PNEUMOCOCCAL VACCINE TO COUNTER
EMERGING INFECTIOUS DISEASE
THREAT IN THE MILITARY

J. A. McKeehan
M. A. K. Ryan
G. C. Gray
for the Pneumococcal Vaccine Study Team

Report No. 00-36

Approved for public release; distribution unlimited.

NAVAL HEALTH RESEARCH CENTER
P O BOX 85122
SAN DIEGO, CA 92186-5122

BUREAU OF MEDICINE AND SURGERY (M2)
2300 E ST. NW
WASHINGTON, DC 20372-5300
Pneumococcal Vaccine to Counter Emerging Infectious Disease Threat in the Military

Guarantor: LCDR Margaret A.K. Ryan, MC USN
Contributors: 2LT Jamie A. McKeelhan, MC USAF*; LCDR Margaret A.K. Ryan, MC USN*; CAPT Gregory C. Gray, MC USN*; for the Pneumococcal Vaccine Study Team†

Streptococcus pneumoniae causes severe morbidity and mortality worldwide and poses a significant threat to the health and readiness of U.S. military personnel. Although a vaccine to prevent pneumococcal infections has been available for almost 25 years, its use has been limited. Recently, increasing antibiotic resistance among S. pneumoniae strains has emerged, prompting health care professionals to reevaluate the benefit of administering pneumococcal vaccine. The Naval Health Research Center, in collaboration with professionals from numerous civilian and military organizations, has initiated a rigorous double-blind, placebo-controlled trial investigating the operational value of vaccinating young adults as they enlist in the military.

Introduction

Diseases caused by Streptococcus pneumoniae (the pneumococcus) are associated with tremendous morbidity and mortality worldwide, and they are a special threat to the health and readiness of the U.S. military. A vaccine to prevent pneumococcal disease has been available for clinical use in the United States for nearly 25 years. Vaccination has been strongly recommended for the elderly, and recently, for very young children, yet its utility in young adults has not been well examined. As a result of recent outbreaks of pneumococcal disease and the emergence of increased antibiotic resistance, a large clinical trial of pneumococcal vaccine among young adults enlisting in the U.S. military is currently being undertaken by the Naval Health Research Center, in San Diego, in collaboration with public health, academic, and military institutions. The study will better define the burden of pneumococcal disease in U.S. military populations and the value of vaccination in protecting healthy young adults.

Pneumococcal Disease

S. pneumoniae are Gram-positive, usually encapsulated cocci that occur singly, in pairs, or in short chains. Of the more than 90 serotypes of S. pneumoniae, types 1, 3, 4, 7, 8, 9, 12, 14, and 23F are the most common causes of infection among adults.1-3 Pneumococci are responsible for a broad spectrum of human disease, ranging from otitis media, mastoiditis, and sinusitis to invasive disease such as pneumonia, meningitis, and sepsis. Some populations are more vulnerable to severe pneumococcal disease, including immunocompromised patients, those with functional or anatomic asplenia, the very old, the very young, and Native American, Native Alaskan, and African-American populations.4 All risk factors are not well defined, however, because otherwise healthy young adults can also suffer from invasive pneumococcal disease.

For nearly two centuries, invasive pneumococcal disease, especially pneumonia, has been recognized as a common and often critical condition.5 The pneumococcus continues to rank among the leading causes of death from infectious disease worldwide.6-8 and it remains a significant cause of morbidity and mortality in the United States.8 Each year, the pneumococcus is estimated to cause approximately 500,000 cases of pneumonia, 50,000 cases of bacteremia, and 3,000 cases of meningitis in this country.3 Surveillance for pneumococcal infections in Soweto, South Africa, and Papua New Guinea reveal that the pathogen is an even greater threat to some subpopulations in those areas.10,11

In addition to the impact S. pneumoniae has had on civilian populations, it has also challenged the health and readiness of the U.S. military population. Navy data from 1981 to 1991 suggest that the pneumococcus has been responsible for 12% of military pneumonia hospitalizations, or 9.5 admissions per 100,000 person-years.12 During the winter of 1989, an epidemic of at least 124 cases of confirmed pneumococcal pneumonia occurred at Camp Pendleton, California,12 affecting troop readiness and placing a strain on medical resources. Other outbreaks have been documented in the military in North Carolina and on a ship in the Mediterranean Sea.13 Most recently, 56 Marine Corps recruits were hospitalized, and many more were treated as outpatients, during an outbreak of pneumococcal pneumonia at Camp Pendleton during the winter of 2000 (CDR Kenneth Earhart, Naval Medical Center, San Diego, personal communication). It is suspected that many more military mem-
Pneumococcal Vaccine

In 1945, the first successful trial of a polyvalent polysaccharide vaccine against pneumococcal pneumonia was completed by MacLeod and collaborators. After the advent of penicillin therapy for treatment, interest in the vaccine seemed to wane. It was not until 1977 that a 14-valent vaccine was finally approved for clinical use in the United States. In 1983, the manufacturer expanded the formulation, creating a 23-valent vaccine. This 23-valent polysaccharide vaccine has since been recommended for the prevention of invasive pneumococcal disease in high-risk groups, including people with chronic illness, asplenia, immune compromise, or age older than 65 years.

Recommendations for more widespread use of pneumococcal vaccine have grown in recent years. In 1997, the Immunization Practices Advisory Committee of the Centers for Disease Control and Prevention recommended that the 23-valent vaccine be evaluated for use in high-risk military populations. Thus far, only one recruit training camp and some elite military groups (Navy SEALs and Army Rangers) have opted to provide vaccine for their trainees. The efficacy of the pneumococcal vaccine in these military populations has not been established.

Despite the 23-valent vaccine’s long history and expanding recommendations for use, some authors have noted conflicting evidence on the vaccine’s efficacy. Although some studies of pneumococcal polysaccharide vaccine show an overall protective efficacy of about 60 to 70%, studies in immunocompromised patients have shown much lower levels of protection. Persons suffering from various states of immunodefi ciency do not consistently develop immunity after vaccination, thus reducing the protective value of the vaccine. However, in the healthy elderly population (immunocompetent persons older than 65 years), the polysaccharide vaccine has a reported efficacy of 75%. The 23-valent vaccine has also been shown to be effective in preventing bacteremia in all groups older than 2 years studied to date. The efficacy of the conjugate 7-valent vaccine in children appears to also be high, at >80% for preventing invasive disease.

The cost effectiveness of the vaccine appears to have been established among high-risk populations by some researchers, although other data suggest that the cost effectiveness may still be in question. It has been proposed that large, rigorous trials investigating the safety, efficacy, and cost effectiveness of the pneumococcal vaccine are necessary before widespread use of the vaccine should be advocated.

New Vaccine Research in the Military

The Naval Health Research Center, in collaboration with professionals from the Centers for Disease Control and Prevention, the Mayo Clinic and Foundation, Wyeth Lederle Vaccines, and a number of military commands, will soon be initiating a large double-blind, placebo-controlled clinical trial of the currently available 23-valent pneumococcal vaccine. The purpose of this study is to determine the operational benefit of vaccinating young adults as they enlist in the military. This $3 million study has been made possible through a competitive research grant administered by the U.S. Army Medical Research and Material Command and a Cooperative Research and Development Agreement with Wyeth Lederle Vaccines.

A population of more than 191,000 Army, Navy, and Marine Corps recruits will be enrolled in the vaccine trial, actively followed during their 8 to 12 weeks of recruit training, and passively followed for respiratory disease outcomes for up to 15 months after training. Four recruit training facilities originally agreed to participate in this operationally complex study. These training facilities—the Marine Corps Recruit Depot, San Diego, California; Navy Recruit Training Command, Great Lakes, Illinois; and Army basic combat training facilities at Fort Leonard Wood, Missouri, and Fort Jackson, South Carolina—have each agreed to take on the challenge of executing this important study with minimal disruption to established training schedules (Fig. I). The Marine Corps Recruit Depot, at Parris Island, South Carolina, will be added to the group of participating facilities within the year.
Recruits will be offered participation in the study from October 2000 through February 2002. Consenting participants will be randomly assigned to receive either pneumococcal vaccine or a placebo injection during routine medical in-processing. All recruits will be followed closely for pneumonia during basic training, and they will receive extensive medical evaluations should they become ill. Laboratory workups will identify infection with *S. pneumoniae*, with serotyping and antibiotic-resistance, as well as the burden of other pathogens (*Chlamydia pneumoniae, Mycoplasma pneumoniae*, adenovirus, influenza, and respiratory syncytial virus) among recruit pneumonia cases. Time lost from training will be carefully tracked among recruits enrolled in this study.

After basic training, computerized medical data containing International Classification of Diseases, Ninth Revision, diagnostic codes for any-cause pneumonia and any-cause acute respiratory disease (codes 460-466 and 480-487) will be tracked for the study group for up to 15 months. Hospitalizations at military medical facilities will be identified using the Standard Inpatient Data Records system. Figure 2 shows the incidence of such hospitalizations from 1997 to 1999. Outpatient encounters at Department of Defense facilities will be identified using the Standard Ambulatory Data Records system, which has only available in the past few years. Data analysts at the Naval Health Research Center have established direct access to these large databases to thoroughly capture all respiratory illness encounters recorded among study participants. These health care databases are robust and standardized. Although identification of pneumococcal disease through these systems may be imperfect, the results will be unbiased because of the randomization procedure performed at study enrollment.

This large vaccine trial will reveal the clinical value of using pneumococcal vaccine in military recruits. Sophisticated laboratory data on *S. pneumoniae* will be closely linked to health care utilization and lost training time to demonstrate the effects on health and readiness that are critical to the Department of Defense. This study received an excellent scientific merit score by the American Institute of Biological Sciences, and it is anticipated to be followed closely by civilian public health officials. The research may prompt new recommendations for the use of pneumococcal vaccine in other young adult populations, including high school and college students, health care workers, other public service occupations, and foreign military groups.

### Conclusion

*S. pneumoniae* is a significant cause of illness in the United States and around the world. In addition to its impact on the health of civilians, the pneumococcus, with its increasing resistance to antibiotics, threatens to compromise the readiness of U.S. military forces. Although an available vaccine against pneumococcal infections might help to reduce this impact, vaccination has not been well studied in healthy young adults without other risk factors. This pneumococcal vaccine study will be one of the largest double-blind, placebo-controlled clinical trials in U.S. military history. This operational research is expected to provide critical information to military policymakers and to have additional value for civilian public health professionals.

### Acknowledgment

This represents Naval Health Research Center report 00-36, supported by the Department of the Navy, under research work unit OH00866-6609.

### References


The public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing the burden, to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302, Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB Control number. PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.

1. Report Date (DD MM YY)  2. Report Type  3. DATES COVERED (from - to)
8-24-00 New Aug 2000

5a. Contract Number:  
5b. Grant Number:  
5c. Program Element: 61102A  
5d. Project Number: M0101  
5e. Task Number: BKX  
5f. Work Unit Number: 6609

4. TITLE AND SUBTITLE
Pneumococcal Vaccine to Counter Emerging Infectious Disease Threat in the Military

6. AUTHORS
JA McKeehan, MAK Ryan, & GC Gray, for the Pneumococcal Vaccine Study Team

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

8. SPONSORING/MONITORING AGENCY NAMES(S) AND ADDRESS(ES)
Chief, Bureau of Medicine and Surgery
Code M2
2300 E St NW
Washington DC 20372-5300

12 DISTRIBUTION/AVAILABILITY STATEMENT
Approved for public release; distribution unlimited.

13. SUPPLEMENTARY NOTES
Published in: Military Medicine, 2001, 166(12), 1089-90

14. ABSTRACT (maximum 200 words)
Diseases caused by Streptococcus pneumoniae (pneumococcus) are associated with tremendous morbidity and mortality worldwide, and they are a special threat to the health and readiness of the US military. A vaccine to prevent pneumococcal disease has been available for nearly 25 years. Vaccination has been strongly recommended for the elderly, and recently, for very young children, yet its utility in young adults has not been well examined. Due to recent outbreaks of pneumococcal disease and the emergence of increased antibiotic resistance, a large clinical trial of pneumococcal vaccine among young adults enlisting in the US military is currently being conducted by the Naval Health Research Center, San Diego, in collaboration with public health, academic, and military institutions. The study will better define the burden of pneumococcal disease in US military populations, and the value of vaccination in protecting healthy young adults.

14. SUBJECT TERMS

16. SECURITY CLASSIFICATION OF:
a. REPORT UNCL  b. ABSTRACT UNCL  c. THIS PAGE UNCL

18. NUMBER OF PAGES 4

18a. NAME OF RESPONSIBLE PERSON
Commanding Officer

18b. TELEPHONE NUMBER (INCLUDING AREA CODE) COMM/DSN: (619) 553-8429

Standard Form 298 (Rev. 8-98)  
Prescribed by ANSI Std. Z39-18