Modelling the Genital Herpes Epidemic

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- GENITAL HERPES
- HSV
- MATHEMATICAL MODELLING
- EPIDEMIC
- ANTIVIRAL THERAPY
- DRUG RESISTANCE
- TRANSMISSION

SUMMARY
Mathematical models are useful tools for summarizing and testing current knowledge about a system and predicting trends. Models have shown that medical and behavioural changes can substantially affect herpes simplex virus type 2 (HSV-2) transmission and can be used to develop rational epidemic control policies. The spread of the genital herpes epidemic and the potential impact of HSV antiviral treatment in the immunocompetent population have been addressed by four models. HSV drug resistance to antiviral drugs is predicted to be minimal. Assuming that drug-resistant mutants are attenuated both in infectivity and reactivity, one model predicted that even after 25 years, only 5 in 10,000 individuals will shed drug-resistant virus, even if rates of usage of antivirals are high. The models show that increased usage of episodic antiviral therapy will be beneficial in reducing the herpes epidemic. Results also show that the transmission rate can be reduced by preventing infection (safer sex), reduced time spent in non-monogamous relationships or the advent of effective therapeutic HSV vaccines. One model has indicated that suppressive therapy will have only a minimal impact on HSV prevalence; however, the results of this modelling study are limited as it assumed that suppressive therapy would only be given to incident infections. More recent research using a model based upon virological core groups (and treating both incident and prevalent infections) shows that suppressive therapy could cause a substantial reduction in HSV-2 incidence rates. Current modelling is also focused on modelling how HSV-2 antiviral treatment will impact the HIV epidemic.

Introduction

MATHEMATICAL MODELS ARE useful tools to summarize existing knowledge about a system and predict its future development. Modelling herpes simplex virus type 2 (HSV-2) transmission can provide insight into the behaviour of the epidemic and the impact of control measures. Four different models have been developed. Two models compare patterns of disease spread under different assumptions about the dynamics of transmission, while two others examine the effects of antiviral drug treatment. These models are reviewed in this paper and their implications for understanding the likely impact of control measures are discussed.

The Basis of Mathematical Models
- Models should be used as health policy tools to predict the impact of interventions on the HSV-2 epidemic (category 3 recommendation)
- Mathematical modelling indicates that high levels of antiviral use will have a minimal impact on levels of drug-resistant HSV-2 (category 3 recommendation)

A mathematical model is a series of equations based on specific assumptions about the transmission dynamics of any specific pathogen. The model can be simple or complex, although it is often best to construct a simple one first and use this as the basis for future, more complex variations as it gives an understanding into key variables that influence dynamics. A model can be explanatory and help understand how epidemics evolve. This aspect can be particularly helpful as epidemics most often develop in a non-linear fashion. Models can also make future predictions, albeit with ‘errors’, thereby quantifying uncertainty. Finally, they can be used to make qualitative and quantitative predictions. The models can be analysed either mathematically or computationally.

MATHEMATICAL ANALYSIS
Mathematical analysis can determine at what prevalence and incidence the epidemic will stabilize. It can also predict the effect of different interventions on $R_0$ (basic reproduction number), which is defined as the number of secondary cases that are produced when one infectious individual is introduced into a population where everyone is susceptible. The value of $R_0$ predicts the severity of the epidemic; the greater the value of $R_0$ above one, the more severe the epidemic. If $R_0$ is less than one, then the epidemic will be eradicated. For HSV-2, $R_0$ is described by three parameters, which are the transmission probability per sexual partnership ($b$), the average number of sexual partners per year ($C$) and the average number of years that an HSV-2-infected individual is infectious during their sexual lifespan (i.e. the sum of all the virus-shedding episodes) ($D$) (Figure 1). These different parameters can all be altered by one or more interventions. For example, condoms and suppressive antiviral therapy can affect the transmission probability for an individual with genital HSV-2 infection. Similarly, behavioural interventions (e.g. sexual abstinence) can decrease the average number of new sex partners per year. Finally, antiviral treatment may reduce the duration of infectiousness even if HSV remains incurable. By deriving an expression for $R_0$ and setting the value to 1, the specific values that are necessary to achieve eradication can be determined for HSV-2 infection (or any infectious disease).

COMPUTATIONAL ANALYSIS
Computational analysis, in which the model is ‘run’ on a computer, can be performed in three different ways: scenario analysis, uncertainty analysis and sensitivity analysis. Each method allows different questions to be answered and has its particular advantages and disadvantages.

Scenario analysis: In scenario analysis, the input parameters are predefined as single values and the model then used to predict an outcome. For example, the effect of a given decrease in infectivity with a vaccine on $R_0$ could be determined. The model can be run several times with different predefined parameters to span a (judgementally determined) range of possible futures. However, the difficulties of scenario analysis are that the value of the parameters is never known precisely. Thus, the relevance of the range of outcomes arising from the different scenarios is likely to be limited. Moreover, there is a trade-off between the size and complexity of the basic model and how much scenario analysis is feasible or interpretable. Therefore, scenario analysis, in which model predictions
**RECOMMENDATIONS AND STATEMENTS**

- Models should be used as health policy tools to predict the impact of interventions on the HSV-2 epidemic (category 3 recommendation)
- Mathematical modelling indicates that high levels of antiviral use will have a minimal impact on levels of drug-resistant HSV-2 (category 3 recommendation)
- To impact on the incidence of HSV-2 and the prevalence of virus shedding, daily suppressive therapy rather than episodic therapy will need to be used. Targeting of suppressive therapy to high frequency shedders would have the greatest impact on reducing the transmission rate. Research is needed to define such core groups (research need recommendation)
- New treatments and HSV-2 vaccines that suppress virus reactivation should be developed (research need recommendation)
- Models should investigate the effect of anti-HSV treatment on the HIV epidemic (research need recommendation)

**RECOMMENDATION AND STATEMENT CATEGORIES**

**Category 1**
Consistent evidence from controlled clinical trials. For example, for an antiviral, this would include results from at least one well-designed, randomized, controlled clinical trial, and, in the case of laboratory studies, consistent evidence from comparative studies.

**Category 2**
Evidence from at least one well-designed clinical trial without randomization, from cohort or case-controlled analytical studies (preferably from more than one centre), or from multiple time-series studies or dramatic results from uncontrolled experiments.

**Category 3**
Evidence from opinions of respected authorities based on clinical experience, descriptive studies or reports of expert committees.

**Research Need**
Area in which research is warranted.

**Sensitivity analysis**: A third method of computational analysis is sensitivity analysis, in which the effect of variation in key input parameters on the output can be examined in a univariate or multivariate manner. This allows the most influential input parameter to be determined. The most comprehensive approach involves specifying probability distribution functions for each input and running the model many times with samples of the input values. The strength of this approach is that it allows simultaneous consideration of how uncertain an input value is and how sensitive important outputs are to it.

**Models of the HSV-2 Transmission Dynamics in Immunocompetent Individuals**

**BLOWER MODEL**

**Description of the model**: A model by Blower et al. has been constructed that links transmission dynamics of drug-resistant and drug-sensitive HSV-2 in an immunocompetent community. To understand this model, it is helpful first to understand the simplest model of HSV-2 transmission, which is the intrinsic dynamics (i.e. the pattern of transmission in the absence of treatment).

Transmission dynamics of an untreated HSV-2 epidemic: In an untreated HSV-2 epidemic, uninfected susceptible individuals ($X$) can become infected. These infected individuals can be in an infectious virus-shedding state ($H$), when they experience a symptomatic outbreak or have an episode of asymptomatic shedding, or they can be in an infected but non-infectious state ($Q$). Thus, an individual can be in one of three states and three differential equations specify the rate of change over time of the number of individuals in each state. The determinants of the flow from each of the states are illustrated in Figure 2. The number of susceptibles (i.e. the number in state $X$) increases as individuals become sexually active at rate $\pi$ and decreases as individuals either experience ‘sexual death’ (i.e. they cease acquiring sexual partners or become sexually abstinent) at a rate $\mu$ or they become infected with HSV-2.

The incidence of HSV-2 infection (i.e. movement into the infectious state, $H$) is modelled by the term $cX\lambda$, where $c$ specifies the average number of sexual partners acquired per unit of time and $\lambda$ is the risk of infection per new sexual partnership. The risk of infection ($\lambda$) is the product of the transmission probability of HSV-2 per sexual partnership and the probability of selecting an infectious individual as a new sexual partner. Assuming random mixing, the probability of selecting an infectious individual reflects the

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**Figure 1**: Factors that can affect the basic reproduction number ($R_0$).

- $R_0 = \beta CD$,
- $\beta = \text{transmission probability per sexual partner}$,
- $C = \text{average number of sexual partners per year}$,
- $D = \text{average number of years that an HSV-2-infected individual is infectious during their sexual lifespan}$.

are made without accompanying estimates of prediction uncertainty, is of limited use for supporting health policy decisions.

**Uncertainty analysis**: A more useful method than scenario analysis for interpreting the impact of different variables within a system is uncertainty analysis, as it accounts for the uncertainty that is often inherent in estimating parameter values. Instead of using a single value for a parameter as in scenario analysis, a range of input variables weighted towards the most likely value (this weighted range is termed a probability distribution function) is used. The advantage of this method is that it translates the uncertainty in parameter estimation (as well as heterogeneity in parameter estimates) into an uncertainty in prediction, making it possible to predict the future with a degree of ‘error’.

One way to perform uncertainty analysis is to simultaneously vary the values of all the input variables according to the probability distribution function and then sample these randomly. The model is run many times with a large sample of the variables determined simultaneously; for methodological details see Blower et al.
proportion of infectious people in the total sexually active population. The size of the $H$ group not only increases because people become infected with HSV-2 (at a rate $c\lambda$) but also because individuals whose infection is in a latent or quiescent state ($Q$) reactivated at rate $r$ and shed virus. The number of individuals who are infectious decreases as their infection naturally returns to latency at rate $q$ or as they experience sexual death at a rate $\mu$.

The size of the quiescent ($Q$) group increases as infectious individuals naturally ‘return’ to latency at a rate $q$, while the size decreases as an individual’s infection reactivates at a rate $r$ or they experience sexual death at a rate $\mu$.

This model is useful as it predicts that both high rates of shedding and partner change enhance the potential for virus spread, while low rates of shedding and partner change reduce this potential. It coincides with studies that indicate that the cohort of people characterised by young age, recent acquisition of HSV-2 and high rates of partner change are likely to have a greater impact on the spread of HSV-2 than older persons with long-standing HSV-2 infections who behaviourally tend to have fewer new partners.

Transmission dynamics of an HSV-2 epidemic with episodic treatment but without the development of resistance: The effects of episodic treatment on the HSV-2 epidemic can be modelled by building upon the intrinsic transmission dynamics model. If episodic treatment is introduced for infectious individuals during a reactivation, then the size of the $H$ group will decrease at a rate $\sigma$ as individuals move from the infectious state to the quiescent state (Figure 3).[^1-2]

Transmission dynamics of an HSV-2 epidemic with episodic treatment and the development of resistance: The basic model has been developed further to include both the effects of episodic treatment and the possibility of the emergence and transmission of drug-resistant strains of HSV-2.[^1-3] A flow diagram of the treatment model is given in Figure 4. The model specifies the rate of change over time in the number of individuals in each of six states: a group of uninfected susceptibles ($X$), two groups of individuals who are infected with drug-sensitive HSV-2 (either the infectious state [$H_1$] or the non-infectious latent state [$Q_1$]) and three groups that are infected with drug-resistant virus (in an infectious state [$H_2$] and [$H_3$] or with virus that is latent [$Q_2$]).

Individuals in the $H_2$ group have permanent drug resistance and their latent virus is drug-resistant; hence they reactivate with permanent drug-resistant virus in all subsequent episodes. In the $H_3$ group, drug resistance is transient and the latent virus is susceptible to the drug and, thus, individuals in this group present with drug-resistant virus for only one episode.

As in the simpler treatment model without the development of resistance, the size of the susceptible group increases as individuals become sexually active but decreases (as do the sizes of all the other states) as they experience sexual death. Individuals also leave the group as they become infectious but they either have infectious susceptible virus (i.e. they enter group $H_1$ at a rate $c\lambda$) or enter an infectious state with resistant virus (i.e. group $H_2$ at a rate $c\lambda_2$). The two terms $\lambda$ and $\lambda_2$ are the product of the transmission probability of HSV-2 per sexual partnership (which can differ between drug-sensitive and drug-resistant strains) and the probability of selecting an infectious individual as a new sexual partner.

The size of the $H_i$ group decreases at rates of $q$ and $\mu$, but also decreases as people are treated. Some of these people will acquire permanent drug resistance at a rate

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[^1-2]: Transcribed from the original text.

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Modelling the Genital Herpes Epidemic using two scenarios for episodic treatment with oral resistance. Using scenario analysis, the model simulated prevalence of HSV-2 infection and the development of antiviral treatment on the pattern of the incidence and predict the impact of more widespread use of episodic treatment.

The exact value of the transmission probability of resistant HSV is unknown; the most common resistance mutation, in the thymidine kinase gene, results in viruses that are less pathogenic and less transmissible than wild-type virus. However, as resistance can influence the dynamics of the infection, for the scenario analyses it was assumed that either transmission of primary drug-resistant virus does not occur, or that the primary drug-resistant virus was half as transmissible as the drug-sensitive virus. As noted above, on the basis that transmission of drug-resistant virus does not occur, then after 50 years the prevalence of aciclovir-resistant HSV-2 at the high treatment rate would be 0.7%.
Findings from the uncertainty analysis: prevalence of a) infection; b) infectiousness; c) drug-resistant infection; d) drug-resistant infectiousness.
These figures were produced from the 1000 simulated epidemics in the uncertainty analyses; prevalence data were plotted, every 2 years, in the form of frequency distributions (as boxplots). Each boxplot shows the median value of the distribution (white horizontal space), the range of the data defined by the upper fourth and the lower fourth of the distribution spread (thick vertical bars), the outlier cutoffs (thin vertical bars) and the outliers (represented individually by dots).


(Upper left) In contrast, for resistant virus that was half as transmissible as drug-sensitive virus, the prevalence of drug-resistant HSV-2 at the high (50%) treatment rate would rise to 2% (Figure 5d).

Uncertainty analysis: The uncertainty analysis considered the effects of episodic treatment rates ranging from 10% to 50% of the HSV-2 seropositive population. 50% was chosen as the maximum value rather than 100% as it was assumed that cases that are asymptomatic are not likely to be treated. In these analyses, the median prevalence of infection was 52% at time zero. Treatment had a very beneficial effect on the HSV-2 epidemic over a period of decades. It decreased the overall prevalence of infection from a median value of 52% to 36% (Figure 6a) and decreased the overall level of infectiousness from 6% to 3% (Figure 6b).

Thus, increasing treatment rates above 10% has the potential to reduce, both rapidly and significantly, the morbidity of genital herpes. However, increasing treatment rates increased the prevalence of drug-resistant infection; the predicted median prevalence of infective drug-resistant virus increased over 50 years from zero to 9% (Figure 6c) and the median prevalence of drug-resistant virus increased from zero to 1% (Figure 6d). Thus, treatment with episodic therapy decreased the overall prevalence of HSV-2 but increased the prevalence of drug-resistant strains. However, even with these high treatment rates, the prevalence of drug resistance remained low.

Findings of the model:
- Mathematical modelling indicates that high levels of antiviral use will have a minimal impact on levels of drug-resistant HSV-2 (category 3 recommendation)
- To impact on the incidence of HSV-2 and the prevalence of virus shedding, daily suppressive therapy rather than episodic therapy will need to be used.
- Targeting of suppressive therapy to high frequency shedders would have the greatest impact on reducing the transmission rate. Research is needed to refine such core groups (research need recommendation).

Treatment evaluation criterion (TEC) findings: Drug treatment has two opposing effects: not only will it decrease the prevalence of susceptible virus but it will also increase the prevalence of drug-resistant virus. A treatment evaluation criteria (TEC) was calculated and used to evaluate whether or not the beneficial effects of antiviral treatment would outweigh the potential detrimental effects. The TEC specifies the average number of drug-sensitive cases that are prevented per prevalent case of drug resistance over the treatment period. Hence TEC is a measure of the net epidemiological benefit of treatment; if TEC>1, the beneficial effects of treatment outweigh the detrimental effects.

The value of TEC calculated from the simulations performed in the uncertainty analysis was always significantly greater than one but decreased steeply with time. Thus, despite the probability of an increase in HSV resistance, treating herpes epidemics would always be beneficial in terms of the number of cases prevented.

The value of TEC was extremely sensitive to the value of p1 (the probability of acquiring drug resistance per treated episode); when the value of p1 was low, the value of TEC was extremely high, indicating that increasing treatment rates had prevented hundreds of new cases of drug-sensitive infections for each prevalent drug-resistant case. This TEC is very different between HSV-2 where virulence of TK mutants is very reduced compared to HIV-drug-resistant mutants, which are only marginally less virulent than wild-type viruses.

Sensitivity analysis of the model identified the average number of infectious episodes per year as the most influential factor both in generating drug resistance and determining the overall value of treatment (i.e. affecting the TEC). Three conclusions can be drawn from the model regarding the impact of increased antiviral therapy use on the prevalence of genital herpes and the development of resistant virus:

- Chronic suppressive therapy is likely to be more beneficial than episodic treatment because it will reduce both symptomatic and asymptomatic infectious episodes;
- Genital herpes treatments should be aimed at decreasing the frequency of HSV reactivation;
- Therapeutic HSV vaccines that reduce the recurrence rate could be very useful in controlling the epidemic.

The results also highlight the importance of implementing behavioural interventions that would decrease β (e.g. increased condom use) and decrease C (reductions in the average number of sex partners). Such interventions would reduce the emergence of drug resistance.

Further findings with the Blower model: Gershengorn and Blower have used this model to make further predictions about the impact of increasing rates of antiviral usage. In keeping with earlier work, increased use of antivirals was always beneficial and the potential detrimental effects due to emergence of drug-resistant strains would be minimal. The authors used the model
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The model determined the effect of increasing levels of episodic treatment on the epidemic (Figure 7). A high level of episodic treatment at the population level has the potential to reduce the size of the herpes epidemic by decreasing transmission. The effect of the episodic treatment rate (at the population level) on decreasing the average number of infectious days per infected individual with 12 recurrences per year and for an individual with four recurrences per year was investigated using the model. The high treatment rates significantly reduced the average number of infectious days per year in patients with four or 12 recurrences per year and, therefore, high episodic treatment rates could significantly reduce transmission (Figure 7).

The probability that an individual will acquire permanent drug resistance during a single treated episode ($p_R$) is very low. However, the lifetime probability of acquiring this ($p_L$) will be higher than $p_1$ as it increases with the number of treated episodes (Figure 8). The model calculated $p_L$ based on a $p_R$ value of 0.001. The value of $p_1$ is likely to be significantly less than this figure, but even at this high value, and assuming a patient is treated for 50 episodes, then their lifetime probability of acquiring permanent drug resistance will be only 0.05.

The model also explored the epidemiological outcome of high levels of episodic antiviral treatment. Although possible, it is unlikely that high levels of episodic usage that could lead to the elimination of herpes would be achieved. However, according to the model, even moderate to low usage of episodic antiviral therapy would substantially reduce prevalence.

Further work considered the potential effect of recent data indicating that drug-resistant strains of HSV-2 are likely to be impaired in their ability to reactivate. Most drug-resistant variants are deficient in the expression of thymidine kinase, a phenotype known to reduce ability to reactivate. Previous models have considered that HSV-2 drug-resistant strains are less infectious than wild-type virus, but have assumed virus reactivation rates were unchanged.

Modelling HSV-2 drug-resistant mutants that are attenuated in both infectivity and reactivation rates predicts that drug resistance will be an order of magnitude lower than stated for earlier predictions. After 25 years of high antiviral usage, only 5 out of 10,000 immunocompetent individuals will be shedding drug-resistant HSV-2. This predicted level is so low that it is unlikely that cases of drug-resistant HSV-2 will be detected in the immunocompetent population.

More recent research by Blower et al. using a model based upon virological core groups (and treating both incident and prevalent infections) shows that suppressive therapy could cause a substantial reduction in HSV-2 incidence rates.

**WHITE AND GARNETT MODEL**

**Description of the model:** The model by White and Garnett describes the spread of genital HSV infection throughout individuals aged 16–35 years, a group representing the most sexually active in a typical Western population. Three compartments were used to describe infection in the population: susceptible, recently infected and long-term infected. The authors assumed that once an individual is infected with HSV they remain continuously infectious. The model population was divided into two groups with different rates of partner exchange and frequency of sexual intercourse within the partnership. Scenario analyses were conducted with a number of predefined parameter values. A transmission probability per sexual partnership of 0.05 was assigned to the group with high sexual activity, while a probability of 0.14 was given to the group with a low sexual activity. These values assumed that the average transmission probability per year was 0.0876, those in the higher activity group would have a shorter duration of partnership (0.28 years) than the low activity group (2.08 years), and those in the high activity partnerships had twice as many sex acts per unit of time.

To assess the effect of suppressive therapy, the model assumed that it would either reduce transmission to zero or increase the transmission probability per sexual partnership to 31.7% in the low-activity group and 9.9% in the high activity group. The higher transmission probabilities were based on the assumption that therapy would prevent symptoms but not decrease infectivity, thereby increasing the rate of transmission of the virus. However, this assumption does not appear to be warranted, as many clinical studies have shown that treatment reduces virus shedding and hence treatment decreases rather than increases transmission, as demonstrated by a recent study on the antiviral drug valaciclovir. A further limitation of the design of the model meant that only the newly infected could be treated and they could only go on therapy once (i.e. they could not be treated again).

**Findings of the model:** As would be expected, the model found that the prevalence of HSV-2 depends on the transmission probability of the virus. The model assessed the impact of suppressive aciclovir under different conditions. If aciclovir prevented transmission completely and 30% of all ‘initially infected’ individuals were treated, then the prevalence of HSV-2 infection would decrease. In
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An intervention could also prevent an epidemic by reducing the length of time that an individual is infectious.

The effect of treatment on the pattern of disease spread can also depend on the extent to which it alters the frequency of reactivations (i.e. infectious episodes), but this effect is critically dependent on the transmission rate. If the transmission rate is below a certain level, the epidemic will die out at any reactivation rate. However, if the transmission rate is high enough, then there will be an epidemic when reactivations are very infrequent or even if there are no reactivations. The analysis indicates that to control the epidemic, affecting the transmission rate is of greatest importance followed by reducing the duration of outbreaks, while reducing the time between outbreaks is of marginal importance.

In summary, the model suggests that lowering the transmission rate will beneficially impact on the epidemic. It also indicates that no epidemic will occur if the time an individual remains infectious is short enough but, in contrast, an epidemic will occur if the transmission rate is high even though the time between infectious periods is very long. Therefore, controlling the recurrence rate alone, while it may be important for an individual, may not be enough to prevent epidemic growth. It would be better to have an intervention that also reduces transmission rate and the duration of an outbreak.

NEWTON AND KUDER MODEL

Description of the model: The Newton and Kuder model simulated transmission among a uniformly mixing population of persons at high risk of acquiring and transmitting HSV-2 infection to multiple partners. The population in the model comprised individuals in their late-teens to mid-twenties. This period was chosen as it represents the time from when individuals embark on sexual activity to when they settle into long-term monogamous relationships.

The model divided the population into compartments representing different stages of the disease (Figure 10). The compartments are S (susceptible but no contact with disease), E (exposed, infected but not yet infectious), I (primary infectious), A (asymptomatic but still infectious) and R (recurrent, symptomatic and infectious). A vaccinated class (V) was included although a vaccine is currently not available. The flow between the compartments is shown in Figure 10. In essence, the flow from the S compartment to the E compartment is determined by the number of people in the susceptible and infectious class (i.e. I, A and R) and the contact rates between them. A factor influencing the likelihood of infection is the length of time that an individual spends in the entire at-risk (i.e. non-monogamous) population and this was incorporated into the model. The time spent in the other compartments is described by differential equations, which depend on the value of certain time constraints (i.e. time spent in other compartments and the time spent in the non-monogamous population). Also included were partner change rates, the probabilities of transmission from persons in each infectious class and a vaccination rate. Estimates for all these variables were obtained from the literature. However, it should be noted that once an individual becomes infected they remain infectious for life – the author does not include any stages where virus shedding is absent.

Findings of the model: In mid-1978, using an overall HSV-2 prevalence of 5% in the modelled population (i.e. those in late-teens and early twenties) based on data from the National Health and Nutrition Examination Survey (NHANES) II from the USA, and using values for the variables obtained from the literature, the model simulated the epidemic for 22 years to the year 2000. This mathematical analysis calculated a base value for $R_0$ of 1.79, which implies that the prevalence will...
eventually stabilize at 44%, and at year 2000 the prevalence in the age group would be 21.5%.

The model identified two aspects of behaviour that exert a strong effect on the epidemiology of genital herpes. The first is the length of time spent in the non-monogamous population. The analysis employed a value of 9 years for this parameter based on studies at age of first intercourse in US men and median ages of first marriage. Reducing the time spent being non-monogamous to 4.5 years brought the value of $R_0$ below 1 to 0.915, meaning that the epidemic would eventually die out in this population and prevalence in year 2000 would be only 2.3%.

The second influential variable is the partner-change rate. For example, halving the rate from the value 1.6 partners per year reported in the literature to 0.8 partners per year reduces $R_0$ to 0.896 and prevalence in year 2000 to only 3.52%. Increasing the partner-exchange rate has a greater effect than increasing the time spent being non-monogamous. Doubling the partner change rate to 3.2 partners per year increases prevalence in 2000 to 70.81%, whereas prevalence reaches only 46.62% when the time spent being non-monogamous is doubled.

The effect of varying the residence times in each of the infectious compartments was much less marked than the behavioural changes. However, varying the transmission probability for the asymptomatic class had a pronounced effect. Changes in the probability of infection in the primary infectious class had little effect, probably because individuals spend little time in this compartment. The effect of varying the probability of transmission for the recurrent infectious class is stronger but even reducing the value to zero does not bring $R_0$ to less than 1. Even when the probability of transmission for both individuals with primary or recurrent disease combined is set to zero, $R_0$ still exceeds 1. This suggests that prevention of transmission during symptomatic episodes alone will not control the epidemic. However, the study found that if the probability of transmission ranged from half to twice its base value, the prevalence in 2000 ranged from 5.76% to 64.35%. Thus, altering the probability of transmission during symptomatic episodes will affect the epidemic to an extent but a reduction in asymptomatic shedding is important.

As the modelled epidemic is sensitive to behavioural parameters, any control programme should incorporate strategies that aim to reduce the rate of partner change and the time spent being non-monogamous. Similarly, reducing the probability of transmission is important. However, because of the importance of asymptomatic shedding, any intervention should be effective during all stages of the genital HSV infection.

**Conclusions**

Once some degree of knowledge of the dynamics of a system is gained, composing a mathematical model allows predictions to be made. These predictions can be useful for healthcare policy and prevention programmes. In developing models, simple ones should be constructed before complex versions, in order to define key variables. Moreover, all complex models should be evaluated against simple models. For each, a variety of treatment evaluation criteria should be defined to help clarify the objectives of an intervention.

The type of analysis applied to the model is critical. Uncertainty analysis of a model of HSV-2 must be performed to test predictions to be made, albeit with a degree of quantifiable error, while sensitivity analysis identifies the most influential variables and can inform strategies for prevention. In any case, results from any scenario analysis should be interpreted with caution, as the results will only have very limited generalizability.

- Models should investigate the effect of anti-HSV treatment on the HIV epidemic (research need recommendation)

Modelling HSV-2 transmission dynamics can provide insights into the behaviour of genital herpes epidemics and the potential impact of medical and behavioural interventions. Four mathematical models of genital herpes epidemics in an immunocompetent population have been developed.

The first model of genital herpes was developed to assess the potential beneficial and detrimental population-level impact of episodic treatment. Analysis of this model revealed that high levels of treatment could substantially reduce the incidence and (over a longer time-scale) the prevalence of HSV-2. Further reductions with high treatment rates, the potential detrimental effects due to the emergence and transmission of drug-resistant strains of HSV-2 would be minimal. More recent elaboration of this model has shown that suppressive therapy may potentially be very effective in reducing herpes epidemics. A scenario analysis of a model that explicitly included short-term suppressive therapy also found that HSV prevalence would be slowly reduced (over a period of decades). However, the generalizability of these particular results for suppressive therapy is limited, as treatment was restricted to those who were newly infected and people could receive suppressive therapy only once.

Modelling analyses have also shown that (as with all sexually transmitted infections) behavioural change can have an impact on the dynamics of HSV transmission. Increasing the time spent in monogamous relationships and decreasing rates of partner change have the potential to reduce the spread of HSV-2. Taken together, the models show that medical and behavioural interventions can substantially affect the epidemiology of HSV-2 infection. As the models identify the key factors and the impact of interventions upon them, they can be used to guide development of rational epidemic control policies.

Given the interaction between HSV-2 and HIV, it is likely to be worthwhile modelling whether or not treating HSV-2 will decrease the HIV epidemic, and also to model the effects of HIV on the HSV-2 epidemic.

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