Global epidemiology of *Trichomonas vaginalis*

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ABSTRACT

Despite having the highest prevalence of any sexually transmitted infection (STI) globally, there is a dearth of data describing *Trichomonas vaginalis* (TV) incidence and prevalence in the general population. The lack of basic epidemiological data is an obstacle to addressing the epidemic. Once considered a nuisance infection, the morbidities associated with TV have been increasingly recognised over the past decade, highlighting the importance of this pathogen as a public health problem. Recent developments in TV diagnostics and molecular biology have improved our understanding of TV epidemiology. Improved characterisation of the natural history of TV infection has allowed us to hypothesise possible explanations for observed variations in TV prevalence with age. Direct and indirect hormonal effects on the female genital tract provide a likely explanation for the greater burden of persistent TV infection among women compared with men. Further characterisation of the global epidemiology of TV could enhance our ability to respond to the TV epidemic.

INTRODUCTION

Trichomonas vaginalis (TV) is the most prevalent curable sexually transmitted infection (STI) globally.[1] A number of studies have highlighted the fact that at least 80% of TV infections are asymptomatic.[2][3] However, even asymptomatic infections are a public health concern. In addition to the risk of transmission to sex partners, TV infection has been associated with as much as a 2.7-fold increase in the risk of HIV acquisition,[4–6] a 1.3-fold increase in the risk of preterm labour, and a 4.7-fold increase in the risk of pelvic inflammatory disease.[w1][w2] (superscript "w"s are references to the WebLink references in the online supplementary document).

In this review, we summarise current knowledge of the global epidemiology of TV infection. Additionally, we highlight recent and interesting advances in our understanding of the epidemiological correlates of TV infections. These include sex differences in the incidence and prevalence of infection, and the potentially important role of female sex hormones, and the menstrual cycle in mediating TV susceptibility and natural history.

WHO has estimated that over half the 248 million new TV infections each year occur in men.[1] By contrast, 89% of prevalent TV cases are found among women.[1] Biological differences between the sexes contribute to these striking differences in the incidence and prevalence of TV infection between men and women. Recent innovations in detection, including the availability of nucleic acid amplification tests (NAATs), have improved our understanding of the natural history of TV infections. These advances in our understanding of TV infection

have been particularly notable in men, as sensitivity of detection by wet mount is so poor in men that it is not used, while culture detection in urethral samples yields variable sensitivity.[w3][w5][7]

Enhanced detection of TV infection in men has facilitated the investigation of different biological mechanisms influencing persistence versus clearance of infection between the sexes. Greater availability of iron in the female genital tract due to menstrual bleeding may contribute to sex-dependent epidemiological patterns of TV infection.[8] One study suggests that the TV genome has adapted to existing in the setting of cyclic variation in iron availability,[9] such as that present during menstrual cycles. Additionally, oestrogen has been identified as an important determinant of the natural history of TV infection.[w5] Recent studies add depth to our understanding of the potential role of female hormones, including both physiological hormonal cycles and hormonal contraceptives, in TV infection.

SUMMARY OF GLOBAL ESTIMATES OF TV PREVALENCE AND INCIDENCE

At the time of this publication, TV is not a reportable infection in any country. As such, there is a lack of TV case-reporting data at national and global levels. Despite this major limitation, WHO has made an effort to generate regional and global estimates of TV incidence and prevalence among adults aged 15–49 years old in 1999 and 2005 (table 1).[1][10] Remarkably, empirical data on TV incidence and prevalence were so scarce that they were not used in developing the 1999 estimates. Instead, TV prevalence among women was estimated to be twice the regional prevalence of *Chlamydia trachomatis* infection. Prevalence of TV infection among men was calculated to be one-tenth of the estimated TV prevalence among women. Estimates of TV incidence were generated by dividing the prevalence by the estimated average duration of infection (females: 1.03–1.36 years, males: 0.11–0.12 years).[10]

By contrast with the 1999 estimates, WHO used data from studies conducted between 1999 and 2005 to generate an estimate of TV prevalence in 2005. Of note, the research studies contributing to the WHO estimate were not designed to measure prevalence in the overall population. Prevalence of TV infection among women was estimated as 8.08% from study data for the Africa, South-East Asia, and Western Pacific regions.[1] By contrast, TV prevalence in men was calculated to be 1.00% from study data available only for the South-East Asia region. For regions in which study data were not available, TV estimates were based on the prevalence of other STIs. When interpreting the 2005 statistics, it is important to bear in mind that the available data represent specific populations of

Table 1 Estimates of the global incidence and prevalence of TV among adults aged 15–49 years

Year	Prevalence estimate (%)				New cases (millions)			
	Total	Female	Male	Estimation method	Total	Female	Male	Estimation method
1995	Not reported			Unavailable	167.12	84.57	82.55	Unavailable
1999	Not reported			Female: 2× the prevalence of Chlamydia. Male: 1/10 the estimated prevalence of females	173.46	87.68	85.78	Estimated prevalence divided by average duration of infection, number of new cases extrapolated from incidence
2005	4.48	8.08	1.00	Female: Compiled data from published reports. Male: prevalence of other STIs used to calculate TV prevalence for all regions except South-East Asia, for which study data were available	248.48	105.63	142.85	Estimated prevalence divided by revised average duration of infection and regional treatment trends to calculate incidence, Number of new cases extrapolated from incidence

Estimates from the World Health Organization 1999 and 2005 reports on STI incidence and prevalence.[1]
STI, sexually transmitted infection.

research interest including pregnant women and women attending family planning clinics. The 2005 incidence estimate was derived by dividing the prevalence by an improved calculation of the duration of TV infection (females: 1.12–1.39 years, males: 0.12 years).[1] This calculation included updated parameters, such as regional treatment trends.[1] A variety of factors including treatment trends and access to care are likely to have contributed to variation in TV prevalence in different areas.

The available estimates suggest that the global incidence of TV infection increased between 1999 and 2005. However, comparison of the WHO 1999 and 2005 prevalence and incidence estimates is problematic because of differences in the methods of estimation. Additionally, only an overall incidence of 54 cases per 1000 person-years was reported in 1999.[10] By contrast, separate estimates were provided for women (63.0 per 1000 person-years) and men (82.2 cases per 1000 person-years) in 2005.[1] Regional comparisons between 1999 and 2005 are not possible due to a restructuring of the regions. Despite these limitations, it is apparent that the global burden of TV infection is enormous, and there is no indication that it is decreasing.

ADVANCES IN UNDERSTANDING TV EPIDEMIOLOGY
Several recent advances have enhanced our understanding of the global epidemiology of TV infection. These include advances in the molecular epidemiology of TV, the development of highly sensitive diagnostic tools, and improved characterisation of the prevalence, incidence and clinical characteristics of TV infection in men.

Molecular epidemiology of TV infection
Publication of the full TV genome in 2007 has fostered significant advances in our understanding of the natural history of the organism.[11] Additionally, the recent development of TV-specific microsatellite and single nucleotide polymorphism genotyping assays[w6] has improved our understanding of TV genetics. Using these technologies, investigators recently identified two distinct genome structure types associated with clinically relevant unique phenotypes. These results confirm previously inconclusive findings that suggest a two-type population structure of TV using less sensitive methods.[w7 12] Type 1 TV isolates have a higher prevalence of infection with TV virus (TVV). These viruses are found in approximately 50% of isolates.[13] The presence of TVV-infected trichomonads triggers mucosal inflammatory responses and may play a role in mediating susceptibility to and the clinical presentation of other STIs.[12] Type 2 TV isolates

are notable for having a higher prevalence of resistance to metronidazole.[14]

One study has characterised the global distribution of types 1 and 2 TV infections. Analysis of 231 clinical isolates from the USA, Mexico, Chile, Italy, South Africa, Mozambique, Australia, Papua New Guinea and India found TV types 1 and 2 to be distributed with equal frequency in most regions, but with two notable exceptions.[14] In isolates from South Africa and Mozambique, all samples 19/19 (100%) were TV type 1 infection. By contrast, samples from Mexico had a significantly higher prevalence of TV type 2 infection.[14]

Diagnostic advances have improved our understanding of TV epidemiology
The sensitivity of diagnostic tools for detecting TV has improved up to 2.7-fold since the parasite was first observed in vaginal secretions by wet mount microscopy in 1837.[w8] Table 2 provides a summary of the trajectory of TV assay development and associated operating characteristics of these tests. Detection of TV by wet mount microscopy remained the gold standard until the emergence of TV culture in 1949.[w9] First-generation PCR assays for detection of TV had a sensitivity of 89% in vaginal samples and 64% in urine samples.[15] In addition to highly sensitive current methods of TV detection including a variety of NAATs, immunochromatographic (IC) antigen detection assays are under development with 83.3% sensitivity in women compared with a composite reference standard of either a positive wet prep or culture.[16]

The evolution of TV diagnostics limits direct comparison of incidence and prevalence data acquired by different detection methods. Studies reporting incidence or prevalence data based on wet mount microscopy, still broadly used in clinical settings, are likely to under-report cases due to inferior diagnostic sensitivity. By contrast, more sensitive tests may detect more cases even if the true incidence and prevalence are unchanged.

Cost and required infrastructure remain as barriers to accurate global TV surveillance using more sensitive methods including culture and NAATs. Nonetheless, serial improvements in diagnostics have greatly expanded our understanding of the epidemiology of TV infection in men,[w4 w10] a population that has previously been largely excluded from TV research. Wet mount microscopy is so insensitive in detecting TV in men that prevalence data were limited until the availability of culture, beginning in 1949. Urogenital swabs analysed by PCR have been considered the most sensitive method of TV detection in men.[17] However, data presented in table 2 shows comparable upper

Table 2 History of TV diagnostics

First use	Assay	Additional details	Sensitivity (men)	Specificity (men)	Sensitivity (women)	Specificity (women)
1837	Wet mount microscopy				36.4–82.0%[w3 w23 w24]	99.1–100.0%[w3 w23 w24]
1949	Culture	Diamond's media	56.0–100.0%[w3 w4 7]	100.0%[w3 w4]	95.7%[7]	100.0%[w3 7]
1993		InPouch TV (BioMed Diagnostics)			69.7–73.3%[w3 w25]	100.0%[w3 w25]
1998	NAAT	APTIMA TV (Gen-Probe, San Diego, California, USA)	91.7%[w3]	86.7–96.9%[w3]	98.6%[w3]	92.5–96.0%[w3]
		PCR: Urine sample	91.7–100.0%[3, w3 w4 7 17]	88.0–99.4%[w3 w4 7]	90.8–100.0%[w3 w23 w26 17]	93.4–99.2%[w3 w23 w26]
		PCR: Urogenital swab	81.6–91.7%[w3 w27]	94.9–95.5%[w3 w27]	97.8–98.6%[w3 w4]	97.4–97.8%[w3 w4]
2002	Immunochromatographic antigen detection assay	OSOM *Trichomonas* Rapid Test (Sekisui Diagnostics, Framingham, Massachusetts, USA)	Limited to vaginal specimens	Limited to vaginal specimens	83.3–98.0%[w28 30]	98.9–99.4%[w28 30]
		XenoStrip-Tv (Xenotype Diagnostics, San Antonio, Texas, USA)			66.7–90.0%[w23 w26 w29]	92.5–100.0%[w23 w26 w29]
2011	NAAT	FDA-cleared APTIMA TV (Gen-Probe, San Diego, California, USA)	96.0%[w3]	90.5–96.3%[w3]	95.2–100.0%[w17 w30]	98.0–100.0%[w17 w30]

NAAT, Nucleic acid amplification test.

ranges of sensitivity among culture, PCR and other NAAT methods. Detection using multiple specimens is more sensitive than single specimen analysis.[w11] First-void urine may be a more readily collected specimen, and a preferred specimen source compared with urogenital swab specimens.

Natural history of TV infection in men

Despite the availability of sensitive diagnostics for TV detection in men, at the time of this publication, no prospective studies present data on male TV incidence rates. Data for TV prevalence among men range from 3% to 17% in STI clinic attendees to as high as 73% for male partners of women diagnosed with vaginal trichomoniasis.[w2 w10 w12 18 19] The mean incubation period of TV infection in men is approximately 10 days.[20] The natural history of untreated TV infection in men is not well characterised. However, one study found a drop in TV prevalence to 30% by the second week postsexual exposure among TV-infected male partners of TV-infected women.[21]

TV susceptibility and persistence across the life cycle

Many aspects of TV infection vary across the life cycle. Infant infection with TV during birth is the only non-sexual mode of transmission. Treatment of asymptomatic infants is often unnecessary. Spontaneous resolution of infant infection occurs within the first 6 weeks of life, as oestrogen concentrations wane to prepubescent levels.[w5]

By sharp contrast with other curable STIs including *C trachomatis* and *Neisseria gonorrhoeae*, significantly higher rates of TV are found in older men[w12 w13] and women[w14] compared with adolescents and younger adults. One retrospective surveillance study of samples from a regional healthcare system found that men infected with TV were significantly older than men presenting with *C trachomatis* and *N gonorrhoeae* (39.9 years vs 27.6 and 25.9 years).[w12] Moreover, TV was the only STI identified in men over 60 years old.[w12] Similarly, one study of women receiving routine gynecological exams demonstrated in multivariate analysis that women 35 years and older were 1.049 (95% CI 1.025 to 1.075) times more likely to have TV infection than younger women.[w15]

RECENT OBSERVATIONS ON SEX DIFFERENCES IN TV INFECTION

Biological differences between the sexes may help to explain why women have a higher prevalence but a lower incidence of TV infection compared with men, as detailed above in our summary of global estimates of the prevalence and incidence of TV infection.

Asymptomatic TV infection

Up to 77.3% of TV infections in men are asymptomatic.[19] These infections represent important vectors for transmission to women. However, no prospective data describing the persistence of asymptomatic TV infection in men are available. In women, over 80% of TV infections are asymptomatic, and these infections can persist for several months.[w5 w16 7] Interestingly, a model assessment of potential strategies for reducing the generalised TV epidemic found screening to be the most efficient method of control.[22] By contrast, syndromic management was ineffective in these models, likely because of high rates of asymptomatic infection.

Symptomatic TV infection

TV infections in men can be symptomatic in about a quarter of cases, and TV was identified as the aetiological agent in 13% of

cases of non-gonococcal urethritis in men attending an STI clinic.[23] This finding is the basis for WHO guidelines that recommend metronidazole for treatment of persistent urethritis in men who fail first-line regimens directed at gonorrhoea and chlamydia. Symptomatic TV infection in men is typically cleared spontaneously within 10 days.[w2 w5 w17] By contrast, symptomatic TV infection in women can persist for years.[24]

HORMONAL EFFECTS AS A MAJOR DRIVER OF TV EPIDEMIOLOGY

Sex hormones may be important in women of reproductive age, directly influencing TV susceptibility and pathogenesis, as well as regulating the availability of iron in the genital tract through menstrual cycles. Sex hormones are known to affect STI acquisition and disease progression through their effects on reproductive tract immune responses.[w18] Thus, sex hormones may contribute to the variation of TV acquisition and persistence over the course of the life cycle. During the reproductive years, availability of iron and oestrogen may facilitate persistent TV infection among females. Likewise, the absence of oestrogen and the iron-depleted environment of the male genital tract may make men poor long-term TV reservoirs.[w19]

Iron availability in the genital tract

In women, hormones could influence TV susceptibility and persistence indirectly through menstrual bleeding. It has been hypothesised that the iron-rich environment of the vagina in menstruating women provides conditions conducive to TV growth and persistence.[8] One unique feature of the TV genome is the duplicity for the majority of genes, of which 117 are upregulated in iron-rich environments, and 78 in iron-restricted environments.[9] The presence of iron facilitates the adherence of TV to the genital tract epithelium.[8] This feature may facilitate survival of the parasite in iron-rich environments, like the vagina in menstruating women, where haeme from the breakdown of menstrual blood provides an abundant supply of iron. By contrast, the zinc-rich environment of the prostate inhibits persistent infection.[w20 25] It is also possible that urination helps to clear TV parasites from the male genital tract, whereas this mechanism would not be expected to influence clearance of vaginal secretions.

Hormonal contraceptive effects on TV growth and persistence

Hormonal contraception appears to influence the risk of TV acquisition and affect persistence. These effects may be mediated through immunological or direct influences of exogenous sex hormones on the parasite. Ecto-5′-nucluetidase, a neutralising enzyme that hydrolyses adenosine monophosphate to adenosine required for parasite growth, may be decreased by oestrogen.[26] This effect, in turn, could serve to attenuate TV pathogenesis.

A number of studies have suggested an association between depot medroxyprogesterone acetate (DMPA) use and lower rates of TV infection.[w14 5 27] Reduced susceptibility to TV infection in women on DMPA could be mediated by reductions in menses, limiting the availability of iron. It is also possible that DMPA lowers TV risk by creating a low-oestrogen environment or by inhibiting exogenous oestrogen and androgen receptors on the TV parasite.[w21 27] Depot medroxyprogesterone acetate has been hypothesised to decrease the risk of TV acquisition by inhibiting exogenous oestrogen and androgen receptors on TV[w21 27] and limiting iron availability through the mechanism of decreased menstrual flow.

Prior to 2009, the widespread use of oestrogen replacement therapy among postmenopausal women[w22] may have contributed to a higher TV prevalence among older women by maintaining oestrogen effects in the female genital tract. On the other hand, low concentrations of oestrogen in postmenopausal women who are not using oestrogen replacement therapy may promote clearance of TV infection.[28]

CONCLUSION

While empirical data remain sparse, the TV epidemic generally appears to be growing by measures of both prevalence and incidence. This review of recent developments in our understanding of the global epidemiology of TV highlights several important points. First, advances in TV genomics suggest important regional differences within the global TV epidemic. Second, a variety of highly sensitive TV detection tests have improved our understanding of the natural history of TV infection in men, and have helped to characterise TV epidemiology across the life cycle in women. Finally, plausible explanations for the differences in TV incidence and prevalence between men and women have emerged as a result of our increased understanding of mechanisms of TV susceptibility and persistence.

The potential morbidity associated with TV infection is described in several of the following reviews in this special issue of *STI*. Increased recognition that TV is not simply a benign infection should lead to greater prioritisation of measures for controlling the epidemic. Advances in our understanding of TV epidemiology point to opportunities for possible intervention. Screening for TV could be a useful case identification strategy in men and women who are tested for *C trachomatis* and *N gonorrhoeae*. Additional screening approaches may be necessary to address the high prevalence of TV in older age groups.[29] High rates of concordant infections in couples underscore the importance of partner notification for male sexual partners of TV-infected women. Further studies into the global epidemiology of TV will offer insight into approaches for successful control of the epidemic.

Key messages

► There are very limited population data to inform global population estimates of *Trichomonas vaginalis* infection.

► The limited data available suggest an exceptionally high global burden of *T vaginalis* infection.

► Developments in diagnostics and molecular biology have improved our understanding of *T vaginalis* infection over the life span.

► Hormonal effects are likely to influence the observed differences in *T vaginalis* incidence and prevalence between men and women.

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Corrections

Poole DN, Scott McClelland R. Global epidemiology of *Trichomonas vaginalis*. *Sex Transm Infect* 2013;89:418–22. A number of citations were incorrect in this paper, the errors were introduced in the process of converting 30 of the references to supplementary web references.

1. Reference 8 is incorrect. The below reference replaces reference 8:
   Sehgal R, Goyal K, Seghal A. Trichomoniasis and lactoferrin: future prospects. *Infect Dis Obstet Gynecol* 2012 2012:536037.
2. Reference 12 is correctly used in the first appearance in the section entitled, "Molecular epidemiology of TV infection." In the second appearance of Reference 12, an alternative reference should be included:
   Fichorova RN, Lee Y, Yamamoto HS, *et al*. Endobiont viruses sensed by the human host – beyond conventional antiparasitic therapy. *PLoS ONE* 2012;7:e48418.
3. Reference 20 is incorrect. The below reference replaces reference 20:
   Krieger JN. Trichomonas in men: old issues and new data. *Sex Transm Dis* 1995;22:83–96.

Weblink References

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