Author’s response to reviews

Title: Differential sexual network connectivity offers a parsimonious explanation for population-level variations in the prevalence of bacterial vaginosis: a data-driven, model-supported hypothesis

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James Moody (Reviewer 1):

This is a very nice review of the role of network structure and dynamics on STI and potential BV variation across populations. I've only one minor quibble, which is that I think the notion of connectivity you end up using (partner degree and concurrency) are all local and not really getting at the level of global network connectivity necessary to assess spread. You'd be better off, in my opinion, looking at things like size of the largest connected component, bicomponent, or forward-reaching-path (in the dynamic case). All of these are of course difficult to measure without global network data, but can be estimated in the simulation tools. That is, use the local collected degree and concurrency data to estimate/simulate global networks, allowing you to assess connectivity per se, rather than these local features by themselves.

Reply:

Thank you for your feedback. We agree that our measures of network connectivity are suboptimal. We have added the following text to incorporate your concerns (P 8 L1):

We acknowledge however that these variables are measures of local sexual networks. Future work could benefit from incorporating better measures of global sexual network connectivity such as the size of connected components and bicomponents.
Ashley Hazel (Reviewer 2): I think the general goal of this paper and its insights are intriguing and important. Understanding more about the transmitted nature of BV and BV-associated microbiota is critical for a comprehensive understanding of STI risk and burden, especially among undertreated populations. I think this paper is on its way to being published, but I recommend a few important changes first.

Major issues:

--A big issue as I read this paper is that I do not understand the fundamental structure of it. Is this a review or an original study? The authors present a single new model of the relationship between concurrency and BV transmission, but the rest of the paper reads like a synthesis of previously reported studies and data, i.e., a review paper. In isolation, both approaches are worthwhile but are rather thin. I suggest reworking the manuscript to have a standard original research paper structure (Introduction, Methods, Results, Discussion, etc.) that focuses on the model and the hypothesis it is testing. The review material can be reframed in Introduction and Discussion sections to motivate the model and expand upon its utility to public health.

--I have a few concerns about how the model is parameterized. As is, I think it is overly simplistic and not reliable to use to understand the likely complex process of BV-VMB transmission. However, the changes I suggest are very doable and would yield much more meaningful results.

First, the high-connectivity model basically allows individuals to choose any new eligible partner at each time step, and any eligible partner is someone of the opposite sex. While it is perfectly sensible when modeling some populations to assume total heterosexuality in sexual partner selection, that choice should be explicitly stated and an argument should be made for this. If the model is kept very simple in order to be more generalizable, than the decision to restrict it to opposite sex partnerships needs to be justified. On the other hand, the total lack of any other kind of sorting beyond heterosexuality constructs a very unrealistic partner-selection landscape and biases the model in favor of stark transmission differences in comparison with the low-connectivity population. If people choose their partners with the same probability across the population, then you essentially have random-mating conditions, which is both unrealistic and well established to lead to much higher transmission rates of STIs. Some type of sorting behavior should be included. I know you mentioned the potential to add such complexities at the end of the manuscript, but I think this is too fundamental to the nature of sex-partner choice to leave it as a hypothetically nice addition down the road.

Also, I think it is unrealistic to assume 100% transmission of BV-VMB after having sex with a partner with a BV-associated microbiota. Surely, there are many factors, including a person's native CST, that would lead to variation in transmission. I realize that you probably do not have enough evidence to confidently estimate the transmission probability, but I would either choose a
more conservative value (even somewhat arbitrarily), or run the model over a distribution of probabilities. Using 100% transmission biases your model to producing positive results for the comparison between high- and low-connectivity populations.

Reply:

We thank the reviewer for the constructive critique of the model. In response, we have made the following modifications to the code and the model description document (Supplementary material):

• We have explicitly stated that all relationships in the model are strictly heterosexual

• Chris, can you add a justification for why we only considered heterosexual relationships in the model?

• Instead of all men having the same probability per time step to go searching for a partner (15% in the original model) and all women having the same probability per time step of accepting a relationship request from a man (also 15% in the original model), we now have variation in these probabilities across the population. Specifically, these probabilities are now assumed to be person-specific and distributed according to a Beta distribution with mean 15% and standard deviation 7.8%. The density distribution of search and acceptance probabilities is shown in the plot below. The result of this modification is that there is more heterogeneity in sexual activity levels within the population, with a small subset of individuals accumulating a very high number of sexual partners. This is true for both the low and high connectivity community.

• We have also imposed assortativity with respect to age in the model: in the new model, relations can only be formed between men and women whose ages differ by not more than five years.

• While these modifications to the model naturally led to changes in the numerical model output, they did not lead to qualitative changes. Indeed, it is still the case in the revised model that a relatively small increase in sexual network connectivity (4.8% versus 0% prevalence of partner concurrency, and a 42% higher total number of relationships formed in the high connectivity community) produced a disproportionately large difference in the prevalence of BV-VMB among women (55.2% versus 17.6%).

• The mention of 100% transmission risk in the original submission was an error, stemming from an older version of the model. In the model that was submitted originally, as well as in the revised model, each partner who is colonized with BV-VMB confers a risk of BV-VMB “transmission” of 20% per one week time step.
Minor issues:

--In the abstract (p3, l5), the authors state that vaginal microbiome types "vary dramatically between different populations around the world." Given that the field is generally in agreement that there are five community state types among women across many populations, I don't understand the characterization "varies dramatically."

Reply:

In our paper on the global epidemiology of BV we note that the prevalence of BV as defined by Nugent's Scoring varies dramatically between different populations around the world 1. In the current paper we review evidence that the same is true for various vaginal Community State Types (CSTs). It is true that studies find that there are 3 to 9 CSTs in different populations around the world. There are large differences in the percent that specific CSTs constitute between different populations. For example, the L. iners CST constitutes a large percentage of all CSTs in certain populations and a small percentage in others.

--Early in the background section (p4, l31-37), the authors state that "Several longitudinal VMB studies have concluded that the VMB can be relatively stable over time, as well as be quite dynamic in a minority of women." What do you mean? These sound like opposite characterizations of the VMB, so can you explain how they can both be true? Are you saying that in most women, the VMB is stable, but in some it is very dynamic? Or are you saying that it can occasionally become very dynamic for short periods of time in some women? Is there any understanding about why or under what conditions stability varies?

Reply:

We have altered this text to remove any ambiguity as follows:

Several longitudinal VMB studies have concluded that the VMB can be relatively stable over time 2-4. In a minority of women and particularly those with BV-VMB, the community composition of the VMB can be fairly dynamic 2,4.

--p12, l31-42, "These considerations leave us to conclude that the most parsimonious explanation for why the prevalence of BV and various STIs is higher in certain populations than other is that these populations have more densely connected sexual networks." I would say "predict" rather than "conclude" because you do not have the ethnographic evidence from a range of high-risk populations to make this conclusion. Rather you are hypothesizing that this is what you would find, if the data were available.

Reply:
Thanks for this useful suggested change which has been made.

--p13, l12: What does "genetically promiscuous" mean?
Reply:
In a genetically promiscuous species successive broods of offspring will have different parents. If the female carries the offspring then this will involve successive broods having different male parentage (and vice versa). All combinations of social and genetic promiscuity are possible. In the species we discuss, Peromyscus maniculatus is both genetically and socially promiscuous whereas Peromyscus californius is genetically and socially monogamous. In the case of the pot-bellied seahorse (Hipocampus abdominalis), it is genetically monogamous but socially monogamous.

--p14, l46: Is enough known about penile microbiota to say that they too should be classified into 5 CSTs?
Reply:
In the only paper that we are aware of that has classified the penile microbiome into CSTs five CSTs were found. This reference has been added to the end of the relevant sentence in the manuscript to further back up the point.

Reply:
This sentence has been expanded the following to provide examples:

Furthermore, interactions with various STI co-infections – most notably chlamydia, gonorrhoea, T. vaginalis, HSV-2 and HIV – should be modelled explicitly, and other non-infectious causal factors (such as douching, smoking, diet) on the pathway to develop BV should be included as well.

--Figure 2: I cannot tell what is happening in the low-connectivity graph over time. Has individual B taken on a new partner? In which case, who is now attached to A? Or, rather, is B representing both nodes now? Please make this graph and its labeling of nodes more clear.
Reply:

Thank you for pointing this out. We have now labeled individuals C and D in all three time periods. In the figure legend we explain that C and D become the new partners of A and B, respectively.

Typos and corrections:

p6, l12: "Consistent condom use has been shown in a meta-analysis to BE[insert] associated..."
Reply:
This has been corrected.

p8, l7: Sentence needs comma immediately after references and before the word "studies."
Reply:
This has been corrected.

p12, l18-22: Sentence needs a comma or colon after phrase "This explanation begs the question...." I also recommend moving "however" to the beginning of the sentence (with a comma following it).
Reply:
This has been corrected.

p12, l27: Remove word "explanation" from sentence. It is unnecessary and sounds redundant with later use of "explain."
Reply:
This change has been made.

p13, l12: "...P. maniculatus had a greater vaginal microbiome diversity...." Delete "a."
Reply:
This has been deleted.

p14, l29: "...rapid spread of BVAB and the various other STIs...." Delete "the."
Reply:
This has been corrected.

p15, l41: "...could translate inTO[insert] large declines...."
Reply:
This has been corrected.

p18, l5: "...study of Zozaya et al...." Should be "by" Zozaya, not "of."
Reply:
This has been corrected.

--Also, I found several typos in the supplemental material file, "Network Model Description." Please look that over and fix.
Reply:
This has been reviewed and corrected.

References


