U.S. Army Center for Health Promotion and Preventive Medicine

Epidemiologic Consultation No. 29-HE-8062-97
Investigation of Adenovirus and Acute Respiratory Disease (ARD) among Recruits
Fort Jackson, South Carolina
November-December 1997

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USCHPPM

Readiness Thru Health

U.S. Army Center for Health Promotion and Preventive Medicine

The lineage of the U.S. Army Center for Health Promotion and Preventive Medicine (USACHPPM) can be traced back over 50 years. This organization began as the U.S. Army Industrial Hygiene Laboratory, established during the industrial buildup for World War II, under the direct supervision of the Army Surgeon General. Its original location was at the Johns Hopkins School of Hygiene and Public Health. Its mission was to conduct occupational health surveys and investigations within the Department of Defense's (DOD's) industrial production base. It was staffed with three personnel and had a limited annual operating budget of three thousand dollars.

Most recently, it became internationally known as the U.S. Army Environmental Hygiene Agency (AEHA). Its mission expanded to support worldwide preventive medicine programs of the Army, DOD, and other Federal agencies as directed by the Army Medical Command or the Office of The Surgeon General, through consultations, support services, investigations, on-site visits, and training.

On 1 August 1994, AEHA was redesignated the U.S. Army Center for Health Promotion and Preventive Medicine with a provisional status and a commanding general officer. On 1 October 1995, the nonprovisional status was approved with a mission of providing preventive medicine and health promotion leadership, direction, and services for America's Army.

The organization's quest has always been one of excellence and the provision of quality service. Today, its goal is to be an established world-class center of excellence for achieving and maintaining a fit, healthy, and ready force. To achieve that end, the CHPPM holds firmly to its values which are steeped in rich military heritage:

★ *Integrity is the foundation*
★ *Excellence is the standard*
★ *Customer satisfaction is the focus*
★ *Its people are the most valued resource*
★ *Continuous quality improvement is the pathway*

This organization stands on the threshold of even greater challenges and responsibilities. It has been reorganized and reengineered to support the Army of the future. The CHPPM now has three direct support activities located in Fort Meade, Maryland; Fort McPherson, Georgia; and Fitzsimons Army Medical Center, Aurora, Colorado; to provide responsive regional health promotion and preventive medicine support across the U.S. There are also two CHPPM overseas commands in Landstuhl, Germany and Camp Zama, Japan who contribute to the success of CHPPM's increasing global mission. As CHPPM moves into the 21st Century, new programs relating to fitness, health promotion, wellness, and disease surveillance are being added. As always, CHPPM stands firm in its commitment to Army readiness. It is an organization proud of its fine history, yet equally excited about its challenging future.

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An acute respiratory disease (ARD) outbreak investigation was conducted at Fort Jackson, SC, the largest US Army basic combat training (BCT) center, during November and December 1997. A total of 79 patients were evaluated with throat swabs (on admission and 24 hrs later), acute serum samples and epidemiologic data. Convalescent serum samples for adenovirus (Adv) antibody testing were collected 14 to 21 days later on 49 of the 79 (62%) patients. Adeno-like viruses were isolated in 71 of 79 (90%) throat cultures; 19 of 20 tested were identified as type 4. Anti-adv antibody testing showed a high degree of susceptibility among incoming recruits; 15-22% of them being seropositive upon arrival at Fort Jackson. Review of ARD surveillance and Adv isolation data revealed that, during the period of June through November 1997, there were 32 and 12 separate military unit clusters, respectively, of ARD and Adv among recruits. Attack rates for ARD were found to be higher among recruits of one of the training brigades (0.95% per week, compared to a rate of 0.44% per week in trainees from other units). At least six separate instances of Adv introduction into training units from off-base were documented during the May-September period. Initial results of a case-control study performed among recruits in affected units (66 hospitalized recruit ARD cases and 189 non-ARD controls) identified prior smoking as an important risk factor (OR=1.89, 95% CI=1.03-3.50, p=0.03). Females were also found to be at significantly lesser risk than males (OR=0.47, 95% CI=0.25-0.87). The impact that Adv had upon training for the period of May-December 1997 was immense; over 2,200 man-days of lost training occurred as a direct result of Adv infections (i.e., admissions to the base military hospital). Air sampling performed at two of the unit barracks involved in the outbreak identified high levels of carbon dioxide, indicative of poor ventilation (especially evident during recruit sleeping times) and may have been a possible environmental risk factor for ARD. Future efforts in the area of Adv prevention, to include vaccination, were identified. Vaccination of recruits was started in early November 1997 and resulted in a subsequent significant reduction in ARD and Adv rates.

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EXECUTIVE SUMMARY

An acute respiratory disease (ARD) outbreak investigation was conducted at the US Army basic combat training (BCT) center, Fort Jackson, SC, during November and December 1997. The principal objective of the investigation was to collect sufficient clinical (throat swab and serum) samples on acutely infected ARD inpatients at Moncrief Army Community Hospital (MACH). These samples were needed to validate end-point measures (eg. lab tests) for evaluation of potential future replacement adenovirus (Adv) vaccines being developed under the auspices of the Adenovirus Vaccine Replacement Program (AVREP) mandated by the Assistant Secretary of Defense for Health Affairs (ASD-HA). Additional objectives of the investigation included: 1) the assessment of the impact of ARD/ADV infections to the military recruit population on-post; 2) investigation of the epidemiology of ARD in the recruit population to include an evaluation of risk factors for illness; and, 3) evaluation of the role of non-vaccine ARD interventions (NOVARDIs) in controlling ARD/Adv transmission in the recruit population.

A total of 79 inpatients presenting with a febrile ARD (oral temperature of 100.5^0F or greater and one or more respiratory symptoms) were evaluated with throat swabs (on admission and 24 hrs later), acute serum samples and clinico-epidemiologic data. Adeno-like viruses were isolated on 71 of 79 (90%) throat cultures; 19 of 20 specimens tested were identified as type 4. The 20th specimen did not contain a transmissible agent. Convalescent serum samples for anti-Adv type 4 antibody testing were collected 14 to 21 days later on 49 (62%) of the 79 inpatients. Pre-existing level of immunity to Adv type 4 among BCT recruits was assessed by testing serum from 78 (64%) of 121 recruits surveyed during the investigation as well as a random sample of pre-accession serum samples (n=76) obtained later in May-June 1998 from the DoD Serum Repository. Baseline levels of anti-Adv type 4 immunity were found to be very low (15-22%). By comparison, seroprevalence in acute samples from patients was found to be 42%, thereby, suggesting an overall Adv infection rate of approximately 20-27% during the first 3 to 4 weeks of training.

Review of ARD surveillance and Adv isolation data available from the Virology laboratory at Dwight D Eisenhower Army Medical Center (DDEAMC) revealed that, during the period of May through December 1997, there were 32 separate ARD outbreaks among company-sized unit clusters. Adv-associated respiratory disease epidemic clusters were detected in twelve separate instances during the months of August and September 1997. In three of these clusters the Adv-confirmed (by culture) attack rates were noted to be as high as 8-10% per week. ARD hospitalization rates were found to be higher among recruits in the 1st Training Brigade (0.95% per week) compared to much lower rates rates among trainees in the 4th Training Brigade (0.44% per week), 120th Reception Station (0.43% per week), and Advanced Individual Training (AIT) units (0.19% per week). At least six separate instances of Adv introduction into training units from off-base were documented during this period. Similar ARD hospitalization rates were noted for recruits housed in newer "Starship" type barracks (0.53% per week) when compared to those billeted in the older "Rolling pin" style barracks (0.50% per week). The impact this

outbreak had in terms of hospitalization days and lost training time was immense. We estimated that over 2,000 hospital days were accrued by over 700 cases of Adv-confirmed cases admitted to MACH (based on an average hospitalization stay of 3 days per case).

A case-control study was conducted comparing the 79 hospitalized cases (66 BCT recruits with a febrile ARD utilized for final analysis) to a total of 304 unit and MTF-based controls. Controls were selected at random from recruits surveyed at the 2/60th Inf Bn, one of the most affected units on-post [n=121, 69 (57%) non-ARD controls] as well as from recruits presenting to the McWethy Troop Medical Clinic (TMC) and battalion aid stations (BAS) for other non-respiratory conditions [n=183, mostly injury-related, 120 (66%) non-ARD controls]. The age distribution of the three groups was similar, however, females were found to be at significantly lower risk of ARD hospitalization than males (OR = 0.47, 95% CI = 0.25,0.87). In addition, smokers were also found to be at higher risk of ARD hospitalization than non-smokers (OR = 1.89, 95% CI = 1.03,3.50). Stratified analysis controlling for gender continued to demonstrate smoking as a risk factor. No major differences in personal hygiene habits were noted between cases and controls.

Air sampling performed at two of the unit barracks involved in the outbreak identified high levels of carbon dioxide, indicative of poor ventilation (especially evident during recruit sleeping times) and may have been a possible environmental risk factor for ARD. Future efforts in the area of Adv prevention, to include vaccination, were identified. Vaccination of all recruits (male and female) was started in early November 1997 and resulted in a significant reduction in ARD and Adv rates.

Subsequent to this investigation, final EPICON team recommendations were developed and discussed with the MEDDAC Commander, COL William Bester and the DCCS, COL Steve Oswald as well as 1st and 4th Tng Bde officials on 31 August 1998. The Commanding General, MG John VanAlstyne, was provided a final briefing on 2 September 1998. The following recommendations were made at that time:

1) continue to provide emphasis on ARD surveillance and adenovirus lab-based surveillance at Fort Jackson to include dedication of funding and manpower resources to maintain lab support at MACH and DDEAMC Virology Laboratory;

2) emphasize need for adherence to industrial hygiene indoor ventilation standards in order to reduce ARD risk in the barracks to include increased use of fans and enforcement of opening of windows in sleeping bay areas;

3) provide training cadre and recruits with increased-level education on how to prevent ARDs and appropriate personal hygiene measures such as mandatory handwashing (at least 5 times per day) and setting up of handwashing stations near the dining facility and training areas;

4) evaluate further the possible role of non-vaccine ARD interventions (NOVARDIs) in collaboration with MAJ(P) Roberto Nang and other DCPM/DEDS-USACHPPM and WRAIR investigators;

5) in collaboration with DEDS-USACHPPM and WRAIR scientists, consider the value of conducting a more comprehensive, prospective study of ARD and respiratory adenovirus infections among non-vaccinated recruits training in the fall and winter (Sept-Nov) of 1998; and,

6) give serious consideration to using Fort Jackson as a top candidate site for conducting future clinical and efficacy trials of candidate adenovirus type 4 (and possibly 7) vaccines being developed in support of the DoDs Adenovirus Vaccine Replacement Program (AVREP).

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1. REFERENCES. Appendix A contains references used in this report.

2. HISTORICAL PERSPECTIVE ON ADENOVIRUS AND ARD IN THE MILITARY.

Acute respiratory diseases (ARD) have long been a problem in military recruit populations (1). Defining the epidemiology of ARD in the military was begun in the midst of World War II, by members of the Commission on Acute Respiratory Diseases at Fort Bragg, NC (2). Prior to WWII, however, the notion that recruits experienced an unusually high incidence of ARD in contrast to "seasoned" troops had already been delineated by Dunham in 1938 (3). A suspected viral cause of ARD (later documented to be an adenovirus) was first recovered from surgically-removed human adenoids by Rowe and coworkers and reported in December 1953 as the "adenoid degeneration (AD) agent" (4). A month later, Hilleman and Werner independently reported the isolation of "respiratory illness agents" during a respiratory disease epidemic among recruits at Fort Leonard Wood, Missouri (5). This included the isolation of an agent, termed RI-67, later identified as adenovirus type 4. Subsequently in 1956, these group of viruses were collectively named adenovirus (Adv) by a committee chaired by Enders (6). With development of tissue culture and serologic tests, adenoviruses were eventually recognized to be the most widely recognized cause of ARD among military recruits (2). For years before its description as a separate agent, however, adenovirus-associated illnesses were recognized as a distinct acute, febrile or "grippe-like" syndrome which was clinically indistinguishable from influenza and which , in 10-25% of cases, could also cause a primary atypical pneumonia syndrome similar to that caused by *Mycoplasma pneumoniae* (2).

Because of factors such as overcrowding (7), frequent travel and contact with indigenous populations in endemic areas of the world (1), physical and mental stress (7), and lack of pre-existing immunity (8), military personnel are subject to respiratory disease epidemics. In the 1950s and 1960s, for example, up to 80% of ARD's in military recruits were due to adenovirus infections. Of these, 20% were hospitalized; ARD hospitalizations reached rates as high as 6 to 17 per 100 soldiers per month (9). Seasoned troops, however, continued to exhibit much lower rates of Adv-associated respiratory disease in military camps, quite possibly due to long-lasting immunity acquired early in military life, such as the first few weeks of initial entry or basic training (2).

ARD's also continued to be recognized for having a severe impact on training and military readiness. During epidemics, the loss of up to 40% of men in a training unit within a 2-week period, the requirement to restart training for those men who were hospitalized, and the hospitalization-associated costs presented real problems for which an immediate solution was urgently needed (10). Thus, a major vaccine development program was launched in the early 1960's. This program focused on producing a live, enteric-coated tablet that could produce asymptomatic enteric infections and which could also trigger an appropriate immune response to

eliminate the vaccine virus infection while at the same time provide long-term immunologic memory to resist future challenges with homologous (e.g. same serotype) strains (11).

By the early 1970's both types 4 and 7 vaccines were available and found to be efficacious when given in combination (12). Well controlled studies among military personnel conducted during the period of 1963-66 clearly demonstrated that use of these vaccines reduced ARD rates by approximately 50% and Adv respiratory infections by more than 90% (13). Thus, in 1971, the Department of Defense (DoD) began routine use of types 4 and 7 vaccines which resulted in a drastic reduction in Adv types 4 and 7-associated ARD in recruits (14). Initially the vaccines were administered during the high-risk winter months only, but, the occurrence of spring and fall outbreaks prompted a change to a year-round policy in 1984 (15). At least two separate reports in the published literature have documented that the military adenovirus vaccination program is a very safe, cost-effective and extremely efficacious method of dealing with this problem (15,16). Given that rates of infection in adult and college-age civilian populations are very low (only 0.5-3% of respiratory pathogens detected) there have been no equivalent efforts to protect civilian populations using Adv vaccines (13).

A problem in production and procurement of vaccine led to a short-term outbreak of type 4 disease at Fort Jackson in the Spring of 1995 (17). One year later, the sole Adv vaccine manufacturer (Wyeth Laboratories) discontinued production (8). Shortage of vaccine caused the US Army to begin vaccinating recruits only during the high-risk season for ARD, October through March. This resulted in peaks of ARD and Adv rates throughout US Army basic combat training (BCT) sites in 1996-97 (1,17,18). One large outbreak of Adv type 4 was thoroughly investigated by USACHPPM and Walter Reed Army Institute of Research (WRAIR) scientists during the period of October and November 1998 (19). These peaks, or mini-outbreaks, were controlled by resuming the vaccination program during high-risk months. Available stocks of Adv vaccine, however, have been utilized and will expire later this year. The DoD is presently attempting to find a new manufacturer so as to limit the time these vaccines will be unavailable (13, Binn L, personal communication).

As described above, adenovirus vaccine types 4 and 7 are the primary means for controlling ARD due to adenoviruses in the U.S. military (13). However, given the shortage and non-availability of these vaccines in the near future, we also wanted to examine the role that personal hygiene practices, type of ventilation systems, type of barracks and indoor air contaminants would have on ARD rates at Fort Jackson, in order to provide medical and post engineering authorities with alternative means of control. In the past, military training authorities have employed non-vaccine ARD interventions (NOVARDIs) consisting mainly of: 1) administrative measures, 2) adherence to industry-accepted standards for heating, air conditioning, and ventilation systems, and 3) enforcement of personal hygiene measures. Administrative measures such as the practice of cohorting (e.g. separate platoons of trainees training/sleeping separately), sleeping in alternate head-to-toe bed arrangements, and hanging sheets from the ceiling to establish barriers between beds, are aimed at reducing contact and transmission among trainees (13). In addition, there are military regulations limiting the density of troops in barracks (20). Additional risk factors increasing risk of ARD in recruits include billeting in enclosed ventilation systems in newly constructed, energy-efficient "Starship" type barracks (21) and clustering of sick recruits in bay areas (22). For practical purposes, however, environmental standards for indoor air temperature, humidity, contaminants, and air exchanges per hour are regulated in accordance with published guidelines which are not based on health-related outcomes (23).

Lastly, the role that personal hygiene measures (such as handwashing) have in decreasing risk of ARD agent transmission has only been well validated in health care settings (24) or in settings involving children (25). Handwashing intervention programs to decrease transmission of ARD agents in military recruits have only been evaluated once before, in an uncontrolled study design, at the U.S. Navy's Great Lakes Naval Training Center, Chicago, IL (26). Results of that study showed that ARD rates decreased for 2 consecutive years following implementation of an education program and mandatory handwashing 5 times-a-day. Many questions, however, still remain regarding this intervention, since potential confounders (such as gender and training unit of assignment) as well as year-to-year variation in ARD rates, were not controlled for in that study. Therefore, we also sought to examine the potential associations between levels of personal hygiene and ARD risk during our investigation.

3. INTRODUCTION TO THE PROBLEM.

The beginning of the 1997 ARD season hit Fort Jackson, South Carolina, particularly hard. Fort Jackson is the largest Army basic combat training (BCT) center. Gender-integrated training has been in place for the past 5 years and increases in ARD rates have been seen to occur for both males and females starting as early as May-June (18,27). Due to the vaccine shortages outlined above, medical authorities at Fort Jackson had stopped routine immunization for adenovirus types 4 and 7 on 31 March. A concomitant adenovirus laboratory-based surveillance program was initiated in late April 1997 in collaboration with laboratories at the Dwight D. Eisenhower Army Medical Center (DDEAMC), Fort Gordon, Ga (COL K. Mills McNeill), and the U.S. Naval Health Research Center, San Diego, CA (CAPT Gregory Gray).

4. OBJECTIVES OF THE EPICON. Concomitant with resumption of vaccination on 3 November, the assistance of an epidemiologic consultation (EPICON) team from the USACHPPM and WRAIR was requested by medical authorities at Fort Jackson on 13 November 1997 (see Appendix B). This EPICON was requested with the principal objective of implementing a plan for the collection of appropriate clinical specimens (throat swabs and paired sera) in Adv-affected patients hospitalized at Moncrief Army Community Hospital (MACH). These samples would permit WRAIR scientists to be able to validate end-point measures for evaluation of potential future replacement vaccines being developed under the auspices of the Adenovirus Vaccine Replacement Program (AVREP) mandated by the Assistant Secretary of Defense for Health Affairs (ASD-HA). Additional objectives of the investigation included: 1) assessment of the impact of ARD/ADV infections to the military recruit population at Fort Jackson; 2) investigation of the epidemiology of ARD in the recruit population to include an evaluation of risk factors for illness; and, 3) evaluation of the role of non-vaccine ARD interventions (NOVARDIs) in controlling ARD/Adv transmission in the recruit population. While at Fort Jackson, preliminary environmental assessments and tentative plans for future non-vaccine intervention strategies were also incorporated into the investigation.

5. COMPOSITION OF THE EPICON TEAM. At the request of COL Oswald, DCCS, MACH, the USACHPPM and WRAIR formed an EPICON team consisting of a group of experts in the areas of epidemiology, virology, infectious diseases and preventive medicine. The EPICON team members (less Dr. Binn) deployed to Fort Jackson during the periods of 16-26 November and 8-10 December 1997. Team members are outlined below:

a. COL Jose Sanchez, Team Chief, Epidemiology Services Program (ESP), Directorate of Epidemiology and Disease Surveillance (DEDS), USACHPPM.
b. Dr. Leonard Binn, Supervisor Research Virologist, Department of Virus Diseases, Division of Communicable Diseases and Immunology, WRAIR.
c. LTC Stephen Craig, Epidemiologist, ESP, DEDS, USACHPPM.
d. SGT Richard Reynolds, Medical Laboratory technician, Division of Preventive Medicine, WRAIR.
e. Mr. Terrence Lee, Epidemiologist, Disease and Injury Control Policy, Directorate of Clinical Preventive Medicine (DCPM), USACHPPM.
f. Mr. Jeffrey Marquez, ORISE Intern, ESP, DEDS, USACHPPM.

6. MATERIALS AND METHODS.

a. Laboratory Methods:

1) Adenovirus Antigen Detection Tests: Two separate new tests are being developed by Dr. Binn at WRAIR utilizing the clinical samples collected in this study. These tests were compared to the standard test, adenovirus culture in replicate tubes (n=2 to 4 tubes) of A549 cells fed weekly and examined for cytopathic effect (CPE) according to already published procedures (28). In the tube isolation test, culture fluids from tubes with 4+ CPE are harvested and the agent is identified by neutralization with reference antiserum. The semi-quantitative endpoint is expressed as negative (0) or positive by day 7 (3+), day 14 (2+), or day 21 (1+). The two new tests being developed at WRAIR are outlined in Table 1 below. For purposes of this report throat culture-positive specimens were those which were positive (1+ to 3+) in the standard A549 cell culture test.

Table 1. Adenovirus detection assays being developed at the WRAIR

Test	Purpose	Specimens required
Rapid plaque assay in A549 cells	Detection of adenovirus types 4 and 7 in body fluids	Throat swab
PCR for adenovirus types 4 and 7	detection of adenovirus types 4 and 7 in body fluids	Throat swab

2) Adenovirus antibody detection assays: Two separate new tests are being developed by Dr. Binn at WRAIR for detection of Adv-specific antibodies. These tests were compared to the standard test, the tube dilution neutralization test in A549 cells (28). In the tube dilution neutralization test, 2-fold dilutions of heat-inactivated test serum from 1:2 upwards are tested in duplicate for neutralization of 10 to 32 $CCID_{50}$ of virus (virus-serum reaction is allowed to go for 1 hour at 37^0C before inoculation). The endpoint titer is defined as the highest dilution affording complete protection against CPE in both tubes, and is read after 7 days. The two new antibody detection tests being developed at WRAIR are outlined in Table 2 below. For purposes of this report antibody-positive serum specimens were those which were positive (titer $\geq$ 1:4) in the standard tube dilution neutralization test.

Table 2. Adenovirus antibody detection assays being developed at the WRAIR

Test	Purpose	Specimens required
Plaque reduction neutralization test	Detection of virus-specific antibody to adenovirus types 4 and 7	Acute and convalescent serum with pre-infection serum if available
Colorimetric micro-neutralization test	Detection of virus-specific antibody to adenovirus types 4 and 7	Acute and convalescent serum with pre-infection serum if available

b. Study Case Definitions: A clinical ARD case was defined as any patient hospitalized with an ARD at MACH and seen by the EPICON team during the period of 17-25 November 1997. This group constituted the hospitalized ARD cohort. An ARD was defined as any patient suffering one or more respiratory symptoms (cough, runny nose, sore throat, headache, sinus pain, trouble breathing, runny eyes, stiff neck, ringing in the ears, trouble breathing, wheezing and dizziness), with or without the presence of a fever (oral temp $\geq$100.5 °F). A febrile ARD was defined as any patient with an ARD and an oral temperature of $\geq$100.5 °F. A clinical adenovirus-positive ARD case is one in which culture-positive samples are detected in throat swabs. A high adenoviral titer was defined as any serum sample with an endpoint titer of $\geq$ 1:32 on tube dilution neutralization test.

c. Clinical Data Collection: Epidemiologic and clinical data were collected on all hospitalized ARD cases seen at MACH (n=79). This information included a sick call questionnaire (see Appendix C) which provided demographic information and illness symptoms, smoking and immunization history. In order to maximize the yield, throat swabs (2 each time) were collected on each of the first 2 days of patient confinement. Initial acute (S_1) and convalescent (14 to 21 days later) sera (S_2) was also collected. Convalescent sera was collected in a follow-up visit conducted by COL Sanchez and SGT Reynolds during the period of 8 to 10 December 1997. This was possible because 62% (49/79) of the cases were initially seen during their 5-7th weeks of training and were still available 2 to 3 weeks later for follow-up. In addition, pre-accession serum specimens from a group of recruits surveyed as part of the case-control study (see below) were obtained later on in May-June 1998 from the DoD Serum Repository bank operated by the Army Medical Surveillance Activity (AMSA), DEDS, USACHPPM. These samples (n=76) were selected at random (anonymously) from the same unit in which the case-control study was performed and served to measure pre-existing (i.e. pre-outbreak) levels of adenoviral immunity in recruits at Fort Jackson. In addition, serum samples were also drawn on 121 recruits surveyed on-site during the investigation (see below); 78 of the 121 samples were tested for adenovirus antibody at WRAIR. A summary of specimen collection procedures is outlined in Table 3 below.

Table 3. Specimens collected during the EPICON investigation

Specimen	Collected when	Processing and storage
Pre-illness serum (S_0)	Accession physical exam	None; requested from serum bank, stored at -20°C
Serum (S_1)	Study day 1	Tiger top, clot RT 1-2h; 3 x 2 ml aliquots, stored at -20°C
Throat swab (T_1)	Study day 1	Prepared 5 x 1 ml aliquots, stored at 4°C
Throat swab (T_2)	Study day 2	Prepared 5 x 1 ml aliquots, stored at 4°C
Serum (S_2)	14-21 days after study day 1	Tiger top, clot RT 1-2h; 3 x1 ml aliquots stored at -20°C

d. Adenovirus (Adv) and ARD Surveillance Data Collection: Systematic surveillance of ARD incidence in U.S. Army BCT centers has been conducted since 1966 (9). Currently, each of the six BCT centers transmits data electronically to a central, automated Army ARD Surveillance System database (managed by the AMSA) on a weekly basis. The following data elements are reported for each training company: company identification, number of men and women assigned, number of male and female ARD cases hospitalized, and week of training. Initially, a separate database was developed on-site and original hard copy reports of the data corresponding to the period of April 1996 through July 1998 examined in collaboration with SPC Michael Escalera, PM technician, MACH (ARD reporting officer). This database was later amended by addition of routinely reported ARD data to the AMSA for the period of January 1996 through September 1999. In addition to ARD cases per week reported, results of viral isolations for adenovirus performed at DDEAMC laboratory were reviewed on-site with Ms. Johnnie Conolly (adenovirus project nurse) and entered into the same database for analysis of trends in ARD and Adv infection rates on-post.

e. Case-Control (Health and Hygiene) Study:

A case-control study was conducted comparing the 79 hospitalized cases (66 BCT recruits with a febrile ARD utilized for final analysis) to a total of 304 unit and MTF-based non-febrile ARD controls. Controls were selected at random from recruits surveyed at the 2/60th Inf Bn, one of the most affected units on-post [n=121, 69 (57%) non-ARD controls] as well as from recruits presenting to the McWethy Troop Medical Clinic (TMC) and battalion aid stations (BAS) for other non-respiratory conditions [n=183, mostly injury-related, 120 (66%) non-ARD controls]. These controls were not documented to be contacts (i.e. sleeping next to) any of the hospitalized cases among BCT recruits.

A pilot health and hygiene questionnaire was initially administered to 20 new patients on the ARD ward on 17 November 1997. This questionnaire was subsequently revised and the final version (see Appendix D) was administered to all 79 hospitalized patients during the period of 18-25 November 1997. In-hospital cases were interviewed individually or in a group upon hospital admission. Controls were administered a similar questionnaire as a group in class (unit survey done on 18-19 November 1997) or individually (TMC/BAS patients seen on 19-20 November 1997). All control questionnaires were answered anonymously without personal identifiers in order to preserve confidentiality and ensure more reliable reporting of risk factors. In addition, serum samples were collected on all 121 unit controls but not in any of the 183 TMC/BAS controls interviewed. No viral isolations were performed on any controls.

We also attempted to discern the effect of handwashing and personal hygiene habits in a more informal fashion. Open-ended conversations were conducted by one of the EPICON team members (Mr. Lee) with at least 12-15 recruits and 5-6 trainers (drill sergeants) in order to assess hygiene habits, handwashing practices, availability of soap and towels in bathrooms, and availability of handwashing stations at the dining facility and field training sites frequented by recruits.

f. Environmental (Indoor Air Quality) Data Collection: In addition to the clinical data, environmental data was also collected by Mr. Greg Shepherd, Industrial Hygienist, MACH. Overnight sampling for CO_2 indoor levels (in ppm), room temperature (in ^{o}F) and relative humidity (in %) were conducted every 15 minutes for a 48-hour period at 3 platoon sleeping bay area locations during the period of 20-25 November 1997. Two platoon sleeping bay areas (one

with males only-A Co, 3rd Plt; one with females only-D Co, 1st Plt) were surveyed at the same battalion where the unit health-hygiene survey was conducted in (2/60th Inf Bn) in. The third platoon sleeping bay area was selected at random from a training unit housed in a "non-Starship" or "Rolling Pin" type barrack (2/39th Inf Bn, B Co, 4th Plt).

g. Data Analysis: Data were coded in a computer database utilizing existing software (SPSS version 7.5, SPSS Inc., Chicago, IL). Univariate analysis was performed and odds ratios (OR) and associated 95% confidence intervals (95% CI) estimated. Stratified analysis (on gender) was performed for the association of smoking with ARD. All significance testing (P values) was done in two-sided fashion.

7. RESULTS.

a. General: A total of 383 individual recruits were interviewed and sampled during the EPICON. This included 79 hospitalized ARD cases (66 recruits meeting the strict febrile ARD case definition), 121 unit controls surveyed at the 2/60th Inf Bn (69 served as non-ARD controls), and 183 controls interviewed at the local TMC and BAS (120 served as non-ARD controls). See Table 4 below. As expected all 3 groups were similar in age distribution. Significantly ($P < 0.05$) more cases were of male gender. In the comparison of all 79 hospitalized ARD cases with all 304 controls interviewed we found that the risk of an ARD for males was approximately 2 times that for females [unadjusted Odds Ratio (OR) = 2.03, 95% CI= 1.19,3.50). Smokers were also found to sustain an higher ARD risk which was 1.5 times that of non-smokers (OR = 1.47, 95% CI = 0.87,2.48).

Table 4. Demographic Characteristics of the study populations.

		Hospitalized ARD Cases (n=79)	**Unit Controls (n = 121)**	**TMC/ BAS Controls (n=183)**	**Unadjusted OR (95% CI) Cases versus All Controls**
Age	Mean (Median)	19.7 (19)	20.6 (20)	20.8 (19)	Not Applicable
Gender	Male Female	50 (63%) 29 (37%)	55 (45%) 66 (55%)	84 (46%) 98 (54%)	2.03 (1.19,3.50)
Current Smoking	Yes No	39 (49%) 40 (51%)	47 (39%) 74 (61%)	74 (41%) 108 (59%)	1.47 (0.87,2.48)

TMC/ BAS = Troop Medical Clinic and Battalion Aid Station controls; OR = Odds Ratio (95% confidence interval)

b. Hospital Cohort and Febrile ARD Hospitalization Rates:

A total of 79 inpatient ARD cases were evaluated during the period of 17-25 November 1997. Of these, 50 (63%) were male; the admission rate (AR) for males was found to be 1.1% (50 cases in 4,468 trainees) compared to that of females which was 0.8% (29 cases in 3,665 trainees). The relative risk for admission, therefore, was 1.4 times higher for men than women (95% CI = 0.88,2.32).

See Table 5 below. Approximately 72% were in the latter half of BCT when admitted to MACH. The peak of case admissions occurred during training weeks 5-7 of BCT; roughly two-

thirds of cases were admitted at this time. The admission rate during weeks 5-7 (50 cases in 2,647 recruits, AR=1.9%) was found to be significantly higher than that for earlier weeks or week 8 of BCT (16 cases in 2,305 recruits, AR=0.7%). The relative risk for admission was, therefore, approximately 2.7 times higher (95% CI = 1.52,5.12) for recruits undergoing weeks 5-7 of BCT. Lower ARD admission rates were seen for those recently arrived into the 120th Reception Battalion (2 cases in 826 recruits, AR=0.2%) or for students undergoing Advanced Individual Training (AIT, 11 cases in 2,355 students, AR=0.5%).

The most affected units (battalions) included the 2/60th Inf (AR=2.1%), the 2/39th Inf (AR=1.7%), the 2/13th Inf (AR=1.5%) and the 1/34th Inf (AR=1.2%). Significantly lower rates were seen in the two AIT units (AR=0.5%), the 120th Rec Sta (AR=0.2%) and in the recently constituted 1/61st Inf (AR=0.2%) undergoing week 2 of BCT. See Table 6 below.

Table 5. Week of Training recruits were hospitalized.

Week of Training	Hospitalized (n=79)	Percent of Total
Rec Sta	2	2.5
3	4	5.1
4	5	6.3
5	**17**	**21.5**
6	**19**	**24.1**
7	**14**	**17.7**
8	7	8.9
AIT	11	13.9

Table 6. ARD Hospitalization Rates by Unit.

Battalion	Hospitalized ARD Cases (n=79)	Total Trainee Population (n=8,133)	Percent Hospitalized
2/60th Inf	19	891	2.13%
2/39th Inf	19	1,089	1.74%
2/13th Inf	13	883	1.47%
1/34th Inf	13	1,120	1.16%
369th AG	6	1,171	0.51%
187th Ord	5	1,184	0.42%
120th Rec Sta	2	826	0.24%
1/61st Inf	2	969	0.21%

See Table 7 below. By definition, all recruits hospitalized and considered as febrile ARD cases had a recorded oral temperature on admission of at least 100.5 ^{0}F. Eleven of the febrile ARD cases were in AIT students and an additional 2 were in recently arrived recruits at the 120th Reception Battalion (i.e. probably acquired their ARD prior to arrival at Fort Jackson). Headache and sore throat were the most common symptoms with over 90% of hospitalized cases

reporting them. Cough, runny/stuffy nose, hoarse voice, muscle aches and dizziness were reported in over two-thirds of cases. Few patients had complaints of lower respiratory tract compromise as reflected by symptoms of chest pain, trouble breathing or wheezing. No cases of pneumonia were detected in this group of patients.

Table 7. Symptoms exhibited by hospitalized patients.

Symptom Reported	No. Hospitalized Cases with Sx	Percent of Total
Fever	79	100
Headache	73	92.4
Sore Throat	73	92.4
Cough	71	89.9
Runny/ Stuffy Nose	70	88.6
Hoarse Voice	57	72.2
Muscle Aches	53	67.1
Dizzy	53	67.1
Sinus pain	34	43.0
Stiff Neck	34	43.0
Chest Pain	30	38.0
Runny Eyes	26	32.9
Ear Ache	25	31.6
Trouble Breathing	23	29.1
Wheezing	15	19.0
Ringing Ears	13	16.5

Febrile ARD patients had an average of 7.3 total sick days (see Table 8 below) with a longer period of illness for females (8.8 days) than males (6.5 days). Females also waited longer (4.5 days) than males (3.1 days) before seeing a health care provider for an ARD-like illness. Continuing this trend, females were also sick longer before being hospitalized for their illness. Once hospitalized, both males and females spent essentially the same number of days in the hospital.

Table 8. Average Clinical Course for ARD Patients.

Illness Period	Male	Female
Days sick before MTF[1] visit	3.1	4.5
Days sick before MTF Hospitalization[2]	0.6	1.4
Days Hospitalized at MACH	2.8	2.9
Total Days Sick	6.5	8.8

[1] Military Treatment Facility;

[2] After MTF visit until hospitalization

c. Adenovirus Isolation Rates in Patients: Seventy-nine sets of throat swabs (2 swabs per patient) were taken on each of 2 days from all hospitalized febrile ARD cases. Of these, 71 (90%) of 79 were culture-positive for an adenovirus-like agent. Nineteen of twenty isolates were typed at WRAIR and all were found to be Adv type 4 (note: the 20th specimen was negative for adenovirus on initial isolation and in the identification test). There was no difference in isolation rates between male and female patients.

d. Anti-adenovirus Antibody Seroconversion Rates in Patients: Acute and convalescent sera were tested using serum neutralization (SN) assays for the presence of antibodies to Adv type 4 (see Table 9 below). A total of 37 (47%) of the 79 patients who had paired sera drawn were tested. Of these, 30 (81%) demonstrated a four-fold rise in antibody titer to Adv type 4. See Table 9 below. All but one of the 31 individuals with a preceding (acute) low titer (titer $\leq$ 1:16) were found to seroconvert as compared to none of the 6 patients who had high titers (titer $\geq$ 1:32).

Table 9. Hospital Patients - Adenovirus Type 4 Serum Neutralization Tests Results

Acute (baseline) SN Titer	No. Patients Tested	No. Four-fold Rises	Seroconversion Rate (%)
< 1:4	22	21	95.5
1:4 – 1:16	9	9	100
$\geq$ 1:32	6	0	0
Total	37	30	81.1

e. Pre-existing Level of Immunity in Recruits:

Recruits' level of immunity upon entry into BCT was estimated from samples obtained from the DoD Serum Repository (n=76). Additionally, 78 of 121 samples collected from recruits during the unit survey and all acute samples on the 79 hospitalized ARD patients were compared. See Table 10 below.

Pre-existing immunity to Adv type 4 was found to be present in only 17 (22%) of 76 incoming recruits. Likewise, pre-existing immunity in non-hospitalized recruits already undergoing training at Fort Jackson was found in only 12 (15%) of 78 recruits tested. By comparison, the level of immunity on admission of ARD patients to the hospital was found to be 42% (33 with type 4 antibody out of 79 acute samples tested). Therefore, it can be deduced that the infection rate with Adv type 4 at Fort Jackson is in the range of 20-27% by weeks 3 to 4 (i.e. the difference between prevalence for inpatients upon admission to the hospital and the prevalence of recruits prior to or immediately upon arrival at the training unit). There were no gender-related differences in baseline immunity; out of 78 recruits surveyed, 6 (18%) of 33 males and 6 (13%) of 45 females were immune.

Table 10. Estimates of immunity to Adenovirus type 4 upon entry and during outbreak, Fort Jackson, SC, November 1997.

Sample Source*	No. Collected	No. Tested	No. Positive (titer ≥ 1:32)	Seropositivity
Pre-accession (DoDSR)	76	76	17	22.4%
Hospitalized ARD Patients (acute)	79	79	33	41.8%
Unit Survey (2/60th Inf Bn)	121	78	12	15.4%

*See text for details.

f. Adenovirus and ARD Surveillance Data Analysis:

As illustrated by the epidemic curve below (Figure 1), Adv isolation rates increased steadily from May until November 1997. Adv type 4 respiratory disease was first detected in late May and type 4 isolations quickly increased to a peak of approximately 2.5% per month during the months of October and November 1997 (18). The concomitant increase in ARD rates, however, did not exceed the "outbreak" threshold of 1.5% per week. In order to combat this continuing increase, routine Adv immunization was restarted on 3 November 1997; a rapid decrease in ARD and Adv rates subsequently followed with the last isolate of Adv type 4 seen in December 1997 (18). A resurgence of Adv-related ARD was noted to occur again starting in July 1998 after cessation of vaccination in late March 1998.

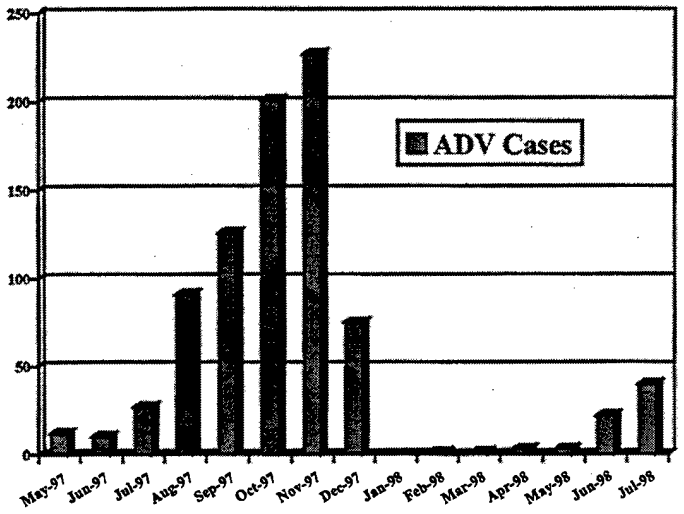
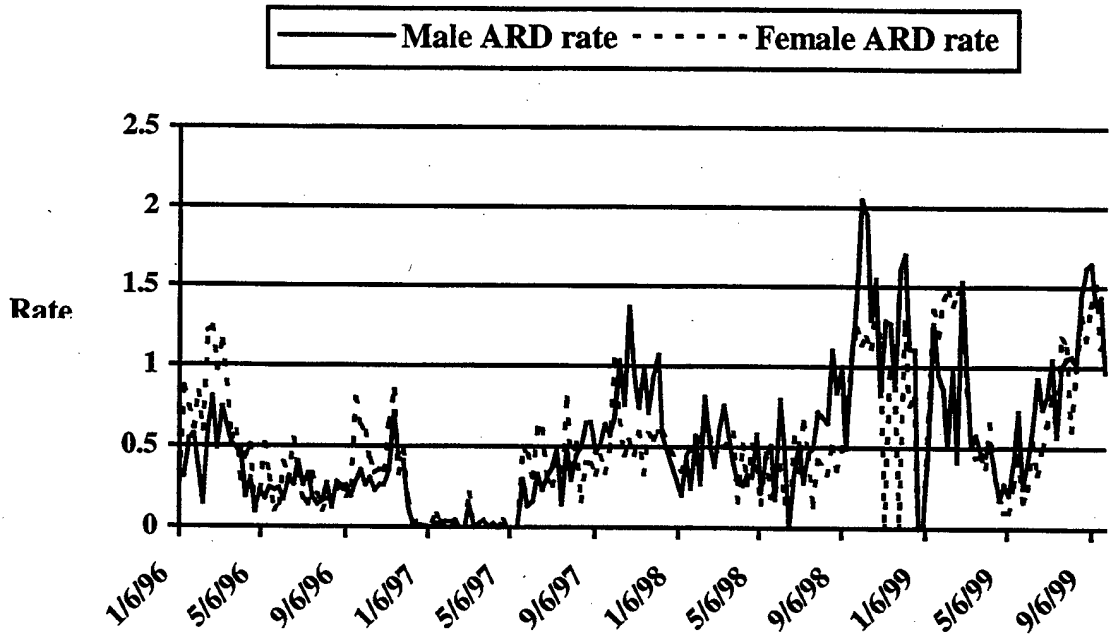


Figure 1. Epidemic Curve of Adenovirus Cases at Fort Jackson, SC, May 97-July 98

See Figure 2 below. Routine surveillance for ARD hospitalizations for the period of January 1996 through September 1999 shows marked seasonal variations in ARD incidence with higher rates in the late fall and winter months (Oct-Nov 97, Oct-Nov 98, Feb & Sep 99). Post-wide ARD hospitalization rates in males appear to peak in October and November and never exceeded 1.5% per week in 1996-97; male rates exceeded the threshold in 7 different weeks in Oct-Nov 98 , Feb 99 and Sep 99. By comparison, rates in females tend to be lower throughout the year and only exceeded the threshold of 1.5% per week on two occasions (Feb and Sep 99). An increasing trend in rates from the period 1996-97 to the period of 1998-99 is evident. This is probably associated with cessation of routine Adv vaccination in 1996-97.

Figure 2. ARD Hospitalization Rates by Week and Gender
Fort Jackson, SC, January 1996 to September 1999



See Figures 3 and 4 below. Although the post-wide ARD hospitalization rate never exceeded the threshold of 1.5% per week in 1997, we found a number of occasions where clusters (3 or more) of ARD hospitalizations as well as Adv-associated ARD hospitalizations occurred. At the training company level ARD attack rates exceeded the outbreak threshold of 1.5% per week in a total of 32 separate instances. In seven of these company-sized ARD outbreaks, attack rates as high as 5-10% per week were noted to occur. Likewise, Adv-associated clusters were noted in twelve separate instances during the months of August and September 1997. In three of these clusters, the Adv-confirmed attack rates were noted to be as high as 8 to 10% per week.

Figure 3. Adenovirus Clusters by Company, May-September 1997, Fort Jackson, SC

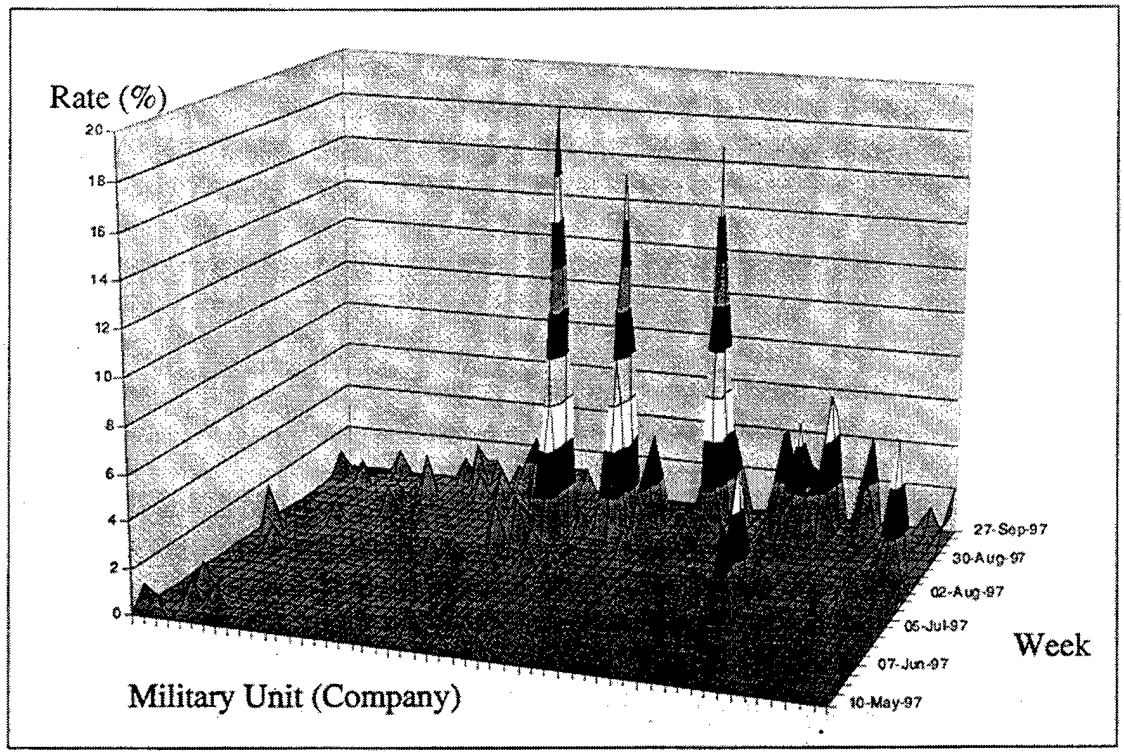
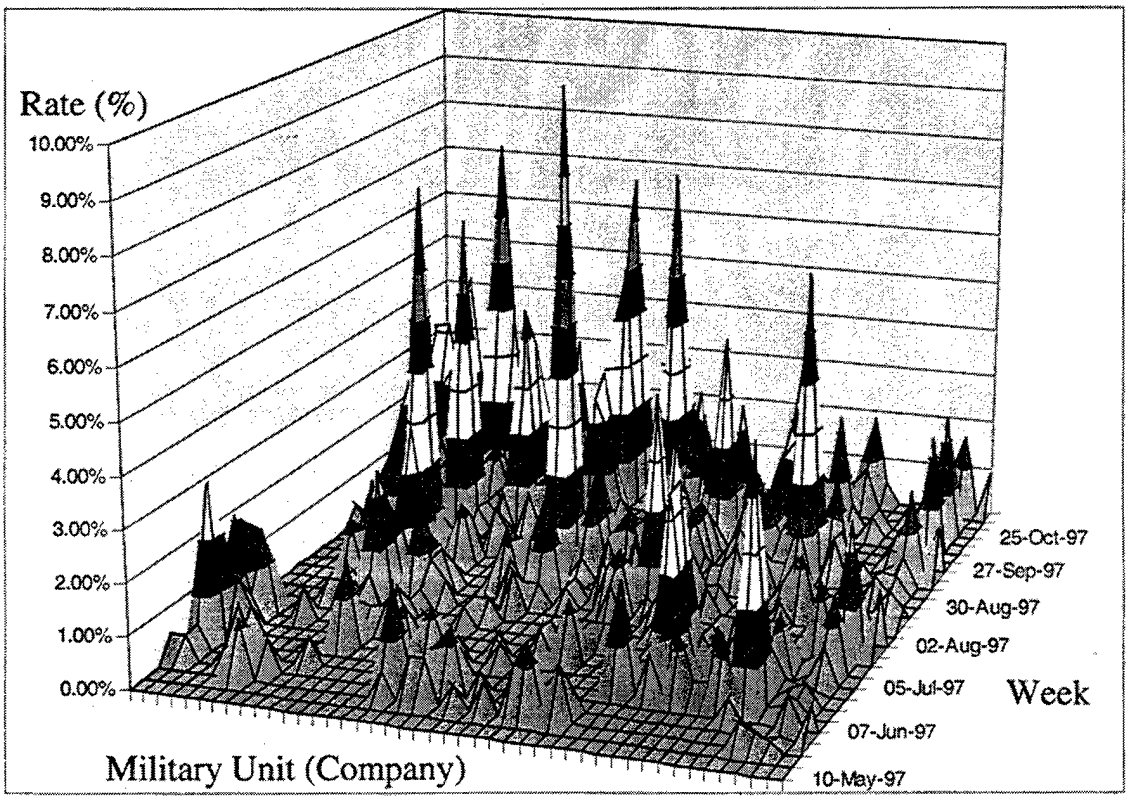


Figure 4. ARD Clusters by Company, May-November 1997, Fort Jackson, SC



Introduction of Adv type 4 was noted to occur in, at least, six separate instances during the 5-month period examined (May-Sept 97). These Adv culture-positive recruits, who had just arrived on-post and were assigned to the 120th Reception Station, were hospitalized within 2 to 3 days of arrival at Fort Jackson. Three of these six culture-positive recruits were detected during the month of May 1997. Thus, it is very possible that these individuals may have introduced the virus on-post.

ARD hospitalization rates were significantly higher (more than twice) for battalions in the 1st Training Brigade (0.95% per week) as compared to battalions in the 4th Training Brigade (0.44% per week) throughout the May through December 1997 timeframe ($P < 0.05$). By comparison, ARD hospitalization rates were similar at the 120th Rec Sta and significantly lower in AIT units (0.19% per week). Likewise, the Adv isolation rates among hospitalized patients from the 1st Training Brigade (42%) were also higher ($P < 0.05$) than those seen for patients from the 4th Training Brigade (34%), AIT units (24%) or the 120th Rec Sta (8%). Similar ARD hospitalization rates were noted for recruits housed in "Starship" type barracks (0.53% per week) when compared to those billeted in the older "Rolling pin" style barracks (0.50% per week).

This outbreak's impact in terms of hospitalization days and lost training time was immense. We estimated that over 2,000 hospital days were accrued by over 700 Adv-confirmed cases admitted to MACH (based on an average hospitalization stay of 3 days per patient, see Table 8 above). The impact is illustrated in Table 11 below.

Table 11. Impact of Adenovirus Outbreak, May – December 1997, Fort Jackson, SC

Unit	Cases	Estimated Hospital Days
120th Rec Sta	15	45 days
1st Tng Brigade	435	1305 days
4th Tng Brigade	240	720 days
AIT Units (2)	69	207 days
Totals	**759**	**2,277 hospital days**

g. Case-Control Study:

As illustrated in Table 12 below, approximately 30 to 42% of study controls reported a febrile illness of any kind during BCT. These febrile illnesses went largely unreported to health care providers and were considered to be minor and self-limited in nature. It is likely that many of these mild febrile illnesses may have been precipitated by extremes in physical stress, exertion, as well as changes in routine dietary and sleeping habits. Approximately 50% of cases and controls interviewed reported some type of self-medication for these symptoms while at Fort Jackson. The more commonly used agents were non-steroidal anti-inflammatory drugs (NSAIDs) and antipyretics such as acetaminophen or aspirin.

Table 12. Comparison of Illness Profile between Study Cohorts.

Prevalence of:		**Hospitalized** (n=79)	**Unit Controls** (n = 121)	**TMC/ BAS Controls** (n=183)
Fever[1]	Yes	79 (100%)	51 (42%)	54 (30%)
	No	0 (0%)	70 (58%)	129 (70%)
Febrile ARD[2]	Yes	79 (100%)	51 (42%)	54 (30%)
	No	0 (0%)	70 (58%)	129 (70%)
Self Medication	Yes	31 (39%)	67 (55%)	56 (31%)
	No	48 (61%)	54 (45%)	126 (69%)

[1] Fever in hospitalized cases is defined as an oral temperature of ≥ 100.5 °F; in unit and BAS/TMC controls it is self-reported.

[2] Febrile ARD (Acute Respiratory Disease) includes: Fever with one or more of following respiratory symptoms: cough, runny nose, sore throat, headache, sinus pain, trouble breathing, runny eyes, stiff neck, ringing in the ears, trouble breathing, wheezing and dizziness.

TMC/ BAS = Troop Medical Clinic and Battalion Aid Station controls; NA = No data available.

Demographic, smoking history and personal hygiene factors were examined in BCT recruit cases who met the febrile ARD case definition (n=66). The remaining 13 hospitalized cases who did not meet our stricter case definition for the case-control study were non-recruits who were undergoing AIT training (n=11) or had just arrived at Fort Jackson and were at the reception station (n=2) awaiting assignment to a BCT training battalion. Table 13 below presents the summary of the case-control study findings comparing the 66 hospitalized ARD cases in recruits with two sets of non-ARD controls, those recruits interviewed/surveyed at the unit-level (n=69) as well as recruits presenting for care of non-ARD related conditions at the local Troop Medical Clinic (TMC) and battalion aid stations (BAS) on-post (n=120).

Table 13. Summary of Case-Control Study Findings, Comparison of Hospitalized ARD Cases (n=66) with Unit (n=69), and TMC/BAS (n=120) non-ARD controls.

Variable	Type[1]	Type of Analysis	Type of Controls		
			Unit	TMC/ BAS	Both
Age	Cont.	Compare Means and Distribution[2]	19.6 (2.50) vs 20.7 (3.4)	19.6 (2.50) vs 21.1 (3.71)	19.6 (2.50) vs 20.9 (3.60)
Gender	Dich.	OR (Female vs Male)	0.75 (0.35,1.57)	**0.34 (0.17,0.67)**	**0.47 (0.25,0.87)**
Smoking Status	Dich.	OR (smoker vs non-smoker)	2.00 (0.94,4.26)	1.84 (0.95,3.56)	**1.89 (1.03,3.50)**
How many times do you wash your hands per day?	Cont.	Compare Means and Distribution[2]	5.3 (3.96) vs 3.2 (1.45)	5.3 (3.96) vs 4.0 (2.03)	5.3 (3.96) vs 3.72 (1.88)
What % of time do you use soap when wash your hands?	Cont.	Compare Means and Distribution[2]	79.2 (28.29) vs 45.8 (31.38)	79.2 (28.29) vs 62.2 (33.45)	79.2 (28.29) vs 56.1 (33.57)
When you use soap, how many seconds do you spend rubbing your hands?	Cont.	Compare Means and Distribution[2]	13.08 (8.82) vs 15.32 (23.34)	13.08 (8.82) vs 18.59 (16.19)	13.08 (8.82) vs 17.4 (19.1)
In the barracks, how do you usually dry your hands?	Disc.	OR (towel vs "Air-Dry")	1.50 (0.67,3.40)	1.10 (0.52,2.09)	1.02 (0.52,2.09)
In the barracks, how do you usually dry your hands?	Disc.	OR (clothes vs "Air-Dry")	0.95 (0.19,4.57)	1.75 (0.86,2.56)	2.51 (1.29,4.93)
What % of time have you covered your mouth when cough /sneeze?	Cont.	Compare Means and Distribution[2]	93.0 (12.01) vs 79.17 (23.96)	93.77 (12.01) vs 89.39 (16.1)	93.77 (12.01) vs 85.6(23.0)
How do you usually cover your mouth when you cough/ sneeze?	Disc.	No analysis because no baseline exposure; Not a risk factor for individual but for those around the individual	NA	NA	NA
How do you usually scratch/rub/wipe your nose?	Disc.	OR (tissue vs finger/hands)	1.29 (0.56,2.99)	0.69 (0.30,1.56)	0.84 (0.41,1.73)
How do you usually scratch/rub/wipe your nose?	Disc.	OR (sleeve vs finger/hands)	1.96 (0.57,6.95)	0.35 (0.13,0.94)	0.62 (0.24,1.55)
Do you pick your teeth with your fingers more than once a day?	Dich.	OR (pick teeth vs no pick teeth)	0.50 (0.15,1.56)	0.49 (0.17,1.39)	0.50 (0.18,1.32)
Do you pick your nose more than once a day?	Dich.	OR (pick nose vs no pick nose)	0.72 (0.23,2.25)	1.73 (0.53,5.60)	1.05 (0.38,2.80)
Have you shared any canteen, cup, face/ hand/ body towel?	Disc.	OR (those who shared anything vs those who did not share)	0.46 (0.21,1.02)	1.48 (0.68,3.20)	0.90 (0.45,1.78)

TMC/ BAS = Troop Medical Clinic and Battalion Aid Station controls; OR = Odds Ratio (95% CI); NA= not applicable; **boldface type** represents statistical significance at the $P < 0.05$ level.
[1]Cont. = Continuous; Dich. = Dichotomous; Disc. = Discrete; [2] Mean (SD) for cases vs. controls

The age distribution of the three groups was similar, however, females were found to be at significantly lower risk of ARD hospitalization than males (OR = 0.47, 95% CI = 0.25,0.87). In addition, smokers were also found to be at higher risk of ARD hospitalization than non-smokers (OR = 1.89, 95% CI = 1.03,3.50). Stratified analysis controlling for gender continued to demonstrate smoking as a risk factor.

Cases reported a higher frequency of handwashing and use of soap, however, they also reported a shorter time for lathering (differences not statistically significant). Methods used for hand drying such as "air drying" or "shake drying" were similar in all groups. As expected, cases reported covering their mouths while sneezing and coughing more often than controls. Lastly, no differences were seen in methods or frequency of nose scratching, rubbing or wiping; picking teeth with fingers; nose picking, or, sharing of personal items such as canteens, cups, or towels.

h. Other Important Observations:

It should be noted that less than 5-10% of recruits informally interviewed by one of us (Mr. Lee) reported being made aware by training cadre of the need to practice frequent hand washing. Head-to-toe arrangement of sleeping bay bunk beds was noted to be enforced as well as general cleanliness of sink areas and showers. Unfortunately, we did not find soap to be readily available in the sinks and no hand washing facility was noted near the dining facility (mess hall).

The windows in the sleeping bay areas were very often noted to be closed even though trainees are instructed to leave every other window open during the day to increase air circulation. Likewise, large room fans used to circulate air were noted to be turned off during peak periods of occupancy in the evenings. We also noted that minimal mixing occurs between trainees in different training companies; interactions occur principally in the dining facility, hospital and during recreational activities.

i. Environmental (Indoor Air Quality) Data: Levels of CO_2 in "Starship" type barracks ($2/60^{th}$ Inf Bn) were noted to consistently exceed NIOSH threshold limits of 1,000 ppm throughout sleeping hours. Peak levels occurred during troop concentration times at 2100 and 0500 hrs. Similar elevated CO_2 indoor levels were detected in "Rolling pin" type barracks surveyed ($2/39^{th}$ Inf Bn). In general, the CO_2 threshold level is exceeded whenever greater than 40 trainees occupy the sleeping bay area; peak levels are reached rapidly within 15-30 minutes of entry. See Appendix E for results of indoor air quality monitoring.

8. DISCUSSION.

Acute respiratory diseases and especially, adenovirus, have re-emerged as a significant and serious problem in recruit healthcare (1). Increasing susceptibility in young adults due to lack of exposure in childhood is a principal factor in the resurgence of adenovirus infections in US military personnel, particularly trainees. Previous seroepidemiologic studies conducted 35-40 years ago in the US and England seemed to indicate that Adv types 4 and 7 infected children less often than other serotypes (29,30). More recently in 1992, in a seroepidemiologic study of Army recruits conducted by Ludwig et al, it was estimated that nearly 90% of incoming recruits were non-immune to Adv types 4 or 7 (8). The low level of pre-existing immunity documented among recruits during our investigation (15-22%) further highlights the increasing risk for adenoviral-associated respiratory illness for young adults in the US. It appears that in the subsequent 5 years after Dr. Ludwig's study the prevalence of antibodies to Adv type 4 has continued to decrease to alarmingly low levels.

The same risk factors for Adv respiratory tract infection which were identified more than 50 years ago by the Commission on Acute Respiratory Diseases at Fort Bragg (2) continue to be present today. The lack of prior military experience of unseasoned troops (2,8), increased time spent indoors with increased transmission of many respiratory infections (31), overcrowding in barracks (1,13,33), training during the winter months (2), introduction and rapid circulation of adenoviruses among a highly-susceptible population (2,8), and poor personal hygiene (26,33) continue to predispose recruits to continued outbreaks of Adv-associated respiratory infections.

In addition to the military experience above, increased reporting of Adv-associated infections among US civilians has occurred. Adenovirus disease outbreaks have recently been identified among adult civilians at a job training facility (32), among staff and patients at a chronic care psychiatric facility (33), among bone marrow transplant (BMT) recipients (34), and among infants and staff at a chronic care facility (35). A similar pattern has also been observed in Japan where reports of endemic Adv type 7 respiratory disease (36) and hospital-acquired Adv type 7 infections (37) have increased since 1995. Thus, it may be inferred that our observations among young adults entering military service constitutes a reflection of a much larger, and greatly under-recognized, problem in civilians in this country and elsewhere.

The clinical and laboratory data presented herein and the reported estimates of morbidity levels seen during our 1997 outbreak investigation at Fort Jackson significantly expand on previously published data (1,17-19,22,27). In our hospital case series of 79 febrile acute respiratory disease (ARD) patients we found a very high rate of Adv infection; 71 (90%) of these patients were infected with an adenovirus (principally type 4). We also found a strong correlation between levels of serum neutralization (SN) test titers (i.e. titers less than 1:32) and susceptibility to illness among patients. Lastly, we found that a SN test titer of 1:32 or higher correlated well with protection from adenovirus infection (as determined by lack of seroconversion). If the results documented in this investigation can be reliably reproduced in ongoing studies with recruits and human volunteers, perhaps the SN test we used may reliably distinguish infected from non-infected persons. This serodiagnostic tool could very well form the basis for the work-up and definition of future Adv outbreaks and could also form the basis for determination of immunogenicity and efficacy of future adenovirus vaccine products.

Our finding that female recruits were at a lower risk (OR=0.43) of hospitalization for an ARD was somewhat unexpected. A male predisposition to human adenovirus infection has been reported infrequently before (38) and has never been well documented among military personnel. The reason(s) for this increased risk among males is(are) unknown. In their initial and brief summary report of this outbreak at Fort Jackson, McNeill and collaborators did not find this association when they examined trends in ARD hospitalizations among recruits (18). It would have been possible to better assess this gender-associated risk by looking at serological (rather than clinical) rates of infection during our investigation, Unfortunately, and as often happens during the course of an epidemic, we could not obtain appropriate "baseline" and post-exposure serum samples in our large cohort since we arrived after the epidemic peak, and immediately after resumption of the vaccination program on-post. We are presently trying to corroborate these findings by conducting a larger, more intensive, prospective seroepidemiologic study of a vaccine-free cohort of recruits at Fort Jackson (19,22).

The association we found between cigarette smoking and an increased risk of ARD hospitalization among US military recruits (OR=1.89) is new, but, hardly surprising. A military physician, Major Joseph John, first raised questions regarding this possible association more than 20 years ago, at a time when he supervised a hospital ward for recruits with ARD (39). Several prior studies have shown an association between cigarette smoking and reported or recorded acute respiratory disease in young people, predominantly males (40). In other selected military populations, increased risk of ARD illnesses (to include influenza but not adenovirus) in smokers has been documented among military cadets (41), in British Army personnel (42), and in two separate male and female recruit camps in Israel (43,44). Thus, it is clear that additional studies are needed to better define the relationship between smoking habits and ARDs (and adenovirus infections) among recruits in the US.

We found little difference between cases and controls in respect to personal hygiene practices although our method of investigating hygienic practices had limitations. Inherently, the self-administered questionnaire which was used in the case-control study, was a poor tool for assessment of hygiene habits. Subjects were probably more likely to report current "now" behaviors as opposed to the behaviors at the time immediately before the outbreak. Subjects may have been unlikely to recall accurately or may have not been truthful about many of their habits on the questionnaire since the subjects may have believed that their responses would affect their rating and treatment during training. A method to accurately determine personal hygiene practices has yet to be developed; further research in this area is warranted.

Our study found that cases washed their hands more frequently and more frequently with soap (albeit not statistically significant). We were unable to determine the role of handwashing in transmission of ARDs but despite the lack of findings in our study and despite the paucity of epidemiological evidence that handwashing decreases transmission of respiratory disease, handwashing has its merits. Handwashing is an inexpensive intervention that has been shown to decrease gastrointestinal and other infectious disease transmission and there is strong theoretical and experimental evidence that suggests efficacy in decreasing transmission of respiratory diseases (24-26).

Brundage et al. (21) observed in a 5-year review of ARD hospitalization data in the military that modern energy efficient barracks ("starship barracks") had higher ARD rates compared to older barracks. The authors hypothesized that closed ventilation systems and decreased outdoor air may have contributed to airborne transmission of infectious agents. In our study, the two barrack styles at Fort Jackson, "starship" and "rolling pin," are both of modern design with closed ventilation systems and there was no statistical difference between the ARD rates. We were able to document inadequate ventilation in our surveys of 2 barracks. It should be noted, however, that according to the American Society of Heating, Refrigerating, and Air Conditioning Engineers (23), the 1,000 ppm limit of indoor CO_2 air concentration which was exceeded, is only an indicator of human bioeffluent (odor) and is used only as a surrogate marker for human comfort. Such levels have not been found to be associated with ulterior health effects of significance. We are unable to definitely determine whether ventilation had a role in the propagation of the outbreak, however, we recommend at a minimum for ventilation to meet the ASHRAE standards.

The high attack rates noted during our study (up to 8-10% Adv-asociated ARD hospitalization rates per week) are of the same magnitude, or higher, to the attack rates seen among recruits during the pre-vaccine era (2,9,15). It should be noted that the experience with the ARD syndrome seen among field artillery recruits at Fort Bragg, NC, in 1942-45 (2), among recruits at the Naval Training Center (NTC), Great Lakes, IL, in 1954-56 (45,46) and among recruits at the NTC and Marine Corps Recruit Depot (MCRD), San Diego, CA, in 1953-63 (47,48) closely resembles what we found at Fort Jackson in 1997. In this sense, we could say that "the more things change, the more they stay the same". The cessation of of adenovirus vaccine production in 1996 has resulted in a well-documented resurgence of adenoviral respiratory disease among military recruits. In this sense, it is apparent that a top prority for military officials at this time should be the re-establishment of a safe, efficacious, and cost-effective adenovirus immunization program (1,13,16).

9. RECOMMENDATIONS. Subsequent to this investigation, final EPICON team recommendations were developed and discussed with the MEDDAC Commander, COL William Bester and the DCCS, COL Steve Oswald as well as 1st and 4th Tng Bde officials on 31 August 1998. The Commanding General, MG John VanAlstyne, was provided a final briefing on 2 September 1998. The following recommendations were made at the time:

1) continue to provide emphasis on ARD surveillance and adenovirus lab-based surveillance at Fort Jackson to include dedication of funding and manpower resources to maintain lab support at MACH and DDEAMC Virology Laboratory;

2) emphasize need for adherence to industrial hygiene indoor ventilation standards (ASHRAE standards in reference # 23) in order to reduce indoor CO2 concentrations, and, possibly, reduce ARD risk in the barracks. This should include an increased use of fans and enforcement of opening of windows in sleeping bay areas, especially at nighttime;

3) provide training cadre and recruits with increased-level education on how to prevent ARDs and appropriate personal hygiene measures such as mandatory handwashing (at least 5 times per day) and setting up of handwashing stations near the dining facility and training areas;

4) evaluate further the possible role non-vaccine ARD interventions (NOVARDIs) may play in collaboration with MAJ(P) Roberto Nang and other DCPM/DEDS-USACHPPM and WRAIR investigators;

5) in collaboration with DEDS-USACHPPM and WRAIR scientists consider conducting a more comprehensive, prospective study of ARD and respiratory adenovirus infections among non-vaccinated recruits conducting training in the fall and winter (Sept-Nov) of 1998; and,

6) give serious consideration to using Fort Jackson as a top candidate site for conducting future clinical and efficacy trials of candidate adenovirus type 4 (and possibly 7) vaccines being developed in support of the DoDs Adenovirus Vaccine Replacement Program (AVREP).

10. ACKNOWLEDGMENTS. We would like to extend our appreciation to the BCT unit personnel and trainers at Fort Jackson, SC, and to the Commanding General, MG John Van Alstyne, for their rapid response and support of this investigation. We would like to specifically acknowledge the support provided by the medical staff at Moncrief Army Community Hospital to include COL Dale Carroll, Commander; COL Stephen Oswald, Deputy Commander for Clinical Services; LTC Rose-Marie Hendrix, Chief, Preventive Medicine Services; LTC Jane Lindner, Community Health Nurse; SPC Michael Escalera, Preventive Medicine Technician; Ms. Johnnie Conolly, Adenovirus Project Nurse; and, SSG Henry Taylor, NCOIC, ARD Ward, Moncrief Army Community Hospital.

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Appendix B

DEPARTMENT OF THE ARMY
HEADQUARTERS UNITED STATES ARMY MEDICAL DEPARTMENT ACTIVITY
FORT JACKSON, SOUTH CAROLINA 29207-5720

REPLY TO
ATTENTION OF

MCXL-P

13 November 1997

MEMORANDUM FOR: COL Sanchez, CHPPM

Subject: Acute Respiratory Distress (ARD) EPICON

1. Pursuant to our recent phone conversation, and on behalf of the Moncrief Army Community Hospital Commander, COL Carroll, an invitation is extended to you and your staff for an on-site visit to this facility during the week beginning 17 November 1997.

2. Purpose of the visit should include as assessment of the impact that ARD and adenovirus (ADV) infection is having on the military recruit population at Fort Jackson, investigation of the epidemiology of ARD in the recruit population to include an evaluation of risk factors of illness, and an evaluation of the role that non-vaccine preventive measures may have in controlling ARD/ADV transmission in recruit population.

3. If you need any assistance prior to or during your visit please do not hesitate to contact this office at 803-751-2280. Your POC during the visit will be LTC Hendrix, Chief, Preventive Medicine Services.

STEPHEN G. OSWALD
COL, MC
Deputy Commander for Clinical Services

Appendix C

JAX EPICON
SICK CALL QUESTIONNAIRE

Name_____ SSN_____ DOB_____ Age____ Sex: M F

Rank____ BN_____ Co____ Platoon_____ Squad_____ Week of Training:____

Date of First Visit :_____ Main Complaint(s): _____ Time (24-hr):____hrs

When did you first start feeling sick (date of onset of symptoms)?_____

Did you take any medicines to make you feel better? Yes No
If yes, what medicines did you take?_____

Did you go to sick-call for this problem before today? Yes No
If yes:
a. Did you receive any medications/antibiotics? Yes No
b. How much duty time did you miss? Hours_____ Days_____

Other symptoms (check all that apply): Highest Oral Temperature:_____°F

Fever	Cough	Runny/Stuffy Nose
Headache	Trouble breathing	Sore Throat/Trouble swallowing
Runny Eyes	Muscle Aches	Earache/Trouble hearing
Sinus pain	Ringing in ears	Stiff neck
Dizziness	Hoarseness	Wheezing
Chest pain/tickling when breathing		

R/O Pneumonia upon admission to ARD Ward (Infirmary)? Yes No

Have you ever had:
Allergies Hay fever Asthma

Did you smoke before basic training? Yes No

If yes, how much did you smoke?
Less than 1 pack/day 1-2 packs/day 3or more packs/day

DO NOT WRITE IN THE AREA BELOW

Immunization History (by records review):

Adenovirus		Yes	No	Unk	RNF	Date_____
Influenza	1996-97	Yes	No	Unk	RNF	Date_____
	1997-98	Yes	No	Unk	RNF	Date_____
Meningococcal		Yes	No	Unk	RNF	Date_____

Specimen/Label #_____

Appendix D

Health and Hygiene Questionnaire for BCT

Offiice Use Only: Mark only One:

□ 1.CASE (In ARD Ward) □ 2.Control other med care □ 3.Control from Unit □4.xSec (unit)

PLEASE FILL OUT:

Chief Complaint :_____

Age ____ Sex: M or F

Unit: battalion_____ company_____

Circle the Most Appropriate
Week of Basic Training: 1 2 3 4 5 6 7 8

Check the Appropriate Box
Have you been sick with a cold or flu (cough, sniffles) ? □ Yes □ No

Did you have a fever ? □ Yes □ No

Have you had nausea, vomiting or diarrhea during BCT ? □ Yes □ No

Did you take any medicines to make you feel better ? □ Yes □ No

If yes, what medicines did you take ? _____

Did you smoke before basic training? □ yes, less than 1 pack/day □ 1-2 packs/day □ 3+ packs/day
□ Non-Smoker

Please answer in terms of your behavior during BCT

How many times do you wash your hands per day ? _____ #

What percentage of the time do you use soap when you wash your hands ? _____%

When you use soap how many seconds do you spend rubbing your hands (lathering) ? ____sec

In the Barracks, how do you dry your hands most of the time ?
Mark Only One
□ towel
□ on clothes
□ "air dry" or "shake dry"
□ other _____

Have you been told to wash your hands Five Times a Day at BCT ? □ Yes □ No

What percentage of time have you covered your mouth when you cough or sneeze during BCT ? ___%

How do you cover your mouth/nose most of the time when you cough or sneeze ?
Mark Only One
□ hand
□ sleeve
□ tissue
□ other

How do you scratch/rub/wipe your nose most of the time
Mark Only One
□ with tissue ?
□ with sleeve ?
□ with fingers/hands ?
□ with other ? _____

Do you pick your teeth with your fingers more than once a day? □ Yes □ No

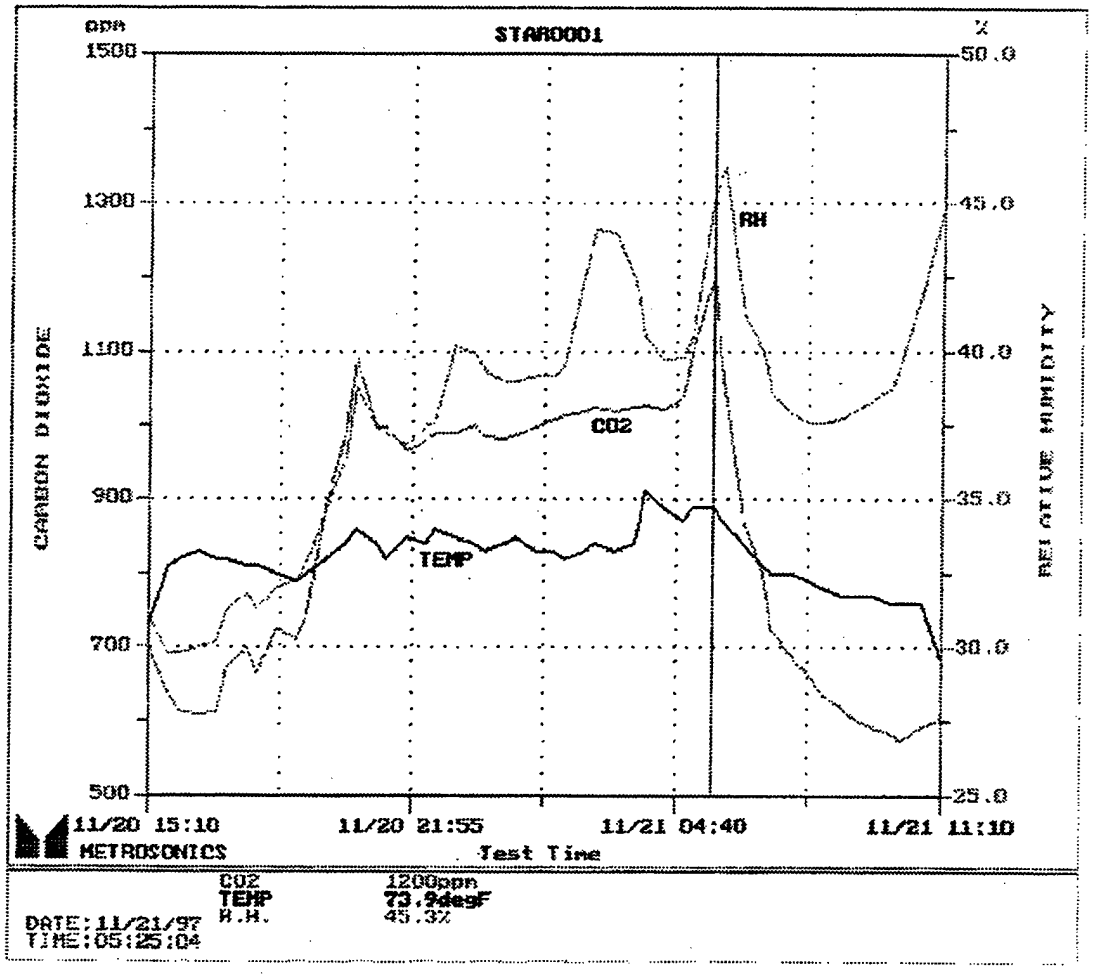
Do you pick your nose with your fingers more than once a day? □ Yes □ No

Have you shared any of the following items (circle all that apply):

Canteens Cups Face towel Handtowel Bodytowel other_____

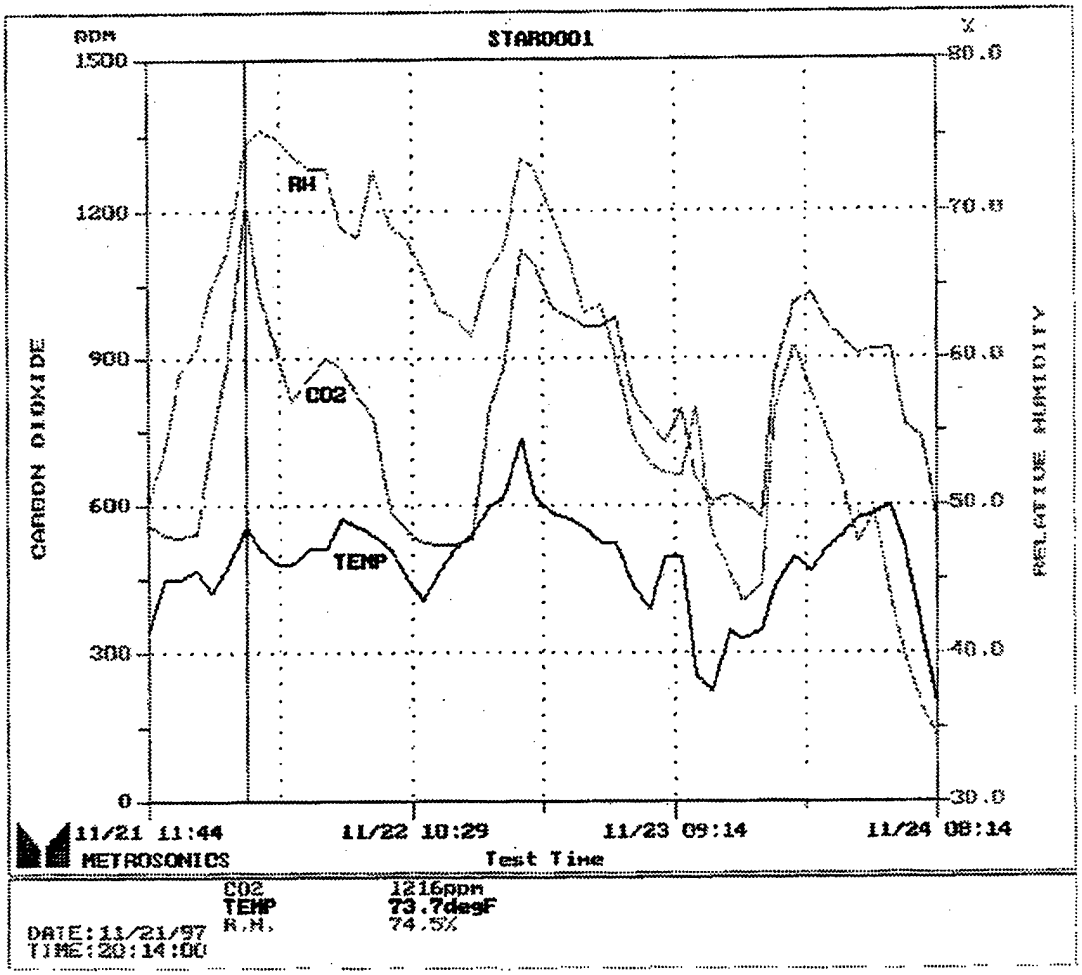
Appendix E-1

Filename.....STAR0001
Test Location...2nd60 1st bde A Co 3rd pn
Building.....11000
Room Number.....A Co 3rd Plt
Department.....bay - 42 males
Placed In rear to rt of
latrine nearest occupied
bed 15 ft
IAQ in conjunction w/
CHPPM



Appendix E-2

Filename.....STAR0002
Test Location...260th 1st Bde D Co 1st Pn
Building.....11000
Room Number.....1st Pn Bay - 43 female
Department.....Starship
IAQ in conjunction w/
CHPPM - AQ502 on 21 Nov
1145 hrs - inst placed
at rear column in middle
of room



Appendix E-3

Filename.....ROLLPIN1
Test Location...239TH B CO 4TH PN
Building.....4260
Room Number.....220
Department.....BASIC TRAINING
IAQ TEST IN CONJUNCTION
W/ CHPPM - RE: ARD RATES
SGT TORRES 3685
7 TRAINEES