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Review Article

# Chemoprophylaxis against group A streptococcus during military training

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ABSTRACT

Chemoprophylaxis with intramuscular benzathine penicillin G has been used widely by the U.S. military to prevent epidemics of group A streptococcus infections during basic training. The recent global shortage of benzathine penicillin prompted a detailed analysis of this issue in 2017 by military preventive medicine and infectious disease authorities in San Antonio, Texas, and San Diego, California, USA. This paper explores the history of group A streptococcus and chemoprophylaxis in the U.S. military training environment, current policy and practice, and challenges associated with widespread chemoprophylaxis. In light of the history presented, preventive medicine authorities at basic training centers should be extremely cautious about discontinuing benzathine penicillin chemoprophylaxis.

## 1. Introduction

### 1.1. Benzathine penicillin G

Due to global supply shortages, the World Health Organization and U.S. Centers for Disease Control and Prevention recently urged judicious stewardship of benzathine penicillin G (World Health Organization, 2017; Centers for Disease Control and Prevention, 2017). The intramuscular antibiotic, which is the first-line agent for the treatment of syphilis and the only recommended treatment for syphilis during pregnancy (Workowski and Bolan, 2015), has been used extensively by the U.S. military since the mid-1950s to prevent group A streptococcus (GAS) outbreaks at basic training centers (Bernstein et al., 1954). The 2016–17 shortage of benzathine penicillin motivated review of the U.S. military's chemoprophylaxis policy, the highlights of which are presented in this paper.

### 1.2. Group a streptococcal disease

*Streptococcus pyogenes* (or GAS) is a Gram-positive, β-hemolytic, catalase negative bacterium that exhibits significant heterogeneity in virulence, transmission route, and clinical presentation (Heyman, 2008). Virulence varies in association with exotoxin production and M protein type—of which over 200 have been identified, and by which the organism is categorized into unique strains (Steer et al., 2009). Transmission occurs predominately through respiratory droplets, although indirect exposure via fomites and ingestion of contaminated food have also been implicated. Clinical presentation ranges from asymptomatic pharyngeal carriage to noninvasive and invasive disease (Heyman, 2008).

GAS is most commonly associated with noninvasive infections, such as exudative pharyngitis and less severe sore throat syndromes. Although streptococcal pharyngitis is typically self-limited, several complications may occur. Suppurative complications in nearby structures can include sinusitis, mastoiditis, lymphadenitis, otitis media, and peritonsillar and retropharyngeal abscesses; meningitis and brain abscess are rare. Nonsuppurative complications include scarlet fever and acute rheumatic fever (ARF). Prevention of the latter is the principal rationale for antibiotic treatment of GAS pharyngitis. Streptococcal impetigo, which is commonly caused by GAS, particularly in young children, may be followed by immune-mediated glomerulonephritis. Unlike poststreptococcal ARF, this complication does not appear to be prevented by antibiotic treatment of the antecedent infection (Shulman et al., 2012).

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**Table 1a**
Group A streptococcus chemoprophylaxis at U.S. military basic training centers, by quarter, 1998–2007.

| | | 1998 | | | | 1999 | | | | 2000 | | | | 2001 | | | | 2002 | | | | 2003 | | | | 2004 | | | | 2005 | | | | 2006 | | | | 2007 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 |
| National benzathine penicillin shortage | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | X | X | X | X | X | X | | | | | |
| Fort Benning, Georgia | Mode | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Antibiotic (primary) | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B+ | B+ | B+ | B+ | B+ | B+ | B+ |
| | Antibiotic (allergy) | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Fort Jackson, South Carolina | Mode | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Antibiotic (primary) | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Antibiotic (allergy) | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Fort Knox, Kentucky | Mode | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Antibiotic (primary) | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Antibiotic (allergy) | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Fort Leonard Wood, Missouri | Mode | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 1 | 1 | 1 |
| | Antibiotic (primary) | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | | | B | B | | | | B | B | B |
| | Antibiotic (allergy) | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Fort Sill, Oklahoma | Mode | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Antibiotic (primary) | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Antibiotic (allergy) | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| NSTC Great Lakes, Illinois | Mode | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Antibiotic (primary) | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | P | P | P | P | B | B | B |
| | Antibiotic (allergy) | E | E | E | E | E | E | E | E | E | E | E | E | E | E | E | E | E | E | E | E | E | E | E | E | E | E | E | E | E | E | E | E | E | E | E | E | E | E | E | E |
| MCRD Parris Island, South Carolina | Mode | 1 | 0 | 0 | 1 | 1 | 0 | 0 | 1 | 1 | 0 | 0 | 1 | 1 | 0 | 0 | 1 | 1 | 0 | 0 | 1 | 1 | 0 | 0 | 1 | 1 | 0 | 0 | 1 | 1 | 0 | 0 | 1 | 1 | 0 | 0 | 1 | 1 | 1 | 1 | 1 |
| | Antibiotic (primary) | B | | | B | B | | | B | B | | | B | B | | | B | B | | | B | B | | | B | B | | | B | B | | | B | B | | | B+ | B+ | B+ | B+ | B+ |
| | Antibiotic (allergy) | E | | | E | E | | | E | E | | | E | E | | | E | E | | | E | E | | | E | E | | | E | E | | | A | A | A | A | A | A | A | A | A |
| MCRD San Diego, California | Mode | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 0 | 3 | 3 | 3 | 3 | 3 |
| | Antibiotic (primary) | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | | ? | B | B | B | B |
| | Antibiotic (allergy) | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | | A | A | A | A | A |
| JBSA Lackland, Texas | Mode | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 1 | 1 | 0 | 0 | 1 | 1 | 0 | 0 | 1 | 1 | 0 | 0 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Antibiotic (primary) | | | | | | | | B | B | | | B | B | | | B | B | | | B | B | | | B | B | | B | B | B | B | B | B | B | B+ | B+ | B+ | B+ | B | B | B |
| | Antibiotic (allergy) | | | | | | | | E | E | | | E | E | | | E | E | | | E | E | | | E | E | | L | L | L | L | L | L | L | L | L | L | L | A | A | A |
| CGTC Cape May, New Jersey | Mode | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Antibiotic (primary) | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | | | | | | | | | | | | | | | | | | | | | | |
| | Antibiotic (allergy) | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |

(*continued on next page*)

**Table 1a** (*continued*)

| 1998 | | | | 1999 | | | | 2000 | | | | 2001 | | | | 2002 | | | | 2003 | | | | 2004 | | | | 2005 | | | | 2006 | | | | 2007 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 |
| 1998 | | | | 1999 | | | | 2000 | | | | 2001 | | | | 2002 | | | | 2003 | | | | 2004 | | | | 2005 | | | | 2006 | | | | 2007 | | | |

Abbreviations: CGTC, Coast Guard Training Center; JBSA, Joint Base San Antonio; MCRD, Marine Corps Recruit Depot; NSTC, Naval Station Training Center.
Legend: *Mode* – 0, surveillance only; 1, automatic initial dose of chemoprophylaxis; 2, automatic initial and second dose; 3, automatic initial, second, and third dose; *Antibiotic* – A, azithromycin; B, benzathine penicillin G; B+, benzathine penicillin G or azithromycin (both used depending on availability of benzathine penicillin); E, erythromycin; L, levofloxacin; P, oral penicillin.

Invasive disease may range from superficial erysipelas to life-threatening infections, such as pneumonia, myositis, necrotizing fasciitis, toxic shock syndrome, and bacteremia with metastatic complications. The annual incidence of invasive GAS infection in the United States is 3.8/100,000 persons, with higher incidence among those aged < 2 or ≥ 50 years and during the winter and early spring, resulting in an overall case fatality rate of 11.7% (Nelson et al., 2016).

Transmission countermeasures include hand hygiene, respiratory etiquette, and social distancing. Chemoprophylaxis of otherwise healthy close contacts is usually not recommended (Shulman et al., 2012). Due to the frequency and severity of GAS epidemics in military training environments, a number of preventive measures have been employed. In addition to engineering controls, such as enhanced air ventilation and head-to-foot bed orientation in the barracks (Lee et al., 2005), U.S. military training centers routinely use intramuscular benzathine penicillin prophylaxis to prevent GAS outbreaks.

## 2. Methods

In order to outline the history of group A streptococcal disease and chemoprophylaxis measures employed in the U.S. military training environment, the authors began by reviewing known publications on the topic. Additional articles were identified in MEDLINE by searching for MeSH major topics “Streptococcal Infections” and “Military Personnel.” A total of 124 English language articles were identified; after exclusion of non-U.S. based and other extraneous articles based on review of the titles, four additional articles were detected. Adverse events associated with alternative macrolide chemoprophylaxis were reviewed by conducting a MEDLINE search with the MeSH major topic “Macrolides” and subheading “Adverse Effects.”

The Naval Health Research Center (San Diego, California) has maintained a record of GAS countermeasures utilized at all uniformed services basic training centers in the United States since 1998. This ongoing active surveillance project involves contacting the preventive medicine authority at each center twice annually to determine the countermeasures utilized during the previous 6 months. Since the 2011 closing of U.S. Army basic combat training at Fort Knox, Kentucky, 9 sites have conducted basic military training. The recent history of GAS outbreaks in U.S. basic training is presented alongside this chronicle of GAS countermeasures (Tables 1a and 1b).

## 3. Results

### 3.1. History of penicillin use in military training

Chemoprophylaxis against GAS was first employed at a U.S. military training center shortly after World War II. Although oral penicillin demonstrated a promising ability to reduce the incidence of streptococcal pharyngitis and the prevalence of nasopharyngeal carriage (Bernstein et al., 1954; Lazar et al., 1957), periodic epidemics in recruit populations persisted (Schreier et al., 1958). Landmark studies conducted in the 1950s at Naval Training Centers Bainbridge, Maryland, and Great Lakes, Illinois, provided three valuable insights: (1) intramuscular benzathine penicillin is more effective than oral penicillin; (2) 1.2 million units offers a greater duration of protection than 600 thousand units; and (3) even with the higher dose, recruits are vulnerable during their second half of training, particularly in late winter during peak GAS season (Schreier et al., 1958; McFarland et al., 1958).

The Navy Medical Department continued to study benzathine penicillin into the 1960s. Given outbreak unpredictability and a perennial baseline endemicity at Great Lakes, policymakers abandoned both seasonal tandem prophylaxis (i.e., providing prophylaxis to new recruits only during peak season) and mass prophylaxis (i.e., using prophylaxis only as an interruptive when outbreaks occurred) in favor of year-round tandem prophylaxis (Frank et al., 1965).

Meanwhile, between July 1964 and January 1966, an aggressive

**Table 1b**
Group A streptococcus chemoprophylaxis at U.S. military basic training centers, by quarter, 2008–2017.

| | | 2008 | | | | 2009 | | | | 2010 | | | | 2011 | | | | 2012 | | | | 2013 | | | | 2014 | | | | 2015 | | | | 2016 | | | | 2017 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 |
| National benzathine penicillin shortage | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | X | X | X | X | X | | |
| Fort Benning, Georgia | Mode | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Antibiotic (primary) | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | | | | | | | | |
| | Antibiotic (allergy) | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Fort Jackson, South Carolina | Mode | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Antibiotic (primary) | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Antibiotic (allergy) | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Fort Knox, Kentucky | Mode | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | [a] | | | | | | | | | | | | | | | | | | | | | | | | |
| | Antibiotic (primary) | | | | | | | | | | | | | | | | [a] | | | | | | | | | | | | | | | | | | | | | | | | |
| | Antibiotic (allergy) | | | | | | | | | | | | | | | | [a] | | | | | | | | | | | | | | | | | | | | | | | | |
| Fort Leonard Wood, Missouri | Mode | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 1 |
| | Antibiotic (primary) | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | M | B | B | B | | | B |
| | Antibiotic (allergy) | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Fort Sill, Oklahoma | Mode | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 0 | 1 | 1 | 1 |
| | Antibiotic (primary) | B | B | B | B | B | B | B | B | B | B | B | B | | | | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | | B | B | | B | B | B |
| | Antibiotic (allergy) | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| NSTC Great Lakes, Illinois | Mode | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 2 | 2 | 1 | 2 | 2 | 2 | 1 | 1 | 2 | 1 | 1 | 2 | 2 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 1 |
| | Antibiotic (primary) | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B |
| | Antibiotic (allergy) | E | E | E | E | E | E | E | E | E | E | E | E | E | E | E | E | E | E | E | E | E | E | E | E | E | E | E | E | E | E | | | | E | E | E | E | E | E | E |
| MCRD Parris Island, South Carolina | Mode | 1 | 1 | 1 | 1 | 1 | 1 | 2 | 2 | 1 | 1 | 2 | 2 | 1 | 1 | 2 | 2 | 1 | 1 | 2 | 2 | 1 | 1 | 2 | 2 | 1 | 1 | 2 | 2 | 1 | 1 | 2 | 2 | 1 | 1 | 2 | 1 | 1 | 1 | 1 | 1 |
| | Antibiotic (primary) | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B |
| | Antibiotic (allergy) | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A |
| MCRD San Diego, California | Mode | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 2 | 2 | 2 | 1 | 1 | 2 | 2 | 2 |
| | Antibiotic (primary) | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B |
| | Antibiotic (allergy) | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A |
| JBSA Lackland, Texas | Mode | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Antibiotic (primary) | B | B | B | B | B | P | P | B | B | P | P | P | P | P | P | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | B | A | B | B | B+ | B+ | B+ | B+ | B+ |
| | Antibiotic (allergy) | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A | A |
| CGTC Cape May, New Jersey | Mode | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Antibiotic (primary) | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| | Antibiotic (allergy) | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |

(*continued on next page*)

**Table 1b** (*continued*)

| | 2008 | | | | 2009 | | | | 2010 | | | | 2011 | | | | 2012 | | | | 2013 | | | | 2014 | | | | 2015 | | | | 2016 | | | | 2017 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 | Q1 | Q2 | Q3 | Q4 |
| | Q1 2008 | Q2 | Q3 | Q4 | Q1 2009 | Q2 | Q3 | Q4 | Q1 2010 | Q2 | Q3 | Q4 | Q1 2011 | Q2 | Q3 | Q4 | Q1 2012 | Q2 | Q3 | Q4 | Q1 2013 | Q2 | Q3 | Q4 | Q1 2014 | Q2 | Q3 | Q4 | Q1 2015 | Q2 | Q3 | Q4 | Q1 2016 | Q2 | Q3 | Q4 | Q1 2017 | Q2 | Q3 | Q4 |

Abbreviations: CGTC, Coast Guard Training Center; JBSA, Joint Base San Antonio; MCRD, Marine Corps Recruit Depot; NSTC, Naval Station Training Center.

Legend: *Mode* – 0, surveillance only; 1, automatic initial dose of chemoprophylaxis; 2, automatic initial and second dose; 3, automatic initial, second, and third dose; *Antibiotic* – A, azithromycin; B, benzathine penicillin G; B+, benzathine penicillin G or azithromycin (both used depending on availability of benzathine penicillin); E, erythromycin; L, levofloxacin; M, multiple (azithromycin, ceftriaxone; cephalexin, or levofloxacin); P, oral penicillin.

[a] Basic military training stopped at Fort Knox in 2011.

outbreak of GAS pneumonia resulted in the hospitalization of 95 Navy and Marine Corps recruits in San Diego, California. The majority experienced a complication—including empyema ($n$ = 54), pneumatocele ($n$ = 2), and pneumothorax ($n$ = 1)—and the mean hospital duration was 74 days. Incidence rates dropped decisively within one month of initiating mass administration of benzathine penicillin prophylaxis to all recruits, although it appears the outbreak may have been past its peak at this point (Basiliere et al., 1968).

In light of "a perceived decrease in the risk for ARF and related streptococcal sequelae," Naval Training Center San Diego elected to terminate its GAS prophylaxis program in 1980. During an 8-month period beginning in December 1986, 10 recruits were diagnosed with ARF, only 6 of whom had reported symptoms of pharyngitis, and 6 recruits experienced GAS pneumonia. Tandem benzathine penicillin G prophylaxis was reinitiated and the outbreak ceased (Centers for Disease Control, 1988b).

U.S. Army basic training centers also discontinued GAS chemoprophylaxis in the early 1980s, likely due to reduced incidence and a perceived lack of theat. In 1988 it was restarted at Fort Leonard Wood, Missouri, arresting a 5-month outbreak in which recruits developed peritonsillar abscess ($n$ = 22), ARF ($n$ = 13), and suppurative axillary lymphadenitis ($n$ = 4) (Centers for Disease Control, 1988a). Universal chemoprophylaxis was not reintroduced across all U.S. Army basic training sites, however, and four additional GAS outbreaks occurred between 1989 and 1991. In addition to usual respiratory presentations, these outbreaks included non-respiratory pathology such as scarlet fever (n = 1), acute glomerulonephritis (n = 1), and streptococcal toxic shock syndrome ($n$ = 2)—one case of which was fatal (Gunzenhauser et al., 1995). When prophylaxis was again discontinued at Fort Leonard Wood, in both 1989 and 1993, GAS rates increased within 2 months (Brundage et al., 1996).

A similar pattern was seen in U.S. Air Force basic training. Universal tandem chemoprophylaxis was stopped in the mid-1970s and reinstituted in January 1989 after a significant 3-week outbreak of GAS pharyngitis ($n$ = 186) among trainees at Lackland Air Force Base, Texas (Centers for Disease Control, 1990).

Three notable invasive GAS outbreaks among military recruits occurred during the first decade of the 21st century—all of which began in the absence of tandem prophylaxis. These outbreaks, which occurred at Fort Knox, Kentucky (2003), and Fort Leonard Wood (2005 and 2006), included cases of pneumonia ($n$ = 7), necrotizing fasciitis ($n$ = 3), streptococcal toxic shock syndrome ($n$ = 2), cellulitis (n = 2), and prepatellar bursitis ($n$ = 1); one case of necrotizing fasciitis was fatal. Notably, the Fort Leonard Wood outbreaks occurred during global shortages of benzathine penicillin, requiring preventive medicine officials to restrict the limited supply of benzathine penicillin to affected units and dispense oral penicillin to all other recruits (Lee et al., 2008).

### 3.2. Current policy and practice

Given geographically disparate GAS epidemiology, the U.S. military defers chemoprophylaxis decisions to each training center: "Routine administration of penicillin for prophylaxis of basic trainees against group A streptococcal infection…should be directed by [the] local preventive medicine authority" (Headquarters, 2017). The Navy provides year-round tandem prophylaxis to all incoming recruits and an automated second dose halfway through the 8-week course from October through March. Year-round tandem prophylaxis is provided to all new recruits at Marine Corps Recruit Depots San Diego and Parris Island, South Carolina; the former also provides second and third doses year-round, while the latter only provides a second dose during peak season. Army policy varies widely among its four training centers due to historic differences in GAS rates (Armed Forces Health Surveillance Center, 2010). Fort Leonard Wood and Fort Sill, Oklahoma, like the Air Force, provide year-round tandem prophylaxis to all incoming recruits. The Coast Guard does not provide tandem prophylaxis. At training

centers using benzathine penicillin, weekly oral azithromycin or erythromycin is prescribed to recruits with a penicillin allergy (Tables 1a and 1b).

## 4. Discussion

Preventive medicine authorities at U.S. basic training centers face a number of challenges related to control of GAS. Of late, the primary challenge has been the shortage of benzathine penicillin subsequent to manufacturing delays by Pfizer, the sole producer of the antibiotic. Even when supply is adequate, however, several issues beset the perpetual application of tandem prophylaxis.

First, penicillin allergy prevents universal administration of benzathine penicillin. Although fewer than 20% of individuals who report a penicillin allergy have demonstrable allergy by skin testing (Salkind et al., 2001), objective confirmatory testing is impractical on a mass scale at military training centers. Total reliance on self-reporting, however, may undermine herd immunity. In one study, over half of Marine Corps recruits ($n = 736$) who did not receive benzathine penicillin due to self-reported allergy were colonized with GAS by the end of training, as compared to 31% of their peers who received chemoprophylaxis (Gray et al., 1991). An outbreak of GAS pneumonia among recruits ($n = 34$) in 2002 was partially attributed to the fact that nearly one-third of incoming recruits reported an allergy. To counteract this issue, authorities began directly observed administration of weekly oral azithromycin for penicillin-allergic trainees (Crum et al., 2005), an alternative therapy found to be superior or non-inferior to benzathine penicillin across several clinical outcomes (Gray et al., 1998).

Second, benzathine penicillin may cause adverse reactions, even among those who report no prior allergy to the penicillin class of antibiotics. In a large U.S. study of nearly 200,000 people prescribed oral penicillin between July 2000 and June 2004, the rate of any allergic reaction and anaphylaxis were 4.7 and 0.1 per 10,000 dispensings, respectively (Johannes et al., 2007). Although large-scale adverse event data are unavailable for benzathine penicillin specifically, intramuscular penicillin injection carries an additional risk of inappropriate administration. Incorrect injection has been linked in pediatric case reports to incomplete cauda equine syndrome (Meyer et al., 1981) and transverse myelitis (Weir and Fearnow, 1983). In the early studies of benzathine penicillin at Naval Training Centers, 0.98% of recruits ($n = 32,419$) were determined to have an allergic reaction, mostly consisting of urticaria, arthralgia, and fever; none experienced anaphylaxis (Schreier et al., 1958; McFarland et al., 1958). A more recent non-blinded randomized clinical trial noted no adverse events among Marine infantry trainees ($n = 346$) who received benzathine penicillin (Gray et al., 1998), and to our knowledge no cases of anaphylaxis have been reported at military training centers since active surveillance began in 1998. Although intramuscular antibiotic administration has not been associated with an increased risk of exertional rhabdomyolysis, most training centers postpone physical fitness training until the day following injection due to the potential for temporary muscle soreness.

Third, antibiotics may disrupt the microbiome—a phenomenon understood nearly since the inception of the modern antimicrobial era (DiCaprio and Rantz, 1950). More recently, the role of the gut microbiota in the development of obesity has come under increased scrutiny (Mikkelsen et al., 2016), including speculation that weight gain among otherwise healthy military recruits taking antibiotics (Haight and Pierce, 1955) was related to antimicrobial effects. Although the gut microbiota is particularly vulnerable to broad-spectrum oral antibiotics (Panda et al., 2014), non-human studies suggest that alternative (i.e., non-oral) administration of antibiotics may be less disruptive (Zhang et al., 2013). An ongoing study among Air Force recruits at Joint Base San Antonio (JBSA)-Lackland aims to determine the effect of intramuscular benzathine penicillin on the dermatologic microbiome.

Fourth, benzathine penicillin currently costs $68.70 (USD) per dose. If the results observed in the aforementioned Marine infantry trial were applicable across the U.S. military training centers, 29 recruits would need to receive benzathine penicillin prophylaxis to prevent one new case of pharyngeal colonization with GAS, and 19 to prevent one GAS infection, as determined by a positive antistreptolysin O antibody titer (Gray et al., 1998). Prevention of one incident colonization and one clinical infection, therefore, would carry respective costs of approximately $2000 and $1300.

Fifth, provision of intramuscular benzathine penicillin in a mass setting requires a significant commitment of recruit time and medical manpower. Given the impact of oral antibiotic non-adherence, however, which compelled one training center to institute directly observed therapy (Crum et al., 2005), benzathine penicillin injection may be logistically superior to oral antibiotic alternatives.

Sixth, ethical issues surround mandatory provision of benzathine penicillin to military recruits, who may comprise a vulnerable population. Although all have freely volunteered to enlist in the armed forces, recruits may feel intimidated to ask questions about the injection because of the high stress environment and a desire to remain inconspicuous. While these risks have not been systematically studied, basic training centers have proactively sought to minimize any real or perceived infraction of informed consent during medical in-processing. At JBSA-Lackland, all recruits receive a detailed presentation concerning the risks and benefits of chemoprophylaxis, complete a standardized questionnaire regarding their current medications and history of antibiotic allergy, and are monitored for adverse reactions by medical staff for at least 20 min after the injection.

Finally, and paradoxically, the effectiveness of chemoprophylaxis undermines its continued application. Given the rarity of GAS outbreaks and of severe GAS infections, military decision makers may mistakenly discount the risk of terminating tandem chemoprophylaxis. This availability heuristic has been implicated in the increased rate of vaccine refusal in the United States (Browne et al., 2015).

These challenges associated with benzathine penicillin have triggered alternative proposals, the two most common of which are targeted chemoprophylaxis based on screening and tandem chemoprophylaxis with an oral antibiotic. Neither is superior to the current policy.

Screening recruits for GAS infection, such as with nasopharyngeal culturing or rapid streptococcal antigen testing, is problematic for multiple reasons. Common GAS pharyngitis symptoms, such as sore throat and subjective fever, are extremely common in the basic training environment, with one cross-sectional study finding a prevalence of over 30% and 10%, respectively (Gray et al., 1998). Conversely, 13% of recruits infected with GAS in one prospective study ($n = 736$) did not report a sore throat, and 37% of infected recruits with a sore throat did not seek care (Gray et al., 1991). This discrepancy between symptoms and infection would require a policy of universal screening, which would be logistically and fiscally unviable.

Oral antibiotics, which have been appropriately utilized as a chemoprophylaxis alternative for penicillin-allergic recruits and during shortages of benzathine penicillin (Tables 1a and 1b), should not supplant benzathine penicillin altogether. Oral penicillin, amoxicillin, and cephalexin would need to be taken at least twice daily, likely for 10 days or longer, to provide appropriate coverage. Moreover, while oral penicillin has been studied for GAS chemoprophylaxis (Wannamaker et al., 1953), the appropriate dosage and duration of amoxicillin and beta-lactam antibiotics for this indication is unknown. Macrolide antibiotics, which are the preferred alternative to benzathine penicillin when necessary, have three major shortcomings when used en masse.

First, due to geographic differences in GAS resistance, macrolide antibiotics may not prevent serious sequelae in a substantial portion of the recruit population. In contrast to beta-lactam antibiotics, which remain universally effective against GAS despite a prolonged history of pervasive clinical use, approximately 5–8% of GAS isolates in the

United States are resistant to macrolides (Shulman et al., 2012). Studies at U.S. military training centers have found a wide range of macrolide resistance among GAS isolates (from 3% to 25%), with the inter-center variation attributed to the geographic divergence of a single M type (M75) (Barrozo et al., 2003; Metzgar et al., 2010).

Second, overuse of macrolide antibiotics may breed antibiotic resistance among other pathogens. Of trainees receiving weekly azithromycin prophylaxis in a Russian military training environment, macrolide resistance in *Streptococcus pneumoniae* isolates emerged rapidly, from 0% at baseline to 40% at week 20 (Guchev et al., 2004). In a small Navy trial, all *S. pneumoniae* isolates recovered from respiratory specimens were resistant to azithromycin in the azithromycin treatment group ($n = 4$) versus only a single isolate with intermediate resistance in the penicillin group ($n = 3$) (Gray et al., 2001). Investigators also found increased azithromycin resistance among GAS isolates in a Marine trainee population after chemoprophylaxis, irrespective of assignment to benzathine penicillin, azithromycin, or no prophylaxis (Putnam et al., 2000). Recently, macrolide resistance has also been detected in *Mycoplasma pneumoniae* (Zheng et al., 2015), another respiratory pathogen prevalent in the basic training environment (Radin et al., 2014).

Third, macrolide antibiotics may prolong the QT interval and precipitate sudden cardiac death. Antimicrobial-induced long QT syndrome is thought to be rare, and most cases occur in persons who are older or who have underlying risk factors, such as heart disease or electrolyte disturbances (Owens Jr and Nolin, 2006). Although these host factors would be uncommon in a relatively young and healthy cohort of military recruits, extensive usage across a large population (i.e., hundreds of thousands annually) could result in arrhythmias.

## 5. Conclusion

Despite the challenges outlined in this paper—periodic shortages of benzathine penicillin; the potential for adverse reactions and microbiome disruptions; fiscal, logistical, and ethical concerns; complacency after extended periods of GAS quiescence; and consequences from the overutilization of macrolide antibiotic alternatives—preventive medicine authorities at military training centers should understand the local GAS epidemiology and be cautious about abandoning chemoprophylaxis. Until the development of a vaccine or other evidence-based alternative, year-round tandem prophylaxis with benzathine penicillin should remain the default policy at most U.S. training centers. Since benzathine penicillin is an important treatment of syphilis, particularly for pregnant women, manufacturing should be increased to meet demand.

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**14. ABSTRACT**

Chemoprophylaxis with intramuscular benzathine penicillin G has been used widely by the U.S. military to prevent epidemics of group A streptococcus infections during basic training. The recent global shortage of benzathine penicillin prompted a detailed analysis of this issue in 2017 by military preventive medicine and infectious disease authorities in San Antonio, Texas, and San Diego, California, USA. This paper explores the history of group A streptococcus and chemoprophylaxis in the U.S. military training environment, current policy and practice, and challenges associated with widespread chemoprophylaxis. In light of the history presented, preventive medicine authorities at basic training centers should be extremely cautious about discontinuing benzathine penicillin chemoprophylaxis.

**15. SUBJECT TERMS**

group A streptococcus, benzathine penicillin G, military basic trainees

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