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# SEX-BIASED RECIPROCAL VIRULENCE AND TRANSMISSION DYNAMICS DUE TO FRIEND VIRUS COMPLEX INFECTION OF MICE

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Historically, biomedical research involves using only one sex in animal studies. Females are primarily used in immunological and metabolic studies, whereas males are more common in studies on nutrition[1]. Doing research in such a way potentially inhibits our understanding of the effects seen in one sex and may lead to a complete misunderstanding of effects in the other sex[2]. In order to avoid such oversights, we have developed a unique system where we can ask how a viral pathogen transmits and causes virulence differentially in each sex[3]. Our methods use semi-natural enclosures and wild-derived mice set up in multiple populations with different infection treatments where each treatment involves infecting one-half of the total group. In the first treatment, half of both the males and females were index (infected); in the second, only half of the males were index; and in the third treatment population, only half of the females were index. Each population had the same number of males and females and all contact (uninfected) mice were sham infected in order to control for the infection procedures. Through this design, we demonstrate that males are 1.5 times more likely to contract the virus and 2.5 times more likely to transmit the virus compared to females. We also demonstrate that both male and female index mice had 2.4 times more virulent infections than contact mice. Although there was no significant difference in virulence between the sexes in either contact or index mice in enclosures, there were significant sex-biased virulence differences in cages. Finally, male contact mice had significantly higher viral titers than female contact mice (by ~1 order of magnitude). These data show that there are large host sex differences for susceptibility, virulence and transmission dynamics during a retro-viral infection, and underscore the emerging realization that there are fundamental differences between males and females relevant to understanding biomedical problems. It is generally thought that increased transmission will lead to higher virulence, but we discovered a sex-biased reciprocal pattern where transmission is highest in males, but virulence is highest in females. One possible explanation is that transmission mechanisms differ between the sexes, primarily physical contests among males, but sexual transmission from females, creating different virulence optima (from the viral perspective) in male and female hosts. These and other data suggest we must evaluate both sexes if we are to understand how disease states might affect the sexes differently and that looking at a single sex may not allow for complete and accurate conclusions to be drawn.

## References

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