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RANDOMIZED, PLACEBO-CONTROLLED CLINICAL TRIAL OF ORAL AZITHROMYCIN PROPHYLAXIS AGAINST RESPIRATORY INFECTIONS IN A HIGH-RISK, YOUNG ADULT POPULATION

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Report No. 00-32

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Randomized, Placebo-Controlled Clinical Trial of Oral Azithromycin Prophylaxis against Respiratory Infections in a High-Risk, Young Adult Population

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Military Special Forces trainees undergo intense psychological and physical stressors that often lead to respiratory infection. During 1998–2000, 477 Navy Special Forces trainees were enrolled in a double-blind trial of oral azithromycin (1 g given weekly) plus a placebo injection, compared with benzathine penicillin G (1.2 million U) plus azithromycin placebo tablets. Among the 464 subjects with complete data, 44 developed acute respiratory infection (20 with pneumonia) during the 2 weeks of most intense training; of these subjects, 12 (27.3%) had evidence of *Chlamydia pneumoniae* infection and 7 (15.9%) had evidence of *Mycoplasma pneumoniae* infection. Trainees who received azithromycin were less likely than were trainees who received benzathine penicillin G to develop acute respiratory infection (risk ratio, 0.50; 95% confidence interval [CI], 0.28–0.92) and less likely at the end of training to report episodes of breathing difficulty (odds ratio [OR], 0.59; 95% CI, 0.34–1.01) or sore throat (OR, 0.66; 95% CI, 0.41–1.05). Compared with benzathine penicillin G prophylaxis, weekly oral azithromycin was superior in preventing respiratory infection in this population at transient high risk.

Epidemics of acute respiratory infection are common among military personnel, particularly among trainees. The US Department of Defense uses a number of vaccines and antibiotic interventions to reduce this morbidity [1–6]. Students attending the 25-week Basic Underwater Demolition/SEAL (BUD/S) school in Coronado, California, undergo some of the most intense physical and mental military training possible and have suffered a number of respiratory epidemics. In 1995, after BUD/S students experienced marked attrition due to pneumonia and necrotizing fasciitis, medical officials initiated aggressive preventive measures: benzathine penicillin G (1.2 million U), influenza vaccine, pneumococcal vaccine, and *Haemophilus influenzae* type B vaccine for incoming trainees. However, the incidence

Received 24 October 2000; revised 13 March 2001; electronically published 5 September 2001.

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Clinical Infectious Diseases 2001;33:983–9

1058-4838/2001/3307-0009

This research has been conducted in compliance with all applicable Federal Regulations governing the protection of human subjects in research.

Financial support: Report no. 00-32, supported by the Department of Defense Global Emerging Infections Systems and US Special Operations Command, MacDill Air Force Base, Florida, under work DoD/HA reimbursable–6609.

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of serious respiratory infections again increased in 1998, and clinicians were unable to determine the etiology. Subsequently, Navy policy officials requested assistance in identifying a more effective intervention to protect trainees.

METHODS

Study population. All Navy SEAL (Sea-Air-Land) special warfare personnel must complete BUD/S training [7]. Trainees are men of ≤28 years of age who must meet high military and physical standards. Every 2 months, a new class of 120 men enters training. Several weeks later, ~90 of these men remain when the class begins the intense "Hell-Week" period, during which students are required to undergo almost continuous physical activity during a 5-day period with a maximum total of 4 h of sleep [8]. After Hell-Week, only an average of 40 students remain to continue BUD/S training. Although most trainees leave voluntarily, epidemics of respiratory infection greatly increase attrition.

Treatment groups. Beginning in September 1998, classes of trainees were introduced to the study. Students who reported an allergy to penicillin or azithromycin or who were already taking those medications were not permitted to participate. Three days before Hell-Week began, study subjects were randomly assigned to 1 of 2 study groups: those subjects who received oral azithromycin (1 g, given as two 500-mg tablets) with placebo injection (vitamin B_{12}), and those who received oral azithromycin placebo (two 500-mg tablets) and 1.2 million U of benzathine penicillin G (standard of care). To cover a 2-week period during and immediately after Hell-Week, the azithromycin or azithromycin placebo tablets were again given 7 days later. Research personnel were blind to the treatments.

Data and specimen collection. On enrollment, students completed a brief baseline questionnaire and permitted collection of serum samples and throat samples for culture. Two weeks later, trainees were again asked to complete a brief questionnaire and to permit another throat sampling. About 5 weeks after enrollment, trainees were asked to donate a second serum sample.

During the Hell-Week period, trainees were continually monitored by Navy Corpsman and closely examined twice each day by clinicians. Study clinical data were collected each time a study participant presented at Special Warfare Center medical clinic with pneumonia, acute respiratory infection, or cellulitis.

Clinical trial outcomes were identified as (1) acute respiratory infection, (2) pneumonia, and (3) cellulitis or folliculitis requiring systemic antibiotics. Acute respiratory infection was defined as ≥6 h of acute respiratory infection symptoms (i.e., cough, wheezing, or shortness of breath). Pneumonia was defined as acute respiratory infection with radiographic evidence of a new infiltrate as read by a radiologist. Cellulitis was defined as dermatologic erythema, calor, and pain on palpation severe enough to warrant antibiotic therapy.

Table 1. Enrollment characteristics of subjects in a study of respiratory infections among Navy Special Forces trainees, by treatment group.

Characteristic	Treatment group	
	Azithromycin (n = 216)	Benzathine penicillin G (n = 248)
Median age, years	23.2	23.6
Race		
White	86.6	81.4
Black	1.8	1.6
Hispanic	7.9	10.1
Other	3.7	6.9
Medical history[a]		
Allergies or hay fever	4.6	4.8
Bronchitis	8.8	7.7
Pneumonia	6.9	6.8
Strep throat	19.9	10.9
Whooping cough	0.5	0.4
Taking antibiotics at time of enrollment[b]	13.4	15.3

NOTE. Data are % of subjects, unless otherwise indicated.

[a] As determined by a questionnaire.

[b] Most subjects who responded positively to this question were applying topical antibiotics; remaining subjects were receiving brief courses of oral regimens that were not expected to interfere with the clinical trial.

Whenever a subject developed acute respiratory infection, he was asked to permit the staff to obtain 4 throat swabs for identification of bacterial and viral pathogens, collection of an acute serum sample, Gram stain and culture of sputum, a complete blood count, and determination of oxygen saturation. Blood samples were obtained from different sites for 2 sets of cultures (anaerobic and aerobic) before antibiotics were administered. Subjects were followed for up to 35 days after enrollment.

Laboratory studies. All laboratory personnel were blind to treatment groups. With the exceptions of blood cultures, blood counts, and sputum studies, respiratory infection work was conducted at the Navy Respiratory Disease Laboratory of the Naval Health Research Center in San Diego [9], as described elsewhere [10, 11]. In brief, the testing included enrollment and 2-week–postenrollment pharyngeal cultures, for *Streptococcus pyogenes* and *Streptococcus pneumoniae* carriage, and acute respiratory infection viral and bacterial etiology studies, by culture, serological testing, and PCR tests.

Statistical analyses. Univariate and multivariate risk factor associations were examined by standard techniques. When data were sparse, exact CIs about ORs were calculated [12]. In Cox proportional hazard modeling, a subject was right-censored

Table 2. Outcomes of study of prophylactic regimens for respiratory infections among Navy Special Forces trainees, according to treatment group.

Outcome	Treatment group: Azithromycin (n = 216)	Treatment group: Benzathine penicillin G (n = 248)	Risk ratio (95% CI)
Clinical event			
All acute respiratory infection	6.5	12.9	0.50 (0.28–0.92)
Pneumonia	3.2	5.2	0.62 (0.25–1.52)
Cellulitis or folliculitis	10.6	13.7	0.78 (0.47–1.28)
Attrition by 35th day of training after enrollment	29.6	31.9	0.93 (0.71–1.22)
Finding of serological studies[a]			
Mycoplasma pneumoniae[b]	3.6	4.2	0.84 (0.28–2.52)
Chlamydia pneumoniae[b]	2.0	2.3	0.87 (0.17–4.09)[c]
Streptococcus pyogenenes[d]	0.5	1.9	0.27 (0.01–2.75)[c]

NOTE. Data are % of subjects, unless otherwise indicated.

[a] Enrollment, acute, and 5-week–postenrollment serum samples were compared. Samples were obtained from 196 subjects in the azithromycin group and 213 subjects in the benzathine penicillin G group, because some subjects did not permit final serum collection.

[b] Methods are described elsewhere [10]. A 4-dilution rise in titer (IgG or IgM) or change in IgM from negative to positive was considered evidence of infection [10].

[c] Because of small cell counts, data are OR (95% CI) determined with exact technique [12].

[d] A 2-dilution rise in antistreptolysin O and deoxyribonuclease B, determined by use of the microtiter plate technique, was considered evidence of acute infection.

Table 3. Self-reported characteristics of subjects in study of respiratory infections among Navy Special Forces trainees, 2 weeks after enrollment, according to treatment group.

Characteristic	Treatment group: Azithromycin (n = 209)	Treatment group: Benzathine penicillin G (n = 233)	OR (95% CI)
Symptom during training of ≥6 h duration			
Cough	48.3	49.4	0.96 (0.65–1.42)
Difficulty breathing	12.9	20.2	0.59 (0.34–1.01)
Feverish feeling	12.9	16.0	0.78 (0.44–1.37)
Runny nose	42.3	43.5	0.95 (0.64–1.41)
Sore throat	19.6	27.0	0.66 (0.41–1.05)
Wheezing	10.5	15.0	0.67 (0.36–1.22)
Possible sign of azithromycin toxicity			
Abdominal pain	1.9	2.2	0.89 (0.17–4.20)[a]
Diarrhea	3.4	3.0	1.11 (0.34–3.60)
Nausea	1.9	2.2	0.88 (0.17–4.16)[a]
Vomiting	—	1.3	0.00 (0.00–2.68)[a]
Diagnosed with cellulitis[b]	14.1	20.5	0.64 (0.37–1.09)
Treated with antibiotics for cellulitis[b]	23.8	29.0	0.76 (0.44–1.31)

NOTE. Data are % of subjects, unless otherwise indicated. Not all enrolled subjects completed the final questionnaire.

[a] Because of small cell counts, data are OR (95% CI), as determined by use of exact technique [12].

[b] As determined by a questionnaire.

Table 4. Laboratory results among subjects from the Navy Special Forces with pneumonia or acute respiratory infection, according to treatment group.

Laboratory finding, method	Treatment group: Azithromycin (n = 14)	Treatment group: Benzathine penicillin G (n = 30)[a]	OR (95% CI)[b]
Mycoplasma pneumoniae	1	6	0.31 (0.01–3.17)
Throat culture	0	1	—
Serological testing[c]	0	1	—
Direct PCR[c]	1	6	—
Chlamydia pneumoniae	4	8	1.10 (0.20–5.40)
Serological testing[c]	1	1	—
Direct PCR[c]	3	8	—
Streptococcus pneumoniae	0	0	—
Throat culture	0	1[d]	—
PCR/EIA[c]	0	0	—
Streptococcus pyogenes	1	0	—
Throat culture	1	0	—
Serological testing[e]	0	0	—

NOTE. Data are no. of subjects with positive results, unless otherwise indicated.

[a] Because of specimen nonavailability, some tests were done on only 27 or 29 specimens.
[b] Derived by exact methods [12].
[c] Methods are described elsewhere [10].
[d] Because of likely asymptomatic carriage, this was not considered evidence of infection.
[e] Methods are described elsewhere [11].

when he quit training or had been followed-up for 14 days after enrollment with no event, whichever came first.

RESULTS

During the study period (September 1998 through March 2000), 477 (93%) of 511 trainees were enrolled. The 2 study groups had very similar enrollment characteristics (table 1). In preparation for enrolling each class of trainees, the enrolling pharmacy technician used randomization software to generate a sequential assignment for each subject based on projected class size. When some members of the class were not enrolled, they failed to contribute to the balanced 1:1 randomization. This process led to unequally sized treatment groups. However, with the exception of "having a history of strep throat," the 2 study arms were very similar with respect to enrollment characteristics (table 1). Among the 477 enrolled subjects, data sufficient for multivariate modeling (complete data) were obtained from 464 subjects.

During the study period, 143 (31.0%) of the 464 study subjects failed to complete training. The attrition percentages were similar for both treatment groups: 64 subjects (29.6%) in the azithromycin group and 79 subjects (31.9%) in the benzathine penicillin G group (table 2) by the 35th day of training after enrollment. The average number of days of completed training was 26.7 for the azithromycin group and 25.6 for the benzathine penicillin G group. The most common reasons for attrition included "drop on request" (quitting), "medical roll" (deferred to another class after convalescence), and "medical drop" (condition prohibits success, e.g., asthma).

Among the 464 study subjects with complete data, 44 developed acute respiratory infection (20 with pneumonia), and 57 were treated with antibiotics for cellulitis or folliculitis. All blood cultures (anaerobic and aerobic) yielded negative results. Gram stain studies of sputum samples were nonspecific. Study outcome risks were lower for the azithromycin group (table 2), as follows: acute respiratory infection (risk ratio [RR], 0.50; 95% CI, 0.28–0.92), pneumonia (RR, 0.62; 95% CI, 0.25–1.52), and cellulitis or folliculitis (RR, 0.78; 95% CI, 0.47–1.28).

During the study, 2 patients in the benzathine penicillin G group developed necrotizing fasciitis. In 1, the right lower extremity was involved, requiring multiple debridements and skin grafts. No organism was recovered. The other patient's necrotizing fasciitis involved his right hand and forearm. Culture of samples taken from the necrotic site yielded penicillin-resistant *Staphylococcus aureus*.

Among the 409 subjects from whom enrollment and 5-week–postenrollment serum specimens were obtained, the RR also favored the azithromycin group; however, the CIs all included 1.0 (table 2), as follows: *Mycoplasma pneumoniae* (RR, 0.84; 95% CI, 0.28–2.52) and *Chlamydia pneumoniae* (RR, 0.87; 95% CI, 0.17–4.09).

A comparison of 2-week–postenrollment questionnaires between groups again suggested better protection among the azithromycin group (table 3), particularly for questions regarding about "difficulty breathing" (OR, 0.59; 95% CI, 0.34–1.01), "sore throat" (OR, 0.66; 95% CI, 0.41–1.05), and "diagnosed with cellulitis" (OR, 0.64; 95% CI, 0.37–1.09). There was no increase in side effects in the azithromycin group (table 3).

Among the 44 subjects with complete laboratory data who developed acute respiratory infection, 12 (27.3%) had evidence of *C. pneumoniae* infection and 7 (15.9%) had evidence of *M. pneumoniae* infection (table 4). Culture of throat samples obtained from 1 subject each yielded adenovirus, parainfluenza virus type 1, and parainfluenza virus type 3.

Cox proportional hazard modeling again suggested a better protective effect for the azithromycin group in preventing acute respiratory infection (RR, 0.48; 95% CI, 0.25–0.89), pneumonia (RR, 0.59; 95% CI, 0.24–1.49), and cellulitis or folliculitis (RR, 0.75; 95% CI, 0.44–1.28). The probability curves also suggest better protection for those subjects who received azithromycin (figure 1). In the Cox modeling, the only risk factor statistically associated with an outcome was season for the cellulitis model. All other models were unadjusted.

Considering throat culture results, there was no indication that either study group was statistically more likely to have a culture positive for *S. pneumoniae* or *S. pyogenes* on enrollment or at the end of training (table 5). However, among end-of-training *S. pneumoniae* isolates, all 4 isolates from the azithromycin group were resistant to azithromycin [13], whereas only 1 of 3 isolates from the benzathine penicillin G group had intermediate resistance to azithromycin. This suggests that azithromycin therapy may select for asymptomatic carriage of resistant organisms.

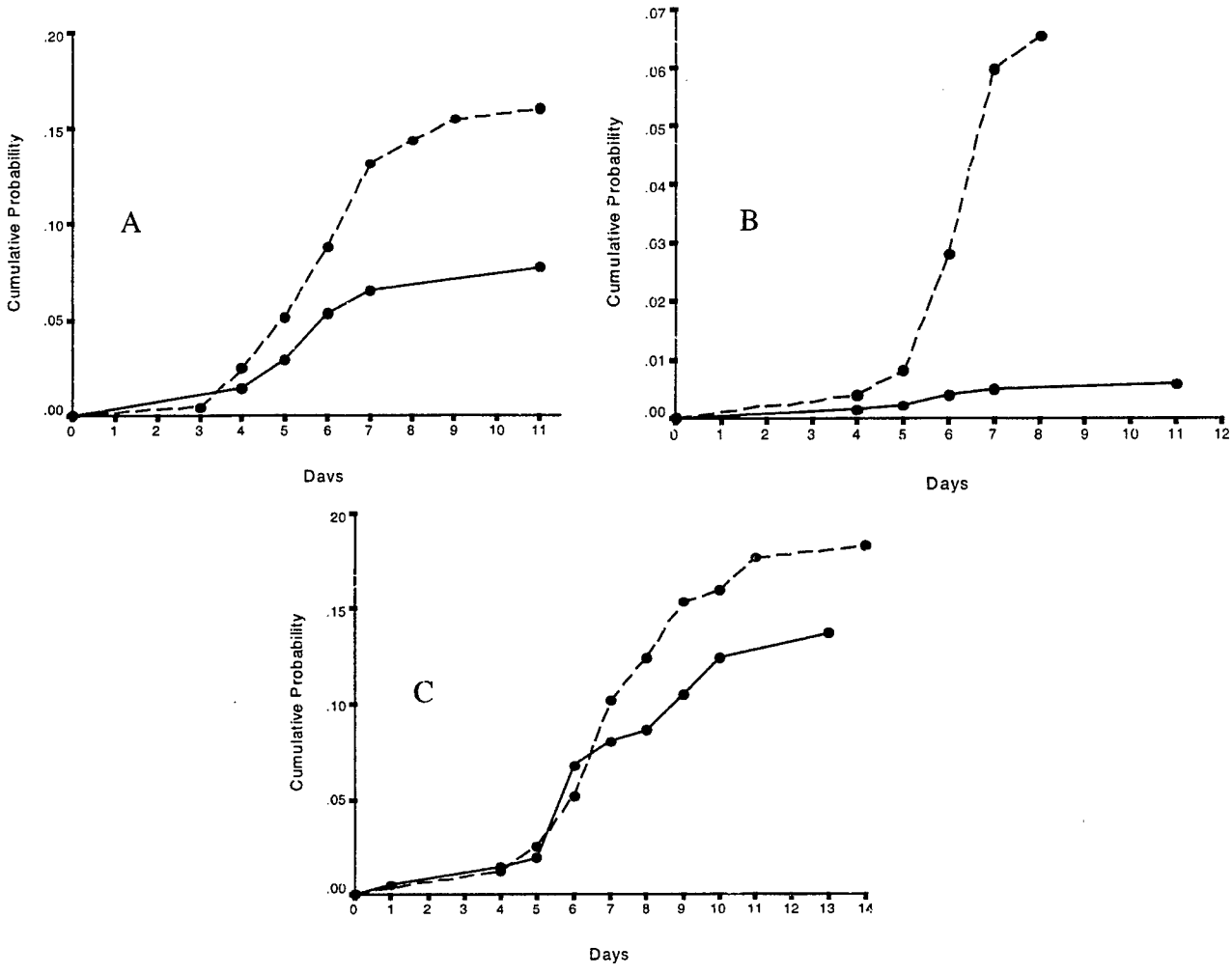

Figure 1. Probability of study subjects developing acute respiratory infection *(A)*, pneumonia *(B)*, or cellulitis *(C)*, according to treatment group. All modeling was done with Cox proportional hazard technique. Subjects were right-censored if they left training or reached 14 days of training after enrollment. *Solid lines*, azithromycin group; *dashed lines*, benzathine penicillin G group.

Table 5. Antibiotic susceptibility of bacterial isolates, determined by use of E test method [13], according to treatment group in study of respiratory infections among Navy Special Forces trainees.

Organism, time point, group	No. of isolates	Penicillin G		Azithromycin		Ceftriaxone		Trimethoprim-sulfamethoxazole	
		R	I	R	I	R	I	R	I
Streptococcus pneumoniae									
Enrollment									
Azithromycin (n = 216)	5	1	1	2	—	—	—	1	—
Penicillin (n = 247)	6	—	1	1	—	—	—	—	—
End of training									
Azithromycin (n = 210)	4	2	1	4	—	—	1	—	2
Penicillin (n = 235)	3	—	3	—	1	—	—	—	—
Streptococcus pyogenes									
Enrollment									
Azithromycin (n = 216)	5	—	—	3	—	—	1	3	—
Penicillin (n = 247)	3	—	—	—	—	—	—	—	—
End of training									
Azithromycin (n = 210)	1	—	—	1	—	—	—	1	—
Penicillin (n = 235)	—	—	—	—	—	—	—	—	—

NOTE. Data are no. of isolates displaying resistance: I, intermediate; R, resistant.

DISCUSSION

Controlling respiratory infection among crowded and stressed military populations is very difficult [14]. Special Forces trainees are particularly susceptible to epidemics of respiratory infection. In addition to the epidemics that we have previously mentioned among Navy BUD/S trainees, US Army Ranger trainees have experienced a series of outbreaks of respiratory infection, often with pneumonia [14–17]. This has led to aggressive use of monthly prophylaxis with benzathine penicillin G. When benzathine penicillin G prophylaxis was halted in March 1998, pneumonia outbreaks occurred soon thereafter and again the following winter. During the spring of 1999, Army investigators documented 29 cases of pneumonia among a cohort of Ranger trainees, for an incidence of 7.1 cases per 100 students per month [16]. *S. pneumoniae* was implicated by laboratory tests. Such outbreaks of respiratory infection are remarkable in that Special Forces trainees are some of the most physically fit persons in military ranks, and they often have years of previous military service, during which they can develop immunity to common respiratory pathogens.

It seems likely that the extreme psychological and physical stressors of Special Forces training are responsible for these outbreaks. Although the research has not specifically targeted Special Forces trainees, there is a growing body of evidence demonstrating the association of psychological stress and acute infections [18–20] or reactivation of latent infections [21]. Data from military populations [22] and research involving elite athletes [23, 24] suggest that Special Forces trainees likely have immunologic compromise due to their intense physical activity.

This double-blind, placebo-controlled study suggests that oral azithromycin (1 g given weekly) is beneficial in reducing the incidence of respiratory infection compared with the previous preventive regimen of benzathine penicillin G (1.2 million U administered im). The azithromycin therapy was well tolerated and had no more side effects than did placebo tablets. It is easy to administer, and the cost is reasonable for protecting small groups of trainees for short periods of time. However, other research teams in other countries have demonstrated an association of macrolide use with increasing macrolide resistance among streptococci [25–27]. We are concerned that wide unmonitored use of azithromycin could lead to endemic resistant strains in the United States.

This study has a number of limitations. A significant number of study subjects had no identified etiology for their pneumonia or acute respiratory infection. Hence, some of the study outcomes might represent a noninfectious process, such as cold submersion–induced pulmonary infiltrates [28]. Trainees often train in the Pacific Ocean, where water temperature may drop to 11.7°C. However, such pulmonary infiltrates are thought to be very rare [29]. Trainees might also develop respiratory infection from aspiration of seawater or gastrointestinal contents.

The study has a number of strengths. The subjects were very closely monitored for study outcomes. Antibiotic prophylaxis was carefully documented, and the population had little mixing with other populations during the study period.

From these study data, azithromycin treatment seems a better choice than injection of benzathine penicillin G for the short-term protection of military trainees who undergo extreme psy-

chological and physical stressors. Should such an intervention be adopted, we strongly recommend concomitant surveillance for macrolide-resistant streptococci in the treated populations.

Acknowledgments

We thank the following for assistance in conducting the trial: Kevin Walters, Norman Moser, James Brixey, Charles Williams, William Schluderberg, Samuel Villareal, Richard Tavernaro, and Jared Reichard (Medical Department, Naval Special Warfare Center, Coronado, California); Steve Giebner (Naval Special Warfare Command, Coronado, California); Cory Beckner (Pharmacy Department, Naval Medical Center San Diego); Scott Thornton (Navy Environmental Preventive Medicine Unit No. 5, San Diego); and Marietta Malasig (Naval Health Research Center, San Diego).

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REPORT DOCUMENTATION PAGE

1. Report Date (DD MM YY)	2. Report Type	3. DATES COVERED (from - to)
September 18, 2000	New	Sept 1998 to Mar 2000

4. TITLE AND SUBTITLE
Randomized, Placebo-Controlled Clinical Trial of Oral Azithromycin Prophylaxis Against Respiratory Infections in a High Risk, Young Adult Population

5a. Contract Number:
5b. Grant Number:
5c. Program Element:
5d. Project Number:
5e. Task Number:
5f. Work Unit Number: 6609

IRB Protocol 31260

6. AUTHORS Gregory C. Gray, MD, MPH, Peter Witucki, MD; Mark T. Gould, MD; Stephen J. Bell, MD; Katia M. Hiliopoulos, MPH; Jamie A. McKeehan; Julie M. Fuller; Christopher P. Barrozo; Marie K. Hudspeth; Tyler C. Smith, MS; Elizabeth K. Ledbetter, MD, MPH; and Mark R. Wallace, MD

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Naval Health Research Center
P.O. Box 85122
San Diego, CA 92186-5122

9. PERFORMING ORGANIZATION REPORT NUMBER
Report No. 00-32

8. SPONSORING/MONITORING AGENCY NAMES(S) AND ADDRESS(ES)
Chief, Bureau of Medicine and Surgery
MED-02
2300 E St NW
Washington, DC 20372-5300

10. Sponsor/Monitor's Acronyms(s)
BUMED

11. Sponsor/Monitor's Report Number(s)

12 DISTRIBUTION/AVAILABILITY STATEMENT
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13. SUPPLEMENTARY NOTES
Published in: Clinical Infectious Diseases, 2001, 33 (Oct), 983-989

14. ABSTRACT (maximum 200 words)

Special Forces military trainees undergo intense psychological and physical stressors that often lead to respiratory disease and soft tissue infections, including necrotizing fasciitis. In an effort to prevent such morbidity, from September 1998 to March 2000, 477 Navy Special Forces trainees were enrolled in a double-blind, placebo-controlled trial. The trial compared 1 g weekly oral azithromycin plus a placebo injection with 1.2 million units benzathine penicillin G (BPG) plus azithromycin placebo tablets as prophylaxis against acute respiratory illness and cellulitis. Subjects were closely observed for the 2 weeks of training when stressors were the most intense. Among the 464 with near-complete data, 44 developed acute respiratory disease (20 with radiographic evidence of pneumonia), and 57 developed cellulitis or folliculitis requiring antibiotics. Twelve (27.3%) of the 44 patients with acute respiratory disease had evidence of *C. pneumoniae* infection and 8 (18.2%) had evidence of *M. pneumoniae* infection. Trainees receiving azithromycin were less likely to develop acute respiratory disease (risk ratio[RR] = 0.50; 95% confidence interval [CI], 0.28-0.92), less likely at the end of training to report episodes of difficulty breathing (odds ratio [OR] = 0.59; 95% CI, 0.34-1.01) or sore throat (OR = 0.66; 95% CI, 0.41-1.05), and had a lower risk by Cox proportional hazard modeling of developing acute respiratory disease (RR = 0.48; 95% CI, 0.25-0.89) over time. There was no increase in side effects associated with azithromycin ingestion. Compared with BPG prophylaxis, weekly oral azithromycin was superior in preventing respiratory disease morbidity in this training population at transient high risk of disease.

15. SUBJECT TERMS
epidemiology, military medicine, acute respiratory disease, clinical trial, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, adenovirus

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b.ABSTRACT	c. THIS PAGE			Commanding Officer
UNCL	UNCL	UNCL	UNCL	7	19b. TELEPHONE NUMBER (INCLUDING AREA CODE) COMM/DSN: (619) 553-8429