A Natural Mouse Model for Neisserial Transmission in the Upper Respiratory Tract

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Background

- Gonorrhea is considered the second most prevalent sexually transmitted bacterial infection worldwide and is caused by *Neisseria gonorrhoeae (Ngo).*
- *Ngo* frequently colonizes asymptomatically the mucosal surfaces of the genital tract, rectum, and pharynx.
- Mechanisms of gonococcal transmission between hosts are poorly understood.
- *In vivo* transmission of *Ngo* are challenging due to high tropism for humans and a lack of natural animal models.
- We have developed the first murine model of *Neisseria* transmission using the model organism *Neisseria musculi (Nmus)*
- *Nmus* is a commensal of wild-caught house mice and the genome of *Nmus* encodes many orthologs of virulence factors candidate vaccine antigens found in human pathogenic *Neisseria* species.
- We plan to use our model system to investigate the role of candidate persistence and transmission factors that have orthologs in human pathogenic species. We are monitoring transmission in two inbred mouse strains, A/J and C57BL/6, following single oral inoculations.

Methods

- A/J and C57BL/6 mice were orally inoculated with a single dose of *Nmus.* 10^8 Colony Forming Units (CFU) were inoculated per mouse.
- Orally colonized mice after 3 weeks were co-housed with non inoculated mice
- Oral swabs were collected weekly and used to quantify CFU/swab up to 10 weeks.

Results

Figure A: Two strains of laboratory mice were used. Left, C57BL/6; Right, A/J. Blue coccobacilli represent *Nmus* cells.

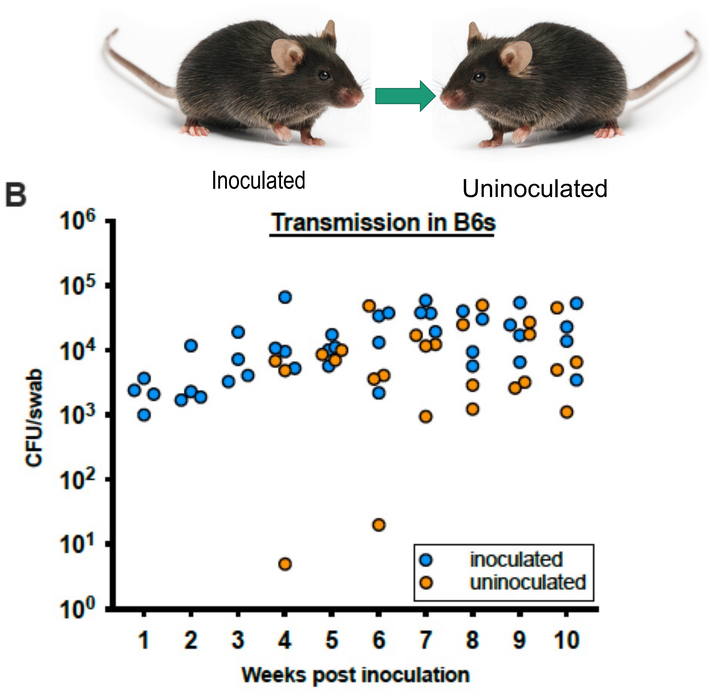

Figure B. Transmission and oral burdens of *Nmus* in B6s. Colored dots represents inoculated (blue) (n=4)or uninoculated (orange) (n=4) mice. At 10-week post inoculation all B6 mice became colonized.

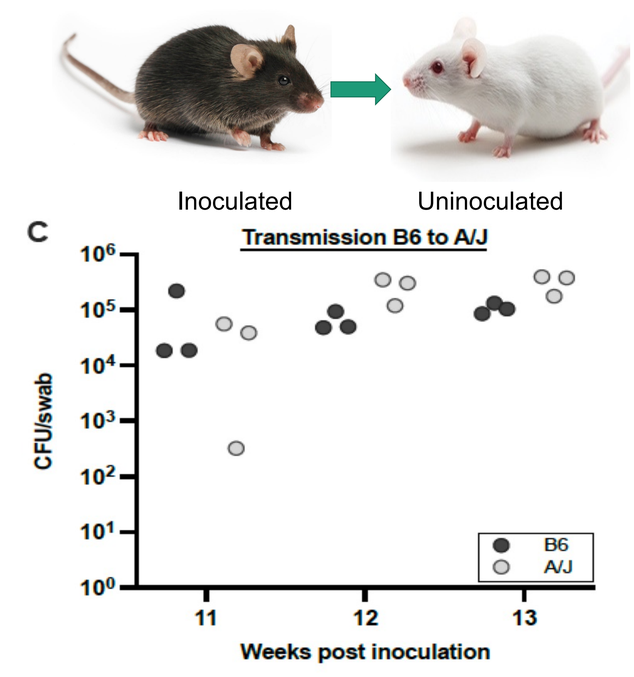

Figure C. Transmission and oral Burdens of *Nmus* in B6s. Colored dots represent inoculated (black) (n=3) and uninoculated (gray) (n=3).

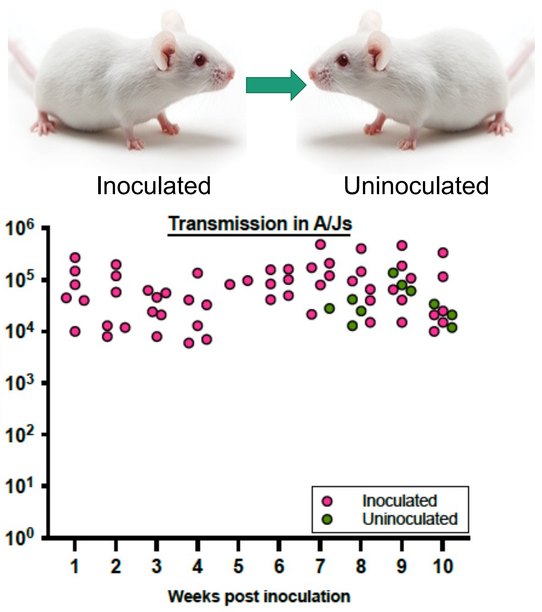

Figure D. Transmission and oral Burdens of *Nmus* in A/Js. Colored (magenta) dots represent inoculated A/Js (n=6) and uninoculated A/Js (green)(n=6). At 10 weeks post inoculation only 50% of the uninoculated A/Js (n=3) mice became colonized .

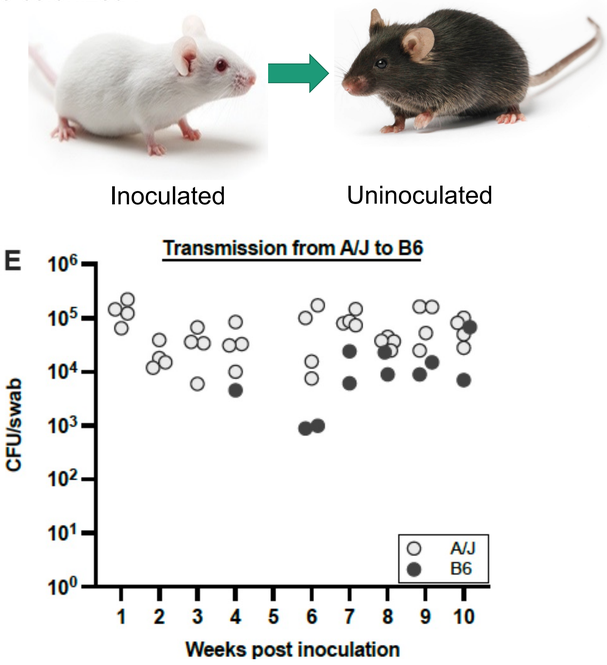

Figure E. Transmission and oral Burdens of *Nmus* in A/Js inoculated mice represented by color gray dots (n=4) and uninoculated dark dots (n=4). At 10 weeks post inoculation only 50% of B6 uninoculated mice were colonized.

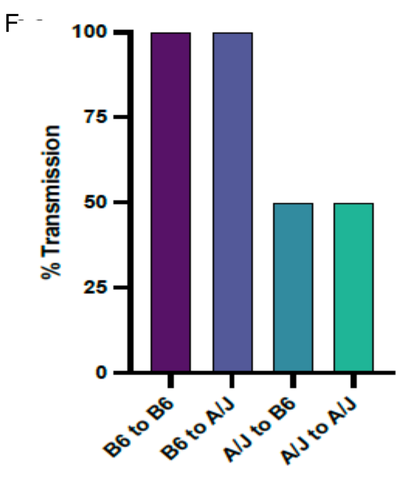

Figure F: Percentage of *Nmus* transmission between indicated mouse strains after seven weeks of co-housing.

Conclusions

- All inoculated B6 and A/Js mice become colonized after a single dose inoculation.
- *Nmus* Transmission Percentages from B6 to B6 or B6 to A/Js were 100%.
- Transmission from A/Js to A/Js and A/Js to B6 were 50%.
- Transmission kinetics were more rapid in the B6 mouse background.

Future directions

- Test *in vivo* colonization and transmission phenotypes for mutated *Nmus* strains.
- Study *in vivo* fitness, persistence and transmission of *Nmus* strains in the oral cavity using a competitive index assay.
- Characterize the normal flora of both A/Js and B6 mice before and after co-houseing.
- Monitor the expression of mouse genes by RNA seq in colonized and mock-infected mice.