bioRxiv preprint doi: https://doi.org/10.1101/090324; this version posted November 30, 2016. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY 4.0 International license.

The risk of sustained sexual transmission of Zika is underestimated

Antoine Allard[1,2,†], **Benjamin M. Althouse**[3,4,5,†], **Laurent Hébert-Dufresne**[3,6,†,*], **and Samuel V. Scarpino**[7,†]

[1]Departament de Física de la Matèria Condensada, Universitat de Barcelona, Martí i Franquès 1, E-08028 Barcelona, Spain
[2]Universitat de Barcelona Institute of Complex Systems (UBICS), Universitat de Barcelona, Barcelona, Spain
[3]Institute for Disease Modeling, Bellevue, WA, 98005, USA
[4]University of Washington, Seattle, WA, 98195, USA
[5]New Mexico State University, Las Cruces, NM, 88003, USA
[6]Santa Fe Institute, Santa Fe, NM, 87501, USA
[7]Department of Mathematics and Statistics and Complex Systems Center, University of Vermont, Burlington, VT, USA
[*]laurent@santafe.edu
[†]These authors contributed equally to this work.

Pathogens can follow more than one transmission route during outbreaks – from needle sharing plus sexual transmission of HIV to small droplet aerosol plus fomite transmission of influenza. Thus, controlling an infectious disease outbreak often requires characterizing the risk associated with multiple mechanisms of transmission. For example, during the Ebola virus outbreak in West Africa, weighing the relative importance of funeral versus health care worker transmission was essential to stopping disease spread [1]. Strategic policy decisions regarding interventions must rely on accurately characterizing risks associated with multiple transmission routes. The ongoing Zika virus outbreak challenges our conventional methodologies for translating case-counts into route-specific transmission risk. Critically, most approaches will fail to accurately estimate the risk of seeing sustained sexual transmission of a pathogen that is primarily vectored by a mosquito – such as the case with the risk of sustained sexual transmission of Zika virus [2, 3].

In conventional models of disease transmission, if the basic reproductive number of a pathogen, R_0 (the average number of secondary infections resulting from a single infected individual in an entirely susceptible population), is less than one, then a large outbreak is unlikely. Therefore, public health officials are interested in both estimating R_0 and evaluating which interventions are most likely to reduce it. Having $R_0 \geq 1$ as a necessary condition for an epidemic, i.e. a large outbreak, relies on the assumption that the infection follows a branching process. With $R_0 \geq 1$, each individual will on average give rise to at least one additional case and the outbreak will be self-sustaining in a large population; while the branching process dies out if $R_0 < 1$ as individuals give rise to less than one additional case on average. In the unique case of sexual transmission of Zika, this underlying assumption is broken in three ways: (1) individuals infected by the vector are not necessarily part of the branching process over the network of sexual contacts; (2) all infections are not equivalent since there is a strong asymmetry in sexual transmission as men are infectious for much longer period than women [4]; and (3) symptoms, and thus probability of detection, are also heterogeneous [5].

First, to estimate the R_0 for sexual transmission correctly, we need to evaluate the number

bioRxiv preprint doi: https://doi.org/10.1101/090324; this version posted November 30, 2016. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY 4.0 International license.

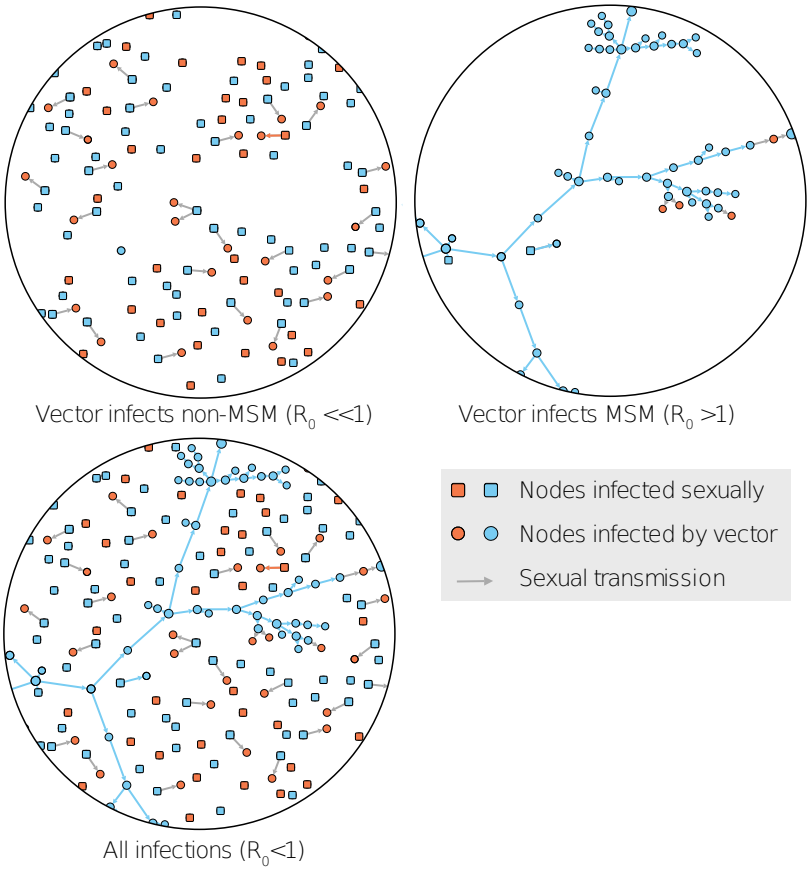

Figure 1. Orange nodes are female, blue nodes are male. Most individuals will be infected by the vector and typically infect 0 or 1 sexual partners. However, within the men who have sex with men community, the probability of transmission is such that an epidemic is possible (with some spillover transmission to bisexual and then heterosexual individuals).

of secondary infections caused by individuals who were infected sexually. For a sexually transmitted infection on a contact network, this means that the key quantity is not the expected number of contacts an individual has, i.e the degree of a node, but is instead the expected *excess* number of contacts: the number of edges other than the one through which they were infected [6]. In contrast, for individuals who are infected by a mosquito we must use the expected number of contacts, because the infection was transmitted to them by the vector, i.e. not by one of their sexual/social contacts (see Fig. 1).

If mosquitoes cause most of the infections in the population, then the average number of sexual transmissions an individual causes is close to what we would expect given the average number of sexual partners. However, if most of the infections in the population are due to sexual transmissions, then the average number of sexual transmissions an individual causes is close to what we would expect given the average excess number of sexual partners. We expect this second average to be larger [7]. As such, measurements of the typical number of sexual transmissions caused by an individual in a population with many vector-caused infections will underestimate the typical number of sexual transmissions caused by an individual in a

bioRxiv preprint doi: https://doi.org/10.1101/090324; this version posted November 30, 2016. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY 4.0 International license.

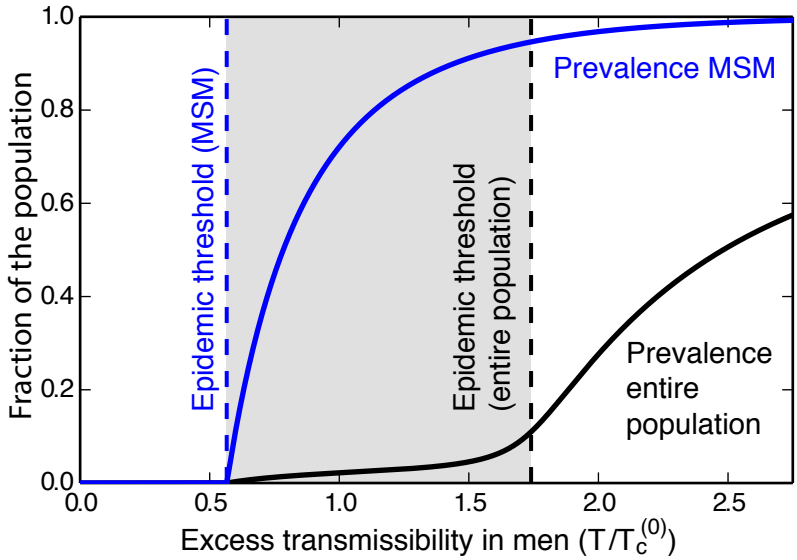

Figure 2. Infection prevalence within the sub-population of men who have sex with men (MSM) and the whole population. Men transmit with probability T, and women with probability εT. The x-axis uses T re-scaled by the classic threshold value, $T_c^{(0)}$, equivalent to $R_0 = 1$ around individuals infected by mosquitoes: $T_c^{(0)}\langle k\rangle(1+\varepsilon)/2 = 1$, using $\varepsilon = 1/10$ and where $\langle k\rangle = 5$ is the average number of contacts of individuals. Also shown are the threshold values for a self-sustained epidemic *within* the MSM sub-population (with subcritical spillovers in the rest of the population, shaded area), and within the whole population (i.e., supercritical outbreaks exist *outside* of the MSM sub-population). The population is assumed to be equally parted between men and women, of which 5% are homosexuals, 3% are bisexuals and 92% are heterosexuals. Individuals have d sexual contacts with probability $p_d = e^{-\langle k\rangle}\langle k\rangle^d/d!$ regardless of their gender or sexual orientation. All results were obtained analytically; see Ref. [9] for further details.

population with few or no vector-caused infections [8].

Second, even ignoring complications due to the vector, the sexual transmission of Zika is itself complicated: males and females are not equally likely to transmit infection due to differences in duration of Zika virus in semen and vaginal fluids. In fact, females are significantly less likely to transmit Zika to their sexual partner than males [4, 10]. Because of the asymmetry in infectious period between males ($>$ 180 days [4]) and females ($<$ 20 days [10]), it is much easier for Zika to invade the men who have sex with men (MSM) community. Consider two infectious males, one in the MSM community and one not in the MSM community: Zika only needs to be transmitted to at least one other individual on average to permit an epidemic in the MSM community, whereas in the non-MSM community, Zika needs to infect enough females such that they will together infect at least one other male. The stronger the asymmetry in infectious period, the more different these conditions become. There are thus two different epidemic thresholds [9, 11]: one for a large-scale epidemic in the MSM community (around which small *subcritical* outbreaks will spillover in the rest of the population); and a higher transmission threshold for an epidemic in the entire population (see

bioRxiv preprint doi: https://doi.org/10.1101/090324; this version posted November 30, 2016. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY 4.0 International license.

Fig. 2).

Third, the most insidious aspect of this double epidemic threshold is that one of the most likely outcomes – an epidemic mostly contained within the MSM community – is also the hardest outcome to detect. Zika virus infections in adults are largely asymptomatic [5] and, therefore, most testing occurs in the roughly 20% of cases that are symptomatic or in individuals seeking to have children [12]. The vast majority of these individuals will be outside of the MSM community [12]. As a result, the group most likely to see sustained sexual transmission is the group least likely to be tested. Given that most infections are asymptomatic in adults [5, 12], this lack of awareness seems less critical; however, it will clearly lead to biased estimates in the potential for sustained sexual transmission of Zika. Additionally, given our evolving understanding of the clinical outcomes for Zika infection in adults, it may be prudent from an individual perspective, as well as a population-level perspective, to increase testing for all adults.

Public health decision- and policy-makers rely on accurate characterizations of transmission risk to decide on interventions and allocate strategic resources. For pathogens, like Zika, which are both vectored by an insect and transmitted sexually, conventional approaches will underestimate the risk associated with sexual transmission. Underestimating the risk of sexual transmission will lead both to biased intervention efforts and to an underestimate of the potential for disease persistence. Additionally, given the differential rates of Zika testing in MSM versus non-MSM communities, the data on sexual transmission are almost certainly biased. Here we advocate for the decision-making and disease modeling communities to better embrace contact network methods when characterizing transmission risk and for increased testing in both MSM and non-MSM communities. The resulting estimates of transmission risk and key epidemiological measures, e.g. R_0 and the likelihood of disease persistence, will be more accurate.

Acknowledgements

The authors thank Joel C. Miller for useful comments on the manuscript. A.A. acknowledges support from the Fonds de recherche du Québec – Nature et technologies. S.V.S acknowledges funding from the University of Vermont. L.H.-D. acknowledges the Santa Fe Institute and the James S. McDonnell Foundation Postdoctoral Fellowship. B.M.A. and L.H.-D. thank Bill and Melinda Gates for their support of this work and their sponsorship through the Global Good Fund.

Author contributions

A.A. and L.H.D performed the calculations; all authors conceived of the project, interpreted the results, and produced the final manuscript. Authors are listed alphabetically.

Conflicts of interest

The authors declare no conflicts of interest exist.

References

[1] M. W. Carroll, *et al.*, *Nature* (2015).

bioRxiv preprint doi: https://doi.org/10.1101/090324; this version posted November 30, 2016. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY 4.0 International license.

[2] C. L. Althaus, N. Low, *PLOS Med.* **13**, e1002157 (2016).

[3] L. Yakob, A. Kucharski, S. Hue, W. J. Edmunds, *Lancet Infect. Dis.* **16**, 1100 (2016).

[4] E. Nicastri, *et al.*, *Eurosurveillance* **21** (2016).

[5] M. R. Duffy, *et al.*, *New England Journal of Medicine* **360**, 2536 (2009).

[6] M. E. J. Newman, *Phys. Rev. E* **66**, 016128 (2002).

[7] S. L. Feld, *Am. J. Sociol.* **96**, 1464 (1991).

[8] J. C. Miller, *arXiv:1609.08108* (2016).

[9] A. Allard, B. M. Althouse, L. Hébert-Dufresne, *In Preparation* (2017).

[10] B. Visseaux, *et al.*, *Lancet Infect Dis* **16**, 1000 (2016).

[11] P. Colomer-de Simón, M. Boguñá, *Phys. Rev. X* **4**, 041020 (2014).

[12] J. T. Lessler, *et al.*, *Bull World Health Organ* **1** (2016).