Association of Bacterial Vaginosis With Chlamydia and Gonorrhea Among Women in the U.S. Army

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Introduction: Bacterial vaginosis (BV) is a common vaginal condition characterized by gray/white, thin, and malodorous discharge. BV is associated with the replacement of normal vaginal lactobacilli by an overgrowth of vaginal anaerobes or Gram-negative bacteria (e.g., Gardnerella vaginalis), which causes an imbalance in the vaginal microflora with a resulting discharge. The BV prevalence varies substantially between countries worldwide. In the U.S., BV is more frequently reported among African-American and Hispanic women than white women.

Methods: A population-based, nested case-control study was conducted of all incident chlamydia and gonorrhea cases reported to the Defense Medical Surveillance System during 2006–2012. Using a density sampling approach, for each chlamydia or gonorrhea case, 10 age-matched (±1 year) controls were randomly selected from those women who were never diagnosed with these infections. Incidence rate ratios were estimated using conditional logistic regression. Statistical analysis was carried out in December 2015.

Results: A total of 37,149 chlamydia cases and 4,987 gonorrhea cases were identified during the study period. Antecedent BV was associated with an increased risk of subsequent chlamydia (adjusted incidence rate ratio = 1.51; 95% CI = 1.47, 1.55) and gonorrhea (adjusted incidence rate ratio = 2.42; 95% CI = 2.27, 2.57) infections. For every one additional episode of BV, the risk of acquiring chlamydia and gonorrhea infections increased by 13% and 26%, respectively. A monotonic dose–response relationship was also noted between antecedent BV and subsequent chlamydia and gonorrhea infection. In addition, an effect modification on the additive scale was found between BV and African-American race for gonorrhea, but not for chlamydia.

Conclusions: Among U.S. Army women, antecedent BV is associated with an increased risk of subsequent chlamydia and gonorrhea infection.

INTRODUCTION

Bacterial vaginosis (BV) is a common vaginal condition characterized by gray/white, thin, and malodorous discharge. BV is associated with the replacement of normal vaginal lactobacilli by an overgrowth of vaginal anaerobes or Gram-negative bacteria (e.g., Gardnerella vaginalis), which causes an imbalance in the vaginal microflora with a resulting discharge. The BV prevalence varies substantially between countries worldwide. In the U.S., BV is more frequently reported among African-American and Hispanic women than white women.

New or multiple male sexual partners have been associated with BV. Lower age at first intercourse, past pregnancy, commercial sex work, and vaginal douching...
are also linked to BV.\textsuperscript{5–8} Since the work of Leopold\textsuperscript{9} and Gardner and Dukes in the 1950s,\textsuperscript{10} the etiologic agent of BV has not been established, and there is debate on whether BV constitutes a sexually transmitted infection (STI).\textsuperscript{11} However, it is also possible that BV is a sexually enhanced disease.\textsuperscript{6}

Data indicate that BV is a risk factor for the acquisition of pathogens such as HIV, herpes simplex virus Type 2, human papillomavirus, \textit{Chlamydia trachomatis}, and \textit{Neisseria gonorrhoeae}.\textsuperscript{12–17} For example, one cohort study conducted among non-pregnant women found that those with BV had a 1.8- and 1.9-fold increased risk for gonorrhea and chlamydia, respectively.\textsuperscript{18} A secondary data analysis of the Project Protect clinical trial indicated that women with a high BV severity had a 2.7-fold increased risk of acquiring an STI.\textsuperscript{19}

According to the Armed Forces Health Surveillance Center, from 2000 through 2012, a total of 87,462 chlamydia and 11,403 gonorrhea cases were reported among military women.\textsuperscript{20} Chlamydia and gonorrhea rates are higher in military than civilian women. This difference may be due to the high prevalence of risky sexual practices among the predominantly younger military women. However, it might also be the result of a screening effect, as women undergo routine annual screening for STIs.

The relationship between BV and STIs has not been examined among military women. Thus, this study sought to determine whether antecedent BV was associated with subsequent chlamydia or gonorrhea infection, with special attention paid to Hispanic women, a minority group not previously evaluated. This study also analyzed the role of the number of episodes of BV on STI risk, as a dose–response relationship has not previously been studied. The identification of BV as risk factor for the transmission of these infections has potential implications for prevention efforts in the U.S. military.

METHODS

Data Sample

Study data were obtained from the Defense Medical Surveillance System (DMSS); details about this surveillance system have been published elsewhere.\textsuperscript{21} Briefly, DMSS is the central repository of medical surveillance data for the U.S. Armed Forces. This relational database contains information on personnel demographics, reportable diseases, deployments, and medical data for all active-duty personnel throughout their careers. DMSS data have previously been used to study HIV and herpes simplex virus Type 2 infections among U.S. military personnel.\textsuperscript{22,23}

In this population-based, nested case-control study, all active duty women in the U.S. Army with a first-time diagnosis of chlamydia or gonorrhea, in either the first or second diagnostic position of an outpatient or inpatient, physician-based, diagnostic encounter reported between January 1, 2006 and December 31, 2012, were selected. For case findings, the ICD-9 was applied. For chlamydia cases, the set ICD-9 codes were 099.41 or 099.5, and for gonorrhea cases, the set ICD-9 codes were 098.0x, 098.1x, 098.4x, or 098.8x. Using a density sampling approach,\textsuperscript{24} a random sample of ten controls composed of women without a chlamydia or gonorrhea diagnosis at the time of diagnosis for the case were matched to each case on age (±1 year). Ten controls per case were chosen to increase the statistical precision of the estimates.\textsuperscript{25}

A BV diagnosis was based on the ICD-9-CM code 616.10 (vaginitis and vulvovaginitis, unspecified) in either the first or the second diagnostic position of an outpatient or inpatient encounter medical record from DMSS, prior to the diagnosis date of chlamydia or gonorrhea. Because recurrent BV episodes are frequent and there is no accepted definition of recurrence,\textsuperscript{26} an episode of recurrent BV was defined as one where a subsequent diagnosis took place ≥30 days from the previously diagnosed BV episode. This criterion was based on the recommendations given by the Centers for Disease Control and Prevention BV Working Group meta-analysis and synthesis report.\textsuperscript{3}

Measures

Demographic variables, including race, education, marital status, region of birth, rank, and years in service, were extracted from DMSS. These were defined as race/ethnicity (white, African American, Hispanic, and other), education (no high school, high school, and some college or higher), marital status (single, married, and other), rank (lower enlisted [E1–E4], higher enlisted E5–E9), and officers), and years of service (≤1, 2–3, and ≥4). Geographic region or residence (birth) was classified into four regions (West, Midwest, Northeast, and South).

Statistical Analysis

The prevalence of BV among cases and controls was compared using the Cochran–Mantel–Haenszel test. To analyze individual matched case-control data, conditional logistic regression was used to estimate the incidence rate ratios with 95% CIs to determine the association between BV and chlamydia and gonorrhea infection. Separate regression models were performed for each variable category. In addition to analyzing BV as a binary variable, BV was treated as a categorical variable to conduct a dose–response relationship analysis. An effect modification analysis on the additive scale was conducted to determine whether the effect of BV on chlamydia or gonorrhea infection differed by race/ethnicity. For analysis, the synergy and the relative excess risk due to interaction [RERI] measures were calculated. Synergy equal to one and RERI equal to zero indicate there is no departure from additivity.\textsuperscript{25}

All \(p\)-values were two-sided and were considered statistically significant if \(p < 0.05\). Analyses were carried out in December 2015 using Stata, version 14.0.

The study was approved by scientific review and IRBs at Lancaster University and the Walter Reed Army Institute of Research.

RESULTS

Chlamydia

Between 2006 and 2012, a total of 37,149 chlamydia case patients were identified among U.S. Army women. Of
these, 89% had high school education, 85% were in the lower enlisted rank, 80% were aged 25 years, 68% were single, 49% had at least 1 year of military service, 48% had home of record in the South, and 34% were African American. Among the 371,490 controls, 84% had high school education, 78% were of lower enlisted rank, 64% were single, 41% had at least 1 year of military service, 40% were from the South, and 21% were African American.

The prevalence of BV was higher among chlamydia cases than their controls (21.4% vs 15.6%, p < 0.001) (Table 1). For both chlamydia cases and controls, the highest BV prevalences occurred among women with senior enlisted rank, those with > 3 years of service, those with “other” marital status, women with college or higher education, married personnel, and among African Americans.

After adjusting for covariates, BV was significantly associated with chlamydia infection (incidence rate ratio=1.51; p < 0.001) (Table 2). These analyses also showed that the association between BV and chlamydia was higher in women with junior enlisted rank, women who had ≤ 2 years of military service, women with single marital status, and who were from the Northeast. Interestingly, the association between BV and chlamydia was higher among white women compared with African-American and Hispanic women.
When BV was treated as a continuous variable, for every additional one episode of BV, the risk of chlamydia infection increased by 13% (95% CI = 12%, 14%) compared with women without BV. A similar estimate was found after controlling for race/ethnicity, marital status, and military rank (data not shown). When BV was treated as a categorical predictor, a dose–response relationship with chlamydia infection was found (Figure 1). Women with one episode of BV had 1.45 (95% CI = 1.40, 1.50) times more risk of acquiring chlamydia infection compared with women without BV. Additionally, for women with two, three, four, five, and six or more episodes of BV, the risk of acquiring chlamydia compared with women without BV was 1.55 (95% CI = 1.47, 1.64), 1.74 (95% CI = 1.61, 1.88), 1.46 (95% CI = 1.29, 1.65), 1.95 (95% CI = 1.68, 2.26), and 2.07 (95% CI = 1.83, 2.33), times higher, respectively.

The analysis did not detect an additive effect modification between BV and chlamydia by race categorized into two groups (African-American race and other race/ethnic groups [white/Hispanic/other]; synergy = 1.02, 95% CI = 0.88, 1.90; RERI = 0.04, 95% CI = –0.24, 0.36).

### Gonorrhea

During the study period, a total of 4,987 gonorrhea case patients were identified (Table 1). Of these, 89% had high school education, 82% were lower enlisted rank, 76% were aged < 25 years, 65% were single, 58% were from the South, 57% were African American, and 41% had at least 1 year of military service. Among the 49,870

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**Table 2. Crude and Adjusted Associations Between BV and Chlamydia and Gonorrhea Among U.S. Army Females**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Chlamydia</th>
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<th>Gonorrhea</th>
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<tr>
<td></td>
<td>IRR (95% CI)</td>
<td>Adjusted^a IRR (95% CI)</td>
<td>IRR (95% CI)</td>
<td>Adjusted^a IRR (95% CI)</td>
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<tr>
<td>All participants</td>
<td>1.52 (1.47, 1.56)</td>
<td>1.51 (1.47, 1.55)</td>
<td>2.42 (2.26, 2.58)</td>
<td>2.42 (2.27, 2.57)</td>
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<tr>
<td>Race/ethnicity</td>
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<tr>
<td>White</td>
<td>1.46 (1.39, 1.54)</td>
<td>1.43 (1.36, 1.50)</td>
<td>2.28 (1.94, 2.68)</td>
<td>2.31 (1.96, 2.71)</td>
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<tr>
<td>African American</td>
<td>1.22 (1.16, 1.29)</td>
<td>1.24 (1.17, 1.31)</td>
<td>1.56 (1.41, 1.73)</td>
<td>1.58 (1.42, 1.75)</td>
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<tr>
<td>Hispanic</td>
<td>1.33 (1.20, 1.49)</td>
<td>1.36 (1.22, 1.52)</td>
<td>2.08 (1.53, 2.62)</td>
<td>2.12 (1.55, 2.90)</td>
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<tr>
<td>Other^b</td>
<td>1.33 (1.15, 1.53)</td>
<td>1.36 (1.18, 1.57)</td>
<td>2.65 (1.76, 3.99)</td>
<td>2.68 (1.78, 4.03)</td>
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<td>Education level</td>
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<tr>
<td>High school</td>
<td>1.44 (1.40, 1.49)</td>
<td>1.50 (1.46, 1.55)</td>
<td>2.32 (1.26, 2.49)</td>
<td>2.44 (1.27, 2.62)</td>
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<tr>
<td>College or higher</td>
<td>1.68 (1.53, 1.84)</td>
<td>1.44 (1.31, 1.59)</td>
<td>2.20 (1.72, 2.81)</td>
<td>1.90 (1.47, 2.46)</td>
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<tr>
<td>Marital status</td>
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<tr>
<td>Single</td>
<td>1.63 (1.57, 1.69)</td>
<td>1.59 (1.53, 1.65)</td>
<td>2.71 (2.47, 2.97)</td>
<td>2.66 (2.42, 2.91)</td>
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<tr>
<td>Married</td>
<td>1.46 (1.38, 1.54)</td>
<td>1.44 (1.36, 1.51)</td>
<td>2.24 (1.97, 2.54)</td>
<td>2.23 (1.96, 2.54)</td>
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<tr>
<td>Other^d</td>
<td>1.38 (1.18, 1.61)</td>
<td>1.37 (1.17, 1.60)</td>
<td>1.68 (1.18, 2.41)</td>
<td>1.66 (1.15, 2.39)</td>
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<td>Region of birth^e</td>
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<tr>
<td>West</td>
<td>1.43 (1.32, 1.56)</td>
<td>1.42 (1.31, 1.55)</td>
<td>2.55 (1.99, 3.26)</td>
<td>2.59 (2.02, 3.32)</td>
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<tr>
<td>Midwest</td>
<td>1.51 (1.36, 1.68)</td>
<td>1.49 (1.34, 1.66)</td>
<td>2.90 (2.16, 3.90)</td>
<td>2.85 (2.10, 3.87)</td>
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<td>Northeast</td>
<td>1.60 (1.40, 1.83)</td>
<td>1.52 (1.33, 1.75)</td>
<td>2.48 (1.75, 3.51)</td>
<td>2.41 (1.69, 3.43)</td>
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<tr>
<td>South</td>
<td>1.47 (1.41, 1.54)</td>
<td>1.48 (1.42, 1.54)</td>
<td>2.12 (1.93, 2.33)</td>
<td>2.14 (1.95, 2.36)</td>
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<tr>
<td>Military rank</td>
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<tr>
<td>Junior enlisted</td>
<td>2.20 (1.78, 2.71)</td>
<td>2.15 (1.74, 2.66)</td>
<td>2.37 (1.28, 4.37)</td>
<td>2.40 (1.29, 4.46)</td>
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<tr>
<td>Senior enlisted</td>
<td>1.47 (1.43, 1.52)</td>
<td>1.50 (1.45, 1.55)</td>
<td>2.46 (2.28, 2.66)</td>
<td>2.53 (2.34, 2.74)</td>
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<tr>
<td>Officers</td>
<td>1.56 (1.45, 1.67)</td>
<td>1.54 (1.43, 1.65)</td>
<td>2.22 (1.88, 2.63)</td>
<td>2.19 (1.85, 2.60)</td>
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<tr>
<td>Years of military service</td>
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<tr>
<td>≤ 1</td>
<td>1.81 (1.71, 1.92)</td>
<td>1.82 (1.72, 1.93)</td>
<td>2.74 (2.36, 3.18)</td>
<td>2.74 (2.35, 3.19)</td>
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<tr>
<td>2–3</td>
<td>1.71 (1.61, 1.81)</td>
<td>1.72 (1.63, 1.83)</td>
<td>2.95 (2.56, 3.38)</td>
<td>2.95 (2.56, 3.40)</td>
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<tr>
<td>≥ 4</td>
<td>1.63 (1.56, 1.71)</td>
<td>1.61 (1.53, 1.69)</td>
<td>2.42 (2.16, 2.70)</td>
<td>2.38 (2.13, 2.68)</td>
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</table>

^aAdjusted IRR for race/ethnicity, marital status, and military rank.
^bOther: American Indian/Alaskan Native, Asian/Pacific Islander, and others.
^cUndefined IRR, zero or infinity.
^dOther: Divorced, widowed, and others.
^eWest (MT, WY, CT, NM, ID, UT, AZ, NV, WA, OR, CA, AK, and HI); Midwest (IL, IN, IA, KS, MI, MN, MO, OH, NE, ND, SD, and WI); Northeast (ME, NH, VT, MA, RI, CT, NY, NJ, and PA); South (FL, GA, NC, SC, VA, WV, MD, DC, DE, AL, KY, MS, TN, AR, LA, OK, and TX).

BV, bacterial vaginosis; IRR, incidence rate ratio.
controls, 83% had high school education, 74% were lower enlisted rank, 61% were single, 41% were from the South, 36% had at least 1 year of military service, and 23% were African American.

The prevalence of BV was higher among gonorrhea cases than their controls (34.7% vs 19.1%, \(p<0.001\)) (Table 1). Similar to the chlamydia results, the highest BV prevalences among gonorrhea cases and controls occurred among senior enlisted personnel, among women with \(\geq 4\) years of service, African-American women, those with other marital status, and among women with college or higher education.

In a regression analysis, BV was significantly associated with gonorrhea (incidence rate ratio=2.42; \(p<0.001\)). After controlling for race, marital status, and military rank, the association between BV and gonorrhea was higher in women with the following characteristics: those with \(< 4\) years of military service, those from the Midwest, single women, and those of other race/ethnic groups.

Analyses also revealed that for every additional episode of BV, the risk of gonorrhea infection increases 26% (95% CI=23%, 28%, \(p<0.001\)) compared with women without BV. This estimate was similar after controlling for race/ethnicity, marital status, and military rank (data not shown). When BV was analyzed as a categorical predictor, the results showed a linear association between the number of episodes of BV and acquisition of gonorrhea infection (Figure 2). According to this dose–response analysis, women with one episode of BV had 1.98 (95% CI=1.82, 2.15) times more risk of acquiring gonorrhea compared with women without BV. Additionally, compared with women without BV, the risk of acquiring gonorrhea among women with two, three, four, five, and six or more episodes was 2.71 (95% CI=2.41, 3.04), 3.22 (95% CI=2.74, 3.79), 3.62 (95% CI=2.87, 4.55), 4.12 (95% CI=3.14, 5.40), and 4.62 (95% CI=3.73, 5.73), respectively.

Analyses also found that using an additive scale, race/ethnicity was a positive effect modifier for the relationship between BV and gonorrhea (synergy=1.29, 95% CI=1.05, 1.58; RERI=1.80, 95% CI=0.25, 3.34). This synergistic relationship indicates that the joint exposure effect of BV and African-American race on gonorrhea was larger than the sum of the effect of African-American race on gonorrhea risk and of BV on gonorrhea risk.

**DISCUSSION**

Antecedent BV was associated with subsequent chlamydia and gonorrhea infection among women in the U.S. Army. This represents the first large study to provide objective evidence of the role of the most common cause of vaginal discharge, BV, on these two STIs. This association was previously reported only among high-risk women in civilian populations.\(^{15-18}\)

Although it is difficult to estimate the exact prevalence of BV, as many women are asymptomatic, limited data on this vaginal condition indicates that among women entering military service in the U.S. Marine Corps during 1999–2000, a high prevalence was found among African-American (32%) and Hispanic women (30%).\(^4\) This finding is in agreement with that observed in this study, in which African-American and Hispanic women had the highest BV prevalences.

The prevalence of BV was two and three times higher among African-American women with chlamydia or gonorrhea compared with white women. This disparity, which has been reported in civilian studies,\(^3,16\) cannot be explained by differences in sexual activity or sociodemographic characteristics.\(^27\) It is possible that it is associated.
with lifestyle factors that are more common among African-American women, such as vaginal douching. Vaginal douching, which causes a disequilibrium in the vaginal microflora, induces inflammation through either physical or chemical irritation, and therefore predisposes women to BV. On the other hand, it is hypothesized that differences in the composition of bacterial vaginal flora between whites and African Americans might explain this disparity, but there is no direct evidence of such a complex relationship.

This study found that women with BV were 1.5 and 2.4 times more likely to have a subsequent chlamydia or gonorrhea diagnosis when compared with their age-matched controls, respectively. These estimates were smaller for chlamydia, and higher for gonorrhea, when compared with estimates from a large cohort study among 3,620 non-pregnant women aged 15–44 years (hazard ratio for chlamydia=1.9; hazard ratio for gonorrhea=1.8). These findings are consistent with previous research suggesting that BV facilitates the acquisition of these STIs.

This study also documents that among Hispanic women, the relationship of BV with chlamydia or gonorrhea infection was higher when compared with African-American women. Data on the dynamics of STI transmission, including gonorrhea, among Hispanic women is limited in the military literature, despite the fact that this minority group has increased its representation in the U.S. military from 4% in 1981 to 13% in 2013. Further studies are warranted in the military to determine what individual, social, or biological factors contribute to the risk of STIs among Hispanic women.

Analyses revealed that among single and enlisted women, the association of BV with chlamydia or gonorrhea was stronger compared with those who were married or officers. Studies of active duty service women, who are mostly single and young, report that they engage in high-risk sexual behaviors (e.g., multiple sexual partners, low condom use, and sex while under the influence of drugs or alcohol). Additionally, among young female recruits (aged 17–21 years), BV has been associated with having more than one sexual partner in the past 3 months. Considering these findings, it is valid to assume that high-risk sexual behaviors might explain the difference between single and married women. On the other hand, in the U.S. Army, enlisted personnel are predominantly young and unmarried. In this enlisted population, 71% of women were young (aged <25 years) and unmarried. Consequently, this high percentage may explain, in part, the high association of BV with chlamydia and gonorrhea among the enlisted ranks.

An important finding from this study was that for every one additional episode of BV, the risk of acquiring chlamydia and gonorrhea infection increased by 13% and 26%, respectively. This increased risk was independent of other covariates. To the best of the authors’ knowledge, there is no evidence in the literature on the risk of STIs by the number of episodes of BV. Although the basis for this increased risk is not known, this study presents evidence for the cumulative effect of BV on the risk for these infections.

This study also found a dose–response relationship between antecedent BV and subsequent chlamydia and gonorrhea diagnosis. The shape of this relationship was monotonic, which indicates that the risk of these infections increases with the number of episodes of BV. For simplicity, the shape of the trend was analyzed descriptively, and not using advanced statistical models, such as splines. This dose–response relationship supports the role of BV in the risk of STI acquisition. In addition to the observed strength of the association, an important component for disease causality, the presence of a dose–response relationship has public health implications in terms of disease prevention because it provides clues to the biology underlying bacterial–STI relationship.

Effect modification analyses found a synergistic effect between BV and African-American race for gonorrhea, but not for chlamydia. Although the mechanisms of this effect remain unclear, biological factors, in addition to individual behavioral and social factors, may explain racial disparities in STI acquisition. However, the nature of STIs among African Americans is complex, multifactorial in nature, and requires further individual and social network–level behavioral research. This is the first study that suggests that African-American race modifies the association between BV and gonorrhea infection.

Taken together, this study provides additional evidence of a probable causal link between BV and chlamydia and gonorrhea infection. These conclusions are supported by the strength of the associations, the temporal sequence of the associations, the consistency of findings with previous studies, and a dose–response relationship.

Limitations

This study has some limitations. It is likely that the reported number of women with BV was affected by the limitations of use of ICD-9 codes as indicators of BV. Therefore, it is probable that some women with BV were misclassified or had other conditions that also cause an inflammation or infection of the vagina, such as candidiasis or noninfectious vaginitis. It was not possible to analyze behavioral risk data, given that this information is not collected in DMSS. Further research should study the influence of behavioral factors (e.g., sexual practices, douching, use of condoms, and frequency of vaginal sex)
on the association of BV with chlamydia and gonorrhea among military women.

CONCLUSIONS

Among women in the U.S. Army, antecedent BV is associated with an increased risk of subsequent chlamydia and gonorrhea infection. This finding is consistent with those observed amongst civilian populations where BV has been reported to represent a strong risk factor for both bacterial STIs. The dose–response relationship between the number of episodes of BV and chlamydia or gonorrhea infection highlights the importance of BV as a clinical risk factor, which can be considered “hypothesis generating” for further research in the field of STIs. The study also provides important evidence-based public health findings for U.S. military authorities to develop prevention strategies such as sexual risk reduction for female service members with BV in order to reduce the acquisition of STIs. These results strengthen the literature that BV constitutes a predisposing condition that increases the risk of both chlamydia and gonorrhea infections.

ACKNOWLEDGMENTS

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