Neglected Parasitic Infections in the United States: Trichomoniasis

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Abstract. Trichomoniasis is one of the most common human parasitic infections in the United States, as well as the most prevalent non-viral sexually transmitted infection. However, it has long received much less consideration than other parasitic and sexually transmitted diseases. Much of this inattention can be attributed to a poor understanding of the public health impact of trichomoniasis. Increasing recognition of the sequelae of infection, including increased risk of infection with human immunodeficiency virus and adverse outcomes of pregnancy, has led to increased interest in T. vaginalis. Recent innovations include development of diagnostic tests that could improve detection of the parasite. A number of important questions, such as the epidemiology among men and women, the true public health burden of symptomatic and asymptomatic T. vaginalis infections, and whether current treatments will be adequate to reduce the substantial health disparities and costs associated with trichomoniasis, need consideration to remedy neglect of this important disease.

INTRODUCTION

Trichomonalis is a sexually transmitted disease (STD) caused by the protozoan parasite Trichomonas vaginalis. With an estimated worldwide incidence of 248 million new cases per year, T. vaginalis infection is more common than Chlamydia, gonorrhea, and syphilis infections combined, making it the most common non-viral sexually transmitted infection (STI).1 Despite this incidence, research and control efforts for T. vaginalis infection have traditionally lagged far behind efforts to control other STIs. It also disproportionately affects minorities and low-income populations, further contributing to its classification as a neglected parasitic infection.2,3

Although it affects both sexes, the health impact of trichomoniasis is manifested primarily in women. Clinically, T. vaginalis infections in women are usually asymptomatic, or symptoms can appear weeks, months or years after an initial infection.4,5 Symptomatic trichomoniasis can cause mild to moderate inflammation of the cervix, vagina, and urethra.6,7 Vaginal discharge can be copious, malodorous, and frothy. Pruritus and pain with urination or sexual intercourse may also be presenting complaints. Punctate hemorrhagic lesions in the genital epithelium can result in colpitis macularis or strawberry cervix, which is a specific sign for trichomoniasis.6,7 Without appropriate treatment, T. vaginalis infection may persist for months to years.8 In addition to these manifestations, trichomoniasis during pregnancy has been associated with premature rupture of the amniotic sac and chorion, preterm labor, and delivery of a low birth weight infant.9–11 Women infected with human immunodeficiency virus (HIV) who are also infected with T. vaginalis have a higher risk of developing pelvic inflammatory disease.12 Trichomonas vaginalis infections have also been linked to increased risks of other STDs,13–21 infection is associated with 1.5–2.7 times greater risks of HIV acquisition and transmission13–17 and up to a four-fold increase in HIV shedding.18

Trichomoniasis in men is not nearly as well studied or understood as it is in women. There are no licensed diagnostic assays for T. vaginalis infection in men, the occurrence of symptomatic infections is rare compared with the estimated prevalence of infection in males, and most infections are believed to resolve in the absence of treatment.2,22 However, this perspective may be incomplete.23 In addition, because infected men are often asymptomatic, they may be unaware of the risks to themselves and their sexual partners. For symptomatic men, the most common syndrome is urethritis. HIV-infected men with urethritis who are also infected with T. vaginalis have higher concentrations of HIV in their semen than HIV-infected men with urethritis who are not infected with T. vaginalis.24 A potential link between T. vaginalis infection and prostate cancer has been hypothesized but remains controversial.25,26

Infection is most commonly diagnosed by identifying the motile parasite during microscopic examination of genital secretions (wet mount), usually cervico-vaginal secretions from women. However, the sensitivity of wet mount is generally poor (51–65%), and decreases by as much as 20% within one hour after collection.27–29 Culture has been considered the gold standard method of diagnosis, but is time-consuming and costly, and therefore is not often performed in the clinical setting. Furthermore, diagnosis by culture requires a return visit for treatment, which can be a barrier to delivery of appropriate therapy. The first nucleic acid amplification test (NAAT) for T. vaginalis infection in women was cleared by the U.S. Food and Drug Administration in 2011.30 The NAAT has high sensitivity and specificity and can be used to test genital secretions or urine specimens. Rapid point-of-care tests that detect parasite antigens or multi-copy genetic biomarkers have also been developed.31–33 Sensitive tests that can provide accurate results within 30 minutes are advantageous because therapy can be prescribed or provided at the initial visit, which decreases missed treatment opportunities because of loss to follow-up.

The Centers for Disease Control and Prevention (CDC) guidelines recommend that all women seeking care for vaginal discharge should be tested for trichomoniasis.34 Screening for T. vaginalis infection is recommended for all HIV-infected women upon entry to care and at least annually thereafter. In addition, screening can be considered for asymptomatic women at high risk for infection or disease (e.g., with a history...
of any STD, new or multiple sex partners, receiving care in a high-prevalence setting, or other risk factors). Few data are available to guide testing or screening recommendations for men.

Nitroimidazoles (i.e., metronidazole or tinidazole) are the only class of antimicrobial medication approved for the treatment of trichomoniasis in the United States. In particular, metronidazole is an inexpensive, widely available, effective and generally well-tolerated treatment option. Treatment of all sex partners is recommended to reduce reinfection. However, nitroimidazoles may not be sufficient to treat all persons with trichomoniasis. Infections with antimicrobial-resistant *T. vaginalis* were identified in women with clinical treatment failure within a few years after metronidazole was introduced in the United States, although these findings might have been the result of naturally occurring nitroimidazole-tolerant strains rather than resistance that developed because of drug pressure. A recent study of STD clinic patients in six U.S. cities found that 4.3% of *T. vaginalis* isolates demonstrated low-level in vitro resistance to nitroimidazoles. Host factors can also influence treatment efficacy. For example, HIV-infected women are less likely to respond to single-dose metronidazole treatment than HIV-uninfected women, even if the parasite isolate is drug sensitive in vitro. A longer nitroimidazole regimen may be needed for effective treatment of HIV-infected women who are also infected with *T. vaginalis*.

In addition, occasional persons may report hypersensitivity reactions to nitroimidazole antimicrobial medications; this sensitivity is believed to be uncommon but the prevalence of this type of allergy is unknown. Most of these persons can be treated successfully for trichomoniasis without severe side effects by using an incremental dosing protocol. However, persons who experience true anaphylactic reactions or Stevens-Johnson syndrome should not be retreated with nitroimidazoles. No other Food and Drug Administration-approved treatments for trichomoniasis are available.

**PUBLIC HEALTH IMPORTANCE OF TRICHOMONIASIS IN THE UNITED STATES**

*Trichomonas vaginalis* is the most prevalent non-viral sexually transmitted infection and arguably the most common parasitic infection in the United States, affecting an estimated 3.7 million persons, including 2.3 million women and 1.4 million men nationwide. A nationally representative study that used a sensitive polymerase chain reaction to detect *T. vaginalis* infections estimated a prevalence of 3.1% in U.S. women of reproductive age (14–49 years). Disparities are a prominent feature of this infection; non-Hispanic black women had the highest rates of infection at 13.3%, which is approximately 10 times higher than rates among Mexican-American (1.8%) or non-Hispanic white (1.3%) women. Other risk factors identified in this study included lower socioeconomic status, lower educational levels, douching, and higher numbers of lifetime sex partners. Another nationally representative study of male and female adolescents tested for *T. vaginalis* infection by polymerase chain reaction reported that women were more likely than men to be infected (prevalence ratio = 1.64, 95% confidence interval = 1.25–2.15).

In contrast to other non-viral STIs, *T. vaginalis* infection rates increase with age. In a metropolitan area with high STI rates, prevalence peaked among 51–60-year-old women, followed by women > 60 years of age and women 41–50 years of age. A similar study conducted in men also showed a peak prevalence of *T. vaginalis* infection among 51–60 year-old men. Thus, national estimates based on studies of persons < 50 years of age probably underestimate the true number of *T. vaginalis* infections in the United States.

Trichomoniasis is not a reportable condition in the United States or in any state. As a result, the true incidence of infection has not been well established. Currently, CDC estimates that at least 1.1 million persons (including 680,000 women and 415,000 men) become infected with *T. vaginalis* each year. Accurate measurements are complicated by the poor sensitivity of commonly used clinical testing methods (e.g., wet mount) and the large number of asymptomatic infections.

The cost and healthcare burden associated with trichomoniasis are substantial, and the direct medical costs are conservatively estimated to be $24 million per year in the United States. The average lifetime cost per case has been estimated at $22, not including any costs associated with complications or associated conditions. However, persons infected with *T. vaginalis* may incur additional unrecognized costs because of adverse outcomes of pregnancy, HIV acquisition, or other health complications. For example, *T. vaginalis* infection may increase the risk of acquiring HIV; an estimated 2–6% of new HIV infections among U.S. women are attributable to trichomoniasis each year. The estimated lifetime cost of these annual *T. vaginalis*-attributable HIV infections approaches $167 million.

**GAPS IN CURRENT KNOWLEDGE AND FUTURE DIRECTIONS**

Despite its high prevalence and associated healthcare costs, many aspects of the pathology and public health impact of trichomoniasis remain poorly understood. The most pressing area of research is the epidemiology of the infection and the disease, including the incidence of symptomatic and asymptomatic infections, their respective risk factors, and sequelae that result if the patient is not treated. These data would help to determine whether there is a public health benefit to screening for *T. vaginalis* infections in persons with risk factors but without recognized symptoms. The recent availability of NAATs and point-of-cares tests may provide a more sensitive tool for identifying infection, but the optimal use of these tests will be difficult to define until there is a better understanding of the public health significance of asymptomatic infections. Clinical guidance is also needed with respect to using sensitive diagnostic tests after treatment to confirm microbiologic as well as clinical cure. One recent innovation has been using the Internet to offer free evaluations of self-collected specimens, a strategy that may reduce barriers to getting tested for STDs, as well as providing an additional source of epidemiologic data. More investigation is also needed into host-parasite interactions that influence whether an infection is symptomatic. For example, parasite surface receptors that promote adherence to host epithelial cells may be key factors in pathogenesis. Studies that investigate the long-term correlates and consequences of...
symptomatic and asymptomatic infections will enable clinicians and public health practitioners to refine screening and treatment strategies.

A better understanding of the effects of trichomoniasis during pregnancy is also needed, including the best management of pregnant women with T. vaginalis infections and the potential long-term consequences for children born to infected mothers.\textsuperscript{50} Despite the associations between infection and preterm delivery, limited data suggest that metronidazole treatment of pregnant women with asymptomatic infections does not reduce the risk of preterm delivery.\textsuperscript{31} However, more well-designed studies using current diagnostic assays are needed to fully evaluate the risks and benefits of treating trichomoniasis during pregnancy.

Another unresolved question is whether some T. vaginalis infections may persist after treatment despite resolution of symptoms. Data that support this phenomenon include the association of increasing prevalence with age and the observation that a previous infection is a strong predictor of subsequent infection.\textsuperscript{52} The association between T. vaginalis infection prevalence and age argue for public health strategies targeted to age groups not typically considered at high risk for STDs. In addition, longitudinal studies have identified some women who were negative for T. vaginalis after treatment, but subsequently were positive for parasites despite reporting no additional sexual activity.\textsuperscript{53,54}

Persistent T. vaginalis infections despite clinical cure suggests that the problem of treatment failure may be more widespread than has been recognized. Although antimicrobial drug-resistant T. vaginalis clearly exists, not all treatment failures are solely attributable to parasite genetic characteristics; for example, many isolates received by the susceptibility testing service at CDC do not display resistance in vitro.\textsuperscript{55} In addition, some women for whom nitroimidazole treatment failed during pregnancy can be cured with the same medication regimen after they have delivered. The exact mechanism of parasite resistance to nitroimidazoles and the host factors that contribute to overt or subclinical treatment failures remain major knowledge gaps that hinder comprehensive management of trichomoniasis.

Finally, the epidemiology of trichomoniasis in men should be evaluated more fully. For example, the putative association with prostate cancer should be confirmed or refuted with well-designed studies using sensitive diagnostic testing. There is also the question of whether more attention to T. vaginalis infections in men might reap public health benefits for women. Typically, men are offered treatment of trichomoniasis only if they have a female sex partner with a diagnosed infection. Although most of these men are infected,\textsuperscript{5,50} their willingness to take antimicrobial medication may be decreased if they are not experiencing symptoms themselves. Many treatment failures in women are likely caused by reinfection after sex with an untreated or undertreated sex partner. Treatment of trichomoniasis in HIV-infected men has been shown to reduce HIV concentration in seminal fluid, leading to the suggestion that programs to control trichomoniasis in men could be a cost-effective approach to reducing HIV transmission.\textsuperscript{24,5} Further study could also clarify the risk of trichomoniasis among men who have sex with men.

Publication of the T. vaginalis genome in 2007 provided a great step forward towards defining the genes responsible for parasite pathology and antimicrobial resistance.\textsuperscript{58} However, fully understanding the genetic correlates of disease has been challenging because of the size, complexity, and repetitiveness of the genome. Nevertheless, population genetic analysis suggests that the preponderance of resistant isolates aggregate into one of two phylogenotypes.\textsuperscript{59} This finding could lead to identification of genetic markers for resistance and the ability to develop molecular tests for isolates from persons who experience treatment failure, which could expedite results on drug susceptibility and improve patient care. Further research on the association of genetic markers with parasite virulence and persistence is also needed, including the effects of parasite infection with the T. vaginalis virus.\textsuperscript{60,61}

One of the most important needs for improving case management will be identification of novel therapeutic regimens in instances when nitroimidazoles cannot be administered (e.g., antimicrobial resistance or hypersensitivity). If 4.3% of existing T. vaginalis infections demonstrate resistance to metronidazole, then more than 159,000 persons in the United States may require some form of alternative therapy. This figure is even higher when also considering the number of persons with severe hypersensitivity to nitroimidazoles. Because metronidazole treatment is inexpensive and effective for most trichomoniasis patients, financial incentives for pharmaceutical companies to develop new therapies are not large. However, we have recently identified some previously approved compounds that increase the efficacy of nitroimidazoles against resistant parasites in vitro\textsuperscript{62}, combinations of these compounds with metronidazole or tinidazole also need in vivo evaluation. Intravaginal treatment with furazolidone or paromomycin sulfate treatment of women with severe hypersensitivity to the nitroimidazoles have been used with limited success,\textsuperscript{63} but further study is needed. Similarly, intravaginal treatment with boric acid or betadine preparations has been effective for some women although additional evaluation will be necessary to confirm their efficacy.\textsuperscript{54–66}

Trichomoniasis has long been overlooked as simply a nuisance infection, and persons who were not cured after treatment may have been judged noncompliant with therapy. Fortunately, these attitudes are changing and more emphasis is being placed on understanding the pathogenesis, burden, natural history, and response to treatment of T. vaginalis infection. Many important questions remain, including the current epidemiology of trichomoniasis among both men and women, the true public health burden of symptomatic and asymptomatic T. vaginalis infections, and whether current treatments will be adequate to reduce the substantial health disparities and costs associated with trichomoniasis. Increased emphasis on detection and treatment of infections is needed to move trichomoniasis out of the neglected category and to provide better care for those most impacted by this parasitic disease.

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