surveillance data on the rates and etiologies of FRI requiring medical care from January 2006 through December 2007; (2) administrative records on BMTs who started and finished training from 1 January through 28 May 2007; and (3) medical records and laboratory test results for BMTs hospitalized with pneumonia in 2007. Additionally, we selected 4 flights and conducted a retrospective cohort investigation to examine rates of Ad14 infection, the spectrum of illness, and risk factors for infection. Because this was an emergency public health response to an outbreak, no review by the human ethics committee of the Centers for Disease Control and Prevention (CDC) was required.

Outbreak description—surveillance data. Since 1996, the US Department of Defense has conducted population- and laboratory-based FRI surveillance among BMTs at military training bases [10, 15, 16]. Any recruit who presents for medical care with a temperature $\geq 38.1^{\circ}\text{C}$ plus a cough or a sore throat or a diagnosis of pneumonia is enumerated, and a weekly rate is calculated. From a subset of these BMTs, a throat-swab sample is collected and tested for respiratory pathogens. On the affected base, we examined the weekly FRI rates in 2006 and 2007 along

with Ad typing data. Additionally, hospital records for 2007 were reviewed to identify cases of pneumonia.

To determine when during training recruits were most at risk of illness and to explore apparent sex differences in Ad14 attack rates, we linked the FRI surveillance data to administrative records, which contained additional information on sex, flight size, and week of training at the onset of illness for BMTs with FRI. Records were examined for recruits assigned to 192 flights that completed training from 1 January through 28 May 2007.

Risk factors for and spectrum of Ad14 disease—cohort investigation. We selected 3 flights (3 for males and 1 for females) with high rates of FRI relative to other flights graduating at the same time. All BMTs who spent any time in one of these flights were considered to have been exposed to Ad14 and were eligible for inclusion in the cohort investigation. However, BMTs assigned to these flights in midtraining were excluded if they (1) had documented respiratory illness when in another flight and might therefore no longer be susceptible to Ad14 infection or (2) were assigned to the flight < 1 week before the end of training, because infections may still have been incubating in these BMTs. Time at risk and rates of Ad14 infection were calculated using the elapsed time from the date of entry into the flight to either the date of exit from the flight or the date of the onset of fever associated with Ad14 FRI.

At the end of the 6.5-week training period, BMTs in these 4 flights were administered a questionnaire by interview to collect data on the clinical symptoms experienced during training, demographic characteristics, and possible risk factors for infection. These factors included smoking history, body mass index (calculated as weight in kilograms divided by the square of height in meters), fitness level (as measured by run times at the initiation of training), and exposure to other sick BMTs. Throat-swab and blood samples were also collected at the time of interview. Additionally, blood samples collected from the BMTs on arrival at the training base were procured from the Department of Defense Serum Repository [17].

We classified self-reported illness as either (1) FRI (self-reported fever plus 1 respiratory symptom [i.e., cough, sinus congestion, runny nose, wheezing, or shortness of breath]); (2) afebrile respiratory illness (self-reported cough plus another respiratory symptom); (3) mild respiratory illness (at least 1 self-reported respiratory symptom but absence of other criteria specified in the case definitions described above); or (4) no respiratory symptoms. Ad14 infection was defined as a throat-swab sample testing positive for Ad14 by polymerase chain reaction (PCR) or a pre- to posttraining rise in the titer of Ad14 neutralizing antibodies.

Investigation of cross-protection conferred by Ad7 antibodies. To determine whether vaccines against Ad7 might mitigate Ad14 disease, we compared the titers of preexisting antibodies to Ad7 in pretraining serum samples from BMTs who

developed severe Ad14 disease during training with those in serum samples from BMTs who developed mild illness or had inapparent infection. Severe Ad14 disease was defined as hospitalization for confirmed Ad14 pneumonia, and mild illness or inapparent infection was defined as confirmed Ad14 infection with self-reported mild or no respiratory disease.

Laboratory methods. Throat-swab samples collected as part of the surveillance program were tested by the Naval Health Research Center (San Diego, CA) by means of a PCR assay that has been described elsewhere [11]. Briefly, nucleic acid was extracted from throat-swab samples and tested by Ad universal and serotype-specific conventional PCR assays. In a subset of Ad14-positive samples, results were confirmed by sequence analysis of part of the hexon gene [11]. For the cohort investigation, testing was performed by the Advanced Diagnostics Laboratory at Lackland Air Force Base (San Antonio, TX). Nucleic acid was extracted from the throat-swab samples as described above and tested using 2 TaqMan real-time PCR assays, one that has been described elsewhere [18] and that detects all Ads and another designed by the CDC that detects only Ad14 (primer and probe sequences are available on request). Both assays were performed using iQ Supermix (Bio-Rad), with each 25- μ L reaction containing 0.5 μ mol/L of forward and reverse primers, 0.1 μ mol/L of probe, and 5 μ L of nucleic acid extract. Thermocycling was performed using an iCycler iQ Real-Time Detection System (Bio-Rad), programmed for 3 min at 95°C and 45 cycles of 15 s at 95°C and 1 min at 60°C. Each run included appropriate positive and no-template controls. Assay specificity was confirmed against all recognized Ad prototype strains and against multiple Ad14 field isolates collected from different temporal and geographic settings.

Serum titers of Ad14 and Ad7 neutralizing antibodies were measured using a modified version of a microneutralization assay [19] incorporating an outbreak Ad14 isolate and the Ad7 reference strain S-1058. Briefly, starting at a dilution of 1:10, 50 μ L of heat-inactivated serum (56°C for 30 min) was 2-fold serially diluted in growth medium (Eagle's minimal essential medium with 10% fetal calf serum) in 4-fold replicates in a microtiter plate. Ten TCID₅₀ units of virus in 50 μ L was added to each well, and the plate was gently agitated and incubated for 1 h at room temperature. Fifty microliters of an A549 cell suspension (400,000 cells/mL) was then added to each well and mixed thoroughly. After incubation for 6 days at 37°C in 5% CO₂, the plate was stained with crystal violet. Appropriate controls were included in each run. A serum sample's neutralization titer was defined as the highest dilution of the serum that fully inhibited 10 TCID₅₀ units of virus. Recent Ad14 infection was defined as any rise in the titer (e.g., from negative to positive) of Ad14 neutralizing antibodies between pre- and posttraining samples. Evidence of prior Ad7 or Ad14 infection was defined as a titer of 1:10 or greater in pretraining serum.

RESULTS

Outbreak description—surveillance data. In 2007, a total of 33,496 BMTs participated in basic training at the US Air Force training facility. Among these, 1147 cases of FRI were identified through surveillance (attack rate, 3.4%). FRI rates increased in March, peaked in late May and early June (with a smaller peak in late September), and remained elevated into November (figure 1A). The average FRI rate in 2007 was 0.57 cases/100 BMTs/week. By comparison, in 2006, a total of 428 FRI cases were detected among 35,872 BMTs, yielding an average rate of 0.20 cases/100 BMTs/week.

Respiratory samples from 482 (42%) of the 1147 patients with FRI whose illnesses began in 2007 were tested. Of the samples tested, 267 (55%) were positive for Ad by PCR, and 231 (87%) of these were typed as Ad14 by PCR (48% of all tested samples). The initial detection of Ad14 correlated with the increase in the FRI rate in March and was detected through year's end (figure 1B). Ad14-negative samples included 23 that were positive for other Ads, including Ad3 and Ad4, and 13 Ad-positive samples that were not typed. By applying the proportion (48%) of all tested samples that were positive for Ad14 to the 1147 cases of FRI that occurred in 2007, we estimate that at least 551 cases of Ad14 FRI occurred in 2007.

In 2007, a total of 66 BMTs were hospitalized with pneumonia, of whom at least 23 (35%) were positive for Ad14. Not all of the BMTs hospitalized with pneumonia were tested for Ad14. Four trainees (3 BMTs and 1 trainee who had recently graduated) with Ad14 pneumonia required admission to an intensive care unit. Three of these trainees required intubation, and one 19-year-old female BMT died of complications after >10 weeks of hospitalization.

In response to the sharp elevation in the rate of cases of severe pneumonia and FRI among BMTs, US Air Force public health officials implemented control measures that included more hand-sanitizing stations, widespread sanitizing of surfaces and equipment with appropriate disinfectants, education of recruits and staff, and contact and droplet precautions for hospitalized patients with Ad14 infection. Additionally, beginning 26 May 2007, BMTs with a fever \geq 38.1°C were not returned to their flight but were isolated in a separate medical bay (the bed-rest flight) until becoming afebrile for 24 h without medication.

From 1 January through 28 May 2007, a total of 192 flights completed training. Overall, approximately two-thirds of flights contained at least 1 case of FRI. Among affected flights, the median attack rate over the training period was 2%. Male flights were more likely to contain FRI cases than were female flights (74% vs. 49%); male flights also had higher attack rates (median, 3% vs. 0%). Moreover, of 104 male flights containing FRI cases, 39 (38%) had at least 1 confirmed case of Ad14 infection, compared with 5 (20%) of 25 female flights containing FRI cases.

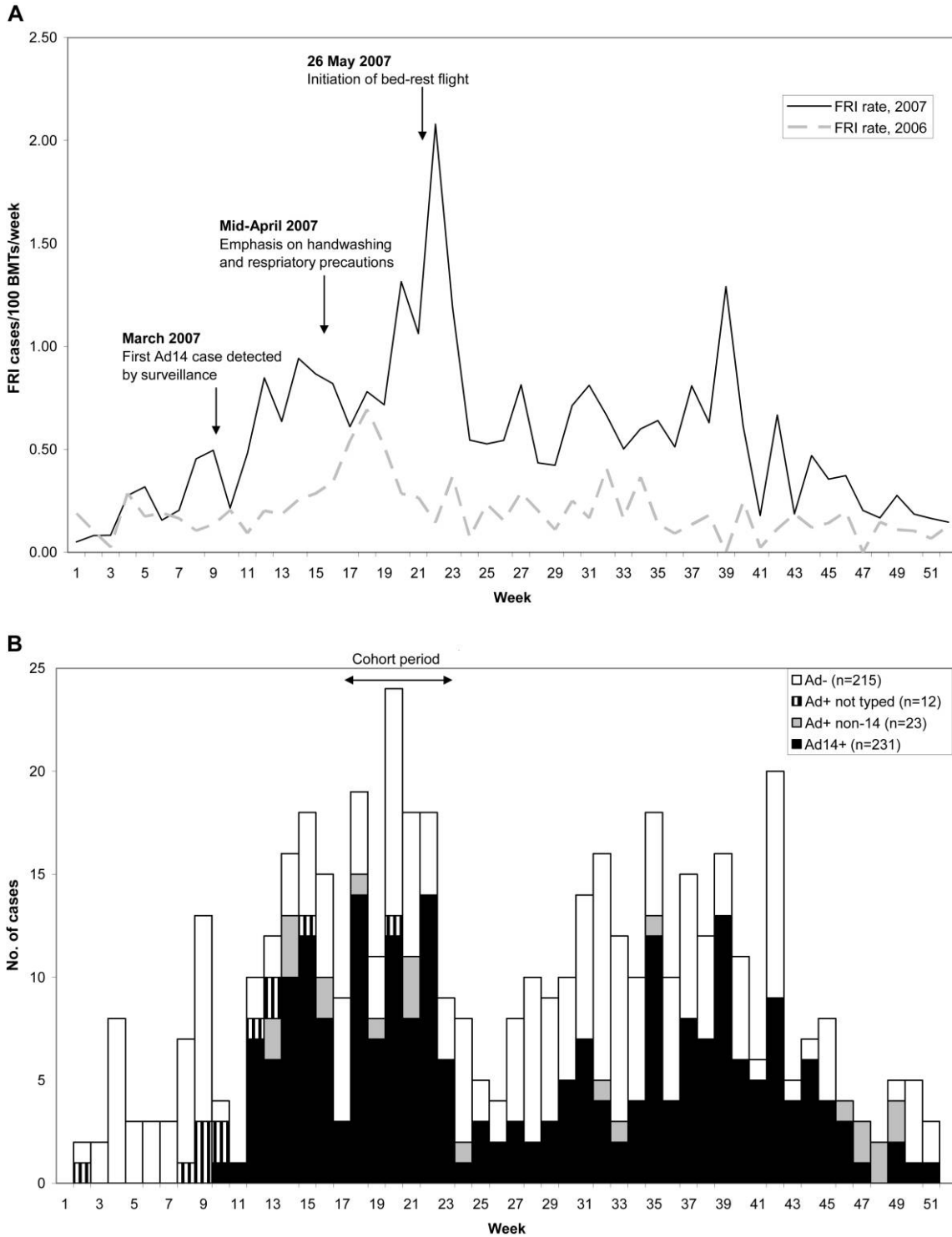


Figure 1. A, Rates of febrile respiratory illness (FRI), by week of detection—Naval Health Research Center Surveillance Program, 2006–2007. B, Human adenovirus test results for 481 tested patients with FRI, by week of detection—Naval Health Research Center Surveillance Program, 2007. —, negative; +, positive.

Finally, male patients with FRI were twice as likely as female patients with FRI to be positive for Ad14 (42% vs. 20%) (table 1). The number of BMTs in male and female flights was similar.

FRI cases occurred throughout a flight's 6.5-week training period but were more common during the second half, which is the more physically arduous part of training. Ad14 was detected

Table 1. Cases of febrile respiratory illness (FRI) and human adenovirus (Ad) serotype 14 infection among flights and corresponding basic military trainees (BMTs), by sex—1 January 2007 through 28 May 2007.

Sex	Flights				BMTs		
	Total	With FRI ^a	With Ad14 ^a	FRI attack rate, median (range), %	Total FRIs	FRIs tested for Ad14	Tested FRIs positive for Ad14
Male	141 (73)	104 (74)	39 (28)	3 (0–15)	278	142	59 (42)
Female	51 (27)	25 (49)	5 (10)	0 (0–9)	47	25	5 (20)
Total	192	129 (67)	44 (23)	2 (0–15)	325	167	64 (38)

NOTE. Data are no. (%), unless otherwise indicated. If a BMT had >1 FRI, then only the first FRI was counted. All flights and BMTs who started and finished training from 1 January 2007 through 28 May 2007 are included.

^a At least 1 confirmed case.

only in samples collected after week 3 of training, coincident with the rise in the number of FRI cases (figure 2).

Risk factors for and spectrum of Ad14 disease—cohort investigation. Of the 227 BMTs who spent any time in 1 of the 4 selected flights, 216 (95%) were eligible for inclusion, of whom 31 (14%) dropped out of training and were unavailable for the investigation, 9 (4%) could not be located, and 3 (1%) were interviewed but did not have samples available for analysis. Of the remaining 173 BMTs included in the investigation, 130 (75%) were in the cohort for the entire training period, 9 (5%) entered the cohort late, and 34 (20%) left early. The median time at risk of infection was 44 days.

Ad14 neutralizing antibody, at titers ranging from 1:10 to 1:160, was present in serum samples from 5 BMTs (3%; 3 males and 2 females) before arrival on the base. These 5 BMTs did not experience a rise in titer during training. Of the 173 BMTs in the cohort, 87 (50%) had evidence of Ad14 infection during training—either a PCR-positive throat-swab sample ($n = 54$) or a

rise in the titer of Ad14 neutralizing antibody ($n = 70$). The rate of Ad14 infection in these 4 flights was 55 cases/100 BMTs/6.5-week training period.

Of the 87 Ad14-infected patients, 35 (40%) reported FRI, 44 (51%) reported afebrile or mild illness, and 8 (9%) reported no respiratory symptoms. Overall, respiratory symptoms were commonly reported by BMTs (75% of cohort members reported such symptoms), but only FRI was significantly associated with Ad14 infection (table 2).

Male BMTs were almost 5 times more likely to have Ad14 infection than were female BMTs (risk ratio [RR], 4.7 [95% confidence interval {CI}, 2.2–10.1]), but male and female BMTs did not differ with respect to other risk factors. There was no difference in the risk of Ad14 infection by race/ethnicity or by age. Self-reported close contact with a person with respiratory symptoms within 10 days before their own onset of illness was associated with Ad14 infection (RR, 1.6 [95% CI, 1.2–2.2]). However, BMTs who slept adjacent to a BMT

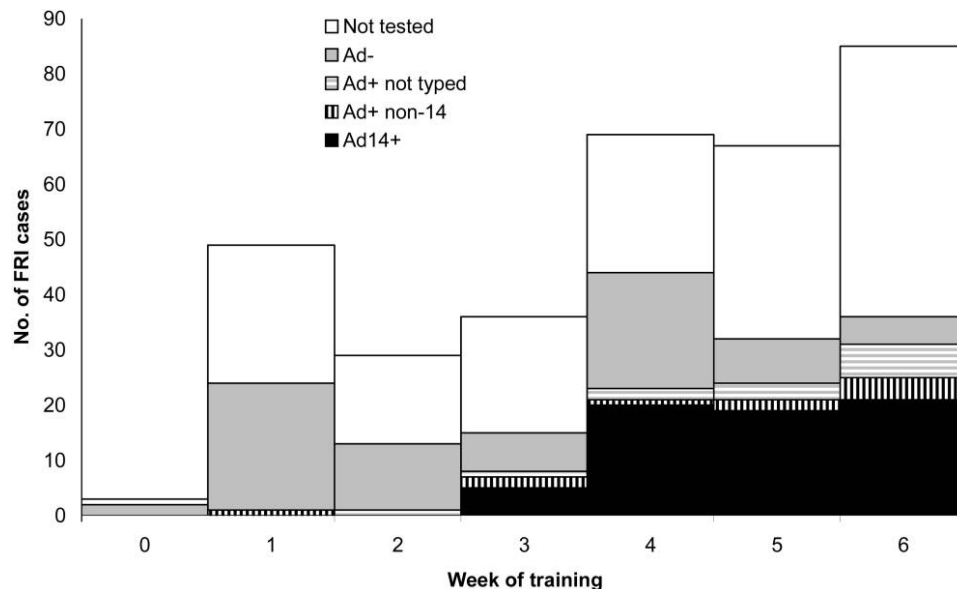


Figure 2. Cases of febrile respiratory illness (FRI) and human adenovirus test results for flights that entered on or after 1 January 2007 and graduated on or before 28 May 2007, by week of training. —, negative; +, positive.

Table 2. Risk factors for and severity of illness due to human adenovirus (Ad) serotype 14 infection among participants in the cohort investigation (n = 173).

Risk factor	Ad14 status		RR (95% CI)	P ^a
	Positive (n = 87)	Negative (n = 86)		
Sex				
Male	81 (63)	47 (37)	4.7 (2.2–10.1)	...
Female	6 (15)	39 (85)	1.0 (reference)	...
Race/ethnicity				
White, non-Hispanic	66 (53)	59 (47)	1.0 (reference)	...
Black, non-Hispanic	10 (50)	10 (50)	0.9 (0.6–1.5)	...
Hispanic	9 (43)	13 (57)	0.8 (0.5–1.3)	...
Other	2 (33)	4 (67)	0.6 (0.2–2.0)	...
Former smoker				
Yes	28 (41)	40 (59)	0.7 (0.5–1.0)	...
No	59 (56)	46 (44)	1.0 (reference)	...
Seasonal allergies				
Yes	16 (43)	21 (57)	0.8 (0.6–1.2)	...
No	71 (52)	65 (48)	1.0 (reference)	...
Age, mean ± SD, years	21.1 ± 1.8	21.6 ± 2.657
Initial BMI, mean ± SD	24.5 ± 3.0	24.2 ± 3.062
Initial run time, mean ± SD, min				
Males	8.02 ± 1.00	8.27 ± 1.1325
Females	10.72 ± 0.89	10.63 ± 1.5184
Childhood region				
West	11 (65)	6 (35)	1.2 (0.8–1.8)	...
Southwest	20 (54)	17 (46)	1.0 (0.7–1.4)	...
Midwest	14 (31)	31 (69)	0.6 (0.3–0.9)	...
South	30 (56)	24 (44)	1.0 (reference)	...
Northeast	10 (67)	5 (33)	1.2 (0.8–1.8)	...
Outside US	2 (40)	3 (60)	0.7 (0.2–2.2)	...
Close contact sick before current illness				
Yes	53 (62)	33 (38)	1.6 (1.2–2.2)	...
No	33 (39)	52 (61)	1.0 (reference)	...
Adjacent sleeper sick before current illness				
Yes	36 (52)	33 (48)	1.1 (0.8–1.5)	...
No	49 (49)	52 (51)	1.0 (reference)	...
Severity of illness				
Febrile respiratory illness ^b	35 (83)	7 (17)	2.5 (1.4–4.5)	...
Afebrile respiratory illness ^c	30 (44)	38 (56)	1.3 (0.7–2.5)	...
Mild respiratory illnesses ^d	14 (36)	25 (64)	1.1 (0.5–2.2)	...
No respiratory symptoms	8 (33)	16 (67)	1.0 (reference)	...

NOTE. Data are no. (%), unless otherwise indicated. BMI, body mass index (calculated as the weight in kilograms divided by the square of height in meters); CI, confidence interval; RR, risk ratio.

^a Wilcoxon rank-sum test.

^b Self-reported fever plus 1 respiratory symptom (i.e., cough, sinus congestion, runny nose, wheezing, or shortness of breath).

^c Self-reported cough plus another respiratory symptom but no reported fever.

^d At least 1 self-reported respiratory symptom but absence of other criteria specified in the case definitions described above.

with respiratory symptoms were not at increased risk of Ad14 infection (table 2).

Investigation of cross-protection conferred by Ad7 antibodies.

BMTs with Ad7 antibodies at the beginning of training were at a lower risk of severe Ad14 illness than were BMTs without Ad7 antibodies. Seven (39%) of 19 Ad14-infected BMTs with mild illness or no respiratory symptoms had serum neutralizing antibodies to Ad7, whereas

none of the 16 hospitalized Ad14-infected BMTs had Ad7 antibodies ($P = .007$).

DISCUSSION

This article reports an outbreak of severe respiratory illness due to an emergent variant of the rarely reported type Ad14 and

highlights the potential of this strain to cause large, protracted outbreaks of illness among otherwise healthy persons. Ad14 infection resulted in a marked rise in the rate of FRI at this US Air Force facility in 2007. In 2006, only 1 case of Ad14 infection, a coinfection with Ad21, was detected at this base [11]. In 2007, of 1147 persons seeking care for febrile respiratory disease, an estimated 551 (48%) were infected with Ad14. The high rate of serious Ad14 illness among BMTs (23 hospitalizations due to pneumonia, including 4 admissions to an intensive care unit and 1 death), compared with the rates of Ad3, Ad4, and Ad7 disease, makes this outbreak especially noteworthy. Consistent with reports of Ad14 infection being rare before 2007, we found a low prevalence of Ad14 antibodies among recruits starting training. Cross-reactivity has been demonstrated among species B Ads, such as Ad7 and Ad14, with hyperimmune animal sera [14], so even this low prevalence may be an overestimate (i.e., some Ad14 neutralizing antibodies may have been induced by other Ads). The presence of cross-reacting antibodies among species B Ads is consistent with our finding that previous natural infection with Ad7 may protect against severe Ad14 disease.

Our investigation provides insights into Ad14 infection and its control. First, Ad14 spread efficiently among BMTs (especially among male trainees), with 50% of the trainees in the cohort investigation becoming infected. Second, although Ad14 caused more-serious illness than did other FRI-associated Ads in BMTs, most infections did not result in serious illness. In fact, in the cohort investigation, many infections were mild or inapparent and did not come to the attention of the health care system. Consequently, control measures for this type of outbreak should be broad-based and applied to all BMTs. Unfortunately, it remains unclear how best to control this type of outbreak. Standard control measures, such as increased handwashing and surface and equipment disinfection, did not appear to prevent a rise in the number of Ad14 cases in early May. The establishment of a medical bay for recruits with fever so they could rest rather than continue training coincided with a sharp drop in the number of cases of FRI and Ad14 infection. However, virus continued to circulate with a relatively high level of infection throughout the year, and it is unclear whether the medical bay decreased transmission, although it may have helped prevent progression to more severe illness. It is likely that person-to-person transmission was important in propagating this outbreak, as suggested by the association between infection and reported close contact with a BMT with respiratory illness. It is also highly likely that environmental contamination contributes to transmission, as suggested by the frequent detection of Ad on surfaces in military training facilities [20].

Ad14 illness at this training facility predominated during the second half of training, possibly because it takes time to establish sufficient numbers of infected recruits to cause disease or because harsher conditions during the second half of training increase the risk of transmission or disease. Previous reports of

Ad4 outbreaks have noted that the number of cases peaked during training weeks 3–5 [15, 21]. Interestingly, there were no reports of increased rates of respiratory illness among other personnel on the base, possibly because they were not exposed or because previous exposures left them less susceptible to infection. This is consistent with reports of lower attack rates among more-seasoned military personnel in Ad outbreaks [22].

The increased risk for Ad infection and disease among male recruits has been reported previously [23, 24], but the reasons for this association are unclear. In relatively homogenous training–environment conditions, it is possible that risk factors for infection are similar for both sexes and that sex-specific host susceptibility factors explain this difference. Alternately, differing hygienic or other behaviors between men and women during training may affect transmission rates.

Few outbreaks of Ad14 have been reported; they include 2 outbreaks of pharynconjunctival fever among college students in Europe in the 1950s and 1960s [25, 26] and outbreaks of acute respiratory disease at military installations in Europe and Asia [27, 28]. Several surveys of respiratory infections in civilian communities found no Ad14 cases in the United States between 1957 and 1976 [24, 29–31], and only a few cases have been identified in Europe and Asia since the 1980s [32, 33]. Ad14 was first reported in the United States among military personnel in 2006 [7, 11], but only as sporadic cases of FRI, and no outbreaks of FRI or hospitalizations were reported [11]. Complete hexon and fiber gene sequences of Ad14 isolates from this outbreak and the outbreaks of severe illness among civilians in 2007 [12, 34] were identical and were similar to, but distinct from, the 1955 prototype strain deWit. There is a single 2-aa deletion in the fiber knob region in proximity to the receptor-binding site. This deletion is not present in the deWit strain, but it is unclear whether this or other changes explain the reemergence of this virus and its apparent increased pathogenicity.

The present investigation had several limitations. Not all recruits seek medical care when they are ill or have samples collected for surveillance, not all surveillance samples are tested for Ad, and many recruits with FRI may avoid presenting for care for fear of delaying completion of training. Thus, the number of FRI and Ad14 cases may be higher than what we observed. Milder respiratory symptoms and risk factors that occur earlier during training, such as close contact with an ill trainee, may have been underreported, because they may be more likely to have been forgotten when cohort members were interviewed at the end of training. A lack of samples collected at the time of the onset of illness hampered the attribution of Ad14 infection to any specific illnesses reported at end of training. Similarly, if not all BMTs in the cohort were actually exposed to Ad14, the risk of infection given exposure has been underestimated. Finally, it is possible that some of the low posttraining Ad14 titers could have been false-positive results.

The protracted nature of this outbreak and the clusters of illness in civilian populations [12, 34] suggest that this Ad14 variant is emergent, widespread, and associated with more-severe disease in some persons than other Ad types. Reassuringly, since 2007, no additional outbreaks of severe Ad14 disease have been reported among civilians, suggesting that Ad14 does not currently present a public health threat to the general population. However, the full extent of Ad14 transmission in civilian populations is uncertain, given that data on Ad infections in civilian populations are limited. In contrast, Ad14 has continued to contribute to sporadic FRI and occasional outbreaks among military trainees [13, 35]. Our finding that natural Ad7 infection may protect against severe Ad14 disease suggests that the Ad7 vaccine being developed may lessen the impact of Ad14 among BMTs. Unfortunately, our study did not clearly determine what other measures might help control the spread of Ad14 or other Ads in military training facilities.

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