

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





EPIDEMIOLOGIC CONSULTATION No. 29-HE-809la-99 PNEUMOCOCCAL PNEUMONIA RANGER TRAINING BRIGADE FORT BENNING, GEORGIA MARCH-APRIL, 1999



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### 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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#### EXECUTIVE SUMMARY EPIDEMIOLOGIC CONSULTATION No. 29-HE-8091a-99 PNUEMOCOCCAL PNEUMONIA, RANGER TRAINING BRIGADE, FORT BENNING, GEORGIA MARCH-APRIL, 1999

1. BACKGROUND AND PURPOSE. On 1 March 1999 the Commander, Martin Army Community Hospital (MACH), Fort Benning, Georgia requested an epidemiologic consultation (EPICON) to investigate a cluster of 7 pneumonia cases in the Ranger Training Brigade (RTB) which had developed during Phase I training. An EPICON team assembled to determine the magnitude of the outbreak, the amount of upper/lower respiratory disease in class 4-99 since the beginning of phase one of Ranger training, the most likely causative agent(s) of the outbreak and possible mode(s) and risk factor(s) for its (their) transmission, and provide recommendations for control of the current and future outbreaks.

2. METHODS. The investigation was conducted in three parts.

a. Part I (Initial visit) consisted of:

1) Reviewing all case histories and lab work.

2) Obtaining throat swabs and sera on all new (non-treated) cases.

3) Medical records review of class 4-99.

4) Administering an epidemiologic survey.

5) Obtaining serum samples and throat cultures on the remainder of the class.

6) Providing the Hospital and Ranger Commanders with a summary of Part I of the investigation.

b. Part II (Follow-Up visit) consisted of:

1) Obtaining all subsequent case histories of upper and lower respiratory illness.

2) Administering an end-of-training (7-8 April) questionnaire, throat swab, and blood draw for determination of end-of-training cumulative illness rates, carriage rates, and serum antibody titers.

c. Part III (Data analysis) consisted of determining the overall rates of illness within the class, the proportion of individuals colonized with *S. pneumoniae*, the proportion of those who had subclinical infections, and the proportion of individuals that developed antibody to *S. pneumoniae*.

#### 3. RESULTS.

- 14 - 14 - 14 a. Seventy-three percent (n=239) of the initial 326 Ranger students in class 4-99 were evaluated during the period of 5-9 March 1999. There were a total of 30 cases of pneumonia detected, 18 of which were hospitalized, during the 5-week period from 1 February to 7 March. The attack rate for this time period was 12.6% (30 of 239). Sixtyfour percent (165 of 239) of the Ranger students reported symptoms of significant flu-like or febrile respiratory illness during the preceding 5 weeks of Ranger training.

b. Review of pre-existing Battalion Aid Station (BAS) visit record data for the period from March 1991 through April 1999 revealed that no clusters of pneumonia were detected between March 1991 and December 1997, concomitant with a period of prophylaxis with 2 doses of benzathene penicillin four weeks apart. Pneumonia clusters were noted to recur in the spring of 1998 concomitant with a cessation of bicillin prophylaxis.

c. At the time of follow-up visit on 7 April, only 1.8% (n=3) of the remaining 166 students were found to suffer from similar conditions during the second half (4 weeks) of training. This included 37.6% (n=61) during the mountain and 2.4% (n=4) during the swamp phases of training. Only one additional case of pneumonia, diagnosed as an outpatient during the swamp phase and treated with a 5-day azithromycin regimen, was documented during the second half of training.

d. Initial results of bacteriologic cultures performed on the 30 ill Rangers had sputum/blood/throat cultures of which 14 [47% (8 sputum, 3 pharyngeal, 1 blood/pharyngeal, 1 sputum/pharyngeal, 1 sputum/blood/pharyngeal)] were positive for *S. pneumoniae* (see Table 1). Of the 18 hospitalized patients, 11 had positive cultures [6 sputum, 2 pharyngeal, 1 sputum/pharyngeal, 1 sputum/blood/pharyngeal, 1 blood/pharyngeal] cultures for *S. pneumoniae*. Additional throat cultures done on 221 students seen at DTC on 7 March showed that a significant number (30, 14%) were found to be positive for *S. pneumoniae*. High-level resistance to penicillin was not found to occur. Eighteen (60%) of the *S. pneumoniae* positive throat cultures obtained on 7 March were sensitive and twelve (40%) were intermediately resistant to penicillin. All *S. pneumoniae* isolate serotypes detected are represented in the 23-valent pneumococcal vaccine (Types 23, 22, 20, 19, 14, 9, 6, 3).

d. Initial rapid control of this pneumonia outbreak appears to have been achieved by mass administration of low-dose azithromycin prophylaxis (250 mg once a week for 2 weeks) of the 221 Ranger students at DTC on 7-8 March and 14-15 March.

#### 4. CONCLUSIONS.

a. An outbreak of pneumococcal pneumonia occurred among students of class 4-99 at the Ranger Training Brigade, Fort Benning, Georgia in the winter and early spring of 1998-1999. This outbreak had been preceded by a spring 1998 outbreak of pneumonia of unspecified etiology.

b. Both outbreaks appear to be the result of the cessation of the two-dose benzathine penicillin (1.2 million units IM) chemoprophylaxis policy instituted by the brigade in March 1991.

c. The mass administration of azithromycin, 250mg once a week for 2 weeks, appears to have rapidly controlled the outbreak in Class 4-99.

#### 5. RECOMMENDATIONS.

a. Year-round vaccination with 23-valent pneumococcal vaccine is recommended for all Ranger classes. Preferably pneumococcal vaccine should be administered prior to arrival at Fort Benning in order to maximize vaccine efficacy. Every Ranger student reporting for training during the period of 1 October through 31 March should also have documentation of a current influenza immunization in his medical record.

b. Routine 2-dose benzathine penicillin prophylaxis, 1.2 million units IM four weeks apart, should be implemented during the period of 1 October 1999 through 31 March.

c. Azithromycin should be reserved for secondary/back-up use for mass post-exposure prophylaxis for rapid control of future pneumonia outbreaks and as first-line treatment of suspected or definite pneumonia cases occurring among Ranger students.

d. Surveillance for febrile acute respiratory diseases (ARDs) and pneumonia among Ranger students, especially during the winter and early spring time frame, should be enhanced.

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e. A future randomized trial comparing the efficacy of antibiotic chemoprophyactic agents and 23-valent pneumococcal vaccine for the prevention of pneumococcal pneumonia among Ranger students should be considered.

f. A reassessment of dietary patterns in Ranger students should be considered.

g. The RTB requires enhanced medical support. Consideration should be given to assigning a full-time medical officer within the training brigade

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

#### 2. INTRODUCTION.

a. Acute Respiratory Disease (ARD) continues to be a significant cause of morbidity among military populations. Training and mobilization centers have traditionally been the foci of epidemics due to close living conditions, stress, and a variety of pathogens brought together by these troops.<sup>1,2</sup> While prophylactic measures are effective when used there appears to be a growing trend in the military to ignore these measures, e.g. adenovirus vaccine. The outbreak of pneumonia in Ranger Class 4-99 also appears to be a result of this disturbing trend.

b. In January 1991, the Centers for Disease Control, Atlanta, Georgia investigated an outbreak of pneumococcal pneumonia in a ranger class at Fort Benning. The class experienced 14 cases of pneumonia (6% of the class). More than 33% of the class were identified as *Streptococcus pneumoniae* carriers, a rate higher than the general population, and 91% of the carriers admitted to having cough or rhinorrhea. The investigation led to the routine administration of benzathine penicillin (bicillin), 1.2 million units IM, at the beginning of training Phases I (Benning) and II (Mountain).<sup>3</sup>

c. Between June 1991-January 1992, the Ranger Training Brigade (RTB) Commander invited a team from the U.S. Army Research Institute of Environmental Medicine (USARIEM) to study the nutritional and physiological impact of Ranger training on the students. They assessed 1) nutritional status by measurement of specific blood-borne biochemical indicators, 2) changes in body composition and muscular strength and endurance, and 3) in vitro and in vivo immune function. Their findings (Figure 1, all tables and figures are in Appendix B) demonstrated a Group A beta-hemolytic streptococcal carrier rate of 3% before chemoprophylaxis. This rate varied from 2% at the end of Phase I to 5% at the end of training. No cases of streptococcal pharyngitis were reported during training. In comparison, the baseline prevalence of Streptococcal pneumoniae carriers was 1%, but increased significantly during the mountain, swamp, and desert phases of training with a peak of 11% during the swamp phase. No cases of pneumococcal pneumonia were reported during training. Immune function studies showed that T-lymphocyte function and systemic production of interleukin-6 are suppressed (Figures 2 and 3). The team concluded this to be the most likely cause of increased rates of infection during the second half of training.<sup>3</sup> The two-dose bicillin regimen continued until the fall of 1997 when it was modified to only one dose administered at the beginning of Phase I. Medical authorities at Fort Benning and the Ranger Training Brigade commander agreed in 19 March 1998 that benzathine penicillin chemoprophylaxis could be terminated altogether if effective streptococcal disease surveillance of Ranger classes was maintained (Major Corr, Preventive Medicine Office, Fort Benning - personal communication).

d. On 1 March 1999 the Commander, Martin Army Community Hospital (MACH), Fort Benning, Georgia requested assistance from the U.S. Army Center for Health Promotion and Preventive Medicine (USACHPPM) in investigating a cluster of 7 pneumonia cases in Ranger Class 4-99 which had developed during Phase I training. At the time of the request, 2 of these cases were in the Intensive Care Unit at MACH, and all throat and sputum cultures were pending. This Ranger class moved from the initial 4-week Phase I training at Fort Benning to the 2-week Phase II (mountain) at Camp Merrill, Dahlonega Training Center (DTC), Georgia on 4 March.

3. OBJECTIVES. The team was tasked to:

a. Determine the magnitude of the outbreak.

b. Determine the magnitude of upper/lower respiratory disease in class 4-99 since the beginning of phase one of Ranger training.

c. Determine the most likely causative agent(s) of the outbreak and possible mode(s) and risk factor(s) for its(their) transmission.

d. Determine the percentage of 1) individuals colonized with *S. pneumoniae*, 2) individuals that have subclinical infection, and 3) those that develop antibodies to *S. pneumoniae*. This information was deemed necessary in order to fully examine risk factors for pneumococcal infection in this cohort.

e. Provide recommendations for control of the current and future outbreaks.

4. EPICON TEAM. An Epidemiologic Consultation (EPICON) team was requested visited Fort Benning/Camp Merrill from 4-9 March. Coordination was effected with COL Frank Helmick, Commander, and CPT George James, Physician Assistant, Ranger Training Brigade (RTB); Ms. Sandra Williams, Research Assistant, Navy Health Research Center (NHRC) Respiratory Disease Surveillance Project; COL Gwen Holeman, Chief, Dept of Pathology, Martin ACH; MAJ William Corr, Preventive Medicine Officer, MAJ Steve Salerno, Chief, Dept of Medicine, and MAJ William Blanke, Dept of Family Practice, Martin ACH.Team members included:

a. COL Stephen C. Craig, Team Chief, USACHPPM.

**1** 1 2 1

b. Dr. Shellie Kolavic, Epidemiologist, USACHPPM.

c. CPT Deborah Hastings, Epidemiologist, USACHPPM.

d. CPT Bryan Alsip, Preventive Medicine Resident, WRAIR.

5. METHODS. The investigation was conducted in three parts.

a. Part I (Initial visit) consisted of:

1) Reviewing all case histories and lab work, establishing a case definition, and determining the most likely cause of the outbreak from cultures of hospitalized cases;

2) Obtaining throat swabs for viral culture (adenovirus, influenza, parainfluenza), detection of *Mycoplasma pneumoniae* (by culture and direct PCR) and *Clamydia pneumoniae* (by direct PCR) and *Streptococcus pyogenes/pneumoniae* (by culture/PCR) on all new cases seen which had not received treatment. Mycoplasma, chlamydial and streptococcal cultures were sent to the Naval Health Research Center Respiratory Disease Laboratory, San Diego, CA (CAPT Greg Gray);

3) Conducting a medical records review of class 4-99 for upper and lower respiratory illnesses since the beginning of training;

4) Administering a baseline survey questionnaire (Appendix C) to obtain basic demographic, training, and risk factor data;

5) Obtaining serum samples on 100% of class 4-99 for IgG and IgM determinations for S. *pyogenes*, S. *pneumoniae*, and C. *pneumoniae*; and

6) Providing the Hospital and Ranger Training Brigade Commanders with a summary of Part I of the investigation.

b. Part II (Follow-Up visit) consisted of:

1) Obtaining all subsequent case histories of upper and lower respiratory illness among the class;

2) Administering an end-of-training (7-8 April) questionnaire (Appendix D), throat swab, and blood draw for determination of end-of-training cumulative illness rates, carriage rates, and serum antibody titers.

c. Part III (Data analysis) consisted of determining the overall rate of illness within the class, the proportion of individuals colonized with *S. pneumoniae*, the proportion of those who had subclinical infections, and the proportion of individuals that developed antibody to *S. pneumoniae*. End-point markers (i.e. dependent variables) such as illness, carriage/colonization and infection (i.e. seroconversion) will be examined for potential associations with demographic, clinical and exposure variables determined (by odds ratios) in univariate and multivariate analyses.

#### d. Case Definitions.

1) A pneumonia case was defined as any student who met the following criteria:

a) Positive sputum culture, blood culture or chest x-ray.

b) Productive cough and adventitious lung sounds, with or without a temperature equal to or greater than 100.5, or a white blood cell count of 10,000 or greater.

c) Positive throat culture with at least one of the above criteria.

2) A respiratory illness was defined as: fever, and/or cough, and/or sore throat and 2 of the following: congestion/rhinorrhea; dyspnea; or hoarseness.

e. The RTB and MACH Commanders were briefed and recommendations discussed at the conclusion of Parts I and II of the EPICON.

#### 6. RESULTS

a. Demographic Data. Seventy-three percent (n=239) of the initial 326 Ranger students in class 4-99 were evaluated during the period of 5-9 March 1999. This cohort consisted of 239 men between the ages of 19-36 years (mean age = 24). Of these, 86.6% were Caucasian, 6.7% Hispanic, 3.8% African-American, and 2.9% Asian. Officers accounted for 51.5% of the cohort.

b. Medical Records Review.

1) A review of pre-existing Battalion Aid Station (BAS) visit record data for the period from March 1991 through April 1999 revealed that no clusters of pneumonia were detected between March 1991 and December 1997, concomitant with a period of prophylaxis with 2 doses of benzathine penicillin four weeks apart. Pneumonia cases at the RTB increased in the spring of 1998 (classes 6-98 and 7-98) and again in the winter

of 1998-99 (classes 2-99, 3-99 and 4-99) concomitant with a cessation of benzathine penicillin prophylaxis (Figure 1).

2) In class 4-99 there were 191 individual medical records available for review. There were a total of 113 visits for ARD in the first 4 weeks of training with an individual range of 0-4 visits per student. Thirty-eight percent (73 of 191) had at least one visit for ARD in the first 4 weeks of training.

c. Pneumonia Cases. There were a total of 30 cases of pneumonia detected, 18 of which were hospitalized, during the 5-week period from 1 February to 7 March (Table 1). The attack rate for this time period was 12.6% (30 of 239). Twenty-five ill students received chest radiographs. Of these 84% (n=21) had radiographically confirmed pneumonia. Twenty-four ill students had complete blood counts with white blood cell (WBC) counts

between 4,400 - 41,200 (mean 16,000), while 75% (18 of 24) had WBC levels greater than or equal to 10,000.

d. Laboratory Results. All 30 ill Rangers had sputum/blood/throat cultures of which 14 [47% (8 sputum, 3 pharyngeal, 1 blood/pharyngeal, 1 sputum/pharyngeal, 1 sputum/blood/pharyngeal)] were positive for S. pneumoniae (Table 1). Of the 18 hospitalized patients, 11 had positive cultures [6 sputum, 2 pharyngeal, 1 sputum/pharyngeal, 1 sputum/blood/pharyngeal, 1 blood/pharyngeal] cultures for S. pneumoniae. Throat cultures done on the 221 students seen at DTC on 7 March showed that a significant number (30, 13.6%) were found to be positive for S. pneumoniae. An additional 18 (8.2%) of students also harbored non-beta hemolytic streptococci (Groups B, C, F or G), and only 3 (1.4%) were found to be positive for group A beta-hemolytic streptococci (GABHS). By comparison, isolation rates of 7 (4.2%), 17 (10.2%) and 0 (0%), respectively, were noted in follow-up throat cultures on 166 Ranger students at the end of training (Table 2). All S. pneumoniae isolate serotypes detected are represented in the 23-valent pneumococcal vaccine (Types 23, 22, 20, 19, 14, 9, 6, 3). Seven students had throat cultures for PCR analysis. Of these, one was positive for C. pneumoniae and one was positive for M. pneumoniae. Analysis of serological specimens is continuing through the Naval Health Research Center to include: anti-pneumococcal serum antibody testing on Ranger students (221 initial, 166 with paired sera).

e. Questionnaire Data Analysis.

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 Sixty-nine percent (165 of 239) of the Ranger students reported symptoms of significant flu-like or febrile respiratory illness during the preceding 5 weeks of Ranger training. By comparison, at the time of follow-up visit on 7 April, only 1.8% (n=3) of the remaining 166 students were found to suffer from similar conditions during the second half (4 weeks) of training (Table 3). This included 36.7% (n=61) of students during the mountain and 2.4% (n=4) during the swamp phases of training. Only one additional case of pneumonia, diagnosed as an outpatient during the swamp phase and treated with a 5day azithromycin regimen, was documented during the second half of training. No significant associations were observed between reporting a respiratory illness and age, rank, race, smoking status, or other demographic characteristics. Further analysis with laboratory data is pending results of serologic data.

2) There were no statistically significant correlations between pharyngeal carriage of S. pneumoniae and self-reported respiratory symptoms. At training week 5, 36.7% (11 of 30) of students with upper respiratory symptoms had a pharyngeal culture positive for S. pneumoniae, compared to 34% (65 of 191) who had upper respiratory symptoms without a concomitant positive culture. Four weeks later, after administration of azithromycin, none of the 7 students with a positive pharyngeal culture met the summary illness definition (one admitted to runny/stuffy nose), and only 1.9% (3 of 159) of the students with a negative culture were symptomatic (Table 4).

f. Antibiotic Sensitivity. Eighteen (60%) of the S. pneumoniae positive throat cultures obtained on 7 March were sensitive and twelve (40%) were intermediately sensitive to penicillin. Only one of the 30 S. pneumoniae sputum isolates was resistant to penicillin. All

thirty cultures were sensitive to erythromycin, ceftriaxone, levofloxacin, vancomycin, and trimethoprim/sulfamethoxazole. Four (57%) of the *S. pneumoniae* follow-up throat cultures obtained on 7 April were sensitive and 3 (43%) were intermediate to penicillin. Two of the follow-up cultures that were intermediately resistant to penicillin were found to be resistant to azithromycin.

g. Interim Control Measures. Initial rapid control of this pneumonia outbreak appears to have been achieved by mass administration of low-dose azithromycin prophylaxis (250 mg once a week for 2 weeks) of the 221 Ranger students at DTC on 7-8 March and 14-15 March. It should be pointed out that the initial recommendation by the EPICON team was for administration of 500 (not 250) mg every week for remainder of Ranger training. Additional control measures also included the administration of one dose of pneumococcal vaccine as well as bicillin prophylaxis (1.2 million units IM) to the subsequent class (5-99), which started Ranger training with approximately 250 students on Monday, 8 March. Class 6-99 (approximately 270 students) which started training on Monday, 5 April did not receive any vaccine or antibiotic prophylaxis.

#### 7. DISCUSSION

a. The cessation of bicillin prophylaxis in March 1998 was found clearly to correlate with this increase of pneumonia cases (Figure 1). While antibiotic chemoprophylaxis has been effective in reducing the rate of pneumonia in this population, the implementation of pneumococcal vaccine is worthy of consideration as a primary prevention modality. Its efficacy in preventing pneumococcal pneumonia in healthy young adults in South Africa and Papua, New Guinea, where incidence of pneumonia is high, has been estimated at approximately 80%.<sup>4-7</sup> Its efficacy in prevention of bacteremia has been estimated at 60-64% based on the pneumococcal surveillance system data from the Centers for Disease Control and Prevention.<sup>8</sup> In addition, it is a relatively inexpensive vaccine (\$23.80 per 5dose vial, \$4.76 per dose, approximately \$1,200 per class) which makes it an ideal first line of prevention in this setting. This vaccine is expected to protect against overt disease due to the most prevalent strains of S. pneumoniae, and may reduce nasopharyngeal carriage rates. If vaccinated prior to arrival at the RTB it would be anticipated that 75-99% (86% overall) of vaccinees would sustain a protective, serotype-specific, antibody response to the vaccine antigens.<sup>9</sup> The 23-valent pneumococcal vaccine would be expected to cover at least 90% of the serotypes responsible for invasive disease in the US.<sup>4,8</sup>

b. To counter outbreaks of *S. pneumoniae* and *S. pyogenes*, the US military has used mass prophylaxis with benzathine penicillin G (1.2 million units intramuscularly) with a high degree of success in the past.<sup>2</sup> Historically, prophylaxis with only one dose led to a reduction of GABHS and *S. pneumoniae* among Ranger students for a period of at least 4 weeks (i.e. phase I of training) (Figure 2). Subsequent experience during the period 1991-1998 gave evidence that indicated a 2-dose bicillin regimen was efficacious and necessary (Figure 1). Based on this prior experience, it is expected that 2 doses will be required 4 weeks apart, with the second dose being administered during the first weekend at DTC. Additional, one-time dosing of the Ranger class undergoing mountain phase training at

DTC in early October 1999 should also be considered. Concerns about adverse effects such as sterile abscesses, immediate hypersensitivity reactions, and muscle pain can be appropriately managed by the medical staff at the Ranger Battalion Aid Station at the RTB and DTC. It is estimated that the cost associated with this prophylaxis will only be around \$3,200 per class (\$6.46 per 1.2 million unit (2 ml) dose). Students who report or have a well-documented history of penicillin allergy should be given azithromycin 500 mg weekly as alternative prophylaxis. The use of oral erythromycin (250 mg two to four times a day), although effective in preventing *S. pyogenes* infections in military recruits is not presently recommended as an alternative prophylaxis regimen given problems with non-compliance and gastrointestinal side effects.<sup>10</sup>

c. From the preliminary data it appears that nasopharyngeal carriage rates for S. pneumoniae and possibly GABHS may have been significantly reduced (4-fold reduction) by only 2 post-exposure doses of azithromycin. In addition, clinically overt illness (i.e. pneumonia) seems to have been significantly curtailed (12-fold reduction). Currently, it is felt that azithromycin should be reserved for secondary/back-up use as mass post-exposure prophylaxis for rapid control of future pneumonia outbreaks. It should also be used as first-line treatment of suspected or definite pneumonia cases occurring among Ranger students. Consideration should also be given for its use in the treatment of "breakthrough" cases of pneumonia who have received bicillin (or erythromycin) prophylaxis as well as any cases of pharyngitis, bronchitis, or cellulitis in this group. This drug has recently been shown to be highly protective as a military prophylactic intervention against infections due to S. pneumoniae (80%), S. pyogenes (84%), M. pneumoniae (64%) and C. pneumoniae (58%) among US Marine Corps personnel at the Infantry Training School, Camp Pendleton, CA.<sup>11</sup> Recommended dosing regimen for mass prophylaxis during outbreaks will be 500 mg weekly for the duration of Ranger training. The expense of this agent (\$111.20 per 30-tablet (250 mg) bottle, \$7.42 per 500 mg dose, \$1,860 per week, \$15,000 per class) is offset by its ease of administration and wide spectrum coverage against bacterial organisms. There is, however, a real concern about potential emergence of resistance to this drug. Therefore, its use will only be reserved for selected instances where "breakthrough" infections occur, even after routine bicillin (or erythromycin) prophylaxis.

d. Results of a previous study <sup>3</sup> have shown that individuals in Ranger training develop a significant reduction in cellular immune function with the greatest decrement occurring after the mountain phase of training (Figures 3 and 4). This reduced immune function parallels a significant degree of weight loss (average of 15.6% of initial weight), and an increased energy deficit due to increased physical stress and decreased caloric intake. Based on the findings of that study conducted almost 8 years ago it may be prudent to consider a reassessment of dietary patterns in Ranger students and the possibility of conducting a follow-on study of the effects of dietary interventions such as long range patrol (LRP) rations.

e. Surveillance for pneumonia cases and cases of pharyngitis, bronchitis, cellulitis and/or febrile, flu-like illnesses among Ranger students should be enhanced, especially for classes training during the period of October-March. A PC-based morbidity (disease and injury)

surveillance spreadsheet program, developed locally by 1LT James Schumacher at the Ranger Regiment TMC, should be utilized to track cases of the above named conditions. In addition, assessment of the types and antibiotic sensitivities of any bacterial isolates found on patients with any of the above conditions should be conducted on a routine basis. Necessary sample collection from patients seen at the Ranger BAS at the RTB or at DTC should be coordinated in advance with Ms. Williams of the NHRC Respiratory Disease Surveillance Project. Collection of antibiotic sensitivity data on bacterial isolates from Ranger students is of paramount importance in order to detect early emergence of antibiotic resistance in this population. Macrolide resistance among streptococcal strains has been previously uncommon among US military populations and infrequent among isolates from civilian personnel in the US.<sup>2</sup>

f. At this time, additional interpretation of study findings is pending the measurement of: a) anti-pneumococcal anti-pneumolysin serum antibody testing on Ranger students (221 initial, 166 with paired sera). A future randomized trial of the efficacy of 23-valent pneumococcal vaccine versus bicillin prophylaxis in the prevention of pneumococcal pneumonia among Ranger students will be planned by USACHPPM in the near future. This operationally relevant study is being requested by COL Martinez-Lopez and COL Helmick in order to better define future prophylaxis measures in this high-risk group. Previously published evidence of a similar outbreak of pneumococcal disease among Rangers in December 1990<sup>12</sup> and historical data from cases occurring in 1997-98 suggests that the best timeframe for conducting this study would be the November 99 through March 00 training cycle (classes 3-00, 4-00 and 5-00). Consideration will also be given to the evaluation of immunogenicity of the 23-valent pneumococcal vaccine initially in order to assess whether adequate immunological responses occur following vaccination. This vaccine-response evaluation is considered necessary given that people who sustain a poor antibody response to this vaccine are considered to be at-risk for serious pneumococcal invasive disease.<sup>4</sup> Details of such a study will be forthcoming in a separate study protocol to be reviewed and approved by the local MEDDAC authorities as well as by the respective human use and institutional review boards at the Naval Health Research Center (NHRC) in San Diego, CA. No studies of newly developed pneumococcal conjugate vaccine candidates are planned at this time. The RTB and medical authorities at Fort Benning do not consider these type studies to be feasible or advisable in this population given their potential for future legal complaints by recipients of an IND vaccine product(s).

8. CONCLUSIONS.

a. An outbreak of pneumonia occurred among students at the Ranger Training Brigade, Fort Benning, Georgia in the spring of 1998 and in the winter of 1998-1999.

b. The outbreaks appear to be the result of the cessation of the two-dose bicillin (1.2 million units IM) chemoprophylaxis policy instituted by the brigade in 1991.

c. The mass administration of azithromycin, 250mg once a week for 2 weeks, appears to have rapidly controlled the winter outbreak.

9. RECOMMENDATIONS. The following were long-term control measures agreed upon for future control of pneumococcal and other bacterial respiratory infections among Ranger students:

a. Pneumococcal vaccine is recommended for all Ranger classes. This vaccine should be administered preferably prior to or immediately upon arrival at RTB on a year-round basis to those Ranger students who have no recorded evidence of previous vaccination. This policy should be started with the next group of Ranger students (class 7-99). Since the peak antibody response to the vaccine takes approximately 2-3 weeks to develop, each Ranger student should receive his dose at least 2 weeks prior to arrival at the RTB in order to ensure peak protective efficacy is attained.<sup>8</sup>

b. In addition to pneumococcal vaccine, every Ranger student reporting for training during the period of 1 October through 31 March should have documentation of a current influenza immunization in his medical record. In the absence of such record, and regardless of students' personal recollection, one dose of influenza vaccine should be administered upon arrival at the RTB.

c. A policy of routine use of 2-dose benzathine penicillin (bicillin) prophylaxis, 4 weeks apart should be implemented during the period of 1 October through 31 March (classes 1-6 each year). Based on prior experience with this regimen from 1991-1998 the second dose should be administered during the first weekend at DTC. Additional, one-time dosing of the Ranger class undergoing mountain phase training at DTC in early October 1999 should also be considered. Students who report or have a well-documented history of penicillin allergy should be given azithromycin 500 mg weekly as alternative prophylaxis.

d. Azithromycin should be reserved for secondary/back-up use as mass post-exposure prophylaxis for rapid control of future pneumonia outbreaks and as first-line treatment of suspected or definite pneumonia cases occurring among Ranger students. Consideration should also be given for its use in the treatment of "breakthrough" cases of pneumonia who have received bicillin (or erythromycin) prophylaxis as well as any cases of pharyngitis, bronchitis, or cellulitis in this group.

e. A future randomized trial of the efficacy of 23-valent pneumococcal vaccine versus bicillin prophylaxis in the prevention of pneumococcal pneumonia among Ranger students will be planned by USACHPPM in the near future. This operationally relevant study has been requested by COL Martinez-Lopez and COL Helmick in order to better define future prophylaxis measures in this high-risk group (see Appendix E).

f. Surveillance for pneumonia cases and cases of pharyngitis, bronchitis, cellulitis and/or febrile, flu-like illnesses among Ranger students should be enhanced, especially for classes training during the period of October-March. In addition, assessment of the types and antibiotic sensitivities of any bacterial isolates found on patients with any of the above conditions should be conducted on a routine basis.

g. Based on the findings of the study conducted almost 8 years ago it may be prudent to consider a reassessment of dietary patterns in Ranger students and the possibility of conducting a follow-on study of the effects of dietary interventions such as long range patrol (LRP) rations.

h. There is a need for enhanced medical support of the RTB. It would be prudent to consider the placement of a full-time medical officer within the training brigade in order to ensure optimal care and timely interventions.

#### APPENDIX A

#### REFERENCES

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### APPENDIX B

### TABLES AND FIGURES

Patient Number	Hospitalized?	<i>S. Pneumoniae</i> Detected by Blood Sample	<i>S. Pneumoniae</i> Detected by Throat Culture	<i>S. Pneumoniae</i> Detected by Sputum Sample
1	Yes	Pos.	Pos.	Pos.
2	Yes	Neg.	None	Pos.
3	Yes	Neg.	Neg.	Neg.
4	Yes	None	Neg.	Neg.
5	Yes	Pos.	Pos.	Neg.
6	Yes	Neg.	Neg.	None
7	Yes	Neg.	None	None
8	Yes	Neg.	Neg.	Pos.
9	Yes	None	None	Pos.
10	Yes	Neg.	Neg.	Pos.
11	Yes	Neg.	Pos.	None
12	Yes	None	Neg.	Pos.
13	Yes	Neg.	None	Neg.
14	Yes	Neg.	Neg.	Neg.
15	Yes	None	None	Pos.
16	Yes	Neg.	None	None
17	Yes	Neg.	Pos.	Neg.
18	Yes	Neg.	Pos.	Pos.
19	No	None	Neg.	None
20	No	None	Neg.	Neg.
21	No	None	Neg.	None
22	No	None	Neg.	None
23	No	None	Neg.	Neg.
24	No	None	Neg.	None
25	No	None	Neg.	None
26	No	Neg.	Neg.	Pos.
27	No	Neg.	Neg.	Neg.
28	No	None	Neg.	Pos.
29	No	None	Pos.	Neg.
30	No	None	Neg.	None

Table 1. Detection of S. pneumoniae by blood, throat or sputum cultures

Pos. = Positive Test Result; Neg. = Negative Test Result

TC Finding	12 Cultures of 18 Hosp	221 Initial TC (wk 4)	166 Exit TC (wk 9)
S. pneumoniae	5 (42%)	30 (14%)	7 (4%)
type 22 type 14 type 9 type 6 Other types	3 (25%) 0 1 (8%) 0 0 1 untyped	0 7 (23%) 12 (40%) 0 4 (0.1%) 1 untyped	0 1 (14%) 3 (43%) 2 (28%) 0
Non-beta hemolytic strep	0	18 (8%)	17 (10%)
Group A beta hemolytic strep	0	3 (1%)	0

Table 2. Results of Ranger student throat cultures (TC), Fort Benning, GA, 1999.

· · · · · · · · · · · · · · · · · · ·	Entry	(n=239)	MT† (	(n=166)	SW†	(n-166)	Exit (	n=166)
· ·	n	%	n	%	n	%	n	%
Fever/chills	18	7.5	15	9.0	3	1.8	0	0.0
Sore Throat	75	31.4	62	37.3	4	2.4	5	3.0
Cough	149	62.3	100	60.2	14	8.4	4	2.4
Stuffy/runny nose	44	18.4	120	72.3	44	26.5	20	12.0
Wheezing	18	7.5	12	7.2	0	0.0	0	0.0
Dyspnea	16	6.7	10	6.0	3	1.8	1	0.6
Chest pain	13	5.4	8	4.8	1	0.6	0	0.0
Hoarse voice	49	20.5	21	12.7	0	0.0	1	0.6
Shortness of breath	28	11.7	13	7.8	4	2.4	. 3	1.8
Summary illness*	89	37.2	61	36.7	4	2.4	3	1.8

Table 3:	Self-reported respiratory signs/symptoms among Ranger trainees,
	Fort Benning, 1999

\* Summary variable: Any two of the following three symptoms: fever, cough, or sore throat and any two of following: stuffy nose, shortness of breath, dyspnea, hoarseness, or sore throat.

† MT = Mountain Phase; SW = Swamp Phase.

	Symptoms	4	C+ 30)	1	C- 191)	OR	95% CI
		No.	%	No.	%		
	Fever/Chills	2	6.7	9	4.7	1.4	0, 7.7
	Sore throat	12	40.0	56	29.3	1.6	0.7, 3.8
	Cough	21	70.0	114	59.7	1.6	0.6, 3.9
Mid-	Runny/Stuff Nose	26	86.7	157	82.2	1.4	0.4, 5.1
Epidemic	Wheezing	0	0	10	5.2	0	0, 3.4
(Week 5)	Dyspnea	0	0	8	4.2	0	0, 4.4
n = 221	Chest pain	0	0	6	3.1	0	0, 6.1
	Hoarse voice	8	26.7	34	17.8	1.7	0.6, 4.4
	Shortness of breath	0	0	15	7.9	0	0, 2.1
	Summary Illness*	11	36.7	65	34.0	1.0	0.4, 2.4
	Symptoms	TC	C+	T	C-		[
	···J — F ····	(n=		(n=159)		OR	95% CI
		No.	%	No.	%		
	Fever	0	0	1	0.6	0	0,450.6
	Sore throat	0	0	5	3.1	0	0, 32.5
After-	Cough	0	0	4	2.5	0	0, 43.3
epidemic	Runny/Stuff Nose	1	14.3	19	11.9	1.23	<sup>†</sup>
(Week 9)	Wheezing	0	0	- 1	0.6	0	0,450.6
n = 166	Dyspnea	0	0	1	0.6	0	0,450.6
	Chest pain	0	0	1	0.6	0	0, 450.6
	Hoarse voice	0	0	1	0.6	0	0,450.6
	Shortness of breath	0	0	3	1.9	0	0,63.2
	Summary Illness*	0	0	3	1.9	0	0, 63.2

# Table 4. Correlation of Symptoms (in %) and S. pneumoniae pharyngeal carriage(TC) in Ranger Students, Class 4-99.

\* Summary variable: Any two of the following three symptoms: fever, cough, or sore throat and any two of the following: shortness of breath, dyspnea, hoarseness, or sore throat.

<sup>†</sup> = Cornfield limits invalid

### Figure 1. Percentage of Ranger students dropped for pneumonia, by class, 1991-99



\*6 were pneumonia cases recycled from class 4-99



Figure 2. The prevalence of positive cultures of Group A  $\beta$ -hemolytic *Streptococci* and *Streptococcus pneumoniae* before and at the end of each phase of Ranger training.

BL = Baseline I = Phase I, Ft. Benning II= Mountain Phase, Dahlonega, GA

t

III= Swamp Phase, Eglin AFB, FLA IV= Desert Phase, Dugway, UT

From: Moore RJ, Friedl KE, Kramer TR, Martinez-Lopez LE, Hoyt RW, Tulley RE, DeLaney JP, Askew EW, Vogel JA. Changes in soldier nutritional status and immune function during Ranger training course. USARIEM Technical Report No. T13-92, September 1992.



Figure 3. Proliferative activity of lymphocytes collected through the course and stimulated with pokeweed mitogen, phytohemagglutinin, concanavalin A, or tetanus toxoid <u>in vitro</u>. Values with dissimilar letters are different at p<0.05.

From: Moore RJ, Friedl KE, Kramer TR, Martinez-Lopez LE, Hoyt RW, Tulley RE, DeLaney JP, Askew EW, Vogel JA. Changes in soldier nutritional status and immune function during Ranger training course. USARIEM Technical Report No. T13-92, September 1992.



Figure 4. The prevalence of positive cultures of Group A  $\beta$ -hemolytic *Streptococci* and *Streptococcus pneumoniae* before (BL=baseline) and at the end of each phase of Ranger training.

From: Moore RJ, Friedl KE, Kramer TR, Martinez-Lopez LE, Hoyt RW, Tulley RE, DeLaney JP, Askew EW, Vogel JA. Changes in soldier nutritional status and immune function during Ranger training course. USARIEM Technical Report No. T13-92, September 1992.

#### APPENDIX C

#### Ranger Respiratory Disease Questionnaire

Last Name:		Firs	t Name:	SSN	•
Birth Date: mm	_/ dd _/yy	Age	In what state h	ave you lived most of y	our life?
Duty Station prior t	o starting Ranger tr	aining:			
Race/Ethnicity:	🛛 White 🛛 B	ack 🗇 Asian	🗇 Hispanic	Native American	Other
Rank MOS	Branch	Co	Platoon	Squad	

Check if you ever had the following: C Asthma C Seasonal allergies/hay fever C Flu Pneumonia In the past 30 days, have you been sick with a flu-like illness (cough, sore throat, fever/chills, etc.)? Yes No

Check any symptom you currently have:

Dfever/chills	🗖 diarrhea	🗇 wheezi			
sore throat	🗖 sinus (facial) pain	trouble breathing	tickling in chest or throat		
🗇 cough	🗇 stiff neck	🗖 chest pain	watery/runny eyes		
🗇 headache	stuffy/runny nose	hoarse voice	shortness of breath		
TYes No	At ANY TIME during Ranger tr	aining, did you seek ca	are for any of the above symptoms?		
TYes No	Have you had any of the above symptoms in the past 7 days? I yes I no				
OYes ONo	Has your Ranger Buddy been sick with any of the above symptoms during training? (if you have had more than one buddy, the answer is <i>yes</i> if ANY of them were sick)				
OYes ONo	Have you been to sick call or see	en a health care provid	er for any other reason during Ranger Training?		
·	If yes, give reason(s)				
OYes ONo	Are you taking any antibiotics?	If yes, what?			
TYes INo	Are you taking any medications	(including over-the-co	ounter) at all? If yes, list them:		

Smoking	Current Smoker	packs per day year started: _				
	G Former Smoker	packs per day	year started:		year quit:	
Alcohol	🗇 Non-drinker	Beers and/or mixed drink	s per week:	0-6	07-12	I more than 12

Since the beginning of Ranger training, have you put the following in, or near, your mouth: OYes ONo A cigarette lighted or smoked by someone else? An eating utensil already used by someone else? OYes ONo TYes DNo A toothbrush already used by someone else? A wash cloth or towel used by someone else (within the last 2 hours of your use)? OYes ONo OYes ONo A canteen used by someone else? OYes ONo A cup used by someone else? During Ranger training have you slept close to (less than 2 feet head-to-head) to other trainees? OYes ONo OYes ONo During the 2 weeks before Ranger training, were you in close contact with someone who had a respiratory illness? Do you feel you get enough food during Ranger training? OYes ONo Since the beginning of Ranger training, how many hours of sleep do you get each night? hours

How stressful is Ranger training for you?

□ Very stressful □ Somewhat stressful

Not stressful at all

### APPENDIX D

#### Ranger Respiratory Disease Questionnaire

Last Name:	First	Name:	SSN
Check any symp	tom you <b>currently have:</b>		
□ fever/chills □ sore throat □ cough □ headache	☐ diarrhea ☐ sinus (facial) pain ☐ stiff neck ☐ ches ☐ stuffy/runny nose	□ wheezing □ trouble breathing□ tic t pain □ wa □ hoarse voice	<ul> <li>vomiting/nausea</li> <li>kling in chest or throat</li> <li>atery/runny eyes</li> <li>shortness of breath</li> </ul>
Check any symp	tom you had during Mountain Phase:	· · · · ·	
☐fever/chills ☐ sore throat ☐ cough ☐ headache	☐ diarrhea ☐ sinus (facial) pain ☐ stiff neck ☐ ches ☐ stuffy/runny nose	□ wheezing □ trouble breathing□ tic t pain □ wa □ hoarse voice	kling in chest or throat
Check any symp	tom had during Swamp Phase:		
☐fever/chills ☐ sore throat ☐ cough ☐ headache	☐ diarrhea ☐ sinus (facial) pain ☐ stiff neck ☐ ches ☐ stuffy/runny nose	☐ trouble breathing ☐ tion st pain	<ul> <li>vomiting/nausea</li> <li>skling in chest or throat</li> <li>atery/runny eyes</li> <li>shortness of breath</li> </ul>
OYes ONo	Has your Ranger Buddy been sick w (if you have had more than one bud	dy, the answer is <i>yes</i> if AN Y	of them were sick)
🗗 Yes 🗇 No	At ANY TIME during Ranger training	ng, did you seek care for ar	iy of the above symptoms?
🛛 Yes 🗖 No			other reason during Ranger Training
	If yes, give reason(s)		, <u>, , , , , , , , , , , , , , , , , , </u>
Beers and/or m	iixed drinks per week: 🛛 Non-drink	er 🖸 0-6 🗍 7-12	I more than 12
During Ranger	training, did you put the following in you	ır mouth:	
YesNoYesNoYesNoYesNoYesNoYesNoYesNo	A cigarette lighted or smoked by son An eating utensil already used by so A toothbrush already used by some A wash cloth or towel used by some A canteen used by someone else? A cup used by someone else?	meone else? one else?	ours of your use)?
⊡Yes ⊡No	During Ranger training did you slee	p close to (less than 2 feet h	ead-to-head) to other trainees?
TYes No	Did you get enough food during Ran		
	Training, about how many hours of sleep has Ranger Training been for you?		
	C Very stressful C Somewhat st	ressful ON	lot stressful at all

- TAR

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#### APPENDIX E

MCXB-CO

22 October 1999

#### MEMORANDUM FOR Commander, U.S. Army Center for Health Promotion and Preventive Medicine, ATTN: MCHB-CG (BG Bettye H. Simmons), 5158 Blackhawk Road, Aberdeen Proving Ground (Edgewood Area), MD 21010-5403

#### SUBJECT: Epidemiologic Consultation (EPICON) Request

1. Request an epidemiologic consultation (EPICON) investigation be conducted at Fort Benning, GA, during the winter of 1999-2000 (Nov 99 to Mar 00). This investigation is necessary due to the continued past occurrence of outbreaks of acute respiratory disease (ARD) and pneumonia among students of the Ranger Training Brigade (RTB). The objectives of this EPICON would be to a) estimate the morbidity that respiratory pathogens have on Ranger trainees, b) identify risk factors for respiratory illness, and, c) suggest methods of reducing rates of respiratory illness among Ranger students and other military trainees.

2. Evidence from previous outbreaks among Ranger trainees, in 1990-1991, indicated that certain pathogens, to include *S. pneumoniae* and *S. pyogenes*, were associated with a large percentage of respiratory illness seen among the affected trainees. Both of these outbreaks were halted by the administration of intramuscular bicillin. During another outbreak of respiratory disease among Ranger trainees, in 1998-1999, *S. pneumoniae* was, again, prominent among the affected cases. It was discovered that during the intervening time period, the use of bicillin as a prophylactic measure against bacterial disease had been discontinued by the spring of 1998. Investigation of the 1998-99 epidemic was conducted by a USACHPPM EPICON team led by LTC(P) Stephen Craig. One of the major recommendations made at the time was that a follow-up study of the nature requested here be conducted among Ranger students conducting training during the winter of 1999-2000.

3. Intramuscular injections of bicillin have been utilized in the control of *S. pyogenes* and *S. pneumoniae* infections among military trainees since the 1950's. Currently, however, bicillin prophylaxis for military personnel is indicated only in response to group A beta-hemolytic streptococcus (GABHS) associated outbreaks. Efficacy studies of bicillin for prevention of pneumococcal pneumonia or febrile ARDs among military populations are lacking. However, the recent experience with the Ranger students would strongly suggest that bicillin has a broader effect in preventing acute respiratory diseases beyond simply eliminating GABHS. In addition, a recent Navy study has suggested some degree of efficacy (38%) of one dose of bicillin in preventing infections due to *S. pneumoniae*.

4. I have discussed these and other issues with the MEDDAC's DCCS, COL Lairie Stabler, LTC Carlos Parrado, and CPT(P) Bryan Alsip, and they agree that a study of this situation is a worthwhile effort. I also understand that the Ranger Training Brigade Commander, COL Frank Helmick, has agreed to offer his support to the study once the logistical arrangements have been finalized. Prior coordination for this study has been established with COL Jose L. Sanchez and Dr. Shellie Ann Kolavic at the USACHPPM. Any help that you could provide us with would be greatly appreciated.

JAMES L. BESON COL, MC Commanding