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Women in the military may have an increased occupational risk of hepatitis B infection. There is currently on clear data available regarding differences in duration of vaccine response between men and women. This study will provide data regarding the prevalence of protective immunity among active duty women in different age groups, under the current guidelines of immunization practice. In addition, a cost-effective vaccine booster strategy will be compared to the standard 1.0 ml dose of vaccine. Since pneumoniae among military recruits is caused by *S.* pneumoniae, data on the prevalence of natural immunity in active duty women would be helpful for future planning of more effective immunization strategies. Using a health assessment questionnaire, serum samples and anergy skin testing, subjects will be screened for eligibility and assessed to determine protective antibody levels to hepatitis B and *S.* pneumoniae. We suspect there is a difference between women and men in antibody response from immunization to hepatitis B and natural immunity to *S.* pneumoniae.

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Renée M Eyle 26 Sept 95

PI - Signature Date

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Introduction

Effective vaccines for the prevention of hepatitis B and pneumococcal disease are available but only hepatitis B surface antigen vaccines are routinely given as a single immunization series.(1-3) There are currently no recommendations for booster doses for hepatitis B for active duty men or women.(4) Loss of protective immunity to hepatitis B carries a risk for active duty members, both male and female, but also for the unborn infant in the event of pregnancy.(1-3,5-7) Pneumococcal disease is increasing in incidence and virulence with reports of antibiotic resistance.(8-9) Active duty men and women, particularly in the health care professions, have an occupational increased risk for infection and secondary morbidity. The 23 valent pneumococcal polysaccharide vaccine has not been formally recommended for healthy adults because of the presumption of natural immunity due to environmental exposure.

It was the purpose of this study to determine the prevalence of protective immunity to hepatitis B and pathogenic pneumococcal polysaccharides (1, 3, 4, 6A, 7F, 8, 9N, 12F, 14, 18C, 19A/F, 23F) in active duty women (in different age groups, compared to active duty men). In addition, those subjects with loss of protective immunity to hepatitis B are to receive booster immunizations by 2 different routes (intradermal 0.1 ml or 2 mcg versus intramuscular 1.0 ml or 20mcg).(5) The goals of the study included the following:

- To enroll three hundred (300) active duty members (150 women, 150 men) defined as normal by history, screening humoral and cellular immunologic studies; 3 different age groups are to be represented (50 subjects from each gender: 18-29 years, 30-44 years, and over 45 years).
- To measure hepatitis B surface and core antibody in all participants and select out those with loss of protective immunity (< 10 IU/ml) for booster immunization by ID versus IM route.
- To determine the prevalence of lack of protective immunity to pathogenic pneumococcal serotypes.
- To assess the levels of measles, mumps and rubella antibody and compare any differences between men and women.

The study design involves enrollment of active duty men and women from the Walter Reed Army Medical Center community as well as the drawing area served by The Stripe and The Pentagon Newspapers. A study coordinator nurse was designed to be an essential component of the project in order to meet the timeline for the project dates and to perform the data collection, special skin testing and blood drawing. Special laboratory studies assaying for humoral immunity were to be contracted out for prompt completion in order to expedite the study. Hepatitis B serology was to be performed in collaboration with the Walter Reed Army Institute of Research (Dr. McCarthy).

Body

One hundred and eighty four (184) subjects (87 women, 99 men) have been enrolled in the study to date. All participants are normal as defined by normal quantitative immunoglobulins, lymphocyte counts and the absence of anergy utilizing the 3 recall antigens tetanus, mumps and candida. The first two age groups (18-29 and 30-44 years) are within 25% of completion of target enrollment but the third age group (>45 years) has been difficult to fill since many within this group have not received a primary hepatitis B vaccine series. Seventy four subjects have been completed in terms of all data accumulated and a letter of discharge (with results of relevant testing being made available to the subjects) having been sent. Due to delays in contracting payments and authorizations, special testing for more than 100 sera remains on hold and will be sent out this month. These delays limit the data available for analysis at this time and prevent identification of subjects for the second phase of the study (immunization arms for hepatitis B). Due to the severe time restrictions on the protocol funding, these delays (not under the investigator's control) may restrict total goal achievements set for the protocol. Numbers remain too small for analysis of gender differences at this time for many of the variables under consideration.

Eighty-four (84) of the 186 subjects enrolled have results for hepatitis B surface (HBsAB) and core (HBcAB) antibody testing. None had evidence of natural infection with hepatitis B (negative core antibody) but 16.7% had HBsAB levels below protective range (< 10 IU/ml). The majority of the participants were health care workers. Twenty-six percent (26%) had HBsAB less than 100 IU/ml, a level previously reported as associated with loss of protective immunity within 3-5 years. To date, there are no significant differences between men and women. Fourteen subjects with borderline or unprotective levels of HBsAB have received either an intradermal or intramuscular booster vaccine dose for hepatitis B. Response data in any of these recipients is not yet available.

Measles, mumps and rubella antibody levels are available for 179 of the 186 subjects enrolled. A limited number (< 10%) of unprotective levels of antibody were found for measles (8.4%), mumps (6.7%) and rubella (2%) in both gender groups and all age groups. As with all other prior vaccination history, a large number of active duty subjects did not have adequate shot records to review and could not by history recall when the date of their last vaccine doses had occurred. Hemophilus influenzae type b specific antibody levels were < 100 ng/ml in 5.7% of 88 subjects. A vaccine for Hemophilus influenzae type b is currently available but is not part of the immunization recommendations for healthy adults or active duty populations. It is also noteworthy that despite this populations increased access to immunizations, 7.8% (N=89) did not have protective antibody levels for diphtheria.

Pneumococcal polysaccharide (PPS) antibody levels to 4 serotypes are available in 88 subjects. For PPS 3, 7F, 9N, and 14, non-protective antibody levels were evident in 16,

17, 42 and 26% of subjects respectively. For the remainder of the serotypes, only 77 subjects have results with percent having nonprotective titers listed by serotype as follows: PPS1 15.6%; PPS4 9%; PPS6b 26%; PPS8 58%; PPS12F 7.8%; PPS18C 15.6%; PPS19F 5.1%; PPS23 7.8%. There has been increasing discussion of developing a modified or conjugated pneumococcal vaccine which produces improved immune responses but would only contain 6 serotypes. This data suggests that future vaccine formulations should include at least serotypes 7F, 9N, 6b and 8 since more than 20% of the healthy population do not have protective immunity. Other serotypes with greater than 15% nonprotection include 7F, 3, 1, and 18C. Considering that PPS3 is the most immunogenic of the serotypes when evaluating immunodeficiency in patients with recurrent bacterial infections, it is surprising that 16% of our study population had no protection to this serotype.

Conclusions

Healthcare workers represent the majority of our study population at this time and actually, due to work contacts to the acute and chronically ill, might be anticipated to have more exposure to bacterial infections such as *Streptococcus pneumoniae* and therefore a higher percent of natural immunity than the rest of the population. Our data to date does not support this hypothesis. This raises the following question: Is the increase in more severe pneumococcal disease related to population decreases in natural immunity and therefore greater susceptibility to infections? If data regarding the serotypes of pneumococcus causing clinical infections at Walter Reed Army Medical Center were available, a potential for defining the environmental exposure risks to the need for enhanced protection might be addressed to further explore the serotypes of greatest relevance to a second generation vaccine. Our data also suggests that immunizing active duty with the pneumococcal vaccine, particularly prior to higher risk situations (such as deployments with close quarters and high stress) might be a reasonable consideration. Those subjects with preexisting high titers of antibody might suffer with large local reactions and mild systemic symptoms described in booster recipients in the past. However, for each serotype, the overall benefit may well outweigh the risks in this population. No clear differences between men and women are appreciated as yet.

References

1. Update on Adult Immunizations: Recommendations of the Immunization Practices Advisory Committee (ACIP). *MMWR* 1991; 40(RR-12, November).

2. Anderson DC, Stiehm ER: Immunizations. *JAMA* 1992; 268(20):2959-63.

3. Proceedings of a Symposium: Hepatitis B: The Disease and its prevention. *Am J Med* 1989;87(3A):1-41S.

4. Lemon SM: Prevention of Hepatitis B virus infections in military forces. *Medical Bulletin of the US Army*, Europe 1983; 40(#2/3):28-30.

5. Jilg W, Schmidt M, Deinhart F: Vaccination against hepatitis B: Comparison of three different vaccination schedules. *J Infect Diseases* 1989; 160(2): 766-760.

6. Barnas GP, Hanacik LJ: Hepatitis B vaccine: Duration of immunity in health care workers. *Clinical Res* 1987; 35(3):731A. (AN ABSTRACT)

7. Simms J, Duff P. Viral hepatitis in pregnancy. *Semin Perinatol* 1993; 17(6):384-93.

8. Musher DM, Groover JE, Rowland JM, Watson DA, et al. Antibody to capsular polysaccharides of Streptococcus pneumoniae: prevalence, persistence, and response to revaccination. *Clin Infect Dis* 1993;17(1):66-73.

9. Roghmann KJ, Tabloski PA, Bentley DW, Schiffman G. Immune response of elderly adults to pneumococcus: variation by age, sex and functional impairment. *J Gerontol* 1987;42(3):265-70.)