Rönn, M. M., & Turner, K. (2018). The dawn of novel STI prevention methods: modelling potential unintended effects of changes in cervical cancer screening guidelines on trichomoniasis. *Sexually Transmitted Infections*, *94*(3), 161-162. https://doi.org/10.1136/sextrans-2018-053534

The dawn of novel STI prevention methods: modeling potential unintended effects of changes in cervical cancer screening guidelines on trichomoniasis

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Trichomonas vaginalis (trichomoniasis) is a parasite of the urogenital area.(1) Trichomoniasis is not a notifiable infection in most countries and, as the majority of infections remain asymptomatic, there is lack of epidemiological data for the infection. In the USA and the UK, screening of trichomoniasis among asymptomatic individuals in the general population is not recommended by the guidelines.(2, 3) In Australia, opportunistic testing for asymptomatic trichomoniasis is done during cervical screening appointments using Pap smear test and wet mount microscopy, which has a sensitivity around 50-60% for trichomoniasis detection. New guidelines were introduced in 2017 to replace cytology-based testing with PCR testing for high-risk (HR) HPV infection, such that cervical cytology is only conducted for those who test positive for HR-HPV.(4)

In this issue, Hui *et al.*(5) have used mathematical modeling to estimate potential indirect effects of the cervical screening guideline changes on trichomoniasis prevalence in Australia. In the study, a deterministic compartmental model of trichomoniasis transmission among heterosexual population was calibrated to low level (0.4%) trichomoniasis prevalence reflecting urban Australian population, and assuming a steady age-specific cytology-based cervical cancer screening rate among women over 18 years. The authors compare the prevalence in the calibrated model to future estimates of trichomoniasis population prevalence in presence of reduced frequency of Pap smear tests. The study suggests that introducing HR-HPV testing could

lead to a substantial increase in trichomoniasis prevalence in the urban population in Australia over a twenty-year period.

Mathematical modelling is a useful analytical tool,(6) which offers a relatively rapid, low cost and low risk method to predict the impact of existing and novel interventions. Models can lead to improved understanding of the ways in which infectious diseases interact, and reveal indirect and unintended consequences of interventions. This provides valuable hypotheses for further epidemiological research, which is one of the major contributions of the study by Hui *et al*. There are few transmission models of trichomoniasis,(7, 8) and the study presented in this issue examines a complex research question in the intersection of two sexually transmitted infections (STI).

Where data are scarce, we need to set appropriate expectations to what mathematical modeling can do. With rich data, a model can be calibrated to multiple data sources, validated, and then used for forecasting, whilst propagating parameter uncertainty. In the absence of such data resources, a modeling study remains at hypotheses generating phase. In their study, Hui *et al.* focused on the indirect effects of cervical cancer screening implementation on trichomoniasis detection. Table 1 describes the broader context of potential interactions between HR-HPV and trichomoniasis, and provides suggestions for future modeling work for trichomoniasis. A key determinant of STI acquisition risk is differences in (unprotected) sexual activity within the population, with higher number of partners being associated with both HR-HPV and trichomoniasis acquisition. In the trichomoniasis model, the transmission dynamics of HR-HPV were not included in the model framework, and the prevalence of trichomoniasis among those who had HR-HPV infection was assumed to be the same as in the general population. Given the same mode of transmission, we might expect there to be a higher prevalence of trichomoniasis among those infected with HR-HPV than those not infected with HR-HPV, and this in turn may

result in larger number of trichomoniasis being detected under new guidelines than estimated in the study. Assumptions of the intensity of control strategies at baseline, prior to comparison to counterfactuals, will also impact the magnitude of change seen in the counterfactuals.(9)

We may also consider variation within the population; increasing heterogeneity in STI distribution in the population makes it easier to sustain a stable, low population prevalence of infection, but it will make the infection harder to control due to subgroups of the population being exposed to the pathogen at higher rate than others.(6) If heterogeneities are epidemiologically important in a given setting, and they have not been included in the model framework, the model estimates of intervention impact can be overestimated. Trichomoniasis prevalence is marked by variation regionally and among minority populations. Trichomoniasis positivity is estimated as 0.4% in Sydney,(10) whilst positivity is 8.4-25% in rural areas and higher among Aboriginal populations.(11, 12) Trichomoniasis is also associated with older age.(13)

In order to take this variation into account in trichomoniasis modeling, we need further data on number of trichomoniasis infections diagnosed in different settings, and how these are changing over time. As an example, the model was calibrated to a single clinic-based positivity estimate of trichomoniasis.(10) There are other plausible scenarios that could have given rise to a good model fit, but that would have resulted in lower contribution of cervical cytology to trichomoniasis control. Furthermore, data are urgently needed now that the field is moving towards point of care testing amid considerations of wider implementation of trichomoniasis testing.(14) It is challenging to limit the scope of a modeling study to what is feasible, and supported by data. Prior assumptions are also required to create any modeling framework, and the study by Hui *et al.* brings about interesting questions to explore in the future.

Table 1. Conceptualizing how proximate and distal factors for trichomoniasis (TV) can create interactions with HR-HPV and further heterogeneity at the population level

	Proximate and distal factors contributing to HR-HPV and TV epidemiology		
	Natural history of Trichomoniasis	**Sexual risk behavior**	**More distal sources of heterogeneity (age, ethnicity, urbanicity, region)**
HR-HPV epidemiology, and cervical screening interventions	It is unclear how many TV cases are detected via cervical cytology. Whether there are biological interactions between HR-HPV and TV is not known.	Individuals with more sexual partners are more likely to have HR-HPV. They may also have different test-seeking behaviors.	Variation in cervical screening and vaccine uptake in the population.
Trichomoniasis (TV) epidemiology	There are a number of uncertainties around the natural history and infection duration for TV among women and men.	Individuals with more sexual partners are more likely to have TV.	There is marked variation in TV prevalence in the population, and higher prevalence of TV among older populations.
Future considerations for modeling TV	Sensitivity analyses similar to those done by Hui *et al.* offer a way to explore the uncertainty around natural history parameters. Time series data are needed for TV testing and diagnoses in different settings to improve model estimates. Impact and cost-effectiveness of testing asymptomatic people for TV is not known.	Individuals with HR-HPV infection are more likely to be infected with TV, resulting in greater co-infection prevalence than if the infections were independently distributed. Future modeling studies should account for this if they examine the impact of cervical screening interventions.	Findings from a model calibrated to one setting may not be applicable to other settings in presence of different epidemiological characteristics. Unexplored heterogeneities may also overestimate the impact of interventions.

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