Analytic characterization of the herpes simplex virus type 2 epidemic in the United States, 1950-2050

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**Key points:** HSV-2 epidemic in the United States underwent a major transition, and has been slowly declining. In addition to 47 million prevalent infections in 2020, high incidence will persist over the next three decades, adding >600,000 new infections every year.

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Abstract

**Background:** We analytically characterized the past, present, and future levels and trends of the national herpes simplex virus type 2 (HSV-2) epidemic in the United States.

**Methods:** A population-level mathematical model was constructed to describe HSV-2 transmission dynamics and was fitted to the data series of the National Health and Nutrition Examination Surveys.

**Results:** Over 1950-2050, antibody prevalence (seroprevalence) increased rapidly from 1960, peaking at 19.9% in 1983 in those aged 15-49, before reversing course to decline to 13.2% by 2020 and 8.5% by 2050. Incidence rate peaked in 1971 at 11.9 per 1,000 person-years, before declining by 59% by 2020 and 70% by 2050. Annual number of new infections peaked at 1,033,000 in 1978, before declining to 667,000 by 2020 and 600,000 by 2050. Women were disproportionately affected, averaging 75% higher seroprevalence, 95% higher incidence rate, and 71% higher annual number of infections. In 2020, 78% of infections were acquired by those 15-34 year-olds.

**Conclusions:** The epidemic has undergone a major transition over a century, with the greatest impact in those 15-34 year-olds. In addition to 47 million prevalent infections in 2020, high incidence will persist over the next three decades, adding >600,000 new infections every year.

**Keywords:** Herpes simplex virus, genital herpes, genital ulcer disease, neonatal herpes, prevalence, incidence, mathematical model
Introduction

Herpes simplex virus type 2 (HSV-2) is a globally prevalent sexually transmitted infection (STI) [1-3] and the most common cause of genital ulcer disease [4]. An estimated 492 million persons had HSV-2 infection in 2016, equivalent to 13.2% of the world’s population aged 15-49 years [5]. Infection is often latent and asymptomatic, but with frequent reactivations and occasional symptomatic episodes causing ulcerative lesions in the genitalia and anus [6, 7]. Infection can cause other clinical disease such as neonatal herpes [8, 9], and its associated stigma can lead to depression [10] and anxiety [10]. HSV-2 infection is considered a principal cofactor in HIV transmission and epidemic growth [11-13], and an effective proxy biomarker for sexual risk behavior and HIV epidemic potential [14-16].

National HSV-2 antibody prevalence (seroprevalence) studies in the United States (US) have been conducted regularly for four decades and suggested a growing but then declining epidemic [17-22]. Despite an improved understanding of seroprevalence, a comprehensive characterization of the epidemic past, present, and future is still lacking. We aimed to fill this gap through mathematical modeling of HSV-2 transmission dynamics over a century, 1950-2050. We assessed the temporal evolution and varying sex and age distributions of seroprevalence, incidence rate, and annual number of new infections. The study aims to inform public health response and ongoing efforts to develop HSV preventive and therapeutic vaccines [23-27]. A major strength of this analysis is the methodological approach allowing rigorous “unraveling” of the epidemic’s history and dynamics, that is “deep-rooted” in ten rounds of quality population-based and sex- and age-stratified data of the National Health and Nutrition Examination Surveys (NHANES) conducted in the US [28].
Materials and methods

Mathematical model

A deterministic compartmental model was developed to describe HSV-2 transmission in the US. Model equations and a schematic diagram describing the model are found in the Supplementary Material (SM) text and in SM Fig. S1, respectively. The model was based on extension and adaptation of earlier models [11, 27, 29-31] and consisted of coupled nonlinear differential equations that stratify the US population into compartments according to infection status and stage, sex, age, and sexual behavior. To reduce complexity, the model did not explicitly distinguish between different forms of sexual transmission.

HSV-2 natural history was divided into three stages: primary infection, latent infection, and infection reactivation (SM Fig. S1). Persons who acquired HSV-2 for the first time developed primary infection followed by latent infection and reactivations. Those with latent infection episodically reactivated their infection, symptomatically or asymptptomatically, and shed the virus during reactivation.

The model categorized the population into 5-year age groups. To account for heterogeneity in exposure risk/sexual risk behavior, the model further incorporated five sexual risk groups based on data of the age-dependent number of sexual partners over the last 12 months [28]. Distribution of risk of infection exposure across risk groups followed a power-law function informed by network and modeling analyses [32-36].

Sexual mixing between age groups and risk groups ranged from fully assortative (choosing partners from own age or risk group) to proportionate (no preferential bias in choosing partners) [37-39]. Force of infection was expressed in terms of sexual-partner acquisition rate, HSV-2 transmission probability per sexual act and per partnership, and mixing among
age and risk groups. Temporal variation in the sexual-partner acquisition rate was incorporated to generate the observed historical patterns of infection.

A detailed description of the model is available in the SM. Analyses were conducted in MATLAB R2019a [40].

**Model parametrization**

The model was parametrized using current data for HSV-2 natural history and epidemiology. We used seroprevalence data from ten rounds of the nationally-representative population-based NHANES surveys (1988-2016) that followed standardized analytical and laboratory procedures [28]. Testing for glycoprotein specific to HSV-2 (designated gG-2) in sera was implemented using solid-phase enzymatic type-specific immunodot assays [28]. The 1976-1980 round used different procedures and was included only in a sensitivity analysis.

NHANES standardized “survey methods and analytic guidelines” [41] were applied in extracting and analyzing demographic, sexual, and seroprevalence data including the 5-year seroprevalence age distribution and reported number of sexual partners in the last 12 months (0 partner, 1 partner, 2 partners, 3 partners, or ≥4 partners), in men and women, along with associated 95% confidence intervals (CIs) [28].

US demographics and trends (SM Fig. S2) were obtained from the United Nations’ World Population Prospects database [42].

Model parameter values and justifications are in SM Table S1.
Model fitting

The model was fitted to NHANES sex-specific, age-specific, and total seroprevalence time-series data for those 15-49 years old [28]. Data fitting was implemented using a non-linear least-square fitting approach, as per previous work [31, 38, 39, 43, 44]. Overall risk of exposure varied with time until a best fit of trend data was reached. Model fitting details are in SM.

Uncertainty and sensitivity analyses

We implemented 500 model runs applying Latin hypercube sampling from a multidimensional distribution of model parameters (SM Table S1)—assuming ±40% uncertainty around parameters’ point estimates, as informed by earlier work [31, 39, 45-47]. In each run, parameters’ values were randomly selected from their specified ranges, and the model was refitted to data. Means and 95% uncertainty intervals (UIs) were derived from resulting distributions for each predicted model outcome.

A sensitivity analysis was conducted to assess impact on model predictions of including a 5-year age gap in sexual partnering between men and women. A second sensitivity analysis assessed impact of including the 1976-1980 NHANES round in model fitting.

Results

The model produced robust fits to HSV-2 seroprevalence of the ten NHANES rounds (Figs. 1-3), and to the US demographics (SM Fig. S2). However, compared to the 1988-1994 NHANES round, the model tended to slightly overestimate the seroprevalence among women 45-64 years old, and to underestimate the seroprevalence among men 30-39 and 75-79 years old. Fig. 3 shows the model-predicted historical and future evolution of seroprevalence in those 15-49 years old in comparison to NHANES rounds. In women and
men, seroprevalence increased progressively from 1950 through early 1980s, but then declined year by year; a decline projected to continue (but slowly) for the next three decades (Fig. 3A). In women, seroprevalence was 19.9% in 1960, increased to 23.6% by 1970, peaked at 25.9% in 1984, but declined to 16.9% by 2020 and 10.5% by 2050. In men, seroprevalence was 11.6% in 1960, increased to 13.3% by 1970, peaked at 14.2% in 1983, but declined to 9.6% by 2020 and 6.5% by 2050. Seroprevalence was ~75% higher in women than men throughout 1950-2050.

In the total (women and men) 15-49 year-old population, seroprevalence was 15.7% in 1960, increased to 18.4% by 1970, peaked at 19.9% in 1983, but declined to 13.2% by 2020 and 8.5% by 2050 (Fig. 3B). Between 1950-1983, seroprevalence increased by 58%, but then declined by 34% between 1983-2020, and by 57% by 2050. Similar trends were found in those aged ≥15 years (SM Fig. S3).

Fig. 4 shows evolution of incidence rate in the 15-49 year-old population. In women and men, incidence rate peaked around 1970 and declined thereafter, with the decline accelerating between 1980-2010 (Fig. 4A). In women, at peak in 1972, incidence rate was 16.8 per 1,000 person-years, but declined by 62% to 6.4 in 2020, and by 74% to 4.4 in 2050. In men, at peak in 1969, incidence rate was 7.8 per 1,000 person-years, but declined by 55% to 3.5 in 2020, and by 65% to 2.7 in 2050. In the total 15-49 year-old population, at peak in 1971, incidence rate was 11.9 per 1,000 person-years, but declined by 59% to 4.9 in 2020, and by 70% to 3.5 in 2050 (Fig. 4B). Similar trends were found in those aged ≥15 years (SM Fig. S4).

Fig. 5 shows annual number of new infections (absolute incidence). In women and men, incidence increased progressively from 1950 through late 1970s, but then declined year by year, with the decline accelerating between 1980-2010 (Fig. 5A). In women, at peak in 1979, there were 649,000 new infections, but declined to 402,000 by 2020, and was projected to
decline to 347,000 by 2050. In men, at peak in 1978, there were 353,000 new infections, but declined to 245,000 by 2020 and 231,000 by 2050.

In the total 15-49 year-old population, at peak in 1978, there were 1,002,000 new infections, but declined to 647,000 by 2020 and 578,000 by 2050 (Fig. 5B). A similar pattern was observed in the total population aged ≥15 years (SM Fig. S5). At peak in 1978, there were 1,033,000 new infections, but declined to 667,000 by 2020 and 600,000 by 2050. The cumulative number of ever infected individuals since 1950 was 17,227,000 by 1970, 27,179,000 by 1980, 60,502,000 by 2020, and 78,384,000 by 2050.

Figs. 6 and 7 show the temporal evolution of seroprevalence and incidence rate, respectively, in the different age groups, indicating a “youth cohort” phenomenon in those aged 15-34 years sometime between 1960 and mid-1980s. Risk of infection (equivalent to incidence rate) soared in this age bracket at this time due to infection seeding within this age group (Fig. 7). In 1970, incidence rate (per 1,000 person-years) among 20-24 year-olds was 24.2 in women and 12.7 in men, but in 2020, it was only 9.2 in women and 5.7 in men.

A distinctive mark of this cohort effect is that seroprevalence between 1960-1990 was higher in mid-age than in older adults (Fig. 6)—persons in this “youth cohort” aggregated in three-decade time-span more cumulative risk of infection than older adults aggregated over their lifetime. However, by 2020 and thereafter, seroprevalence increased monotonically with age, as expected for a “typical” HSV-2 epidemiology.

Fig. 7 illustrates the consistency in the age-specific pattern of incidence rate over time. Throughout 1950-2050, incidence rate increased rapidly following sexual debut, reached its maximum among 20-24 year-olds, remained rather stable for the 25-34 year-olds, and declined rapidly among those aged ≥35 years. For instance, in 2020, 78% of total infections were acquired by those aged 15-34 years. As for seroprevalence, other than the “youth
cohort” generation, it increased steadily with age, most rapidly for 15-34 year-olds (Fig. 6), reflecting the incidence rate pattern (Fig. 7).

SM Fig. S6 shows results of the uncertainty analysis for the temporal evolution of seroprevalence, incidence rate, and annual number of new infections. The analysis affirmed above findings.

SM Fig. S7 shows results of the sensitivity analysis including a 5-year age gap in sexual partnering between men and women. Predictions were affirmed but with slight quantitative differences; incidence rate for women and men peaked in mid-1970s instead of early 1970s, and peaked in those aged 25-29 years instead of those aged 20-24 years. The sensitivity analysis forcing inclusion of the 1976-1980 NHANES round in model fitting produced inferior fitting metrics (SM Fig. S8), and spurious predictions that contradicted available evidence (note discussion below).

Discussion

Results indicate an evolving epidemiology (rapidly at times) for HSV-2 infection in the US. Current infection pattern implicitly reflects two distinct experiences of two generations. The epidemic expanded after World War II and accelerated post-1960 (Fig. 5). For those aged 15-34 years sometime between 1960 and mid-1980s, a time often associated with the “sexual revolution” and discovery of the “pill” [48, 49], risk of infection was high leading to high incidence and seroprevalence for this specific (“youth cohort”) generation (Figs. 3-7). At peak incidence in late 1970s, one million infections occurred every year, nearly two-thirds of which were among women.

Nonetheless, by mid-1980s, notably when HIV/AIDS was first recognized [50], risk of infection went into a steep decline for three decades, before settling into a slowly declining
pattern at present (Fig. 4). Even though the US population expanded substantially since 1980s (SM Fig. S2), the rapid decline in incidence rate more than compensated the larger influx of new susceptibles—there were only 667,000 new infections in 2020, two-thirds of the number of infections in 1978 at the epidemic peak (Fig. 5 and SM Fig. S5).

Commercial tests discriminating HSV-2 from HSV-1 antibodies became widely available only in the 1990s. By 1999-2001, a number of tests were approved by the US Food and Drug Administration [51, 52], and seroprevalence measures began to proliferate in the literature. Early measures identified high levels of ~20% in the general population [1], leading to alarming projections for epidemic expansion [53, 54] that never materialized. To the contrary, repeated NHANES rounds have shown declining seroprevalence (Fig. 3) [19-22, 28]. Our findings indicate that seroprevalence measures from that earlier era largely reflected the demographic contribution of the high-incidence “youth cohort” generation, whereas subsequent seroprevalence measures increasingly reflected the contribution of the low-incidence younger cohorts—earlier projections [53, 54] erred for not recognizing the implied and distinct dynamics of the two generations. As the demographic contribution of the “youth cohort” generation faded by 2010, HSV-2 epidemiology settled into a somewhat stable seroprevalence, a pattern (based on current trends) that is projected to continue for the next three decades (Fig. 3).

A highlight of the above results is the subtle role of sexual behavior change in driving the epidemiology. A change in population sexual behavior, whether it is a change in the sexual partnering rates and/or structure of the sexual networks, translates first into a change in incidence rate, then absolute incidence, and lastly seroprevalence (Figs. 3-5)—seroprevalence pattern at a given point in time is a delayed manifestation of behavior change two decades earlier. Therefore, emphasis on examining trends based only on observed seroprevalence is
inadequate and will miss opportunities for prevention at the right time. There should be more emphasis on assessing trends of incidence rate of HSV-2 infection and its disease sequelae to be able to capture changes in sexual behavior patterns at the right time and address them with appropriate interventions.

Despite the major epidemic transition over the last few decades, HSV-2 epidemiology appears to be stabilizing with key features (Figs. 3-7). Incidence will persist at >600,000 new infections every year (Fig. 5)—a total of 18 million new infections will be added to the population by 2050, in addition to the currently prevalent 47 million infections. Seroprevalence will remain >10% among women and >6% among men. Incidence rate (per 1,000 person-years) will hover around 5 for women and 3 for men (Fig. 4). Women will continue to be disproportionately affected. Those 20-34 years of age will endure the highest incidence rate and absolute incidence with about three-quarters of infections occurring among them. Of note that these estimates assume continuation of current trends in population sexual behavior over the coming three decades. Increases in population sexual behavior in the future will drive even higher incidence. This demonstrates how tenuous is HSV-2 control and supports the need for interventions that can tackle infection acquisition and transmission.

At present, there is no national program specific for genital herpes prevention and control given lack of a prevention modality, such as a vaccine [20, 55]. Our findings demonstrate the need for prophylactic and therapeutic vaccines, a current focus of ongoing international effort spearheaded by the World Health Organization [56-58]. Several vaccine candidates are already in phase I and II trials [56, 59]. An example is a therapeutic candidate that demonstrated sustainable reductions in shedding and lesions over 12 months, with no serious adverse events [23, 56, 59]. While available prevention modalities, such as condoms and antiviral therapy, are insufficient to control infection spread, vaccination is perhaps the only feasible strategic approach to control transmission and to curb the clinical, psychosexual, and
economic burden of this infection [26, 60]. A recent modeling study assessed the impact of both HSV-2 prophylactic and therapeutic vaccination in the US [26]. The study showed that a therapeutic vaccine of intermediate efficacy can reduce HSV-2 incidence by >10% and avert 76,000 infections per year. Meanwhile, a prophylactic vaccine of intermediate efficacy can reduce HSV-2 incidence by >50% and avert >350,000 infections per year. The impact of these vaccines was found to be optimal by prioritizing them to young adults and those at higher risk of infection.

The predicted epidemic evolution and declines in seroprevalence are in concordance with the historical pattern of genital herpes diagnosis [61] and statistical analyses of NHANES rounds [19-22]. Our results are, however, inconsistent with the seroprevalence of the 1976-1980 NHANES round (SM Figs. S9 and S10) [17], and a trend analysis using this round to report increasing seroprevalence, particularly among youth, between the 1976-1980 and 1988-1994 rounds [18]. Despite using different analytical approaches and sensitivity analyses (such as in SM Fig. S8), we could not produce the 1976-1980 round seroprevalence, though the model fitted robustly and consistently all other ten rounds (Figs. 1-3).

While earlier modeling studies, with input data including only the 1976-1980 and 1988-1994 rounds, projected increasing seroprevalence over time [53, 54], these projections contradicted what actually occurred (Fig. 3) [19-22]. It seems implausible that sexual risk behavior underwent sudden transient surge during mid-to-late 1980s and early 1990s to drive higher incidence, exactly when it was expected to decline considering recognition of HIV/AIDS [50], launch of national prevention programs with focus on youth [62], doubling of condom use [63], and declines in HIV [64] and STI incidence [65, 66]. These lines of evidence suggest that the reported 1976-1980 round seroprevalence underestimated actual seroprevalence, particularly among youth, and by as much as 30% (SM Fig. S10). While this
discrepancy remains unresolved, there was a change in the serological testing protocol between the 1976-1980 round and subsequent rounds [17, 18]. For NHANES 1976-1980, a non-type-specific enzyme-linked immunoassay was applied prior to testing positive specimens with a type-specific HSV-2 test [17, 67-69]. It could be that persons with low antibody titers or recent infection evaded infection detection [17, 70, 71]. Conversely, in subsequent rounds, seropositivity was directly tested for using a type-specific immunodot assay [18]. It remains unknown whether differences in sampling weights, or in response rate and survey adjustments, may also contributed to this discrepancy [17, 18, 72]. This discrepancy argues for reexamination of stored sera of that round, or other stored sera from that era, and testing it using current gold standard methods to clarify actual seroprevalence.

Limitations may have affected this study. Model projections are conditioned on quality of input data. Future projections were generated by fitting the model to past and current data which may not hold as sexual behavior could change from one generation to another. These projections could also be influenced by factors that are difficult to predict at present, such as roll-out of interventions/vaccines. HSV-2 shedding was assumed to continue at a fixed frequency, but evidence suggests shedding declines with time [73]. HSV-2 infectiousness was assumed invariable despite symptoms, but this is probably of limited impact as most shedding is asymptomatic [4, 7, 74]. We did not investigate implications on disease outcomes such as genital ulcer disease and neonatal herpes, nor impact on the HIV epidemic given the exiting evidence supporting synergy between HIV and HSV-2 infections [11-16]. However, the present model provides a framework that could be extended to investigate and estimate HSV-2 disease burden and impact on the HIV epidemic.

This study has strengths. We used an elaborate yet minimalist model to capture the complex transmission dynamics. This is (to our knowledge) the first such study to analytically model
the intricate epidemiology of this infection and its transition over a century, at a level of
detail not amenable to empirical studies. Model outcomes fitted data robustly with predicted
trends matching actual trends. The model was anchored on quality data for HSV-2 natural
history and transmission. Importantly, the model was grounded on over three decades of
standardized and nationally-representative population-based NHANES data [28].
Remarkably, with such rigorous and large-scale data input, model predictions were well-
constrained, limiting uncertainty around predictions, despite assuming wide uncertainty
intervals for the model parameters (SM Fig. S6). Findings were also affirmed by the
sensitivity analyses.

In conclusion, the US HSV-2 epidemic underwent a major transition over a century, leading
to two distinct experiences for two generations. From 1950 to mid-1980s, the epidemic
expanded massively to add thirty million new infections and to affect nearly a quarter of the
US population. From mid-1980s, however, the epidemic reversed course with rapid declines,
followed by stabilization that is projected to continue over the next three decades. Despite
epidemic decline, incidence will persist at >600,000 infections every year, adding close to 20
million new infections by 2050. These findings highlight the scale of HSV-2 burden in the
US and demonstrate the need for continuous surveillance and criticality of development of
HSV-2 vaccines.
Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Patient Consent Statement

The study does not include factors necessitating patient consent.

Availability of data and materials

Data and results are available in the cited literature, main manuscript, and supplementary material. The model computer codes programmed in MATLAB can be obtained by contacting the authors.

Potential Conflicts of Interest

The authors declare that they have no competing interests.

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Authors’ contributions

HHA and IA designed, coded, and parametrized the mathematical model, conducted the analyses, and wrote the first draft of the article. SFA and RO contributed to the modeling analyses. HC supported the model parameterization, conducted statistical analyses, and participated in the drafting of the article. LJA conceived and led the design of the study and model, analyses, and drafting of the article. All authors have read and approved the final article.

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Fig. 1. **Fitting of the age-specific distribution of HSV-2 seroprevalence among women in the United States.** The fitted HSV-2 seroprevalence in each five-year age band, compared to the National Health and Nutrition Examination Surveys (NHANES) data from 1988 up to 2016.

Fig. 2. **Fitting of the age-specific distribution of HSV-2 seroprevalence among men in the United States.** The fitted HSV-2 seroprevalence in each five-year age band, compared to the National Health and Nutrition Examination Surveys (NHANES) data from 1988 up to 2016.

Fig. 3. **Temporal evolution of HSV-2 seroprevalence in the United States.** A) Estimated HSV-2 seroprevalence for women and men aged between 15-49 years, compared to the National Health and Nutrition Examination Surveys (NHANES) data. B) Estimated HSV-2 seroprevalence in the total population aged between 15-49 years, compared NHANES data.

Fig. 4. **Temporal evolution of HSV-2 incidence rate in the United States.** A) Estimated HSV-2 incidence rate for women and men aged between 15-49 years. B) Estimated HSV-2 incidence rate in the total population aged between 15-49 years.

Fig. 5. **Temporal evolution of new HSV-2 infections in the United States.** A) Estimated annual number of new HSV-2 infections for women and men aged between 15-49 years. B) Estimated annual number of new HSV-2 infections in the total population aged between 15-49 years.

Fig. 6. **Age-specific distribution of HSV-2 seroprevalence in the United States.** A) Estimated age-specific distribution of HSV-2 seroprevalence among women in 1960, 1970, 1980, 1990, 2020, and 2050. B) Estimated age-specific distribution of HSV-2 seroprevalence among men in 1960, 1970, 1980, 1990, 2020, and 2050.

Fig. 7. **Age-specific distribution of HSV-2 incidence rate in the United States.** A) Estimated age-specific distribution of HSV-2 incidence rate among women in 1960, 1970, 1980, 1990, 2020, and 2050. B) Estimated age-specific distribution of HSV-2 incidence rate among men in 1960, 1970, 1980, 1990, 2020, and 2050.
References

1. Smith JS, Robinson NJ. Age-specific prevalence of infection with herpes simplex virus types 2 and 1: a global review. J Infect Dis 2002; 186 Suppl 1:S3-28.
2. Weiss H. Epidemiology of herpes simplex virus type 2 infection in the developing world. Herpes 2004; 11 Suppl 1:24A-35A.
3. Looker KJ, Magaret AS, Turner KM, Vickerman P, Gottlieb SL, Newman LM. Global estimates of prevalent and incident herpes simplex virus type 2 infections in 2012. PLoS One 2015; 10:e114989.
4. Tronstein E, Johnston C, Huang ML, et al. Genital shedding of herpes simplex virus among symptomatic and asymptomatic persons with HSV-2 infection. JAMA 2011; 305:1441-9.
5. James C, Harfouche M, Welton NJ, et al. Herpes simplex virus: global infection prevalence and incidence estimates, 2016. Bull World Health Organ 2020; 98:315-29.
6. Nahmias AJ, Dowdle WR, Naib ZM, Josey WE, McLone D, Domescik G. Genital infection with type 2 Herpes virus hominis. A commonly occurring venereal disease. Br J Vener Dis 1969; 45:294-8.
7. Mark KE, Wald A, Magaret AS, et al. Rapidly cleared episodes of herpes simplex virus reactivation in immunocompetent adults. J Infect Dis 2008; 198:1141-9.
8. James SH, Kimberlin DW. Neonatal Herpes Simplex Virus Infection. Infect Dis Clin North Am 2015; 29:391-400.
9. Looker KJ, Magaret AS, May MT, et al. First estimates of the global and regional incidence of neonatal herpes infection. Lancet Glob Health 2017; 5:e300-e9.
10. Mindel A, Marks C. Psychological symptoms associated with genital herpes virus infections: epidemiology and approaches to management. CNS Drugs 2005; 19:303-12.
11. Abu-Raddad LJ, Magaret AS, Celum C, et al. Genital herpes has played a more important role than any other sexually transmitted infection in driving HIV prevalence in Africa. PLoS One 2008; 3:e2230.
12. Looker KJ, Elmes JAR, Gottlieb SL, et al. Effect of HSV-2 infection on subsequent HIV acquisition: an updated systematic review and meta-analysis. Lancet Infect Dis 2017; 17:1303-16.
13. Looker KJ, Welton NJ, Sabih KM, et al. Global and regional estimates of the contribution of herpes simplex virus type 2 infection to HIV incidence: a population attributable fraction analysis using published epidemiological data. Lancet Infect Dis 2020; 20:240-9.
14. Omori R, Abu-Raddad LJ. Sexual network drivers of HIV and herpes simplex virus type 2 transmission. AIDS 2017; 31:1721-32.
15. Kouvoumjian SP, Heijnen M, Chaabna K, et al. Global population-level association between herpes simplex virus 2 prevalence and HIV prevalence. AIDS 2018; 32:1343-52.
16. Abu-Raddad LJ, Schiffer JT, Ashley R, et al. HSV-2 serology can be predictive of HIV epidemic potential and hidden sexual risk behavior in the Middle East and North Africa. Epidemics 2010; 2:173-82.
17. Johnson RE, Nahmias AJ, Magder LS, Lee FK, Brooks CA, Snowden CB. A seroepidemiologic survey of the prevalence of herpes simplex virus type 2 infection in the United States. N Engl J Med 1989; 321:7-12.
18. Fleming DT, McQuillan GM, Johnson RE, et al. Herpes simplex virus type 2 in the United States, 1976 to 1994. N Engl J Med 1997; 337:1105-11.
19. Xu F, Sternberg MR, Kottiri BJ, et al. Trends in herpes simplex virus type 1 and type 2 seroprevalence in the United States. JAMA 2006; 296:964-73.
20. Fanfair RN, Zaidi A, Taylor LD, Xu F, Gottlieb S, Markowitz L. Trends in seroprevalence of herpes simplex virus type 2 among non-Hispanic blacks and non-Hispanic whites aged 14 to 49 years--United States, 1988 to 2010. Sex Transm Dis 2013; 40:860-4.
21. McQuillan G, Kruszon-Moran D, Flagg EW, Paulose-Ram R. Prevalence of Herpes Simplex Virus Type 1 and Type 2 in Persons Aged 14-49: United States, 2015-2016. NCHS Data Brief 2018;1-8.
22. Chemaitelly H, Nagelkerke N, Omori R, Abu-Raddad LJ. Characterizing herpes simplex virus type 1 and type 2 seroprevalence declines and epidemiological association in the United States. PLoS One 2019; 14:e0214151.

23. Gottlieb SL, Giersing BK, Hickling J, et al. Meeting report: Initial World Health Organization consultation on herpes simplex virus (HSV) vaccine preferred product characteristics, March 2017. Vaccine 2019; 37:7408-18.

24. Johnston C, Koelle DM, Wald A. Current status and prospects for development of an HSV vaccine. Vaccine 2014; 32:1553-60.

25. Sandgren KJ, Truong NR, Smith JB, Bertram K, Cunningham AL. Vaccines for Herpes Simplex: Recent Progress Driven by Viral and Adjuvant Immunology. Methods Mol Biol 2020; 2060:31-56.

26. Ayoub HH, Chemaitelly H, Abu-Raddad LJ. Epidemiological Impact of Novel Preventive and Therapeutic HSV-2 Vaccination in the United States: Mathematical Modeling Analyses. Vaccines 2020; 8.

27. Alsallaq RA, Schiffer JT, Longini IM, Jr., Wald A, Corey L, Abu-Raddad LJ. Population level impact of an imperfect prophylactic vaccine for herpes simplex virus-2. Sex Transm Dis 2010; 37:290-7.

28. NHANES. National Health and Nutrition Examination Survey: http://www.cdc.gov/nchs/nhanes/nhanes_questionnaires.htm, 1976-2016.

29. Abu-Raddad LJ, Longini IM, Jr. No HIV stage is dominant in driving the HIV epidemic in sub-Saharan Africa. AIDS 2008; 22:1055-61.

30. Abu-Raddad LJ, Patnaik P, Kublin JG. Dual infection with HIV and malaria fuels the spread of both diseases in sub-Saharan Africa. Science 2006; 314:1603-6.

31. Ayoub HH, Chemaitelly H, Abu-Raddad LJ. Characterizing the transitioning epidemiology of herpes simplex virus type 1 in the USA: model-based predictions. BMC medicine 2019; 17:57.

32. Watts CH, May RM. The influence of concurrent partnerships on the dynamics of HIV/AIDS. Math Biosci 1992; 108:89-104.

33. Watts DJ, Strogatz SH. Collective dynamics of ‘small-world’networks. nature 1998; 393:440.

34. Barthelemy M, Pastor-Satorras R, Vespignani A. The architecture of complex weighted networks. Proc Natl Acad Sci U S A 2004; 101:3747-52.

35. Boccaletti S, Latora V, Moreno Y, Chavez M, Hwang D. Complex Networks: Structure and Dynamics Physics Reports, Vol. 424, 2006.

36. Barthelemy M, Pastor-Satorras R, Vespignani A. The architecture of complex weighted networks. Proc Natl Acad Sci U S A 2004; 101:3747-52.

37. Garnett GP, Anderson RM. Balancing sexual partnerships in an age and activity stratified model of HIV transmission in heterosexual populations. IMA J Math Appl Med Biol 1994; 11:161-92.

38. Awad SF, Abu-Raddad LJ. Could there have been substantial declines in sexual risk behavior across sub-Saharan Africa in the mid-1990s? Epidemics 2014; 8:9-17.

39. Awad SF, Sgaier SK, Tambatamba BC, et al. Investigating voluntary medical male circumcision program efficiency gains through subpopulation prioritization: insights from application to Zambia. PloS One 2015; 10:e0145729.

40. MATLAB®. The Language of Technical Computing. The MathWorks, Inc. 2019.

41. Centers for Disease Control and Prevention. Survey Methods and Analytic Guidelines.: https://www.cdc.gov/nchs/nhanes/analyticguidelines.aspx, 2016.

42. United Nations Department of Economic and Social Affairs. World Population Prospects, the 2015 Revision, 2015.

43. Lagarias JC, Reeds JA, Wright MH, Wright PE. Convergence properties of the Nelder-Mead simplex method in low dimensions. Siam Journal on Optimization 1998; 9:112-47.

44. Ayoub HH, Al Kanaani Z, Abu-Raddad LJ. Characterizing the temporal evolution of the hepatitis C virus epidemic in Pakistan. J Viral Hepat 2018; 25:670-9.

45. Chemaitelly H, Awad SF, Abu-Raddad LJ. The risk of HIV transmission within HIV-1 sero-discordant couples appears to vary across sub-Saharan Africa. Epidemics 2014; 6:1-9.
46. Chemaitelly H, Awad SF, Shelton JD, Abu-Raddad LJ. Sources of HIV incidence among stable couples in sub-Saharan Africa. Journal of the International AIDS Society 2014; 17:18765.
47. Ayoub H, Abu‐Raddad LJ. Impact of treatment on hepatitis C virus transmission and incidence in Egypt: A case for treatment as prevention. Journal of viral hepatitis 2017; 24:486-95.
48. Allyn D. Make love, not war: the sexual revolution: an unfettered history. routledge, 2016.
49. Chadwick KD, Burkman RT, Tornesi BM, Mahadevan B. Fifty years of “the pill”: risk reduction and discovery of benefits beyond contraception, reflections, and forecast. Toxicol Sci 2012; 125:2-9.
50. Greene WC. A history of AIDS: looking back to see ahead. Eur J Immunol 2007; 37 Suppl 1:S94-102.
51. Wald A, Ashley-Morrow R. Serological testing for herpes simplex virus (HSV)-1 and HSV-2 infection. Clin Infect Dis 2002; 35:S173-82.
52. Ashley RL. Performance and use of HSV type‐specific serology test kits. Herpes 2002; 9:38-45.
53. Fisman DN, Lipsitch M, Hook EW, 3rd, Goldie SJ. Projection of the future dimensions and costs of the genital herpes simplex type 2 epidemic in the United States. Sex Transm Dis 2002; 29:608-22.
54. Armstrong GL, Schillinger J, Markowitz L, et al. Incidence of herpes simplex virus type 2 infection in the United States. Am J Epidemiol 2001; 153:912-20.
55. Douglas JM, Jr., Berman SM. Screening for HSV-2 infection in STD clinics and beyond: a few answers but more questions. Sex Transm Dis 2009; 36:729-31.
56. World Health Organization. World Health Organization preferred product characteristics for herpes 2 simplex virus vaccines. https://www.who.int/immunization/research/ppc-tppp/HSV_Vaccine_PPCs_for_Public_Comment.pdf. Accessed on: February 3, 2020. 2019.
57. Gottlieb SL, Giersing B, Boily MC, et al. Modelling efforts needed to advance herpes simplex virus (HSV) vaccine development: Key findings from the World Health Organization Consultation on HSV Vaccine Impact Modelling. Vaccine 2017.
58. Gottlieb SL, Deal CD, Giersing B, et al. The global roadmap for advancing development of vaccines against sexually transmitted infections: Update and next steps. Vaccine 2016; 34:2939-47.
59. Johnston C, Gottlieb SL, Wald A. Status of vaccine research and development of vaccines for herpes simplex virus. Vaccine 2016; 34:2948-52.
60. Giersing BK, Vekemans J, Nava S, Kaslow DC, Moorthy V, Committee WHOPDIVA. Report from the World Health Organization’s third Product Development for Vaccines Advisory Committee (PDVAC) meeting, Geneva, 8-10th June 2016. Vaccine 2019; 37:7315-27.
61. Becker TM, Blount JH, Guinan ME. Genital herpes infections in private practice in the United States, 1966 to 1981. JAMA 1985; 253:1601-3.
62. Ku LC, Sonenstein FL, Pleck JH. The association of AIDS education and sex education with sexual behavior and condom use among teenage men. Fam Plann Perspect 1992; 24:100-6.
63. Sonenstein FL, Pleck JH, Ku LC. Sexual activity, condom use and AIDS awareness among adolescent males. Fam Plann Perspect 1989; 21:152-8.
64. Rosenberg PS, Biggar RJ. Trends in HIV incidence among young adults in the United States. JAMA 1998; 279:1894-9.
65. Centers for Disease C, Prevention. Summary of notifiable diseases, United States, 1997. MMWR Morb Mortal Wkly Rep 1998; 46:ii-vii, 3-87.
66. Groseclose SL, Zaidi AA, DeLisle SJ, Levine WC, St Louis ME. Estimated incidence and prevalence of genital Chlamydia trachomatis infections in the United States, 1996. Sex Transm Dis 1999; 26:339-44.
67. Lee FK, Coleman RM, Pereira L, Bailey PD, Tatsuno M, Nahmias AJ. Detection of herpes simplex virus type 2-specific antibody with glycoprotein G. J Clin Microbiol 1985; 22:641-4.
68. Lee FK, Pereira L, Griffin C, Reid E, Nahmias A. A novel glycoprotein for detection of herpes simplex virus type 1-specific antibodies. J Virol Methods 1986; 14:111-8.
69. Coleman RM, Pereira L, Bailey PD, Dondero D, Wickliffe C, Nahmias AJ. Determination of herpes simplex virus type-specific antibodies by enzyme-linked immunosorbent assay. J Clin Microbiol 1983; 18:287-91.
70. Ashley RL, Militoni J, Lee F, Nahmias A, Corey L. Comparison of Western blot (immunoblot) and glycoprotein G-specific immunodot enzyme assay for detecting antibodies to herpes simplex virus types 1 and 2 in human sera. J Clin Microbiol 1988; 26:662-7.
71. Nahmias AJ, Lee FK, Pereira L, Reid E, Wickliffe C. Monoclonal antibody immunoaffinity purified glycoproteins for the detection of herpes simplex virus type 1 and type 2 specific antibodies in serum. Human herpesvirus infections Raven Press, New York 1986:203-9.
72. Forthofer RN. Investigation of nonresponse bias in NHANES II. Am J Epidemiol 1983; 117:507-15.
73. Ramchandani M, Selke S, Magaret A, et al. Prospective cohort study showing persistent HSV-2 shedding in women with genital herpes 2 years after acquisition. Sex Transm Infect 2018; 94:568-70.
74. Gnann JW, Jr., Whitley RJ. Genital Herpes. New England Journal of Medicine 2016; 375:666-74.
Figure 2

[Graphs showing trends over different years (1988-1994, 1999-2008, 2001-2002, 2003-2004, 2005-2006, 2007-2008, 2009-2010, 2011-2012, 2013-2014, 2015-2016). Each graph compares HbA1c and body mass index (BMI) across age groups (20-24, 45-49, 70-74, 95-99). NHANES data and model prediction are indicated.]
Figure 3

(A) HSV-2 seroprevalence among women and men aged 15-49 years.

(B) HSV-2 seroprevalence among all individuals aged 15-49 years.

- NHANES data for women
- Model prediction for women
- NHANES data for men
- Model prediction for men

Year: 1950, 1960, 1970, 1980, 1990, 2000, 2010, 2020, 2030, 2040, 2050
Figure 4

(A) HSV-2 incidence rate among women and men aged 15-49 years per 1000 person-years.

(B) HSV-2 incidence rate among all individuals aged 15-49 years per 1000 person-years.

Model prediction for women
Model prediction for men
Figure 5

(A) Annual number of new HSV-2 infections among women and men aged 15-49 years

(B) Annual number of new HSV-2 infections among all individuals aged 15-49 years
Figure 7

(A) Women

 HSV2 Incidence rate (per 1000 person-years)

Age group

15-19 20-24 25-29 30-34 35-39 40-44 45-49 50-54 55-59 60-64 65-69 70-74 75-79

(B) Men

 HSV2 Incidence rate (per 1000 person-years)

Age group

15-19 20-24 25-29 30-34 35-39 40-44 45-49 50-54 55-59 60-64 65-69 70-74 75-79

Colors represent different years: 1980, 1970, 1980-2000, 2010-2020, 2020-2050.