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Analytic Characterization of the Herpes Simplex Virus Type 2 Epidemic in the United States, 1950–2050

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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 Survey.

Results. Over 1950–2050, antibody prevalence (seroprevalence) increased rapidly from 1960, peaking at 19.9% in 1983 in those aged 15–49 years, before reversing course to decline to 13.2% by 2020 and 8.5% by 2050. Incidence rate peaked in 1971 at 11.9 per 1000 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 years of age.

Conclusions. The epidemic has undergone a major transition over a century, with the greatest impact in those 15–34 years of age. In addition to 47 million prevalent infections in 2020, high incidence will persist over the next 3 decades, adding >600 000 new infections every year.

Keywords. genital herpes; genital ulcer disease; herpes simplex virus; HSV-2; incidence; mathematical model; neonatal herpes; prevalence.

Herpes simplex virus type 2 (HSV-2) is a globally prevalent sexually transmitted infection [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 human immunodeficiency virus (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 4 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 10 rounds of quality population-based and sex- and age-stratified data of the National Health and Nutrition Examination Survey (NHANES) conducted in the US [28].

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

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Supplementary Text and Supplementary Figure 1, 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 3 stages: primary infection, latent infection, and infection reactivation (Supplementary Figure 1). 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 asymptomatically, 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 5 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 Supplementary Materials. Analyses were conducted in MATLAB R2019a [40].

Model Parameterization

The model was parameterized using current data for HSV-2 natural history and epidemiology. We used seroprevalence data from 10 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, 1, 2, 3, or ≥4 partners), in men and women, along with associated 95% confidence intervals [28].

US demographics and trends (Supplementary Figure 2) were obtained from the United Nations World Population Prospects database [42].

Model parameter values and justifications are shown in Supplementary Table 1.

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 nonlinear least-squares 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 shown in the Supplementary Materials.

Uncertainty and Sensitivity Analyses

We implemented 500 model runs applying Latin hypercube sampling from a multidimensional distribution of model parameters (Supplementary Table 1)—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 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 10 NHANES rounds (Figures 1–3), and to US demographics (Supplementary Figure 2). 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 aged 30–39 and 75–79 years. Figure 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 the early 1980s, but then declined year by year, a decline projected to continue (but slowly) for the next 3 decades (Figure 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 approximately 75% higher in women than men throughout 1950–2050.

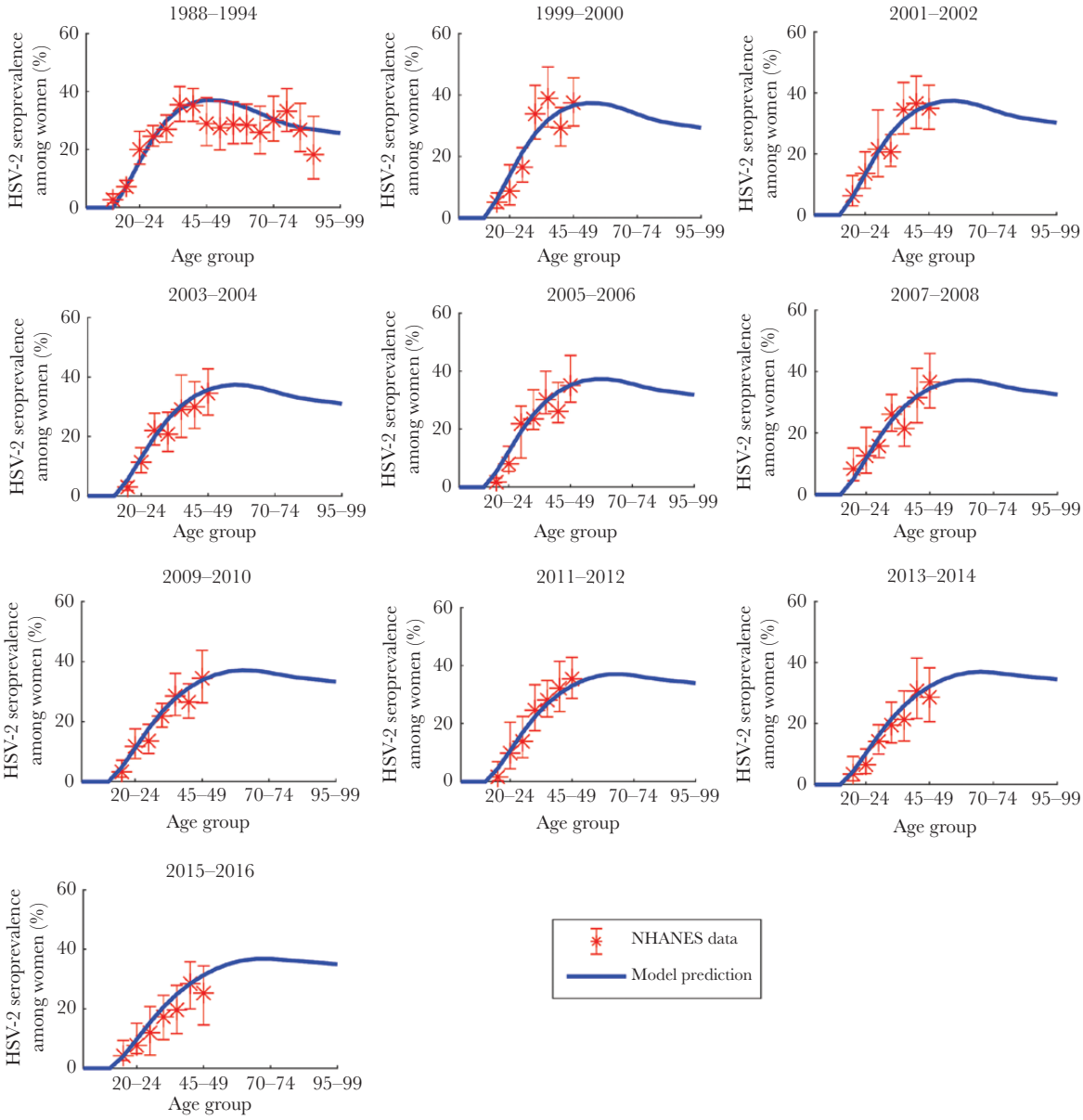

Figure 1. Fitting of the age-specific distribution of herpes simplex virus type 2 (HSV-2) seroprevalence among women in the United States. The fitted HSV-2 seroprevalence in each 5-year age band, compared to the National Health and Nutrition Examination Survey (NHANES) data from 1988 to 2016.

In the total (women and men) population of 15- to 49-year-olds, 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 (Figure 3B). Between 1950 and 1983, seroprevalence increased by 58%, but then declined by 34% between 1983 and 2020, and by 57% by 2050. Similar trends were found in those aged ≥15 years (Supplementary Figure 3).

Figure 4 shows evolution of incidence rate in the 15- to 49-year-old population. In women and men, incidence rate peaked around 1970 and declined thereafter, with the decline accelerating between 1980 and 2010 (Figure 4A). In women, at peak in 1972, incidence rate was 16.8 per 1000 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, the incidence rate was 7.8 per 1000 person-years, but declined by 55% to 3.5 in 2020, and by 65% to 2.7 in 2050. In the total 15- to 49-year-old population, at peak in 1971, incidence rate was 11.9 per 1000 person-years, but declined by 59% to 4.9 in 2020, and by 70% to 3.5 in 2050 (Figure 4B). Similar trends were found in those aged ≥15 years (Supplementary Figure 4).

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

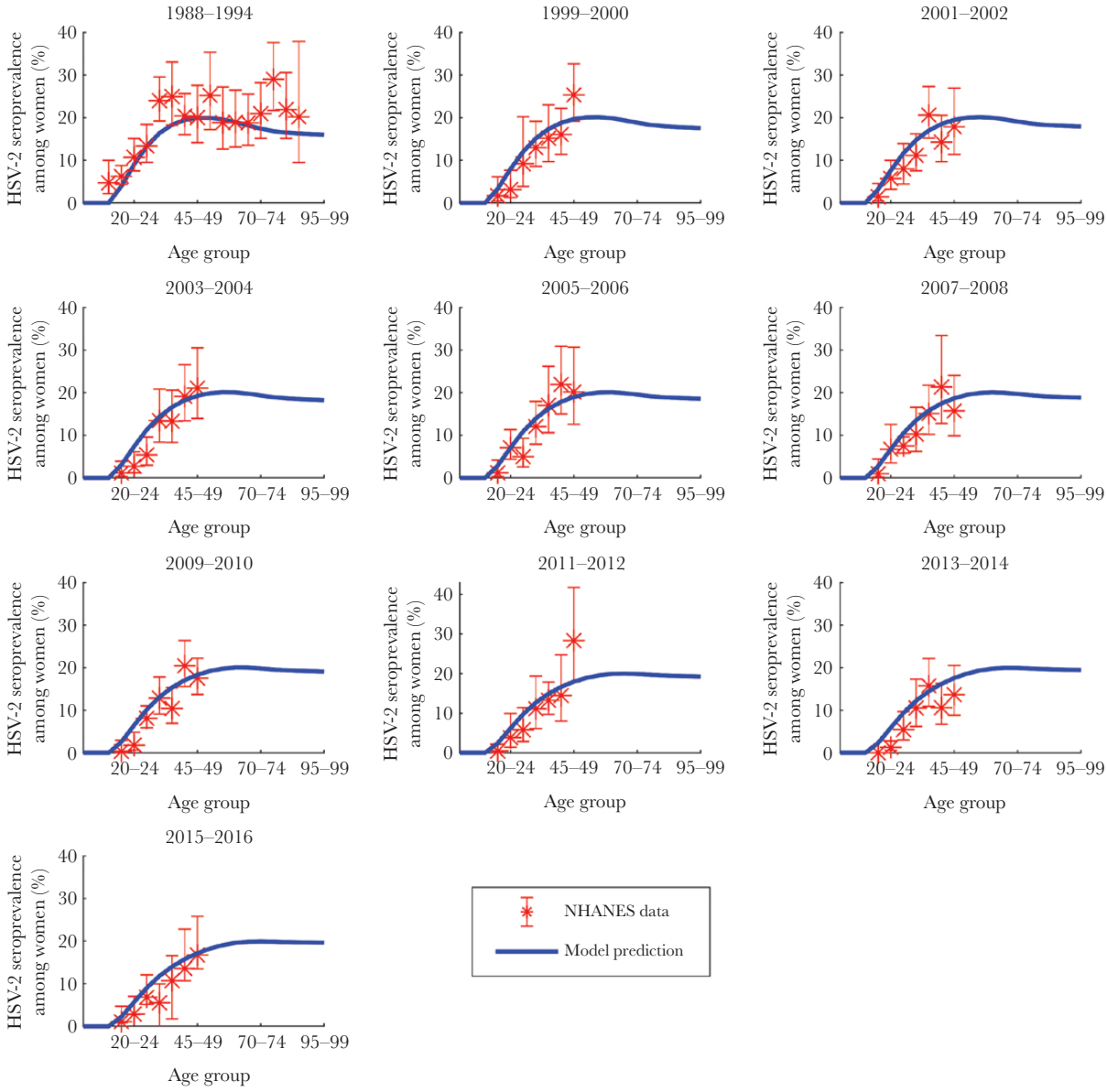

Figure 2. Fitting of the age-specific distribution of herpes simplex virus type 2 (HSV-2) seroprevalence among men in the United States. The fitted HSV-2 seroprevalence in each 5-year age band, compared to the National Health and Nutrition Examination Survey (NHANES) data from 1988 to 2016.

and was projected to decline to 347 000 by 2050. In men, at peak in 1978, there were 353 000 new infections, declining to 245 000 by 2020 and 231 000 by 2050.

In the total 15- to 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 (Figure 5B). A similar pattern was observed in the total population aged ≥15 years (Supplementary Figure 5). At peak in 1978, there were 1 033 000 new infections, declining 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.

Figures 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 the 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 (Figure 7). In 1970, incidence rate (per 1000 person-years) among 20- to 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 and 1990 was higher in middle-aged than in older adults (Figure 6); persons in this "youth cohort" aggregated in a 3-decade time span more cumulative risk of infection than older adults aggregated over their lifetime. However, by 2020 and thereafter, seroprevalence increased

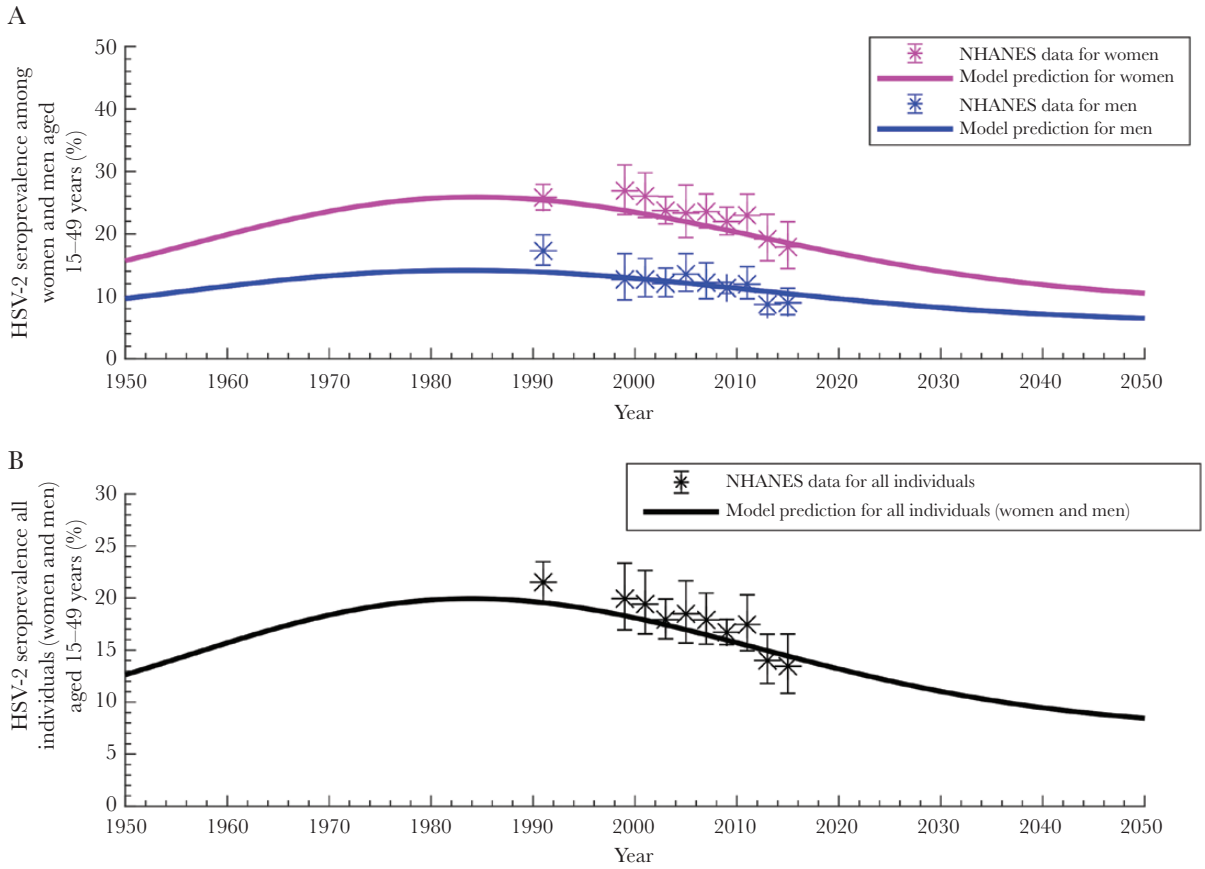

Figure 3. Temporal evolution of herpes simplex virus type 2 (HSV-2) seroprevalence in the United States. *A*, Estimated HSV-2 seroprevalence for women and men aged 15–49 years, compared to the National Health and Nutrition Examination Survey (NHANES) data. *B*, Estimated HSV-2 seroprevalence in the total population aged 15–49 years, compared to NHANES data.

monotonically with age, as expected for a "typical" HSV-2 epidemiology.

Figure 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- to 24-year-olds, remained rather stable for 25- to 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- to 34-year-olds (Figure 6), reflecting the incidence rate pattern (Figure 7).

Supplementary Figure 6 shows results of the uncertainty analysis for the temporal evolution of seroprevalence, incidence rate, and annual number of new infections. The analysis affirmed the above findings.

Supplementary Figure 7 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; the incidence rate for women and men peaked in the mid-1970s instead of the 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 (Supplementary Figure 8) and spurious predictions that contradicted available evidence (see Discussion).

DISCUSSION

Results indicate an evolving epidemiology (rapidly at times) for HSV-2 infection in the US. The current infection pattern implicitly reflects 2 distinct experiences of 2 generations. The epidemic expanded after World War II and accelerated post-1960 (Figure 5). For those aged 15–34 years sometime between 1960 and the mid-1980s, a time often associated with the "sexual revolution" and introduction of "the pill" [48, 49], risk of infection was high leading to high incidence and seroprevalence for this specific ("youth cohort") generation (Figures 3–7). At peak incidence in late 1970s, 1 million infections occurred every year, nearly two-thirds of which were among women.

Nonetheless, by the mid-1980s, notably when HIV/AIDS was first recognized [50], risk of infection went into a steep decline for 3 decades before settling into a slowly declining pattern at present (Figure 4). Even though the US population

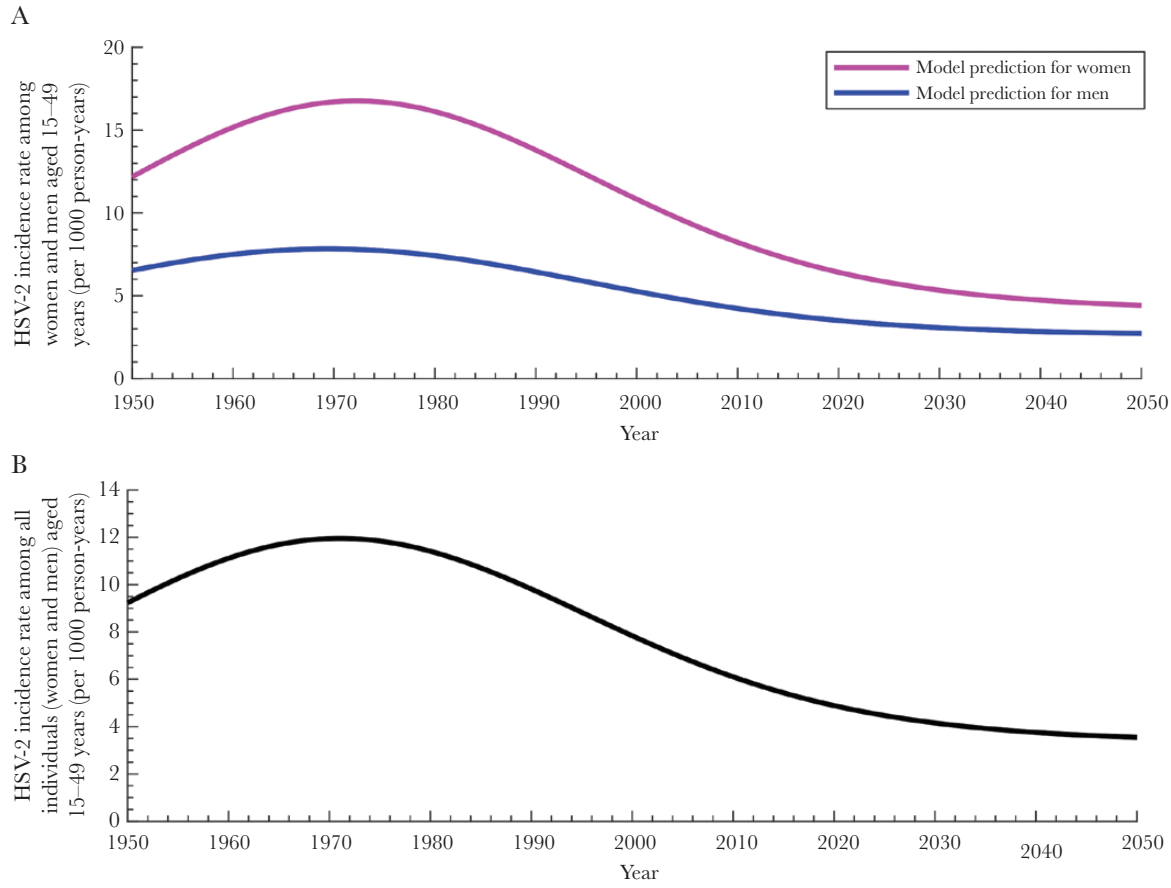

Figure 4. Temporal evolution of herpes simplex virus type 2 (HSV-2) incidence rate in the United States. *A*, Estimated HSV-2 incidence rate for women and men aged 15–49 years. *B*, Estimated HSV-2 incidence rate in the total population aged 15–49 years.

expanded substantially since the 1980s (Supplementary Figure 2), the rapid decline in incidence rate more than compensated for the larger influx of new susceptibles—there were only 667 000 new infections in 2020, two-thirds the number of infections in 1978 at the epidemic peak (Figure 5 and Supplementary Figure 5).

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 approximately 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 (Figure 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 2 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 3 decades (Figure 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 (Figures 3–5)—a seroprevalence pattern at a given point in time is a delayed manifestation of behavior change 2 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 sequalae 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 (Figures 3–7). Incidence will persist at >600 000 new infections every year (Figure 5)—a total of 18 million new

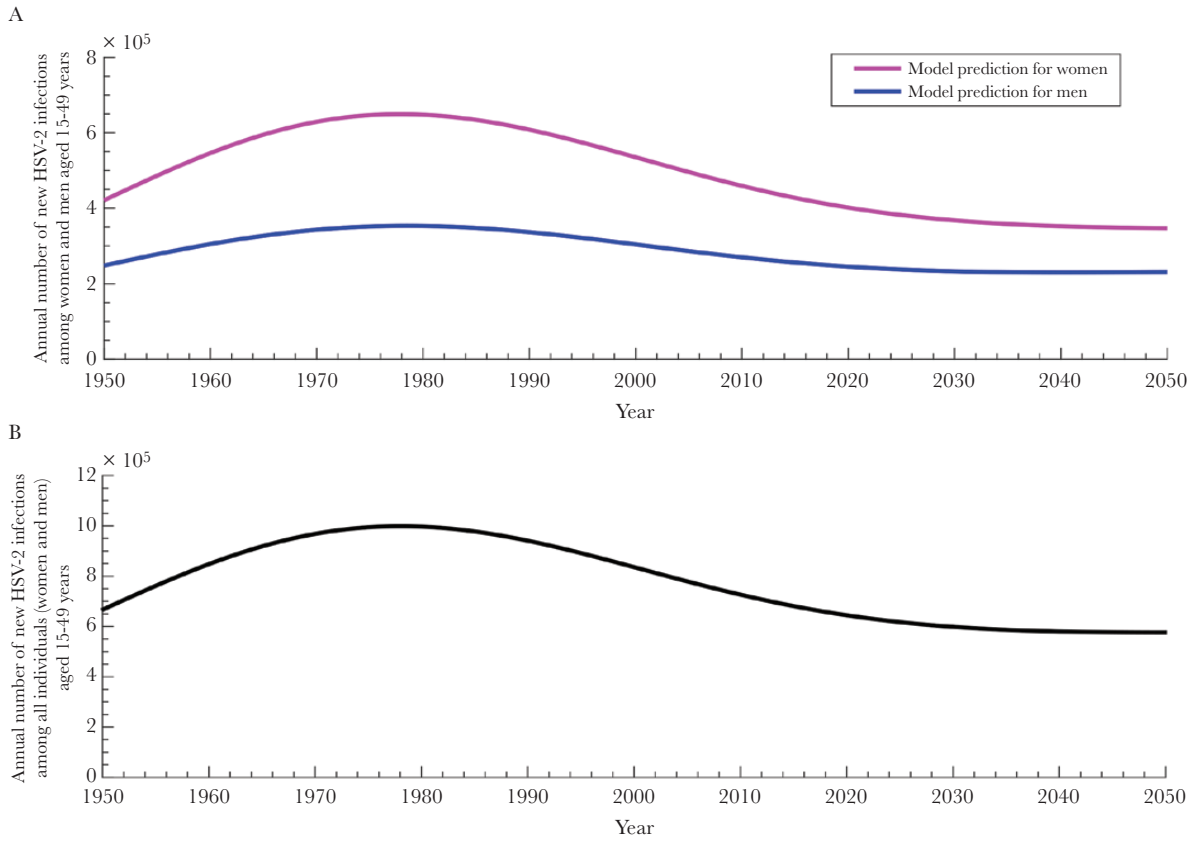

Figure 5. Temporal evolution of new herpes simplex virus type 2 (HSV-2) infections in the United States. *A*, Estimated annual number of new HSV-2 infections for women and men aged 15–49 years. *B*, Estimated annual number of new HSV-2 infections in the total population aged 15–49 years.

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 1000 person-years) will hover around 5 for women and 3 for men (Figure 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 is that these estimates assume continuation of current trends in population sexual behavior over the coming 3 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 1 and 2 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 (Supplementary Figures 9 and 10) [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

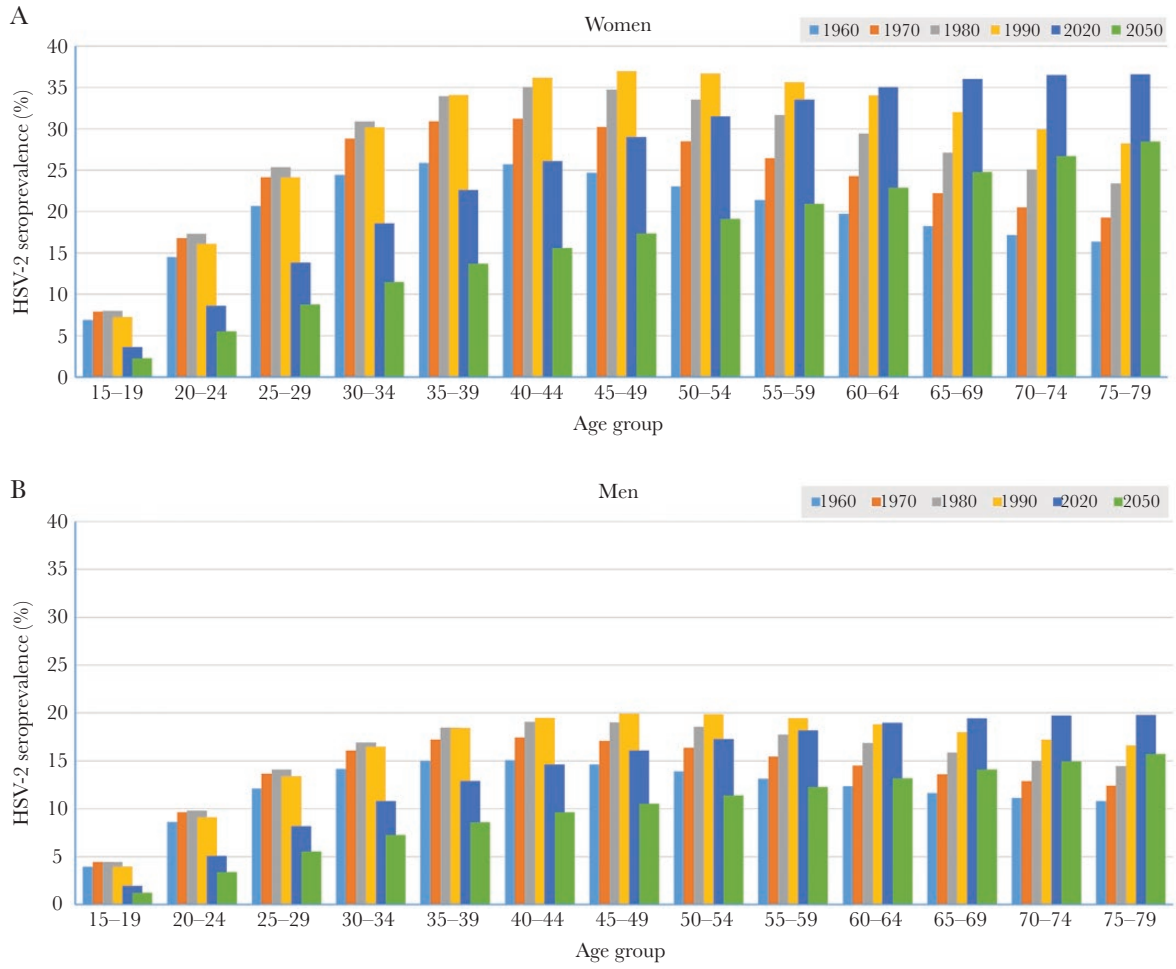

Figure 6. Age-specific distribution of herpes simplex virus type 2 (HSV-2) seroprevalence in the United States. *A*, Estimated age-specific distribution of HSV-2 seroprevalence among women in 1960, 1970, 1980, 1990, 2020, and 2050. *B*, Estimated age-specific distribution of HSV-2 seroprevalence among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

sensitivity analyses (eg, Supplementary Figure 8), we could not produce the 1976–1980 round seroprevalence, though the model robustly and consistently fitted all other 10 rounds (Figures 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 (Figure 3) [19–22]. It seems implausible that sexual risk behavior underwent a sudden transient surge during the 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 sexually transmitted infection 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% (Supplementary Figure 10). 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, 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

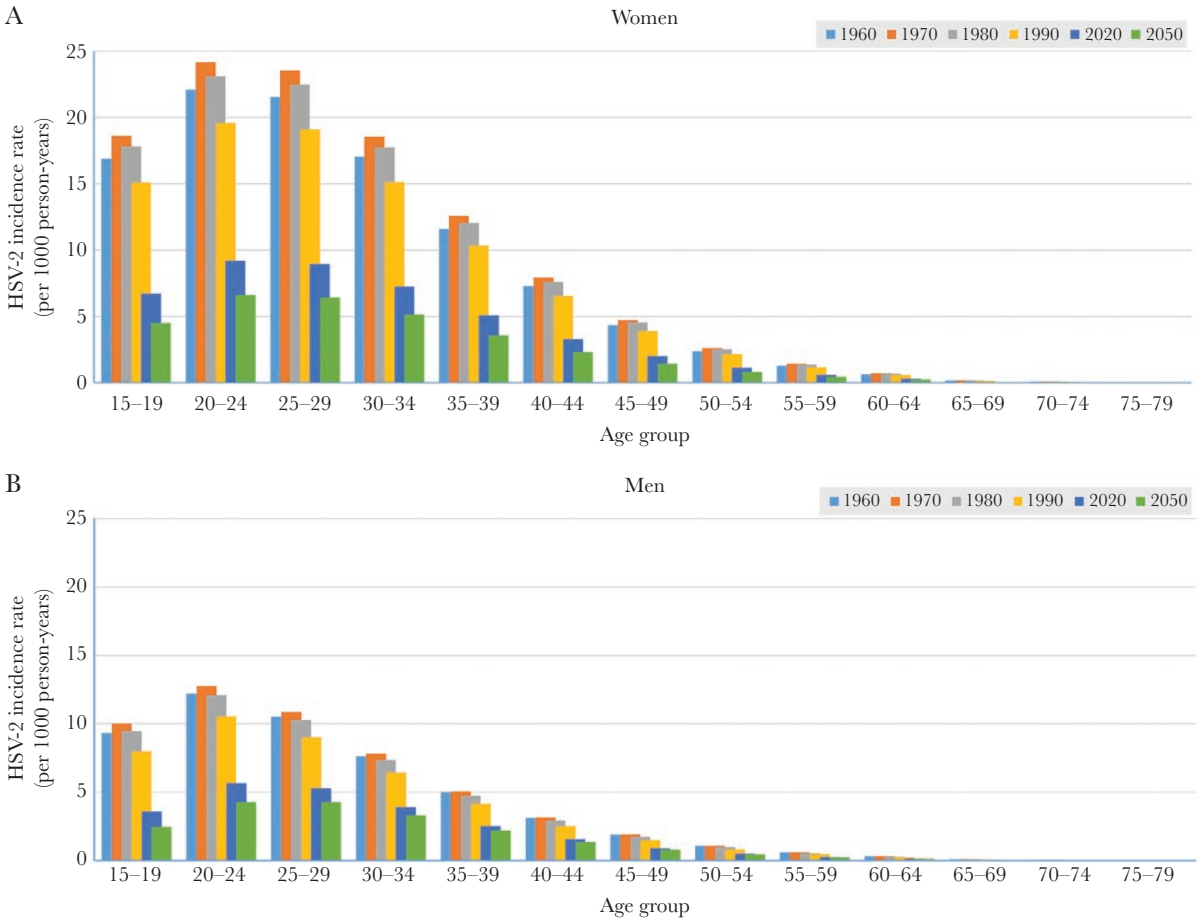

Figure 7. Age-specific distribution of herpes simplex virus type 2 (HSV-2) incidence rate in the United States. *A*, Estimated age-specific distribution of HSV-2 incidence rate among women in 1960, 1970, 1980, 1990, 2020, and 2050. *B*, Estimated age-specific distribution of HSV-2 incidence rate among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

as roll-out of interventions/vaccines. HSV-2 shedding was assumed to continue at a fixed frequency, but evidence suggests that 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 the impact on the HIV epidemic given the existing 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 >3 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 (Supplementary Figure 6). Findings were also affirmed by the sensitivity analyses.

In conclusion, the US HSV-2 epidemic underwent a major transition over a century, leading to 2 distinct experiences for 2 generations. From 1950 to the mid-1980s, the epidemic expanded massively to add 30 million new infections and to affect nearly a quarter of the US population. From the mid-1980s, however, the epidemic reversed course with rapid declines, followed by stabilization that is projected to continue over the next 3 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 the HSV-2 burden in the US and demonstrate the need for continuous surveillance and criticality of development of HSV-2 vaccines.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. H. H. A. and I. A. designed, coded, and parameterized the mathematical model, conducted the analyses, and wrote the first draft of the article. S. F. A. and R. O. contributed to the modeling analyses. H. C. supported the model parameterization, conducted statistical analyses, and participated in the drafting of the article. L. J. A. 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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Disclaimer. The findings achieved herein are solely the responsibility of the authors.

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Potential conflicts of interest. All authors: No reported conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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