Risk factors for hepatitis B virus infection in US Army soldiers in Europe

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SUMMARY Cross-sectional and case-control studies were conducted in a US Army unit which had experienced a protracted outbreak of viral hepatitis. Serological, demographic, and exposure data were collected. The cross-sectional study found that there was no association between the prevalence of hepatitis B virus (HBV) infection and ethnicity, education, and rank. There was an association with age and duration of assignment to the unit. Having social contact with an identified hepatitis patient and the sharing of personal hygiene items with a case were significant risk factors for HBV infection. Through the use of anonymous questionnaires, the case-control study evaluated various behavioural factors. Univariate analysis indicated moderate but not significant increases in risk associated with a history of multiple sex partners and a history of disciplinary problems while in the military. Six drug-use related risk factors were significantly associated with HBV infection on univariate analysis. When evaluated with multivariate analysis, the only risk factor that was significantly associated with HBV infection was injection of drugs while assigned to the study unit. Two sources of misclassification bias were identified, both of which acted to underestimate the true risk associated with identified risk factors.

Historically, viral hepatitis has produced significant morbidity in members of the US military during periods of peace and war. Data from the second world war yield rates ranging from 0.75 to 46 cases per 1000 per year. More recent data from the Vietnam conflict show rates from 4 to 10 cases per 1000 per year.^{1 2} Viral hepatitis has been an important cause of morbidity among soldiers of the United States Army, Europe (USAREUR) since the early 1970s. A large protracted outbreak of hepatitis began in 1972 and resulted in a peak yearly case rate of approximately 20 cases per 1000 population in 1974. From this peak in mid-1974, case rates gradually decreased to approximately 1.6 cases per 1000 in 1982. Several studies of hepatitis in military populations have been conducted and have found that the aetiological agent for most non-outbreak associated infections is the hepatitis B virus (HBV).^{3–7}

Studies have established that transmission of HBV occurs as a result of both environmental and behavioural factors.^{8–10} Behavioural issues have been examined for the military in various population-based studies. Lemon *et al* reported that the specific behavioural factor most frequently reported in Germany was illicit self-injection of drugs, while in Korea sexual activity was most important.⁶ In 1975,

an outbreak of hepatitis cases in US Army soldiers prompted a case-control study in Nuremberg which evaluated transmission factors through serological studies and questionnaires. This study revealed that most disease was due to hepatitis B, and that drug abuse was the most frequently reported antecedent factor.¹¹ A study of US military personnel conducted during 1973–74 in Thailand determined that social or sexual contact with the indigenous population, and marijuana use, were associated with hepatitis B infection.¹² In none of these studies were multivariate methods of analysis reported. A study by the authors of drug screen results and reported cases of hepatitis from 1978 to 1982 in US Army soldiers in Germany found a strong correlation ($r=0.84$, $p<0.001$) between the proportion of urine tests positive and the incidence of hepatitis,⁷ as shown in the figure. A later report, also by the authors, found that a USAREUR unit experiencing a protracted outbreak of hepatitis B had significantly higher rates of positive drug screens than did two identical units located in the same area, or the USAREUR population in general.¹³

The present study involves the same USAREUR hepatitis outbreak reported,¹³ in which we examine specifically the importance of behavioural variables known to be linked to HBV transmission.

Total hepatitis and positive drug screen tests per 10 000 tests, by quarter, 1978-82

Methods

The unit of concern has a population of approximately 930 men organised into six subunits (companies). Normal tours of duty with the unit range from 18 months to three years. During the period of interest the unit strength was constant. The unit experienced an outbreak of hepatitis which lasted two years and generated 46 identified clinical cases. On-site investigation occurred in June 1983. Descriptive epidemiology of the outbreak has been presented.¹³

To obtain a cross-sectional demographic, historical, and serological profile of the unit, 879 personnel (95% of the population) answered a non-confidential questionnaire and provided a 15ml sample of venous blood for viral analysis. All specimens were tested for hepatitis B surface antigen (HBsAg) and antibody to hepatitis B core antigen (anti-HBc) by radioimmunoassay at the USAREUR Blood Bank. At the time of the study, the serological capability to differentiate recent infection from previous infection with the IgM fraction of anti-HBc did not exist in USAREUR.

In addition to demographic data, information was solicited about social contacts and the sharing of personal hygiene items such as razors, towels, and toothbrushes with hepatitis cases.

To address the sensitive behavioural issues involved more directly a case-control study was planned. In this study an anonymous questionnaire was administered to all available personnel positive for either HBsAg or anti-HBc (cases). Two personnel negative for these markers (controls) were also selected for each case, matched for rank, ethnic group, age group, and company. To preserve anonymity, questionnaires were coded so that it was possible for the investigators to determine whether the respondent was a case or control but not to identify the individual. Completed

questionnaires were folded and placed into a sealed container. The questionnaire addressed non-specific drug use, use of injectable drugs, history of self-injection, and use of marijuana, heroin, amphetamines, cocaine, barbiturates, and diet pills. In addition, information was solicited about history of venereal disease, number of sexual contacts, homosexual behaviour, and a history of disciplinary problems while in the military. As a measure of internal validity, two additional questions were asked: "Did you answer the questionnaire honestly", and "Do you feel your privacy was preserved".

Statistical analysis was accomplished using the Statistical Package for the Social Sciences,¹⁴ BMDP Statistical Software,¹⁵ and the University of Texas School of Public Health Epidemiology Package.¹⁶ Statistical significance was determined using the chi-square test for categorical data, and the Armitage test for trends for dose-response relation. For specific exposures, an odds ratio and 95% confidence interval estimate (CIE) was calculated. An odds ratio was considered significant if unity was not included in the CIE. To evaluate the relation of each risk factor to markers for hepatitis infection in the presence of other risk factors, multiple logistic regression analyses were performed using BMDPLR.

Results

Of the 879 soldiers sampled, six were positive for HBsAg. Two of these six were previously identified cases of clinical hepatitis B. An additional 73 soldiers were negative for HBsAg but positive for anti-HBc, giving a 9.0% prevalence of markers representing current or past HBV infection.

There were no significant differences in HBV marker prevalence between ethnic groups, rank, and educational groups. There were trends towards an increase in prevalence with increasing age (slope coefficient = 0.006, $p = 0.005$) and months assigned to the unit (slope coefficient = 0.006, $p = 0.042$). Having a friend who was a case of clinical hepatitis and sharing personal hygiene items with a hepatitis case were both associated with marker positivity and yielded odds ratios of 3.18 and 3.16, respectively, both of which were significantly greater than 1.0.

Approximately 20% of the cases and controls that were identified at the time of the cross-sectional study had transferred out of the unit by the time the case-control study was conducted. One person, a case, responded that he had not answered the questionnaire honestly. This questionnaire was excluded from further analysis, giving a total of 29 cases and 57 controls.

The univariate odds ratios and 95% confidence interval estimates for the behavioural variables

collected via the anonymous questionnaire were calculated and are presented in table 1. Significant risk factors for HBV infection were: use of heroin, use of diet pills, history of ever injecting drugs, and history of injecting drugs since joining the study unit.

Further analysis utilised multiple logistic regression to evaluate the contribution of each risk factor in the presence of other risk factors. Variables were set to enter in a step-wise manner. The only variable that entered the regression equation was a history of injecting drugs since joining the study unit. The associated odds ratio was 8.00, with a 95% confidence interval estimate of 1.46 to 43.87. In the presence of this variable, the use of heroin, diet pills, and history of ever having injected drugs lost significance. No other variable was significantly associated with HBV infection.

Overall there were no significant differences between cases and controls in response to the question about preservation of privacy. When the questions about use of heroin and injection of drugs since joining the unit were stratified by response to the privacy question, however, the odds ratios were markedly increased for those who felt their privacy had been preserved, as shown in table 2. These results were interpreted as evidence of misclassification on exposure, in that those who felt their privacy had been maintained reported more exposure to risk factors than those who felt that their privacy had been compromised. This misclassification biases results towards minimising differences in the exposed and unexposed groups, with the crude odds ratios underestimating the true risk associated with these two

Table 2 Effect of misclassification of exposure on odds ratios

Variable	Odds Ratios			Ratio of odds ratios*
	Crude	Stratified on privacy preserved		
		Yes	No	
HEROIN	9.00	20.42	0.65	2.27
INJUNIT	8.83	39.44	0.41	4.47

*Privacy preserved—Yes' odds ratio divided by crude odds ratio.

drug-use variables. The magnitude of this underestimation is given as the ratio of odds ratios.

Discussion

The relation of hepatitis B to drug abuse and sexual behaviour has been well established in both civilian and military populations. Because of the negative impact that admitting to drug abuse or homosexual contact would have on an individual's military career, inquiries about these matters must be approached circumspectly. This was accomplished in this study through the use of an anonymous questionnaire. Even with efforts to ensure anonymity for the study subjects, the potential remains that a lack of confidence will result in soldiers inaccurately reporting behaviour which could compromise their military record. An attempt to quantify the misclassification on exposure which results from such inaccuracies prompted the inclusion of questions concerning truth and privacy.

Despite these potential inaccuracies, analysis of responses to the anonymous questionnaire yielded a strong association between injectable drug abuse and infection with HBV. Further analysis using multiple logistic regression indicated that the most important factor was injection of drugs while assigned to the study unit. In the presence of this variable, all other variables lacked significance.

There are two important sources of misclassification bias identified in this study, both of which should result in underestimation of the odds ratio associated with the risk factors examined. First, all persons with serological markers for HBV were considered equally, with no method to differentiate between those who were infected while in the unit ('true' cases) and those who had been infected before being assigned to the unit ('false' cases). Therefore, the group of cases includes an unknown proportion of soldiers with markers of HBV infection who should be excluded from analysis, as they were not at risk of new infection. This results in bias on outcome or disease status. The magnitude of the bias that this introduces is unknown. The resulting bias, however, should lower the risk estimate associated with the variables

Table 1 Univariate odds ratios and 95% confidence intervals (95% CIE) for risk factors for hepatitis B infection

Variable description	Variable name	Odds ratios	95% CIE
Ever use any drugs	ANYDRUG	2.43	0.96-6.15
Ever use marijuana	MARIJUAN	1.53	0.62-3.76
Ever use heroin	HEROIN	9.00	1.72-46.88
Ever use cocaine	COCAINE	3.55	0.91-13.81
Ever use barbiturates	BARBIT	2.17	0.50-9.40
Ever use diet pills	DIETPILL	4.29	1.25-14.77
Ever inject drugs	EVRIJECT	3.96	1.16-13.51
Inject drugs since joining study unit	INJUNIT	8.83	1.70-46.03
Ever have a positive urine test for drugs	URINE	2.23	0.70-7.12
Ever had gonorrhoea	GONORREA	0.95	0.34-2.71
Ever had syphilis	SYPHILLIS	9.73	0.45-209.76
Ever had non-specific urethritis	NSU	2.17	0.50-9.47
Ever been jailed	JAIL	4.15	0.36-47.78
Ever had rank reduced	RANKRED	2.72	0.87-8.47
Had two or more sexual contacts since joined study unit	SEXCONT	1.66	0.60-4.58
Ever had sex with another male	HOMOSEX	0.66	0.03-16.74

examined. If the misclassification is non-differential on exposure (ie, equal proportions of individuals with and without the exposure variable are improperly considered cases), the resulting odds ratios are biased towards one.¹⁷

Secondly, the differences in odds ratios associated with HEROIN and INJUNIT (table 2) for those who felt that their privacy had been preserved as compared to those who did not indicates that there may have been misclassification of individuals on exposure, at least for these risk factors. It appears that those who felt their privacy had been compromised falsely stated that they had not been exposed to these risk factors. As it seems unlikely that an equal proportion of non-exposed persons would falsely claim that they had been using heroin or injecting drugs, this would represent differential misclassification on exposure. The bias resulting from this would also be towards one.¹⁷

Considering that both the non-differential and differential biases introduced would be towards one, the odds ratio associated with injection of drugs while with the unit has probably been underestimated by a factor greater than four. Given the strength of the observed association, the multivariable analyses conducted, and the probable underestimation of the odds ratio, it is felt that the identified drug use risk factor is the only important factor involved in transmission of HBV in this population.

Disclaimer

The views expressed in this paper are those of the authors and do not necessarily represent the official position or policy of the Department of Defense, Department of the Army, or the United States Army, Europe.

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