Title: Relationship between community-level alcohol outlet accessibility and individual-level HSV-2 infection among young women in South Africa

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Summary:
A study of young women in rural South Africa found that living in communities with more alcohol outlets was associated with increased likelihood of herpes simplex virus type 2 infection.

Abstract
Background: Exposure to alcohol outlets may influence sexual health outcomes at the individual- and community-level. Visiting alcohol outlets facilitates alcohol consumption and exposes patrons to a risky environment and network of potential partners, while presence of alcohol outlets in the community may shift social acceptance of riskier behavior. We hypothesize that living in communities with more alcohol outlets is associated with increased sexual risk.
Methods: We performed a cross-sectional analysis in a sample of 2,174 South African schoolgirls (ages 13-21) living across 24 villages in the rural Agincourt sub-district, underpinned by long-term health and socio-demographic surveillance. To examine the association between number of alcohol outlets in village of residence and individual-level prevalent HSV-2 infection, we used generalized estimating equations with logit links, adjusting for individual- and village-level covariates.
Results: The median number of alcohol outlets per village was three (range zero to seven). HSV-2 prevalence increased from villages with no outlets [1.4%, (95% CI: 0.2, 12.1)], to villages with one to four outlets [4.5% (3.7, 5.5)], to villages with more than four outlets [6.3% (5.6, 7.1)]. An increase of one alcohol outlet per village was associated with an 11% increase in odds of HSV-2 infection [adjusted odds ratio (95% CI): 1.11 (0.98, 1.25)].
Conclusions: Living in villages with more alcohol outlets was associated with increased prevalence of HSV-2 infection in young women. Structural interventions and sexual health screenings targeting villages with extensive alcohol outlet environments could help prevent the spread of sexually transmitted infections.

Introduction

Exposure to alcohol outlets (places where alcohol is sold and consumed, such as taverns, bars, and bottle shops) may influence sexual risk. At the individual level, easy access to alcohol outlets is associated with increased alcohol consumption,(1-3) which increases sexual risk behaviors, such as unprotected sex,(4-6) and results in poor sexual health, including HIV infection.(7-9) Similarly, characteristics of alcohol outlets (e.g. music, dim lights, unisex bathrooms) (10) and the network of potential sex partners who typically frequent them (11, 12) may provide environments with heightened potential for risky sexual activity. At the community level, the presence of alcohol outlets may influence or reflect community norms around acceptable behaviors, yielding heightened risk for all community members, whether they patronize the establishments or not.

Community-level alcohol outlet accessibility is typically quantified with a community density measure, but can include other measures such as hours/days of alcohol sale and price. Alcohol outlet accessibility is associated with increased measures of population-level (13-15) and individual-level (16) sexually transmitted infections (STIs). However, the relationship between alcohol outlet accessibility and sexual risk has been underexplored in areas outside of the United States and entirely unexplored in adolescent-specific populations that are at heightened risk for STI. As adolescents may have different alcohol outlet utilization patterns and alcohol-using behaviors than adults, generalization from adult population studies to adolescents could be problematic.

South African law prohibits the sale of alcohol to minors under the age of 18.(17, 18) However, this regulation is not widely enforced: about half of South African teens report having consumed alcohol in their lifetime, and the age of alcohol initiation is often substantially lower than 18, with many youth initiating alcohol consumption even prior to age 13.(19-21) In practice, South African minors are also often afforded access to outlets that sell alcohol; over 40% of young women living in rural Mpumalanga report recently visiting taverns.(22) Further, alcohol use and misuse are temporally connected to risky sex in this population: up to a quarter of South African teens who are sexually active report having used alcohol before sex.(19, 21)

Young women in South Africa are at exceptionally high risk for STIs; nearly a third are HIV positive by the time they reach age 21 and up to 70% are infected with herpes simplex virus type 2 (HSV-2) in their lifetime.(24, 25) Thus, the need to identify potential interventions for STI reduction in this population is critical. Alcohol outlet accessibility is attractive as a potential intervention target because it is relatively modifiable through strengthening or more strictly enforcing existing government regulations.(26-28) In this study, we aim to explore the association between alcohol outlet accessibility and sexual risk among adolescents in the developing world, using a population-based sample of young women in rural South Africa. We also explored the potential effect of neighborhood-level alcohol interventions using a marginal modeling approach.

Materials and Methods

Population

To explore the relationship between alcohol outlet accessibility and sexual risk, we analyzed baseline data collected in the HPTN 068 HIV prevention trial.(29) HPTN 068 is a Phase III randomized controlled trial in rural Mpumalanga province, South Africa within the Agincourt Health and Demographic Surveillance System site (HDSS).(30) The aim of the study is to assess whether cash transfers conditional on school attendance can prevent HIV. School-attending young women aged 13-21 were enrolled in the study between March 2011 and December 2012 (n=2533). Biological HIV and HSV-2 data were collected during routine baseline procedures completed by each young woman enrolled in the study. Data on alcohol outlets were collected as part of a community mapping exercise administered in 2010. A group of key informants from each village (average 11 key informants per village; n=24 villages) completed a questionnaire to enumerate, by consensus, a broad number of village assets, including schools, businesses, social organizations, and government services. Taverns and bottle shops were enumerated separately. Taverns generally sell alcohol for on-premises consumption and bottle shops generally sell alcohol for off-premises consumption; however, these are not rigid definitions. In practice, alcohol consumption can occur outside of bottle shops, and, conversely, taverns can sell alcohol to take home.

Ethical approval for the parent studies (HPTN 068 and community mapping study) was provided by the Office of Human Research Ethics at the University of North Carolina-Chapel Hill, the University of the Witwatersrand's Committee for Research on Human Subjects, and the Mpumalanga Province Research and Ethics Committee. The community mapping study received additional ethical approval from the Committee for Human Research at the University of California, San Francisco. Ethical approval for this secondary analysis was provided by the Office of Human Research Ethics at the University of North Carolina-Chapel Hill (#13-2013).

Key measures

Alcohol outlet accessibility was quantified as the *number of alcohol outlets per village*, defined as the combined number of taverns and bottle shops within each village. For analysis, we considered the alcohol outlet measure in two ways: 1 - categorically with categories None (zero outlets), Low (one to four outlets), and High (above four outlets); and 2 – numerically using the absolute number of alcohol outlets per village. The categorical cutpoints were chosen by 1. Enumerating plausible categorizations based on visual inspection of histogram of number of alcohol outlets per village, then 2. Choosing the categorization that minimized QIC (quasilikelihood under the independence model criterion) model fit statistic.

We used an absolute number instead of alcohol outlets per area measure because village area exhibited minimal variation (interquartile range: 1.3 to 3.2 square kilometers). Furthermore, we theorize that in small areas like the villages in the study region, absolute number is more important than density because all outlets were within reasonable walking distance to all inhabitants. We used a community- as opposed to individual-level exposure because we were interested in capturing contextual as well as individual effects.

From a directed acyclic graph, we identified a minimally sufficient adjustment set of three potential village-level confounding variables. Each variable was derived from the Agincourt HDSS census dataset. *Total population* was defined by the 2011 estimated population size of each village. *Proportion male* was defined as the number of male residents divided by the total population of each village in 2011. *Proportion employed* was defined by the proportion of village residents reporting employment in the most recent labor survey in 2008. Final coding decisions were informed by comparing quasi-likelihood under the Independence model criterion fit statistics for a variety of categorizations and transformations to best reflect each covariate's association with HSV-2 prevalence. Individual-level covariates predictive of the outcome (age, household socio-economic status (SES), relationship of young woman to her primary caregiver) were also included in the adjusted model to improve their precision and predictive ability.

The outcome was individual-level prevalent *HSV-2 infection* at the time of enrollment in the study. Baseline testing for HSV-2 was performed at Johns Hopkins University using Kalon™ HSV-2 gG2 ELISA (Kalon Biological, Ltd., Surrey, United Kingdom) according to the manufacturer's protocol using standard laboratory practices.(31) HIV status was not considered as an outcome due to the small number of prevalent infections at baseline HIV and the likelihood that at least some of the cases were a result of perinatal, as opposed to sexual, transmission.

Statistical modeling

To estimate the association between number of alcohol outlets per village and HSV-2 infection, we used generalized estimating equation (GEE) log binomial and logistic models with exchangeable working correlation matrices. The GEE models corrected the standard errors of our estimates for the clustered nature of the data. First, GEE log binomial models were used to estimate the unadjusted prevalence of HSV-2 among participants in villages with different alcohol outlet exposure categories. In all subsequent analyses, we treated the alcohol outlet number exposure numerically, as indicated by visual inspection of the categorical results. GEE logistic regression models were used to calculate the relative difference in odds of HSV-2 infection with each one-unit increase in number of alcohol outlets per village of residence.

Next, we used a causal inference approach to predict the population-level HSV-2 prevalence in the study population, across a range of alcohol outlet exposure levels.(32) First, we imputed the probability of HSV-2 infection for each participant given their particular set of covariates, across the range of alcohol outlet exposures observed in the data (zero to seven alcohol outlets per village of residence). These predicted probabilities were calculated based on the parameters estimated in the fully adjusted

GEE logistic regression model. We then averaged these imputed probabilities for all participants in the study sample at each level of alcohol outlet exposure. These values estimate the HSV-2 prevalence in the study population had the alcohol outlet exposure been set to each level (from zero to seven outlets) for the entire population. We used a bootstrapping technique to estimate 95% confidence intervals around each predicted prevalence. All analyses were performed in SAS statistical software, v9.1.2 (Cary, NC).

Results

Overall, 2,533 young women were enrolled in HPTN 068 and 2,174 (86%) lived in one of the 24 villages mapped in the community survey. The overall prevalence of HSV-2 infection among young women in the sample was 5% (n=108). The young women ranged in age from 13 to 21 years with a median age of 15 years (Table 1). Households in which the young women resided had an average of 164 Rand ($15USD) in food and non-food expenditures per capita each month. Neither age nor SES varied significantly by number of alcohol outlets per village of residence. Approximately three-fourths of the young women reported a mother or father as their primary caregiver (74%), though young women who lived in villages with high numbers of alcohol outlets (five to seven) tended to be more likely to have a parent caregiver (85%).

The population of the 24 villages ranged in size from 171 to 9836; median population size was 3544. The proportion of males per village ranged from 37% to 50% and the proportion of employed residents per village ranged from 12% to 21% of the total population. The number of alcohol outlets per village ranged from zero to seven. A total of four villages had no alcohol outlets, 16 villages had one to four outlets, and four villages had more than four outlets. Number of alcohol outlets was positively correlated with population size (r=0.88), proportion male (r=0.42), and proportion employed (r=0.29).

Young women who lived in villages with more alcohol outlets were more likely to have prevalent HSV-2 infections (Table 2). The estimated prevalence of HSV-2 increased from young women living in villages with no alcohol outlets [prevalence 1.4%, (95% CI: 0.2, 12.1)], to those living in villages with low numbers of alcohol outlets [prevalence 4.5% (3.7, 5.5)], to those living in villages with high numbers of alcohol outlets [prevalence 6.3% (5.6, 7.1)]. The prevalence estimate for the zero exposure level was imprecise, likely due to the small sample size and single HSV-2 infection in this category.

Treating the alcohol outlet exposure numerically, for every one-unit increase in number of alcohol outlets per village, the odds of prevalent HSV-2 infection increased 8% [odds ratio (OR) (95% CI): 1.08 (1.01, 1.15)]. The point estimate changed minimally after adjustment for village- and individual-level covariates [OR (95% CI): 1.11 (0.98, 1.25)]; however, this adjusted estimate was less precise. Visually, the numerical model provided a reasonable representation of the pattern suggested by the categorical model (Figure 1).

Using estimates from the adjusted GEE logistic regression model above, we calculated the predicted population-level HSV-2 prevalence across the observed range of alcohol outlet exposures (zero to seven alcohol outlets) (Figure 2). For example, if the entire study population lived in villages with seven alcohol outlets, the expected HSV-2 prevalence would be 6.4% (95% CI: 2.7, 10.0). If the entire study population lived in villages with zero alcohol outlets, the expected HSV-2 prevalence would be 3.8% (95% CI: 0.0, 7.5). However, the absolute differences should be interpreted with caution as the predicted probabilities are imprecisely measured with wide confidence intervals and the causal relationship between alcohol outlets and HSV-2 is unconfirmed.

Discussion

Overall, we found that living in villages with higher numbers of alcohol outlets was associated with increased HSV-2 prevalence among young women in rural South Africa. This finding is consistent with previous studies linking alcohol outlet density to prevalent STI among adults (13-16), and to risk factors for STI, like binge drinking and intimate partner violence.(33, 34) Further, the use of individual-level HSV-2 biological data strengthens inference over prior ecological studies (13-15) and studies with self-reported STI outcomes.(16) We also estimated the predicted population-level HSV-2 prevalence across a range of alcohol outlet exposure levels, exploring the potential benefits of interventions to limit exposure to alcohol outlets. To our knowledge, this approach has not previously been employed with regards to alcohol outlets and sexual risk.

In order to interpret the findings causally, we must assume the exposure (alcohol outlets) occurs prior to the outcome (HSV-2 infection). Yet, due to the cross-sectional nature of this analysis, certainty about the temporality of the relationship between alcohol outlets and HSV-2 infection is not possible. Based on key informant reports, we believe that the absolute number of outlets likely remained constant over recent history. Conversely, although we used a prevalence measure, since this was a young cohort, those with HSV-2 infection were likely to have acquired the infection recently. Under these assumptions the alcohol outlet exposure likely predates the HSV-2 outcome, though the findings should be interpreted with caution.

The observational nature of the data also limited our ability to assess a causal relationship between alcohol outlets and sexual risk. Self-selection of where one lives could theoretically be influenced by alcohol outlet accessibility. However, adolescents are presumably less likely to make decisions about where the family lives as they live with parents or other adult caregivers who are more likely to make that decision. Also, other unmeasured village characteristics, such as social disorganization or normative constraints against sexual activity, may vary with alcohol outlet accessibility and influence sexual risk.(35) Although the association between alcohol outlets and HSV-2 remained after adjusting for measured individual- and village-level covariates, the possibility remains that confounding by other unmeasured characteristics influenced the results.

This study found that young women who live in communities with more accessible alcohol environments have higher HSV-2 prevalence than those who do not. These findings point to potential opportunities for intervention to improve sexual health among young women. Policies limiting the number of venues distributing alcohol show promise in reducing alcohol consumption in both low- and middle-income settings, which may also result in improved sexual health.(36, 37) South Africa has recently enacted some alcohol policies aimed to reduce harmful alcohol consumption (e.g. reducing hours of sale, establishing a minimum legal age for consumption), though the extent of their enforcement and the extent to which they have reduced consumption is uncertain.(18) At minimum, our results suggest that high-risk young women may be found in higher proportions within alcohol-accessible communities and that sexual health interventions may be appropriately targeted at communities based on their alcohol environment characteristics. Future research should focus on establishing the temporal relationship between alcohol outlet exposure and sexual risk, and on identifying the pathways through which the association exists. A better understanding of how alcohol outlets are associated with sexual risk could inform recommendations about whether reducing access to outlets could reduce sexual risk, or whether the number of outlets is more likely a reflection of community norms.

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Tables and Figures

Table 1. Demographic characteristics of cross-sectional sample of 2,174 rural South African young women across 24 villages, by number of alcohol outlets in village of residence

	Total population N=2174 Villages=24	**No AO N=67 Villages=4**	**1 to 4 AOs N=1333 Villages=16**	**5 to 7 AOs[a] N=774 Villages=4**	
Individual-level variables	*Median (IQR)*	*Median (IQR)*	*Median (IQR)*	*Median (IQR)*	*ANOVA p*[d]
Age	15 (14-17)	16 (15-17)	15 (14-17)	16 (14-17)	0.1
Household SES[b]	164 (110-236)	174 (104-239)	167 (111-237)	161 (108-233)	0.9
	N (%)	*N (%)*	*N (%)*	*N (%)*	χ^2 *p* [d]
Primary caregiver relationship					
Parent	1608 (74.1)	594 (76.8)	957 (71.9)	57 (85.1)	0.005
Non-parent	563 (25.9)	179 (23.2)	374 (28.1)	10 (14.9)	
Village-level variables	*# Villages*	*# Villages*	*# Villages*	*# Villages*	*r (p)* [e]
Total population[c]					0.88 (<0.001)
Quartile 1 (<2258)	6	4	2	0	
Quartile 2 (2258-3543)	6	0	6	0	
Quartile 3 (3544-5352)	6	0	6	0	
Quartile 4 (>5353)	6	0	2	4	
Proportion male[c]					0.42 (0.04)
At or above median (≥48.3%)	10	0	8	2	
Below median (<48.3%)	14	4	8	2	
Proportion employed[c]					0.29 (0.2)
Quartile 1 (<18.2%)	9	4	4	1	
Quartile 2 (18.2-18.4%)	4	0	1	3	
Quartile 3 (18.4-19.0%)	5	0	5	0	
Quartile 4 (≥19.0%)	6	0	6	0	

[a]Note: no village had exactly five alcohol outlets.

[b]Household SES measured as per capita household expenditures, in South African Rands

[c]Quartiles for population size were computed based on village-level data. Median for proportion male and quartiles for proportion employed were computed based on individual-level data, as used in the final statistical models. Total population size was coded linearly in the final statistical models.

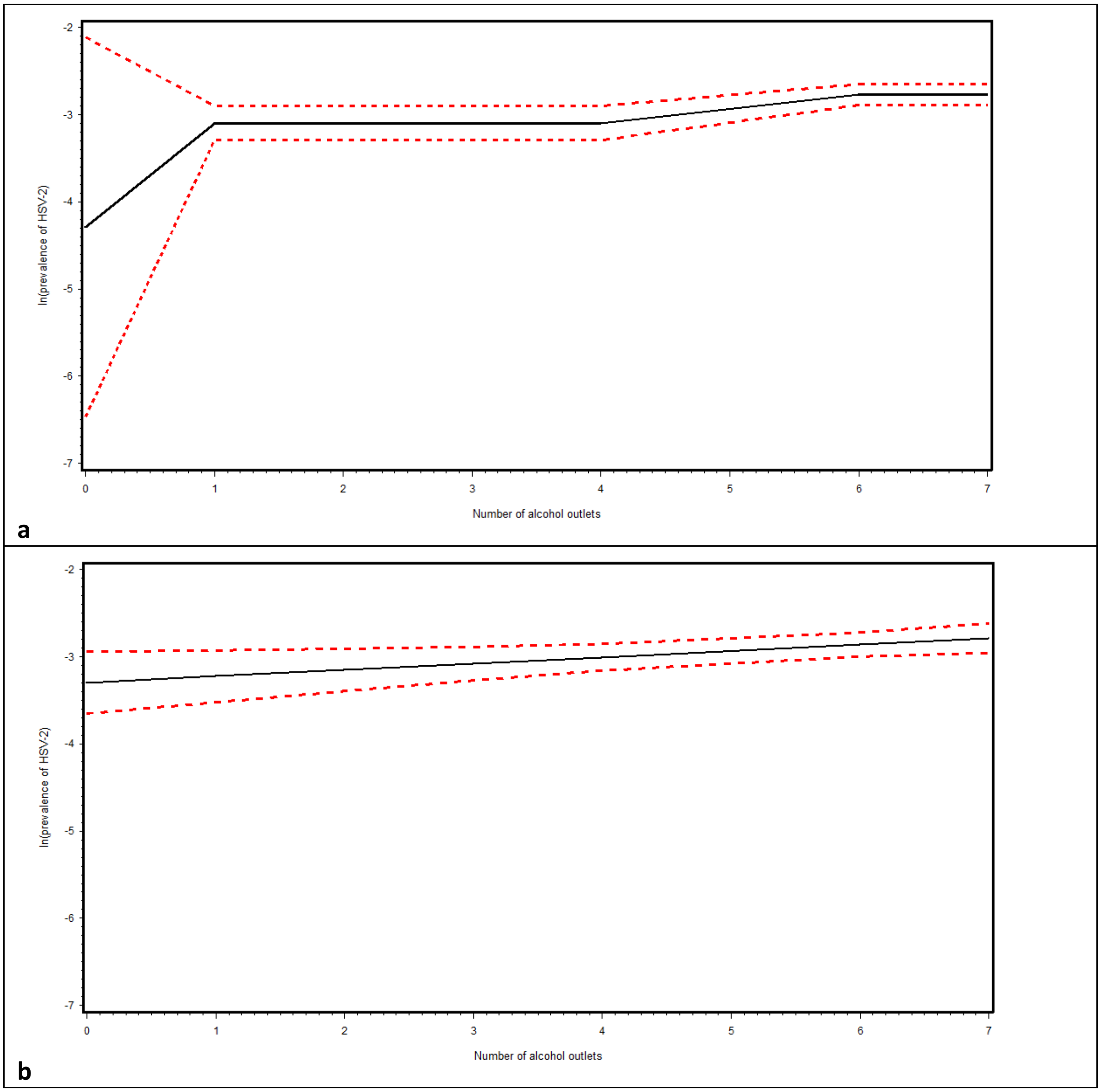
[d]p-values for continuous covariates are for ANOVA tests, p-values for categorical covariates are for chi-square tests. Note that the statistical significance of these relationships is likely inflated as these tests are not adjusted for the clustered nature of the data. For this test, the household SES variable was log-transformed to meet assumption of normality.
[e]Pearson correlation coefficient and p-value for the village-level correlation between each covariate (treated linearly) and number of alcohol outlets (treated ordinally)
AO=alcohol outlets; IQR=interquartile range; SES=socio-economic status; ANOVA=analysis of variance between groups test; r=Pearson correlation coefficient

Table 2. Association between number of alcohol outlets in village of residence and prevalent HSV-2 infection among 2,174 South African young women

# AO per village	# Villages	# Young women	# HSV-2+	HSV-2 prevalence (%) (95% CI)[a]
0	4	67	1	1.4 (0.2, 12.1)
1 to 4	16	1333	61	4.5 (3.7, 5.5)
5 to 7[b]	4	774	46	6.3 (5.6, 7.1)
Model description				**OR (95% CI)**
Unadjusted GEE model, ordinal AO exposure				1.08 (1.01, 1.15)
Adjusted GEE model, ordinal AO exposure[c]				1.11 (0.98, 1.25)

[a]Results from an unadjusted GEE model with log link, with categorical AO exposure, per 100 young women
[b]Note no village had exactly five alcohol outlets
[c]Adjusted for village population size (coded linearly), proportion of village population male (coded dichotomously with cutpoint at median – 48.3%), proportion of village population employed (coded categorically in quartiles), age (coded categorically in two-year increments), household SES (coded as the log-transformed per capita expenditures with a quadratic term), and primary caregiver relationship (coded dichotomously as parent/non-parent)

AO=alcohol outlets; OR=odds ratio; CI=confidence interval; GEE=generalized estimating equation



(a) Number of alcohol outlets treated categorically at 0, 1 to 4, and 5 to 7 outlets per village in an unadjusted generalized estimating equation (GEE) model with a logit link. Note: No village had exactly five outlets.

(b) Number of alcohol outlets treated numerically in an unadjusted GEE model with a logit link.

Figure 1. Graphical representations of the association between number of alcohol outlets in home village and prevalent HSV-2 infection among 2,174 South African young women. Solid line indicates ln (odds of prevalent HSV-2 infection) across varying number of alcohol outlets per village. Dashed line indicates 95% confidence intervals around the ln(odds) estimates.

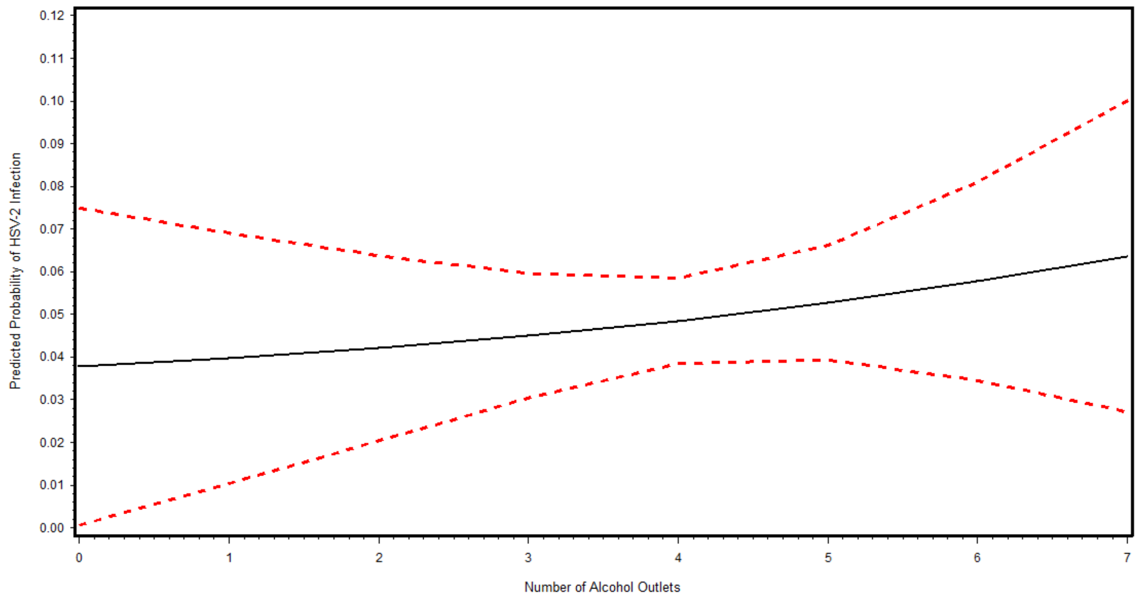


Figure 2. Predicted HSV-2 prevalence corresponding to a range of counterfactual neighborhood alcohol outlet exposure levels (zero to seven alcohol outlets per village of residence). Solid line indicates the predicted probability of prevalent HSV-2 infection across varying number of alcohol outlets per village. Dashed line indicates 95% confidence intervals around the predicted probability estimates.