Weekly Oral Azithromycin as Prophylaxis for Agents Causing Acute Respiratory Disease


Since the 1950s the U.S. military has used intramuscular injections of benzathine penicillin G (BPG) to control outbreaks of respiratory disease. In an effort to find an alternative prophylaxis, a randomized field trial was conducted among 1,016 male U.S. Marine trainee volunteers at high risk for respiratory disease. Participants were evaluated for evidence of acute respiratory infection by serological tests on pretraining and posttraining sera (63 days apart). Oral azithromycin prophylaxis (500 mg/w) outperformed BPG, preventing infection from Streptococcus pyogenes (Efficacy [E] = 84%; 95% confidence interval [CI], 63%–93%), Streptococcus pneumoniae (E = 80%; 95% CI, 50%–92%), Mycoplasma pneumoniae (E = 64%; 95% CI, 25%–83%), and Chlamydia pneumoniae (E = 58%; 95% CI, 15%–79%) in comparison with results in a no-treatment group. Azithromycin group subjects reported few side effects and less respiratory symptoms than the BPG and no-treatment groups. According to serological tests, oral azithromycin is an effective alternative prophylaxis to BPG for military populations.

Both in the preantibiotic era and in recent years, acute respiratory infections have been frequent causes of outpatient and inpatient morbidity among adults in the United States, especially military personnel [1–6]. Studies of respiratory disease in military personnel have led to a number of vaccine and antibiotic prophylactic therapies [4, 5]. These interventions have been proven effective in both civilian and military populations.

Since the 1950s, intramuscular injections of benzathine penicillin G (BPG) have been used to prevent Streptococcus pyogenes infections [7–10] and to combat Streptococcus pneumoniae pneumonia epidemics [11] among new military personnel. Generally, BPG has been safe and effective; however, reports of penicillin tolerance among S. pyogenes isolates [12–14] and penicillin resistance [15] among S. pneumoniae isolates threaten military preventive strategies. At least one authority has suggested that penicillin resistance among S. pyogenes isolates is likely to occur [16]. The emergence of more virulent S. pyogenes strains [17, 18] and their severe disease manifestations [19–21] are further causes for concern.

Easily administered and safe alternative therapies to BPG are needed, particularly for persons allergic to penicillin [22]. Recently, low-dose oral erythromycin has been used with some success, although the twice-daily dosing requirements and gastrointestinal side effects have caused compliance problems [22–23]. Ideally, new prophylactic therapies should be effective in preventing other common causes of upper and lower respiratory tract infection among military populations, such as Mycoplasma pneumoniae, Chlamydia pneumoniae, and Haemophilus influenzae [24–26].

New macrolides, with long half-lives and activity against many bacterial respiratory pathogens, are logical candidates for such alternative therapy. The purpose of this study was to examine the prophylactic efficacy of one such macrolide, azithromycin, in a military population at high risk for acute respiratory infection.

Methods

Study Population

The Infantry Training School at Camp Pendleton, California, known for recent epidemics of acute respiratory disease and pneumonia [4], was selected as the study site. This school
provides 9 weeks of combat training to new Marines after they complete 11 weeks of initial recruit training in San Diego. Training takes place in companies of ~320 men and involves many stresses, including exhaustive tests of physical endurance. Marines are housed in open-bay barracks with ~80 men per bay. Their beds are oriented head to toe, with an estimated 75 square feet of living space per man. Marines spend ~2 weeks in the field in 2- to 3-day intervals, sleeping in small tents. All Marines have unlimited access to medical care. A large medical clinic, providing 24-hour care, is supplemented by field medical teams whenever the Marines leave the immediate training area.

During four enrollment periods between November 1994 and January 1995, Marines were screened and enrolled in the study within 24 hours of arrival at the Infantry Training School. Marines were excluded from enrollment if they had a penicillin, erythromycin, or azithromycin allergy or if they were taking a theophylline preparation. Medical providers were notified of the study participation of all study volunteers.

### Treatment Groups

Participants were assigned to one of three treatment groups, on the basis of a random number procedure: (1) azithromycin, two 250-mg tablets orally, once every week; (2) BPG, 1.2 million units intramuscularly, once, upon enrollment (standard epidemic intervention); or (3) no prophylaxis (standard of care). A research assistant strictly managed azithromycin administration by checking weekly rosters of subjects selected to receive the therapy and issuing the corresponding number of tablets to small training groups. Staff noncommissioned officers monitored and verified ingestion with open-mouth checks.

### Data and Specimen Collection

Before reporting to Infantry Training School, many study participants had received pneumococcal and adenovirus (types 4 and 7) vaccines during their recruit camp training 3–4 months earlier (table 1). Vaccine data were abstracted from the records of the Marine Corps Recruit Depot Medical Clinic (San Diego).

Both upon enrollment and at the end of training (median, 63 days later), study participants completed a questionnaire, donated 15 mL of blood, and permitted a throat culture. The enrollment questionnaire collected demographic information and recent data about symptoms. The posttraining questionnaire requested information regarding symptoms of respiratory illness and also asked subjects if they had sought treatment for respiratory illness since enrolling in the study. For subjects in the azithromycin group, additional information was requested, including the number of doses taken and reasons for missing any doses.

Study subjects were considered to have an acute respiratory infection if they visited military sick call with any of the following: a sore or inflamed throat, a cough, difficult or rapid breathing, or physical-examination findings consistent with respiratory infection. These persons were further evaluated with throat swab sampling and nasopharyngeal aspiration with use of 3 mL of a sterile solution wash and a Delee suction catheter with trap. If the nasopharyngeal aspirate was inadequate, a calcium alginate swab was used to collect a nasopharyngeal culture specimen. A research assistant also administered a clinical evaluation questionnaire that collected information on the duration of the current illness, physical examination findings, whether chest radiography was performed, diagnosis, antibiotic regimen prescribed, and medical conditions contributing to the current illness.

### Laboratory Studies

All laboratory personnel were blinded with regard to specimen linkage with treatment groups.

### Table 1. Enrollment characteristics of study subjects assigned to the three treatment groups for prophylaxis against acute respiratory infection.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Oral azithromycin (n = 366)</th>
<th>Benzathine penicillin G (n = 366)</th>
<th>No treatment (n = 370)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (y)</td>
<td>19</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>15.3</td>
<td>15.3</td>
<td>16.9</td>
</tr>
<tr>
<td>Black</td>
<td>4.2</td>
<td>5.1</td>
<td>5.9</td>
</tr>
<tr>
<td>White</td>
<td>73.2</td>
<td>71.1</td>
<td>73.5</td>
</tr>
<tr>
<td>Other</td>
<td>7.3</td>
<td>8.5</td>
<td>3.7</td>
</tr>
<tr>
<td>Home of record</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>California</td>
<td>20.5</td>
<td>20.9</td>
<td>15.5</td>
</tr>
<tr>
<td>Texas</td>
<td>15.1</td>
<td>17.3</td>
<td>18.2</td>
</tr>
<tr>
<td>Illinois</td>
<td>8.5</td>
<td>9.6</td>
<td>10.1</td>
</tr>
<tr>
<td>Missouri</td>
<td>4.9</td>
<td>3.6</td>
<td>4.9</td>
</tr>
<tr>
<td>Washington</td>
<td>4.7</td>
<td>3.0</td>
<td>3.5</td>
</tr>
<tr>
<td>Other</td>
<td>46.3</td>
<td>45.3</td>
<td>47.8</td>
</tr>
<tr>
<td>Vaccination</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenovirus</td>
<td>43.0</td>
<td>44.4</td>
<td>43.4</td>
</tr>
<tr>
<td>Pneumococcal</td>
<td>57.3</td>
<td>55.9</td>
<td>58.3</td>
</tr>
<tr>
<td>Symptoms during previous week</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(all for &gt;1 d)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>44.5</td>
<td>44.3</td>
<td>48.9</td>
</tr>
<tr>
<td>Fever</td>
<td>13.2</td>
<td>9.0</td>
<td>12.5</td>
</tr>
<tr>
<td>Runny nose</td>
<td>49.3</td>
<td>50.0</td>
<td>51.4</td>
</tr>
<tr>
<td>Sore throat</td>
<td>31.4</td>
<td>29.7</td>
<td>33.2</td>
</tr>
<tr>
<td>Breathing illness</td>
<td>8.3</td>
<td>8.5</td>
<td>12.8</td>
</tr>
<tr>
<td>Pharyngeal colonization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S. pyogenes</td>
<td>2.5</td>
<td>1.1</td>
<td>2.2</td>
</tr>
<tr>
<td>S. pneumoniae</td>
<td>1.7</td>
<td>0.8</td>
<td>1.4</td>
</tr>
</tbody>
</table>

NOTE. The clinical trial groups received oral azithromycin (500 mg/w), 1.2 million units intramuscularly of benzathine penicillin G, injected upon enrollment, or no treatment (standard of care). Data were available for at least 96% of subjects for each characteristic.
Streptococcus identification. Throat and nasal swabs were plated onto a 5% sheep blood agar plate within 4 hours of sample collection and incubated in 5% CO2 at 35°C. Plates were examined at 24 and 48 hours for ß- and/or ß-hemolytic colonies, which were subcultured for isolation. Isolation and identification of S. pyogenes and S. pneumoniae were accomplished with standard procedures [27, 28]. All ß-hemolytic, catalase-negative, gram-positive cocci were screened for streptococcal antigens (Lancefield groups A, B, C, F, G; Difco, Detroit), and biochemical confirmation was done with the API 20S kit (bioMérieux Vitek; Hazelwood, MO). α-Hemolytic streptococci that were gram-positive and catalase-negative and had a positive optochin disk reaction were presumed to be S. pneumoniae. Biochemical confirmation was done by bile-solubility evaluation and with use of the API 20S kit.

Streptococcus antimicrobial testing. The MICs of azithromycin, erythromycin, penicillin, and cefotaxime against S. pyogenes and S. pneumoniae were determined with the Etest (AB Biodisk, Solna, Sweden). Isolates were resuspended in 1 mL of sterile PBS. Suspensions were inoculated onto Mueller-Hinton sheep blood agar plates (Hardy Diagnostic; Santa Maria, CA), and after 10–15 minutes of drying, the Etest strips were applied. Susceptibility plates were incubated at 35°C under 5% CO2 for 24 hours. MICs were defined as the concentrations of antimicrobial present on the E-test strips at the point of intersection with the elliptical zone of inhibition of growth on the plates. MIC breakpoints defined by the National Committee for Clinical Laboratory Standards [29, 30] were used to interpret results.

Serological testing. Sera were tested for S. pyogenes antibodies by the antistreptolysin O (ASO) and the antideoxyribonuclease B microtiteration (DNase B) procedures, with use of a 0.10-log scale [31, 32]. Bacto-Streptolysin O reagent (Difco), Streptolysin-B reagent and enzyme (Wampole; Cranbury, NJ), and Bacto-Streptolysin O buffer dried (Difco) were prepared and used as described by the manufacturers. A two-dilution rise (0.2-log change) in titer (pretraining to posttraining) of either antigen was considered evidence of recent S. pyogenes infection [33].

C. pneumoniae—specific IgG, IgA, and IgM were measured by the microimmunofluorescence test, with elementary bodies of C. pneumoniae Kajaani 6 as the antigen [34]. Sera were tested in serial twofold dilutions from 1:32 for IgG and 1:16 for IgA to the endpoint. IgM antibodies were first screened at a dilution of 1:16, and positive sera were retested after treatment with goat antibody to human IgG antibody (Gullsorb; Gull Laboratories, Salt Lake City). A positive, acute C. pneumoniae infection was defined as a fourfold rise in IgG or IgA titer (with enrollment IgM <1:16) or a pretraining to posttraining change in IgM titer from <1:16 to ≥1:16 [35].

EIAs for IgM and IgG on paired sera were performed with use of a whole-cell lysate of M. pneumoniae, as previously described [36]. Endpoint titration was performed on every serum, and a fourfold rise in IgG or IgM titer or a change in IgM titer from negative to positive was considered serological evidence of acute infection.

Antibodies to pneumolysin (specific for S. pneumoniae), H. influenzae, and Moraxella catarrhalis were also measured by EIA [37, 38]. These results were recorded in optical density units on a continuous scale (not a titered dilution scale). As per previous published reports, a twofold (100%) rise in IgG titer (pretraining to posttraining) against pneumolysin was considered evidence of recent infection [37, 39]. Similarly, a 2.5-fold increase in IgG titer was considered evidence of recent infection in the EIAs for H. influenzae and M. catarrhalis [38].

Nucleic acid detection for C. pneumoniae. Nasopharyngeal aspirates were evaluated for C. pneumoniae with use of PCR. Nucleic acid was extracted from 400 µL of aspirate by means of QIAamp DNA isolation columns (Qiagen, Chatsworth, CA), as described by the manufacturer. Twenty µL of eluate from each column was used for specific PCR amplification of C. pneumoniae DNA. Positive controls consisting of C. pneumoniae organisms and several negative controls were included in each assay.

Primers used for C. pneumoniae amplification were CpnA and PTW51, which resulted in a 369-bp amplified fragment [40]. The PCR reaction was performed in 10 mM of Tris (pH 8.3), 75 mM of KCl, and 2.5 mM of MgCl2 (with use of primers at 0.5 µM), 0.2 mM of dNTPs, 0.5 U of uracil DNA glycosylase, 1.8 U of Tth DNA polymerase (Perkin-Elmer Cetus, Norwalk, CT), and 1.4 µM of Tth antibody (Clontech Laboratories, Palo Alto, CA). Amplification parameters were 25°C for 10 minutes and 95°C for 5 minutes, followed by 40 cycles of 94°C for 10 seconds, 58°C for 30 seconds, and 72°C for 30 seconds. Following amplification, PCR products were detected in a liquid hybridization format using a 32P-labeled C. pneumoniae—specific probe, PTW50 [40].

Statistical Analyses

Potential risk factors for the various clinical and laboratory outcomes were evaluated for relative risk. Confidence intervals about relative risk calculations were determined by the Taylor series method [41]. Efficacy calculations were made with the following formula:

\[
Efficacy (E) = 1 - \text{relative risk (RR)}
\]

Results

Study Participation

Written informed consent was obtained from 1,102 Marines (95% participation). Of these, 1,038 (94%) were followed throughout their Infantry Training School experience. Upon enrollment, subjects assigned to the three treatment arms were similar with regard to distribution of age, race, home of record, vaccine history, colonization with streptococci, and recent acute respiratory disease symptoms (table 1).
 Azithromycin Side Effects

Thirty-four (10.2%) of 334 azithromycin group Marines who completed postraining questionnaires reported at least one episode of upset stomach after therapy; however, only three of these subjects stopped taking the tablets. Other reported side effects included drowsiness or weakness (n = 5), change in appetite (n = 3), “feeling hot” (n = 3), and dizziness (n = 2). There was no statistical difference between the three study groups in reports of ≥1 day of diarrhea.

Evidence of Clinical Respiratory Disease

To reduce potential confounding, three subjects who had <55 or >100 days of training were excluded from analyses. An additional 19 azithromycin group subjects were excluded because they missed ≥1 week of therapy. Despite prophylactic interventions among two-thirds of the 1,016 remaining subjects, considerable evidence of clinical respiratory disease was apparent.

Overall, 730 (71.9%) of the Marines had evidence of acute respiratory disease; 133 (13.1%) visited the medical clinic with symptoms of acute respiratory disease; 286 (28.1%) had serological evidence of infection with at least one bacterial pathogen; and 638 (62.8%) reported ≥1 day of cough, fever, sore throat, or trouble breathing during training.

Clinical Evaluations

As evidence of characteristic stoicism, only 133 (18.2%) of the 730 Marines with evidence of acute respiratory disease sought medical attention. These 133 ill subjects were more likely than other subjects to report cough, fever, runny nose, or sore throat for ≥1 day on the postraining questionnaire (data not shown). The ill subjects also had a higher relative risk (RR = 2.3; 95% CI, 1.3–4.1) of serological evidence of C. pneumoniae infection over the 63 days of training.

Clinical data were obtained from 83 (62.4%) of the 133 ill subjects during their medical clinic visits. Clinicians confirmed the following signs and symptoms during these clinical visits: cough in 88%, sore or inflamed throat in 77%, runny nose in 52%, and oral temperature of ≥100°F in 32%. Patients experienced a median of 3 days of illness (range, 1–21 days) before seeking medical attention. Twelve (14.6%) of 82 ill patients who permitted nasopharyngeal aspirate sampling had PCR evidence of C. pneumoniae (no difference among treatment groups).

Three subjects (one from the no-treatment group and two from the BPG group) were hospitalized because of radiographic evidence of pneumonia. The no-treatment patient had received both adenovirus and pneumococcal vaccines during recruit training. His sputum gram stain result was not reported, but he had serological evidence of C. pneumoniae infection. Neither patient from the BPG group with pneumonia had received either vaccine. The sputum gram stains for both were consistent with S. pneumoniae infection, and both had serological evidence of M. pneumoniae infection.

Treatment Group Comparisons

Clinical evaluations, self-reported symptoms, postraining colonization with streptococci, and serological findings were evaluated by treatment group (table 2). Azithromycin group subjects experienced fewer hospitalizations for pneumonia and fewer medical visits for acute respiratory infection (table 2) than did subjects in the other two groups; however, these differences were not statistically significant.

Serological evidence of infection. Azithromycin group subjects were less likely than the no-treatment group subjects to have serological evidence of infection with 1 or more bacterial pathogens (RR = 0.38; 95% CI, 0.28–0.51). Azithromycin protected subjects against infection from a number of specific pathogens, as shown in table 2.

<table>
<thead>
<tr>
<th>Outcome variable</th>
<th>Oral azithromycin (n = 319)</th>
<th>Benzathine penicillin G (n = 346)</th>
<th>No treatment (n = 351)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median no. of follow-up days</td>
<td>63</td>
<td>63</td>
<td>63</td>
</tr>
<tr>
<td>Hospitalized for pneumonia</td>
<td>0</td>
<td>0.6</td>
<td>0.3</td>
</tr>
<tr>
<td>Visited clinic with acute respiratory symptoms*</td>
<td>11.6</td>
<td>13.9</td>
<td>13.7</td>
</tr>
<tr>
<td>Symptoms during training (all for &gt;1 d)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>37.0</td>
<td>57.8</td>
<td>54.2</td>
</tr>
<tr>
<td>Fever</td>
<td>20.4</td>
<td>28.9</td>
<td>28.7</td>
</tr>
<tr>
<td>Runny nose</td>
<td>52.5</td>
<td>61.0</td>
<td>54.0</td>
</tr>
<tr>
<td>Sore throat</td>
<td>35.4</td>
<td>46.0</td>
<td>45.3</td>
</tr>
<tr>
<td>Breathing illness</td>
<td>11.3</td>
<td>19.7</td>
<td>16.9</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>13.2</td>
<td>17.3</td>
<td>14.3</td>
</tr>
<tr>
<td>New pharyngeal colonization at end of training†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With S. pyogenes</td>
<td>0.3</td>
<td>4.8</td>
<td>8.3</td>
</tr>
<tr>
<td>With S. pneumoniae</td>
<td>2.1</td>
<td>0.7</td>
<td>0.6</td>
</tr>
<tr>
<td>Serological evidence of infection‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antistreptolysin O</td>
<td>1.9</td>
<td>6.5</td>
<td>11.9</td>
</tr>
<tr>
<td>Antideoxyribonuclease B</td>
<td>3.9</td>
<td>10.3</td>
<td>12.9</td>
</tr>
<tr>
<td>S. pneumoniae</td>
<td>1.6</td>
<td>5.0</td>
<td>8.2</td>
</tr>
<tr>
<td>M. pneumoniae</td>
<td>2.9</td>
<td>7.6</td>
<td>8.2</td>
</tr>
<tr>
<td>C. pneumoniae</td>
<td>3.2</td>
<td>6.8</td>
<td>7.6</td>
</tr>
<tr>
<td>H. influenzae</td>
<td>0.6</td>
<td>0.0</td>
<td>0.3</td>
</tr>
<tr>
<td>M. catarrhalis</td>
<td>1.0</td>
<td>1.2</td>
<td>0.6</td>
</tr>
</tbody>
</table>

* Patients had clinical evidence of an acute respiratory infection or they reported that they visited the medical clinic with a “breathing illness.”
† Percentage of subjects whose enrollment pharyngeal cultures were negative for this agent.
‡ Due to exhaustion of sera, some assays were run on fewer pairs of sera, but every test was run on at least 94% of serum pairs.
bacterial pathogens: *S. pyogenes*, per ASO (E = 84%; 95% CI, 63%–93%); *S. pyogenes*, per DNAse B (E = 70%; 95% CI, 44%–84%); *S. pneumoniae* (E = 80%; 95% CI, 50%–92%); *M. pneumoniae* (E = 64%; 95% CI, 25%–83%); and *C. pneumoniae* (E = 58%; 95% CI, 15%–79%) (table 3). In contrast, the BPG group had serological evidence of protection against only *S. pyogenes* by the ASO assay (E = 45%; 95% CI, 10%–66%). The pneumococcal vaccine, as shown by the pneumolysin serological test, offered no protection against *S. pneumoniae* infection (E = 3%; 95% CI, 0–43%). When the 82 subjects who sought medical care for respiratory illness and permitted nasopharyngeal aspiration were considered, those with PCR evidence of *C. pneumoniae* infection were more likely to also show serological evidence of infection (RR = 4.7; 95% CI, 1.5–14.9) than those without PCR evidence.

**Symptoms reported.** Azithromycin group subjects were less likely than BPG recipients to report ≥1 day of respiratory symptoms during training (RR = 0.79; 95% CI, 0.70–0.90). Fewer subjects in the azithromycin group reported a ≥1-day history of cough (table 2) (RR = 0.68; 95% CI, 0.57–0.81), fever (RR = 0.71; 95% CI, 0.54–0.93), sore throat (RR = 0.78; 95% CI, 0.65–0.94), and breathing illness (RR = 0.67; 95% CI, 0.45–0.98). In contrast, the BPG treatment offered no reduced risk of posttraining reporting of any respiratory symptom.

**Streptococcal pharyngeal colonizations.** Compared with the no-treatment group, azithromycin protected subjects with no throat-culture evidence of *S. pyogenes* upon enrollment from having an *S. pyogenes*–positive throat culture at training’s end (table 2) (E = 96%; 95% CI, 69%–99%). The BPG group’s corresponding efficacy was 42% (95% CI, 0–69%). Newly colonized study subjects were more likely to have ASO serological evidence of *S. pyogenes* infection than were subjects who were not newly colonized at the end of training (RR = 6.91; 95% CI, 3.8–12.7). Neither the azithromycin nor the BPG was protective against new colonization with *S. pneumoniae*.

For all *S. pyogenes* (n = 79) and *S. pneumoniae* (n = 24) pharyngeal isolates (from pretraining, acute respiratory disease episodes, and postraining) the Etest MICs of azithromycin, erythromycin, penicillin, and cefotaxime were well under resistance breakpoints.

**Discussion**

This randomized field trial of two prophylactic treatments was conducted in a population of young adult males at high risk for acute respiratory disease. Five years earlier, this training population suffered the largest *S. pneumoniae* pneumonia epidemic recorded since the development of antibiotics [11]. This population also had the highest pneumonia-related hospitalization rate among Navy and Marine Corps personnel [4]. During several recent winters, military public health officials had employed mass BPG and pneumococcal vaccine interventions to control epidemics at this site.

Despite an intervention among two-thirds of the study population, 72% of the trainees had evidence of a clinically significant respiratory infection, yet only 18% of the ill trainees sought medical care. This is consistent with the medical literature concerning military trainees. In 1962, researchers at the Naval Training Center in Great Lakes, Illinois, reported that only 12%–14% of recruits with clinical respiratory disease sought medical attention [42]. Similarly, it was noted in 1989 that only 36% of Marine Corps trainees sought medical attention despite reporting a sore throat for ≥6 hours and having serological evidence of *S. pyogenes* infection [22]. This reluctance to seek medical attention makes evaluating public health interventions difficult in military populations.

Exclusive measurement of clinical outcomes will underestimate disease incidence and may misrepresent other disease characteristics. In addition, it is difficult in this clinical setting to determine the etiologic agent(s). More than 65% of hospitalizations for pneumonia in the military are reported without a specific agent being identified [4]. Intensive efforts to define a pathogen fail in 50% of instances [4]. Surveying trainees with serial throat cultures is inadequate because most bacterial respiratory tract pathogens can also exist as part of the normal oropharyngeal flora. For these reasons, serological evidence of infection is the most useful measure by which to assess respiratory tract infections.

Consistent with the military medical literature, clinical and serological data in the current study demonstrated that *S. pyogenes, S. pneumoniae, M. pneumoniae*, and *C. pneumoniae* were important pathogens in this population (table 2) [5, 22, 25, 33, 43]. Azithromycin protected subjects against infection with each of these agents (table 3). A single dose of BPG, the standard military intervention, was effective against only *S. pyogenes*. Throat culture studies corroborated serological
studies and did not suggest that the interventions induced antibiotic resistance. PCR studies of nasopharyngeal aspirates from ill subjects confirmed the presence of \textit{C. pneumoniae}. Data about posttraining symptoms additionally supported azithromycin’s protective effect.

It was interesting that pneumococcal vaccine failed to protect the recipients from serologically evident \textit{S. pneumoniae} infection. This poor efficacy might be explained by endemic strains that are distinct from the strains used to prepare the 23-valent vaccine. However, serotyping studies of the \textit{S. pneumoniae} isolates were not performed.

The poor performance of BPG in this setting is likely explained by the 63-day period of study. The effect of BPG against \textit{S. pyogenes} is thought to last for 1–4 weeks for an individual recipient [44–47]; however, applying the antibiotic uniformly in a single dose to a large, confined population may reduce the endemnicity of the pathogen and thereby have a more prolonged protective effect. Such is the strategy employed by both the U.S. Army and U.S. Air Force in protecting their recruit trainees for 6–8 weeks by giving them a single BPG injection when they enter training camp [48, 49].

This strategy also is used in combating Navy and Marine Corps epidemics of acute respiratory disease that occur outside of recruit training [11]. Hence, administration of a single dose of BPG to Infantry Training School entrants was used in this field trial as the standard prophylactic intervention for this postrecruit training population. A previous report suggested that such one-time BPG therapy reduced the incidence of infection from pathogens other than streptococci [48]; however, present study data do not support such a premise.

Azithromycin is an attractive alternative to BPG for prophylaxis. Military respiratory epidemics often occur without identification of a specific etiologic agent [4], and an intervention with a broad spectrum of effectiveness is desired. Study data suggest that azithromycin offers significant protection against infection from \textit{S. pyogenes}, \textit{S. pneumoniae}, \textit{C. pneumoniae}, and \textit{M. pneumoniae}. Assuming that ASO is a marker of pharyngeal invasion and DNAse B is a marker of both pharyngeal and cutaneous invasion, azithromycin may help prevent both acute rheumatic fever and invasive forms of \textit{S. pyogenes} infection, such as those resulting in necrotizing fasciitis, bacteremia, and streptococcal toxic shock syndrome [50]. Azithromycin is also attractive in that subjects are likely to comply with therapy.

Oral erythromycin, the U.S. military’s only alternative therapy, requires twice-a-day dosing, and compliance suffers accordingly [23]. The limited data from this study suggest that weekly oral azithromycin is safe and well tolerated.

Although efficacy, compliance, and safety suggest that azithromycin is superior to BPG for prophylaxis in this population, the cost of azithromycin may be a limitation. The current government cost of azithromycin for 1 person-month of therapy ($29.04) is considerably higher than that of a 1.2-million-unit injection of BPG ($6.95). Although the broader spectrum of protection may be cost-effective, analytical comparisons have yet to be made.

In addition, although the MICs were well below resistance breakpoints for all \textit{S. pyogenes} and \textit{S. pneumoniae} isolates in this study, azithromycin has the potential to select for antibiotic-resistant streptococci, and prophylactic use of azithromycin should be followed with routine surveillance for azithromycin resistance. With these problems, azithromycin is not likely to immediately supplant BPG for routine prophylactic therapy in military training populations. However, it may have a role in certain acute respiratory epidemics, especially when the suspected etiologic agents are not likely to respond to BPG.

In summary, 500 mg weekly of oral azithromycin and 1.2 million units of intramuscular BPG were compared with no treatment as prophylactic agents against a number of bacterial respiratory pathogens. Over their 63 days of military training, 1,016 young-adult male study subjects had considerable clinical and serological evidence of acute respiratory infection. Oral azithromycin recipients reported fewer respiratory symptoms and were protected from pharyngeal colonization and infection with \textit{S. pyogenes}. Azithromycin recipients also were protected from infection with \textit{S. pneumoniae}, \textit{M. pneumoniae}, and \textit{C. pneumoniae}. BPG recipients were only partially protected from \textit{S. pneumoniae} infection. Weekly oral azithromycin was well tolerated and may be an effective alternative to BPG prophylaxis in preventing bacterial respiratory infections among military populations.

Acknowledgments

The authors thank Gary Doern, Ph.D., of the Department of Microbiology, University of Iowa, Iowa City, IA, for his most helpful review of the manuscript. They also thank the following individuals for their most helpful assistance and recommendations in conducting the field trial: Maj. Robert R. Parker, USMC, and Lt. Col. Dennis Judge, USMC, of the Infantry Training Battalion, Camp Pendleton, CA; Debbie C. Brummitt, Leslie Hennigan, Michelle Wyckoff, and Capt. Stephanie F. Brodine, M.C., USN, of the Naval Health Research Center, San Diego; Capt. Elizabeth L. Ledbetter, M.C., USN, HM2 Carlos A. Lewis, USN, HM2 James L. Clark, USN, and HM Graydon M. Webster, USN, of the Navy Environmental and Preventive Medicine Unit #5, San Diego; Cdr. Robert K. Hanson, M.C., USN, of the 1 Marine Expeditionary Force, Camp Pendleton, CA; Ms. Lynn Duffy and Ms. Ginger Gambil of the University of Alabama School of Medicine, Birmingham, AL; Cdr. Barbara Roberts, N.C., USN, HMC Barney Card, USN, HM2 Kevin Dodd, USN, and PFC Jason Kelly, USMC, of the Area 52 Medical Clinic; Cdr. Jeannie Berg, M.S.C., USN, HMC Vernon Carr, USN, HMC Debra Dunning, USN, HM1 Patrick Malone, USN, HM1 Clinton Garrett, USN, HM1 Leslie Cablin, USN, HM1 Robert Sweeten, USN, HM2 Brandia Coker, USN, HM2 Gerald Nowden, USN, and HN Jorge Sanchez, USN, of Naval Hospital Camp Pendleton, Camp Pendleton, CA.

References


