Murine Models of Vaginal Trichomonad Infections

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Abstract. Trichomonas vaginalis and Tritrichomonas foetus cause common sexually transmitted infections in humans and cattle, respectively. Mouse models of trichomoniasis are important for pathogenic and therapeutic studies. Here, we compared murine genital infections with T. vaginalis and T. foetus. Persistent vaginal infection with T. foetus was established with 100 parasites but T. vaginalis infection required doses of 10^4, perhaps because of greater susceptibility to killing by mouse vaginal polymorphonuclear leukocytes. Infection with T. vaginalis persisted longest after combined treatment of mice with estrogen and dexamethasone, whereas infection was only short-lived when mice were given estrogen or dexamethasone alone, co-infected with Lactobacillus acidophilus, and/or pretreated with antibiotics. Infection rates were similar with metronidazole-resistant (MR) and metronidazole-sensitive (MS) T. vaginalis. High dose but not low dose metronidazole treatment controlled infection with MS better than MR T. vaginalis. These murine models will be valuable for investigating the pathogenesis and treatment of trichomoniasis.

INTRODUCTION

Trichomoniasis is a common human and bovine sexually transmitted infection caused by flagellated trichomonads. The human pathogen, Trichomonas vaginalis, causes vaginitis, cervicitis, adverse pregnancy outcomes (i.e., preterm birth, premature membrane rupture, and low birth weight infants) and increases the risk of human immunodeficiency virus (HIV) transmission.1 Similarly, infection with Tritrichomonas foetus in cattle results in vaginitis, cervicitis, and endometritis and reproductive failure.2–3 The pathogenesis of human and bovine trichonomiasis is incompletely understood. Immune protection against human trichonomiasis is not well studied, but vaccination of cattle protects against persistent infection,4 suggesting that vaccination of targeted human populations against trichomoniasis may be feasible.

Studies of the pathogenesis, immunology, and therapy of trichonomiasis would be greatly facilitated by availability of small animal models of genital infection, yet only a few such models have been reported and robustness and reproducibility of the infections remain a major challenge. For example, estrogen administration and pretreatment with certain Lactobacillus spp. permitted infection with T. vaginalis in some studies,5,6 but this regimen was not successful in our preliminary studies or those of another group.7 Mouse models of trichonomiasis are important for pathogenic and therapeutic studies. Here, we tested. Therefore, we took a systematic approach in investigating the impact of inoculum size and various pretreatments to improve and standardize vaginal murine infection models with T. foetus and T. vaginalis for investigations of chemotheraphy and immunoprophylaxis.

MATERIALS AND METHODS

Strains of trichomonads. One strain of T. foetus and several of T. vaginalis were used in these studies. The T. foetus D1 strain was originally isolated from a cow with T. foetus pyometra.8 The T. vaginalis genome strain G3 was from the ATCC (strain PRA-98).9 The T. vaginalis 12047, 12321, and 11418 strains were obtained from pregnant women at the first prenatal visit in our previous studies (Corbeil LB, unpublished data). The T. vaginalis F1623 strain was obtained from a man who later cleared infection with tinidazole treatment.10 The T. vaginalis B7268 strain was obtained from a woman with recurrent infection for 18 months.11 The T. vaginalis LA-1 strain was obtained from a patient who had multiple treatment failures for trichomoniasis.12 Strain 12047 was passed via the mouse vagina and multiple vials were frozen in liquid nitrogen. Initial experiments revealed no difference between mouse-passed and non-passed 12047. Subsequent experiments used the mouse-passed 12047 strain. Trichomonads were grown axenically at 37°C in trypsin-yeast-iron (TYI) medium supplemented with Diamond vitamins and 15% adult bovine serum and adjusted to pH 7.0 for T. foetus and pH 6.2 for T. vaginalis.13

Bacterial cultures. Lactobacillus acidophilus (ATCC 3456) was kindly supplied by Dr. Gary Garber (Ottawa University) and frozen at −80°C in 60% glycerol.14 Lactobacilli were grown in 5% CO2 at 37°C in Lactobacilli MRS Broth pH 6.5 (Difco, Becton-Dickinson, Sparks, MD).

Animals. Female BALB/c mice (6–7 weeks of age from Charles River Laboratories, Hollister, CA) maintained under specific pathogen-free conditions, were used for these studies. All animal studies were reviewed and approved by the University of California, San Diego, Institutional Animal Care and Use Committee.

Intravaginal inoculation of mice. Trichomonads were harvested by centrifugation and washed twice in Dulbecco’s phosphate-buffered saline (PBS). The final pellet was suspended in TYI medium with 0.32% agar (Bacto Agar, Becton-Dickinson) at a density of 10^6 trichomonads/mL. Each mouse was inoculated intravaginally with 10 μL of this suspension containing ~10^5–10^6 T. foetus or 10^7 T. vaginalis using a plastic tipped micropipette. A second inoculation of T. vaginalis was given the next day. Dilutions of the inoculum were tested to determine the lowest dose of T. foetus that resulted in persistent infection.

Pretreatment of mice for T. vaginalis genital infection. (I) Estradiol. Mice were treated with estradiol as previously described with minor modifications.3 Mice were given either
500 or 50 μg of estradiol valerate (Delestrogen, JHP Pharmaceuticals, Rochester, MI) suspended in 100 μL of sesame oil (Sigma-Aldrich, St. Louis, MO) subcutaneously 9 and 2 days before infection.

(II) Dexamethasone. Mice were given 1–10 mg/kg of dexamethasone sodium phosphate (APP Pharmaceuticals, Schaumburg, IL) diluted in 100 μL of PBS intraperitoneally daily from 4 days before challenge to 6 days after challenge.

(III) Lactobacillus acidophilus. Mice were inoculated intravaginally with L. acidophilus (ATCC 4356) as described by others. Before inoculation, 500 mL of MRS media was inoculated with 5 μL of a culture of L. acidophilus, incubated overnight, and washed three times in PBS with centrifugation (5,000 × g, 4°C, 10 min). The final pellet was resuspended in MRS at a density of 7 × 10^9 CFU/mL. Mice were inoculated into the fornix of the vagina with 10 μL of MRS containing ~10^9 L. acidophilus 7 and 6 days before challenge. The inoculum was standardized by spectrophotometry at 650 nm and confirmed by CFU assay on plates with MRS plus 1.5% agar (Becton-Dickinson).

(IV) Antibiotics. Mice were treated with a combination of antibiotics to reduce the vaginal commensal microbiota as described for gonococcal infections, but with minor modifications. Vancomycin hydrochloride (1.2 mg/day) (Sigma-Aldrich) and streptomycin sulfate (2.4 mg/day) (Sigma-Aldrich) were suspended in 100 μL PBS and injected intraperitoneally daily from 4 days before challenge to 7 days after challenge. Mice also received trimethoprim (Teknova, Hollister, CA) orally at 0.4 mg/mL in the drinking water given ad libitum for the same period of time.

Treatments I–IV was given singly or in combination to groups of 5 mice each. Control mice without treatment were included in each experiment.

Treatment of T. vaginalis infection with metronidazole. Inhibition in vitro of T. vaginalis by metronidazole was evaluated as previously described for Giardia lamblia. A 10 mM stock of metronidazole (Sigma-Aldrich) in dimethyl sulfoxide was diluted in PBS to 75 μM, and 1:3 serial dilutions were made in 40 μL TYI medium in 96-well plates. Final concentrations ranged from 20 μM to 0.4 nM, covering a -5-log_10 range. Strains of T. vaginalis were added at 1–2 × 10^5 trophozoites in 10 μL of TYI/well. Plates were incubated for 24 hr at 37°C under anaerobic conditions (AnaeroPack, Mitsubishi Gas Chemical, Remel, Lenexa, KS). Cell growth and viability of T. vaginalis was determined with an ATP assay (BacTiter-GloMicrobial Cell Viability Assay Promega, Madison, WI) and the luminescent signal was measured in a microplate reader (SpectraMax, Molecular Devices, Sunnyvale, CA). The metronidazole concentration, which inhibited T. vaginalis growth by 50% compared with parallel cultures without added metronidazole (50% effective concentration or EC_50) was determined by graphic extrapolation of the concentration-response curves and expressed as negative log_10 value of the EC_50 (pEC_50).

Mice infected with T. vaginalis were given metronidazole (10 or 50 mg/kg) diluted in 100 μL of PBS orally by gavage using a blunt curved needle (22 G) five times, twice at 2 and 3 days and once at 4 days after infection. Metronidazole was administrated orally rather than genitally because of a higher bioavailability and greater efficacy in women. Vaginal samples were collected by flushing with 50 μL of sterile PBS before inoculation and at 3, 5, and 7 days after infection. Samples were cultured in 500 μL of TYI medium containing penicillin (200 U/mL)-streptomycin (200 μg/mL) (Gibco, Invitrogen, Grand Island, NY), amphotericin B (0.5 μg/mL) (CellGro Mediatech, Herndon, VA), kanamycin sulfate (200 μg/mL) (AllStar, Sunnyvale, CA), and gentamicin sulfate (10 μg/mL) (Fisher, Fair Lawn, NJ). In some cases, 10 μL of the vaginal washing was dried on clean glass slides before fixation with methanol (Fisher) for 10 min and staining with 0.25% crystal violet stain (Fisher, Kalamazoo, MI).

Statistical analysis. Vaginal trichomonad culture results were analyzed by the non-parametric Wilcoxon signed-rank test. Data are expressed as mean and standard error of the mean. The Pearson correlation test was used to analyze the data comparing the percentage of mice with PMNs in the vaginal secretions at the time of inoculation of trichomonads (Day 0) with the percentage of mice still infected at Day 7 post inoculation. The level of significance was set at P < 0.05.

RESULTS

Murine vaginal infection with T. foetus. Infection persisted for at least 34 days in all mice inoculated with all doses of T. foetus (from 10^6 to 10^10) (Figure 1). Vaginal culture and direct counting of trichomonads gave comparable results, because all mice were positive on every sampling day (Figure 1A and B). Thus, no pretreatment was needed and even an inoculum as low as 100 trophozoites of T. foetus persisted in resulting infection.

Murine vaginal infection with T. vaginalis. Normal mice were challenged intravaginally with five strains of T. vaginalis (10^6 trichomonads/mouse) on two consecutive days (Days 0 and 1). Cultures were used to assess infection, because direct counting and culture results were closely correlated for T. vaginalis infection (data not shown), as with T. foetus (Figure 1). Infection with the different T. vaginalis strains was achieved in 20–60% of mice after 3 days post inoculation, yet no T. vaginalis infection was detected after 11 days for any of the strains (Figure 2). Although the proportion of infected mice did not differ significantly between the five strains, we selected T. vaginalis strain 12047 for further studies, because it infected the highest proportion of mice for the longest duration (Figure 2).

Treatments of mice with either estradiol (500 μg), or dexamethasone (10 mg/kg), or L. acidophilus (10^7), or antibiotics (vancomycin-streptomycin-trimethoprim) did not result in a higher proportion of infected mice or a longer duration of genital infection (P > 0.05) (Figure 3). We next evaluated if a combination of pretreatments would result in more frequent and prolonged vaginal T. vaginalis infection. Estradiol and dexamethasone, with or without antibiotics, resulted in a significantly higher infection rate (60–100% of mice) compared with non-pretreated mice (0% of mice infected) from 5 to 16 days post challenge (P < 0.05) (Figure 4). Vaginal infection persisted in 20–40% of the pretreated mice for at least 45 days (Figure 4). Two of 10 mice that received estradiol, dexamethasone, and antibiotics and 2 of 5 mice that received estradiol and...
dexamethasone died between 10 and 26 days after challenge. Because high doses of estrogen are known to cause illness in mice, we reduced the estradiol dose to 50 μg in subsequent experiments. Pretreatment of mice with low-dose estradiol (50 μg) and 10 mg/kg dexamethasone (with the same schedule as above) resulted in comparable rates of infection with strain 12047 at Day 7 (Figure 5) as high-dose estradiol pretreatment (Figure 4). On the basis of these results, robust vaginal T. vaginalis infection of mice can be obtained after pretreatment with estradiol (50 μg) subcutaneously at 9 and 2 days before T. vaginalis inoculation and dexamethasone (10 mg/kg) intraperitoneally from 4 days before until 6 days after challenge.

Polymorphonuclear leukocytes and T. vaginalis infection. The role of PMNs in greater murine resistance to T. vaginalis than to T. foetus was investigated because PMN infiltration of the vaginal mucosal surface occurs in waves during the estrus cycle, especially at diestrus. PMNs are known to kill T. vaginalis more efficiently than T. foetus in vitro. To assess whether the presence of PMNs in vaginal secretions at Day 0 of inoculation of 10^6 T. vaginalis strain 12047 or T. foetus D1 may be related to the rate of infection by Day 7 post-trichomonad inoculation, vaginal smears at inoculation were evaluated for the presence of PMNs. These vaginal smears were obtained from mice reported in Figures 1–5. The presence of PMNs was not related to infection rates with T. foetus (Table 1), as we noted previously. However, PMNs in vaginal secretions at Day 0 were negatively correlated with the percentage of mice still infected with T. vaginalis 12047 at Day 7 (P < 0.05).

Pretreatment with estrogen and dexamethasone was next investigated to further examine the role of PMNs in killing T. vaginalis because both estrogen and corticosteroids depress PMN numbers. As expected, mice treated with dexamethasone and estrogen had the lowest percentage of vaginal PMNs at inoculation and the highest percentage of infection with T. vaginalis after 7 days (Table 1). These results suggest that the success in establishing robust T. vaginalis infection was related to the ability of dexamethasone to inhibit PMN migration to the vaginal surface and the ability of estrogen to arrest the estrus cycle and the associated cycle-specific occurrence of PMNs in vaginal secretions.

Evaluation of metronidazole treatment of murine infection with metronidazole resistant or sensitive strains of T. vaginalis. To begin to determine the utility of the new murine T. vaginalis infection models, we used treatment with metronidazole as “proof of concept” study, because 5-nitroimidazoles (including metronidazole and tinidazole) are the only approved drugs to treat human trichomoniasis. Furthermore, resistance of T. vaginalis against 5-nitroimidazoles is increasingly reported, making the establishment of a suitable murine trichomoniasis model for studying metronidazole resistance particularly relevant. We first tested metronidazole sensitivity in the different strains of T. vaginalis in vitro. Using an ATP assay to determine growth and survival, we found that T. vaginalis strains B7268 and LA-1 (pEC50 of 5.09 ± 0.34 and 5.13 ± 0.08, respectively) exhibited > 10-fold metronidazole resistance (MR) compared with the metronidazole-sensitive (MS)
Infection of mice, pretreated with estradiol (50 μg) and dexamethasone (10 mg/kg), with 10^6 of each of these strains showed that MR-strain B7268 and MS-strain 12047 infected more mice after 5 and 7 days than the other strains (Figure 5). Infection with *T. vaginalis* B7268 and 12047 strains persisted until sacrifice of mice at 28 and 47 days post challenge, respectively (data not shown). Therefore, these two strains were chosen for further study. Mice infected with B7268 (MR) and 12047 (MS) strains were treated with two doses of metronidazole (10 and 50 mg/kg) orally five times. Vaginal culture showed most of the control mice (60–80%) remained infected with both *T. vaginalis* strains for at least 7 days post inoculation (Figure 6). Metronidazole at 50 mg/kg eliminated infection with *T. vaginalis* MS strain 12047 at 3 days post challenge and thereafter, which was significantly lower than the infection rate in the control group (*P* < 0.05) at 5 and 7 days post inoculation (Figure 6). In contrast, treatment of mice infected with *T. vaginalis* MR strain B7268 with the same metronidazole dose did not cause a significant decrease in the proportion of infected mice compared with untreated controls at 5 and 7 days post inoculation (*P* > 0.05) (Figure 6).

**DISCUSSION**

This study shows that careful optimization of infection conditions and selection of suitable infecting strains allows establishment of vaginal infection of mice with trichomonads. In the case of *T. foetus*, infection was established and maintained in 6-week-old BALB/c mice with an inoculum as low as 100 trichomonads without any pretreatment. This dose is markedly lower than in our previous studies in which 90–100% of non-estrogen treated mice were persistently infected only after inoculation with 10^4 or 10^6 trichomonads. The lower dose of 10^2 was not tested in previous studies. This low inoculum (10^2) is similar to that required for infection of 50% of female cattle (the natural host) with the same D1 strain of *T. foetus*. The success of low *T. foetus* inoculum in untreated mice is in contrast to the results with *T. vaginalis* where a dose of 10^6 trichomonads and pretreatment with both estrogen and dexamethasone was necessary for robust vaginal infection. Although the reason for this difference in murine vaginal infection with bovine versus

![Figure 3. Effect of treatments with single agents—estradiol, dexamethasone, Lactobacillus acidophilus, or antibiotics (ATB) to sustain *Trichomonas vaginalis* infection. Five mice per group were infected intravaginally with *T. vaginalis* 12047 strain at Days 0 and 1 and then cultured for *T. vaginalis*. (A) Mice received estradiol (500 μg/dose) at Days −9 and −2, Lactobacillus acidophilus intravaginally at Days −7 and −6, or ATBs (vancomycin, streptomycin, and trimethoprim) daily from Days −2 to 7 days. (B) Mice received dexamethasone daily from Days −4 to +6. Control mice did not receive any treatment (no pretreatment). No single treatment increased infection rates significantly as compared with control mice (*P* > 0.05).](image)

![Figure 4. Combination treatment consisting of estradiol, dexamethasone (Dx) and antibiotics (ATB) to increase *Trichomonas vaginalis* infection. Five mice per group were infected intravaginally with *T. vaginalis* 12047 strain at Days 0 and 1 and then cultured for *T. vaginalis*. (A) Dexamethasone plus ATB was compared with a combination of estradiol, dexamethasone, and ATB. (B) Estradiol plus dexamethasone compared with a combination of estradiol, dexamethasone, and ATB. Mice received estradiol (500 μg/dose) at Days −9 and −2, and/or ATBs vancomycin, streptomycin, and trimethoprim daily from Days −2 to +7, and/or dexamethasone daily from Days −4 to +6. Control mice did not receive any treatment (no pretreatment). Pretreatment of mice with estradiol and dexamethasone (with or without ATB) resulted in more mice infected for a prolonged time than treatment with dexamethasone plus ATB or no treatment. “a” indicates *P* < 0.05 compared with control group.](image)
human trichomonads is not clear, possible factors can be suggested. For example, both the bovine and murine vaginal pH is close to neutral,\textsuperscript{20,22} whereas the human vagina has a pH of five or less,\textsuperscript{23} making the pH of the murine vagina possibly more hospitable to \textit{T. foetus} than \textit{T. vaginalis}. Second, attachment to vaginal epithelial cells is thought to be an important step in colonization. Surface lipophosphoglycan (LPG) plays a key role in attachment of both trichomonads,\textsuperscript{24–26} but the terminal sugars of LPG differ in \textit{T. foetus} and \textit{T. vaginalis}.\textsuperscript{27} Perhaps murine vaginal epithelial cells bind \textit{T. foetus} LPG better than \textit{T. vaginalis} LPG. PMNs are another important innate immune factor in defense against bovine\textsuperscript{18,19} and human\textsuperscript{17} trichomonads. Pretreatment with both estrogen and dexamethasone suppressed vaginal PMNs, and PMNs can kill \textit{T. vaginalis},\textsuperscript{17} making it likely that these cells interfered with the establishment of \textit{T. vaginalis} by early parasite killing in the vagina. In contrast, mouse neutrophils are not efficient at destroying \textit{T. foetus} in vitro.\textsuperscript{11} Most of the mice infected with \textit{T. foetus} had PMNs in the vaginal secretions at the time of infection but remained infected for several weeks. These data suggest that PMNs did not interfere with \textit{T. foetus} infection in the murine vagina. Finally, persistence of the two infections may also vary in the natural host. Experimental infection of female cattle with \textit{T. foetus} (strain D1) can be detected by vaginal cultures for many weeks or months.\textsuperscript{10,28} Because comparative data on experimental infection with \textit{T. vaginalis} in humans are not available, it is possible that \textit{T. vaginalis} infection of the even the natural host is less persistent than that of \textit{T. foetus}.

Pretreatment of mice with steroids and sex hormones was critical for achieving robust and extended vaginal infections with \textit{T. vaginalis}. Of importance, single drug regimens were not sufficient for success, because estradiol, \textit{L. acidophilus}, or antibiotics alone did not increase persistence, even though similar treatments were reported to increase susceptibility to murine vaginal infection with \textit{Mycoplasma hominis}, \textit{Neisseria gonorrhoeae}, or \textit{Ureaplasma urealyticum}.\textsuperscript{20–31} The combination of estradiol and \textit{L. acidophilus} increased the rate and duration of murine \textit{T. vaginalis} infection in some studies,\textsuperscript{32} but this could not be reproduced, for unknown reasons, in our work or that of others.\textsuperscript{2} Instead, we found that lowering vaginal PMNs by a combination of estradiol and dexamethasone was the best pretreatment strategy for obtaining persistent infection of mice with \textit{T. vaginalis}. Furthermore, strain-dependent differences in \textit{T. vaginalis} colonization of the murine vagina were detected in our study as well as those of others.\textsuperscript{4} This underlines that it is important to test several trichomonad strains, especially clinical isolates, to identify the most suitable ones for use in mouse models to investigate new approaches to controlling trichomoniasis.

Nitroimidazoles, including metronidazole and tinidazole, remain the mainstay chemotherapeutic agents against human trichomoniasis. We infected mice with MR and MS strains of \textit{T. vaginalis} to assess the mouse model for evaluation of chemotherapy. Treatment with 50 mg/kg metronidazole cleared infection with the MS strain 12047 but no significant difference was observed between treated mice and controls with the MR strain at this dose. In contrast, differences between groups were not apparent at the lower metronidazole dose, which is consistent with previously reported results indicating that \textit{T. vaginalis} metronidazole resistance or susceptibility is not correlated with metronidazole treatment outcome.\textsuperscript{32} The success in eliminating murine MS \textit{T. vaginalis} with oral metronidazole was comparable to other studies with intravaginal metronidazole gel in mice.\textsuperscript{7} The regimen of five doses of metronidazole at 50 mg/kg applied in mice was similar to treatment of women for \textit{T. vaginalis} infection. A recommended metronidazole regimen for women consists of either a single dose of 2 g (~40 mg/kg in a woman of 50 kg) or, in case of resistance, 500 mg (~10 mg/kg in a woman of 50 kg) twice daily for 7 days.\textsuperscript{4}

In conclusion, this study shows infection conditions and selection of suitable infecting strains to establish vaginal infection of mice with two important reproductive pathogens,

![Image](https://via.placeholder.com/671)

**Figure 5.** Infectivity of different strains of metronidazole resistant (MR) or metronidazole sensitive (MS) strains of \textit{Trichomonas vaginalis} in estradiol and dexamethasone pretreated mice. Five mice per group were infected intravaginally with different strains of \textit{T. vaginalis} at Days 0 and 1 and then cultured for \textit{T. vaginalis}. Mice received estradiol (50 μg/dose) at Days −9 and −2 and dexamethasone daily from Days −4 to +6. MR \textit{T. vaginalis} strain B7268 and MS strain 12047 infected more mice than the other strains for up to at least 7 days post challenge, although only strain B7268 was significantly different from the other strains. Different letters indicate significantly different results (P < 0.05).

<table>
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<th>% Of mice infected at Day 7*</th>
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*The percentage of mice with PMN at Day 0 and the percentage of mice infected at Day 7 are negatively correlated (Pearson correlation: P < 0.05).
T. foetus and T. vaginalis. The differences in infectious doses and duration of infection may be related to the differences in susceptibility to killing by PMNs in the murine vaginal secretions during the estrus cycle. The mouse model of human trichomoniasis may be a useful tool for studying the efficacy of therapeutic drugs.  

Figure 6. Effect of oral metronidazole treatment of Trichomonas vaginalis infection in estradiol and dexamethasone pretreated mice. Five mice per group were infected intravaginally with T. vaginalis metronidazole resistant (MR) strain B7268 and metronidazole sensitive (MS) strain 12047 at Days 0 and 1 and then cultured for T. vaginalis. Mice received estradiol (50 μg/dose) at Days −9 and −2 and dexamethasone daily from Days −4 to +6. They were treated with metronidazole (2–50 mg/kg) 5 times twice daily at Days +2, 3, and 4 (see arrows). Doses of 50 mg/kg of metronidazole eliminated infection of T. vaginalis MS strain 12047 with a significantly lower percentage of infected mice at 5 and 7 days post challenge ("a" = significantly lower than controls. P < 0.05). Other doses of metronidazole were not significantly different from the untreated controls and no treatments reduced MR strain B7268 infection rates in comparison with untreated controls (P > 0.05).

REFERENCES