# Clinical Presentations for Influenza and Influenza-Like Illness in Young, Immunized Soldiers

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**Concern about respiratory diseases in soldiers increased in the late 1990s as production of the successful adenovirus vaccines stopped and the possibilities of an emergent pandemic influenza strain and use of bioweapons by terrorists were seriously considered. Current information on the causes and severity of influenza-like illness (ILI) was lacking. Viral agents and clinical presentations were described in a population of soldiers highly immunized for influenza. Using standard virus isolation techniques, 10 agents were identified in 164 (48.2%) of 340 soldiers hospitalized for ILI. Influenza isolates (29) and adenoviruses (98) occurred most frequently. Most influenza cases were caused by influenza A and probably resulted from a mismatch between circulating and vaccine viruses. Most (58.5%) patients with an adenovirus had a chest radiograph; 31.3% of these had an infiltrate. Clinical findings did not differentiate ILI caused by the various agents. Only 29 cases of influenza occurred in ~7,200 person-years of observation, supporting the use of influenza vaccine.**

## Introduction

During the period from 1994 to 1999, three events increased interest in the causes and severity of influenza-like illness (ILI) in soldiers and the ability of providers in the military health system to identify the agent or agents causing acute respiratory diseases. The first event was the loss of two important vaccines. Beginning in 1971, the primary causes of acute respiratory disease in military basic trainees, adenovirus types 4 and 7, were controlled by oral enteric-coated vaccines.[1] In 1994, the sole manufacturer of the vaccines announced that vaccine production would be terminated permanently.[2] In response, the military services limited administration of the existing vaccine supply to the higher-risk colder months, with the depletion of all vaccine stocks occurring in 1999.[2] Some medical leaders called for quickly awarding a contract to reestablish production of the vaccines. Others argued that adenovirus-associated acute respiratory disease in previously healthy soldiers was a mild disease that did not warrant an expensive, multiyear vaccine initiative. The second event was more of a growing concern that terrorists would use as bioweapons respiratory pathogens such as *Bacillus anthracis*. This fueled discussions on the range of respiratory pathogens that might occur in military populations and the ability of providers to quickly identify the agents.[3] The third event was the appearance of a threatening H5N1 influenza A strain with pandemic potential in Hong Kong in 1997.[4] This event highlighted the possibility that the effectiveness of the mandatory, annual military influenza immunization program could be compromised by the emergence of an influenza virus antigenically different from the viruses used to make the vaccine. Formal meetings of medical leaders in the Department of Defense (DoD) followed to address the likelihood that novel, unexpected influenza viruses would be detected in a timely fashion so that vaccine effectiveness could be determined and outbreak interventions expeditiously implemented.[5]

Interruption in the routine year-round administration of the adenovirus vaccines resulted in a resurgence of ILI at military training centers and prompted the initiation of enhanced laboratory-based surveillance at selected Army installations in 1997.[1,2,6–8] The enhanced surveillance program was initiated to monitor changes in ILI, project increases in clinical work load, and provide epidemiological data needed to develop a contract for a new vaccine producer and to test the next generation of adenovirus vaccines.[6–8] Data and information from this surveillance program also provided an opportunity to address concerns about the causes and severity of ILI in soldiers. Using data from the surveillance initiative at Fort Gordon, Georgia, we identified the viral agents causing ILI and the proportion of ILI cases for which no agent could be identified. We also determined whether the identified pathogens were associated with clinically distinguishing features and assessed the clinical severity of ILI. Lastly, we defined the occurrence of clinical influenza in a highly immunized U.S. Army population.

## Methods

Fort Gordon is an Army advanced training installation. Soldiers come to Fort Gordon after completing initial entry (basic) training at other military installations. The epidemiological assessment of the occurrence of acute respiratory disease at Fort Gordon during the time of this study has been reported elsewhere.[7] From April 1, 1997 to March 31, 1999, we studied 340 Army trainees hospitalized with acute, febrile respiratory illness at Dwight D. Eisenhower Army Medical Center (DDEAMC) at Fort Gordon. The case definition for study enrollment was fever (≥38.1°C or ≥100.5°F orally) with one or more symptoms of an acute respiratory illness.[7] This case definition has been used in the military to define cases of acute respiratory disease, which is also referred to as febrile respiratory illness. In this study, we

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refer to our patients as having ILI. The approximate size of the Fort Gordon trainee population during the study period was 3,600 individuals, of which approximately 20% were women.[7] The age range of our patients was 17 to 34 years (median age, 19 years); 19.7% were women. An estimated 80% of soldiers hospitalized with ILI during the study period were evaluated.[7]

Demographic information and a clinical history were recorded for each patient, and a pharyngeal swab was obtained for virus culture. Specimens for virus isolation were quickly transported from the medical treatment facility to the laboratory for processing. The DDEAMC clinical laboratory routinely offered virus isolation services on site. The laboratory procedures used for virus isolation and identification have been described elsewhere.[6] Only laboratory tests available at the DDEAMC were used. Influenza isolates were not subtyped. Serological tests and rapid laboratory tests for influenza and respiratory syncytial virus were not readily available. Results of other relevant laboratory and radiographic studies were obtained from medical records. These included, in most instances, a pharyngeal swab for isolation of *Streptococcus pyogenes*, group A, using standard bacteriological methods. Cultures or other diagnostic tests were not performed for rhinoviruses, respiratory syncytial virus, *Chlamydia pneumoniae*, *Legionella* spp., *Mycoplasma pneumoniae*, *Streptococcus pneumoniae*, or *Bordetella* spp. Cerebrospinal fluid (CSF) was not cultured for viruses, but standard bacteriological culture was performed. This study was in compliance with standards established by the Institutional Review Committee of the DDEAMC.

All or nearly all soldiers studied had received influenza vaccine, although vaccination records were unavailable for review. Before and during the study, soldiers entering the Army were vaccinated for influenza on a year-round basis. Senior immunization personnel at Fort Jackson, South Carolina, the Army's largest basic training center, estimated one or less exemption per 5,000 soldiers entering basic training was given for documented egg or vaccine allergy. After basic training, soldiers proceeded to Fort Gordon and other posts for advanced training where they again received influenza vaccine during the annual, fall influenza immunization campaign.

Analyses of 45 signs, symptoms, and laboratory findings to assess possible differences in clinical presentations associated with specific viral agents were performed using SAS Software (SAS Institute Inc., Cary, North Carolina). For analyses, hospitalized soldiers were placed into one of five groups based on virus isolation laboratory results. These five groups were: adenovirus 4 (ADV 4), herpes simplex virus, influenza A, other viruses isolated, and no virus isolated. Statistical analyses were done using the $\chi^2$ test and Fisher's exact test for small cell size. Statistical significance was set at $p < 0.05$. Study variables were first evaluated by virus isolation group in a $5 \times n$ table. When statistical significance was found in the table or the $\chi^2$ values were unevenly distributed, the occurrence of the variable in each virus etiology group was compared with the occurrence in all other virus etiology groups for a total of 10 different comparisons. The *t* test was used to compare means. Variables observed to have statistical significance were studied in a multivariate analysis model.

## Results

Viral agents were identified in 164 (48.2%) of 340 individuals studied (Table I). Influenza (29 isolates; 23 influenza A, 6 influenza B) was second only to adenoviruses (98 isolates) in frequency of isolation. Twenty-one of the 23 isolates of influenza A occurred as an outbreak in late January and early February of 1998; the two additional isolates occurred in March and May 1998. Six influenza B isolates were identified sporadically over the study period.

**TABLE I**

VIRAL AGENTS ISOLATED

| Viral Agent | No. of Isolates (%) |
|---|---|
| ADV 4 | 82 (24.1) |
| Herpes simplex | 24 (7.1) |
| Influenza A | 23 (6.8) |
| Adenovirus 21 | 10 (2.9) |
| Parainfluenza 3 | 8 (2.4) |
| Influenza B | 6 (1.8) |
| Coxsackie A-21 | 5 (1.5) |
| Adenovirus 2 | 4 (1.2) |
| Adenovirus 2/3 | 1 (0.3) |
| Adenovirus not typed | 1 (0.3) |
| No virus isolated | 176 (51.8) |
| Total | 340 (100.0) |

In addition to fever ranging from 38.1°C to 40.1°C (100.5°F to 104.2°F), the most common presenting symptoms were cough and sore throat in 60.1% and 69.6% of all patients, respectively. Our analyses failed to identify any variable or combination of variables, other than virus culture, that significantly differentiated the clinical cases by virus isolation group. The number of days of illness before hospitalization, age, gender, mean oral temperature, cough, sore throat, other signs and symptoms of a respiratory infection, and the results of chest radiographs, blood leukocyte counts, and tests for mononucleosis were evaluated. Upper respiratory congestion, head or nasal congestion, and rhinorrhea occurred infrequently in the 340 hospitalized patients (5.9%, 7.9%, and 19.4%, respectively).

Among the 340 individuals studied, 246 (72.4%) had a throat culture for isolation of group A, β-hemolytic *Streptococcus pyogenes* (GABHS; Table II). Fifteen (6.1%) of the patients tested positive for GABHS. Patients who were positive for influenza A were more likely to demonstrate a positive culture for GABHS than patients who were positive for ADV 4 (Fisher's exact test, $p = 0.04$); no other statistically significant associations were present.

A total of 226 patients (66.5%) had chest radiographs performed during their hospitalization (Table III). Of those with radiographs, 83 (36.8%) exhibited abnormal findings: 75 presented with infiltrates, 6 with increased interstitial markings,

**TABLE II**

BACTERIAL THROAT CULTURE RESULTS

| Virus Isolation Group | Throat Cultures Done/ Patients in Group (%) | Isolations of GABHS (%) |
|---|---|---|
| ADV 4 | 61/82 (74.4 ) | 1 (1.6) |
| Herpes simplex | 19/24 (79.2 ) | 1 (5.3) |
| Influenza A | 18/23 (78.3 ) | 3 (16.7) |
| Influenza B | 3/6 (50.0 ) | 0 (0) |
| Other viruses | 20/29 (69.0 ) | 1 (4.3) |
| No virus isolated | 125/176 (71.0) | 9 (7.2) |
| Total | 246/340 (72.4) | 15 (6.1) |

TABLE III

FREQUENCY OF OBTAINING CHEST RADIOGRAPHS AND OCCURRENCE OF INFILTRATES IN 340 SOLDIERS HOSPITALIZED WITH ILI

| Virus Isolation Group | No. Radiographs/ Patients in Group (%) | No. with Infiltrates/ Patients with Radiographs (%) |
|---|---|---|
| ADV 4 | 48/82 (58.5) | 15/48 (31.3) |
| Herpes simplex | 15/24 (62.5) | 2/15 (13.3) |
| Influenza A | 12/23 (52.2) | 2/12 (16.7) |
| Influenza B | 4/6 (66.7) | 1/4 (25.0) |
| Other viruses | 18/29 (62.1) | 0/18 (0) |
| No virus isolated | 129/176 (73.3) | 55/129 (42.6) |
| Total | 226/340 (66.5) | 75/226 (33.2) |

and 2 with hyperinflation. Among patients with an identified viral agent and a chest radiograph, those from whom ADV 4 was isolated had the greatest frequency of infiltrates (31.3%). One (25.0%) of four patients with influenza B and a chest radiograph and two (16.7%) of 12 patients with influenza A and a chest radiograph had an infiltrate (Table III).

Focal infiltrates predominated (88.0%, 66 of 75 patients with infiltrates; Table IV). All pulmonary lobes were involved, but most had only lower lobe infiltrates (66.7%); 25.3% of those with infiltrates had only upper lobe involvement. Statistical analyses revealed that similar percentages of patients in the virus isolation groups had chest radiographs performed, and the occurrence of abnormal findings was similar in all groups.

Eighteen patients underwent lumbar puncture; eight (44.5%) of these had an adenovirus isolate and eight had no virus isolated. Within these two groups, respectively, five (62.5%) of eight and four (50%) of eight had abnormal CSF test results, the most common finding being elevated monocyte and lymphocyte counts. The other two patients undergoing lumbar puncture had pharyngeal isolates: one yielded parainfluenza 3 and the other influenza A. CSF results were normal in each. Bacterial meningitis was not diagnosed. Statistical analyses revealed no significant differences between virus isolation groups with regard to lumbar puncture. All patients completely recovered and were discharged after 48 hours or less of hospitalization.

## Discussion

Our study demonstrated the occurrence of clinically significant adenovirus-associated acute respiratory disease when the routine schedule for administering adenovirus vaccines was disrupted, the ability of a variety of viral agents to present as clinically indistinguishable ILI, and the occurrence of breakthrough influenza in a highly immunized population. Using a case definition that differed only slightly from that established by the Centers for Disease Control and Prevention (Atlanta, Georgia) for ILI surveillance (fever of ≥37.8°C with cough and/or sore throat),[9] illness associated with several different viral agents that resulted in hospitalization was documented. Among 340 individuals studied, 66.5% had a chest radiograph and 33.2% of these had infiltrates. Additionally, 5.3% received a lumbar puncture and 9 (50%) of these had an abnormal finding.

Only 8.6% of the hospitalized soldiers had an influenza virus isolated. Among the patients from whom influenza was isolated, 3 (18.8%) of 16 had chest radiographs with an infiltrate, a level somewhat higher than the reported 4% to 8% in individuals infected with influenza between the ages of 5 and 50 years.[10] ADV 4 was the most frequently isolated pathogen (82 patients). Eight (9.8%) of the 82 underwent lumbar puncture, and 15 (18.3%) of the soldiers with ADV 4 had chest radiographs showing infiltrates. Similar results for pulmonary findings were reported for military trainees with adenovirus-associated acute respiratory disease in the prevaccine era.[11] In patients without a viral isolate, 55 (42.6%) of 129 with chest radiographs had an infiltrate. Likely causative agents for pneumonia in these soldiers with infiltrates were undetected viruses or bacterial pathogens for which laboratory testing was not done. It was not possible to differentiate between patients with different viral isolates on the basis of clinical signs, symptoms, or laboratory test results (other than virus culture). Nasal congestion and rhinorrhea were identified by the Centers for Disease Control and Prevention as features of ILI cases not associated with anthrax.[12] In our hospitalized soldiers, none of whom had anthrax, upper respiratory, head, or nasal congestion and rhinorrhea occurred infrequently. Small sample sizes may have limited our ability to identify differences.

In the 340 soldiers studied, ADV 4 (24.1%), herpes simplex (7.1%), and influenza A (6.8%) were the viral agents most often isolated. Despite emphasizing the rapid transport of specimens to the laboratory for processing, we were able to identify a viral or bacterial agent in only 50.8% of our patients. Long turnaround times for laboratory results precluded consideration of this information in decisions regarding the use of antimicrobial drugs. Our inability to identify a possible causative agent in 49.2% of our cases probably reflects both the limitations of virus isolation as a diagnostic test and failure to use testing for other agents such as *C. pneumoniae, Legio-*

TABLE IV

DISTRIBUTION OF INFILTRATES IN 75 SOLDIERS HOSPITALIZED WITH ILI BY VIRUS ISOLATE

| Finding | Influenza A (%) | Influenza B (%) | ADV 4 (%) | All patients (%) |
|---|---|---|---|---|
| Total Infiltrates | 2 (100) | 1 (100) | 15 (100) | 75 (100) |
| Type Infiltrate(s) | | | | |
| Focal | 2 (100) | 1 (100) | 14 (93.3) | 66 (88.0) |
| Multifocal | 0 (0) | 0 (0) | 1 (6.7) | 3 (4.0) |
| Bilateral | 0 (0) | 0 (0) | 0 (0) | 6 (8.0) |
| Location | | | | |
| Lower lobes | 0 (0) | 1 (100) | 5 (33.3) | 50 (66.7) |
| Middle lobes | 0 (0) | 0 (0) | 2 (13.3) | 3 (4.0) |
| Upper lobes | 2 (100) | 0 (0) | 7 (46.7) | 19 (25.3) |
| Upper/lower | 0 (0) | 0 (0) | 1 (6.7) | 3 (4.0) |
| Effusions | 0 (0) | 0 (0) | 1 (6.7) | 5 (6.7) |

*nella* spp., *Mycoplasma pneumoniae*, *S. pneumoniae*, *Bordetella* spp., rhinoviruses, and respiratory syncytial virus. Tests for human metapneumovirus and severe acute respiratory syndrome-associated coronavirus, both newly recognized respiratory pathogens, should also be considered for future ILI studies.[13,14] A battery of rapid diagnostic tests for both bacterial and viral agents could assist in the timely identification of pathogens of concern, identify mixed infections, and aid in assessing the need for antibiotics or antiviral drugs.[15]

In early 1998, we identified 21 soldiers from a highly immunized population who were hospitalized with influenza A. Although the influenza A isolates were not further characterized, all cases occurred during the peak incidence of ILI caused by A/Sydney/5/97-like viruses, a drifted variant of the vaccine strain and the predominant circulating A(H3N2) virus in early 1998.[16] Breakthrough influenza may occur in highly immunized populations because influenza vaccine is considered to be only 70% to 90% effective in healthy individuals younger than 65 years of age.[17,18] When there is a poor match between vaccine antigens and circulating strains of influenza virus, vaccine efficacy may be reduced to 40% to 60%.[18] The ineffectiveness of influenza vaccine against a drifted variant in the crew of a U.S. Navy ship in 1996 demonstrated the importance of matching the vaccine antigens to circulating influenza viruses.[19] Despite the limitations of influenza vaccine, data from our 2-year study support the value of influenza vaccine as an effective public health intervention. During approximately 7,200 person-years of observation of young adults immunized for influenza, only 29 soldiers were hospitalized with influenza (23 with influenza A and 6 with influenza B).

Concerns continue about adenovirus-associated and other respiratory diseases in military training centers, the possible emergence of a pandemic influenza strain, and the potential use of bioweapons, but progress is being made. A contract has been negotiated to reestablish a production base for the adenovirus vaccines, but large-scale use of these vaccines is years away.[2] Several programs have been implemented to address respiratory disease threats in an ongoing fashion.[5,20–22] The Air Force Institute for Operational Health, Brooks City Base, Texas, conducts the DoD Laboratory-Based Global Influenza Surveillance System to quickly identify novel influenza strains.[20] The Naval Health Research Center Respiratory Disease Laboratory, San Diego, California, closely monitors viral and bacterial respiratory diseases in the military training community.[21] Additionally, the Armed Forces Institute of Pathology, Washington, DC, has compiled a directory of public health laboratory services to assist DoD providers worldwide in identifying the resources available for expeditiously obtaining a laboratory-confirmed diagnosis.[22] However, the need persists for rapid, reliable laboratory tests in proximity to where patient care is given. The Naval Health Research Center and the Walter Reed Army Institute of Research, Silver Spring, Maryland, are evaluating and developing rapid diagnostic tests for onsite use at military training centers and with deployed forces. Recent recognition of the severe acute respiratory syndrome-associated coronavirus and the human metapneumovirus as significant causes of disease suggests surveillance for emerging respiratory pathogens and development of rapid, reliable tests for these pathogens are medical missions that will continue far into the future.[13,14]

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