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Lack of effectiveness of the 23-valent polysaccharide pneumococcal vaccine in reducing all-cause pneumonias among healthy young military recruits: A randomized, double-blind, placebo-controlled trial

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ABSTRACT

Background: Streptococcus pneumoniae infections have periodically caused significant morbidity and outbreaks among military personnel, especially trainees. This study evaluated the effectiveness of the 23-valent polysaccharide pneumococcal vaccine (PPV23) in reducing pneumonia in healthy military trainees.
Methods: From 2000–2003, 152 723 military trainees from 5 US training camps were enrolled in a double-blind, placebo-controlled trial of PPV23. Participants were closely monitored during basic training for radiographically confirmed pneumonia etiology and loss-of-training days. Participants were also followed using electronic medical encounter data until 1 June 2007 for three additional outcomes: any-cause pneumonia, any acute respiratory disease, and meningitis.
Results: Comparison of demographic data by study arm suggested the randomization procedures were sound. During basic training, 371 study participants developed radiographically confirmed pneumonia. None had evidence of *S. pneumoniae* infection, but other etiologies included adenovirus (38%), *Chlamydophila pneumoniae* (9%), and *Mycoplasma pneumoniae* (8%). During the follow-up period, many study participants, in both the vaccine and placebo groups, had clinical encounters for the medical outcomes of interest. However, Cox's proportional hazard modeling revealed no evidence of a protective vaccine effect during recruit training (radiographically confirmed pneumonia) or up to 6.7 years after enrollment (any-cause pneumonia, any acute respiratory disease, or meningitis).
Conclusions: Data from this large, double-blind, placebo controlled trial do not support routine use of PPV23 among healthy new military trainees. This clinical trial was registered at clinicaltrials.gov (registration number NCT02079701, http://www.clinicaltrials.gov/ct2/show/NCT02079701?term=NCT02079701&rank=1).

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1. Background

Streptococcus pneumoniae infections are recognized to cause significant morbidity and mortality especially among persons younger than 2 and older than 65 years of age. The 23-valent polysaccharide pneumococcal vaccine (PPV23) was first approved for use in the United States in 1983 [1,2]. Initially it was recommended for children older than 2 years of age and adults with chronic illnesses, as well as for adults aged 65 years or older [2]. Numerous studies were conducted evaluating the effectiveness of this vaccine in various populations. Inconsistent protection against

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community-acquired pneumonias was noted, but later studies more consistently demonstrated the vaccine's best protection was against invasive pneumococcal disease [3–9].

S. pneumoniae is recognized as a major cause of morbidity among US military populations. During the influenza pandemic from 1918 to 1919, death was far more common among patients with influenza who developed secondary *S. pneumoniae* infection [10]. This predisposition to *S. pneumoniae* or bacterial infection after influenza infection has subsequently been well described [11]. Additionally, a study by Hakansson and colleagues in the early 1990s documented increased adherence of *S. pneumoniae* to human respiratory tract epithelial cells previously infected with adenovirus, suggesting an increased expression of receptors for *S. pneumoniae* after adenovirus infection [12]. This is particularly important to consider in the military training setting where adenovirus infections are prevalent [13].

US Navy data from 1981 to 1991 suggest that *S. pneumoniae* caused approximately 12% of military pneumonia hospitalizations or 9.5 admissions per 100 000 person-years [14,15]. An epidemic of 124 cases of pneumococcal pneumonia occurred during winter 1989 at a military training facility. Reichler et al. suggested that PPV23 be used as a preventive strategy where potential exposure to respiratory pathogens occurs in crowded settings such as these military training camps [16]. Other outbreaks have been documented, particularly in US military training scenarios [14,17,18]. Pneumococcal pneumonia outbreaks have also occurred in Israel, Russia, and Finland [19–21]. Because the incidence of outpatient disease is unknown and there are diagnostic difficulties in identifying *S. pneumoniae*, these reports likely underestimate the true impact of this pathogen [14].

Civilian cost-benefit and cost-effectiveness studies performed prior to this study suggested that vaccination against pneumococcal pneumonia would create net health improvements in every age group and that vaccination programs for those considered at high risk were economically justified [22,23]. Beutels and Postma demonstrated that vaccination of those between 65 and 75 years of age, immunocompromised individuals, and military populations was cost-effective [24]. In 2000, Vold Pepper and Owens suggested that if all Navy and Marine Corps members were vaccinated, savings of $5.7 million could be achieved during members' active-duty service [25].

An increasingly important problem regarding *S. pneumoniae* infections is antimicrobial resistance. Data collected from the United States for the SENTRY Antimicrobial Surveillance Program beginning in 1998 showed an overall increasing trend of *S. pneumoniae* non-susceptibility to penicillin, amoxicillin, ceftriaxone, erythromycin, and clindamycin [26]. From 1998 to 2011, percent susceptible *S. pneumoniae* isolates dropped from 97.1 to 81.1 for amoxicillin ($\leq$2 μg/mL); from 96.8 to 85.2 for penicillin ($\leq$2 μg/mL); and from 82.2 to 55.2 for erythromycin ($\leq$0.25 μg/mL) [26]. Prior to this study, data from Naval Medical Center San Diego from May 1995 to May 1997 showed that the prevalence of penicillin resistance among non-sputum clinical isolates of *S. pneumoniae* was as high as 43% (18% intermediately resistant, 25% highly resistant) [27]. As the prevalence of antibiotic resistance increases in military populations, alternate public health interventions, such as routine pneumococcal vaccination of all military trainees, have been considered [14].

With frequent outbreaks, potential cost savings, increasing resistance to antibiotics, and the availability of the safe PPV23, public health officials at several US military training centers have opted to routinely employ the vaccine, despite the lack of effectiveness data and a specific policy requirement. A number of scientific reports posit success with the vaccine among military trainees in the United States, Russia, and Finland [17,19,21,28]. In 1998, to address the need for compelling data, the US Armed Forces Epidemiological Board (USAFEB), a volunteer board composed of civilian experts in various fields of infectious disease and public health, recommended the US Department of Defense (DoD) conduct a research study on the effectiveness of the pneumococcal vaccination in military populations [29]. The hope was that the PPV23 might be clearly established to reduce morbidity and mortality within military groups already known to bear a high burden of respiratory illness, and address the need for more evidence to guide policy decisions for pneumococcal vaccination in military populations. Spurred by the USAFEB's recommendation, the goal of this study was to determine the effects, if any, of PPV23 on the outcome measures of S. pneumonia infections, any-cause pneumonia, any-cause respiratory disease, recruit training clinical pneumonia (radiographically confirmed during the recruit training period), and days lost from training among military recruits.

2. Methods

2.1. Study participants, enrollment, and follow-up

Given their documented high rates of respiratory illness, US military trainees were selected for participation. The procedures followed were in accordance with DoD ethical standards and the Helsinki Declaration of the World Medical Association. The study was approved by multiple DoD institutional review boards. Using a written informed consent process, basic training recruits at five recruit training centers (in South Carolina, Missouri, Illinois, and California), where rates of respiratory illness are consistently high, were invited to participate during their first week of training. Pregnancy screening was performed on all women, and those with positive results were not enrolled. Exclusion criteria included known history of PPV23 vaccination within the past 5 years or having a medical condition that either required or precluded pneumococcal vaccination. Study participants completed a study questionnaire and were administered a prepackaged, blinded, and randomized intramuscular deltoid injection containing either the PPV23 (Wyeth Pharmaceuticals or Merck & Co., Inc.) or saline. Randomization was conducted by a third party in a simple 1:1 ratio, and tubes were labeled with a unique identifier. The identifier was then followed on each subject's enrollment paperwork for later unblinding. Study injections were administered at the same time as other recruit in-processing vaccinations, which may have included vaccines against polio, measles–mumps–rubella, varicella, tetanus–diphtheria, hepatitis A virus, hepatitis B virus, meningococcal disease (A/C/Y/W135), and influenza. At the end of recruit training, a questionnaire was administered to capture symptoms and signs of illnesses that might have been missed by the active and passive surveillance.

Since enrollment continued for more than 2 years, the person-year contributions of those first enrolled were greater than those enrolled near the trial's end. The original planned surveillance period was 1.7 years. This was later extended to 6.7 years from enrollment of the first participant, for continued monitoring of impact in this large double-blinded trial.

2.2. Specimen collection

During the active surveillance period, study participants with suspected pneumonia were identified by the attending physician. Study personnel obtained three throat swabs, blood cultures (aerobic and anaerobic), sputum sample (if producible), and acute serum samples from participants. Samples were processed on all participants that received radiological confirmation. From these, attempts were made to also capture a convalescent serum sample 2 weeks after the acute presentation. These attempts were not always

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