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Estimated global and regional incidence and prevalence of herpes simplex virus infections and genital ulcer disease in 2020: mathematical modelling analyses

Manale Harfouche,[1,2] Sawsan AlMukdad,[1,2] Asalah Alareeki,[1,2] Aisha M M Osman,[1,2] Sami Gottlieb,[3] Jane Rowley,[4] Laith J Abu-Raddad ,[1,2,5,6,7] Katharine J Looker[8]

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For numbered affiliations see end of article.

Correspondence to
Dr Laith J Abu-Raddad; lja2002@qatar-med.cornell.edu

LJA-R and KJL are joint senior authors.

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ABSTRACT

Objectives Genital herpes simplex virus (HSV) type 1 and 2 infections are lifelong and can cause symptomatic genital ulcer disease (GUD). HSV-2 almost always causes sexually transmitted genital infection, while HSV-1 mainly causes oral infection but can be sexually transmitted to cause genital infection. This study estimated genital infection with both HSV types and associated GUD globally in 2020, breaking down the data by WHO region and sex for females and males.

Methods A calibrated mathematical model was employed to generate estimates for the incidence and prevalence of HSV-2 infection, genital HSV-1 infection, and GUD caused by both HSV types. Estimates for non-genital infections caused by HSV-1 were also generated. Model input was derived from a comprehensive systematic review and meta-analyses of HSV prevalence data for all WHO regions.

Results Globally in 2020 there were 25.6 million (95% uncertainty interval (UI) 23.1–29.4 million) people aged 15–49 years with new HSV-2 infections, and 519.5 million (95% UI 464.3–611.3 million), or 13.3% (95% UI 11.9–15.6%), with existing (prevalent) HSV-2 infections. In addition, there were 16.8 million (95% UI 10.6–22.4 million) people aged 15–49 years with new genital HSV-1 infections and 376.2 million (95% UI 235.6–483.5 million), or 10.2% (95% UI 6.4–13.1%), with prevalent genital HSV-1 infections. The estimated number of people aged 15–49 years with at least one episode of HSV-attributable GUD in 2020 was 187.9 million (95% UI 116.0–291.8 million) for HSV-2, and 16.7 million (95% UI 9.3–25.2 million) for HSV-1, totalling 204.6 million (95% UI 132.3–306.5 million).

Conclusion Genital HSV infections have a high incidence and prevalence worldwide, contributing to a significant GUD disease burden. New prevention and treatment measures, such as prophylactic and therapeutic HSV vaccines, are needed critically to control HSV infections and reduce the associated disease burden.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Herpes simplex virus (HSV) type 1 and type 2 infections are lifelong, globally prevalent, and cause a significant disease burden, including symptomatic genital ulcer disease (GUD), and economic costs. Making a case for investing in HSV prevention and care for GUD requires current estimates of the numbers of HSV infections and GUD, along with their distribution across populations by geographical region, age, sex, and infection site (genital vs oral).

WHAT THIS STUDY ADDS

⇒ This study was conducted to generate current estimates, updating the 2012 and 2016 WHO estimates. Based on comprehensive regional systematic reviews and meta-analyses of HSV-1 and HSV-2 prevalences for all WHO regions, and methodological enhancements on previous HSV estimation rounds, this study estimated HSV infection and GUD levels in 2020 globally and by region, and for females and males. The estimates show that globally, in 2020, 26 million new HSV-2 infections occurred among individuals aged 15–49 years, adding up to a total of 520 million people living with HSV-2. Also globally, in 2020, 122 million new HSV-1 infections occurred among individuals aged 0–49 years, including 16.8 million who acquired the infection genitally, adding up to a total of 3.8 billion people living with HSV-1 infection. Of these totals, 188 million and 17 million people had at least one episode of HSV-2 or HSV-1 GUD in 2020, respectively.

INTRODUCTION

Herpes simplex virus (HSV) type 1 and type 2 cause lifelong infections and are widespread worldwide, resulting in significant disease and economic burden.[1–3] Both infections are characterised by frequent infectious subclinical shedding, along with symptomatic reactivations in a proportion of those infected.[4–8] HSV-2 infection is almost always acquired through sexual transmission and is the leading cause of recurrent clinical genital ulcer disease (GUD) in most countries.[9–12] In addition to the painful genital sores, genital herpes is associated with a range of social and psychological adverse outcomes, including effects on sexual relations, quality of life, and mental health issues such as depression, anxiety, and low self-esteem.[13–16] HSV-2 infection is believed to increase the risk of

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HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Estimates of the incidence and prevalence of HSV infections and GUD are essential for informing policy, advocacy, resource planning, and guiding the development of new products such as vaccines. HSV infections are at a high incidence and prevalence in all global regions leading to significant disease and economic burden with repercussions on clinical sequelae and psychosocial, sexual, and reproductive health, neonatal transmission, and HIV transmission. Available prevention modalities are insufficient to control infection transmission, and have had, at best, modest population impact. There is a need for HSV prophylactic and therapeutic vaccines as a strategic approach to control transmission and to curb the disease and economic burden of these infections.

HIV acquisition and transmission by threefold,[17 18] potentially resulting in an epidemiological synergy between these two infections.[18–20]

HSV-1 infection is typically acquired orally in childhood and commonly manifests as cold sores,[21 22] but it can also cause more serious neurological, corneal, and mucocutaneous complications.[23–25] Adults can acquire genital HSV-1 infection if they were not infected orally during childhood.[26] Particularly in high-income countries, HSV-1 infection has been increasingly acquired sexually,[9 26–28] and in several countries it is now the leading cause of first-episode genital herpes.[9 27 28] Recurrences of genital HSV-1 are much less frequent compared with HSV-2 recurrences.[4]

HSV-1 and HSV-2 infections can both be transmitted, although rarely, from genitally-infected mothers to their neonates during birth and through oral contact from caregivers postnatally,[29] leading to neonatal herpes, a disabling disease in newborns with a high fatality rate.[14 30] In response to the clinical disease burden of these two infections and their impact on sexual and reproductive health and HIV transmission, the WHO has advocated for efforts to reduce HSV disease burden by advancing the development of new prevention and treatment measures, such as vaccines.[31]

In this article, we present global and regional modelling estimates of the incidence and prevalence of genital HSV infections as well as HSV-related GUD for the year 2020. In addition to updating earlier estimates,[1 32 33] the present estimates benefit from methodological enhancements. The main enhancement is that HSV-1 and HSV-2 prevalence data, which provided the modelling input, are based on a series of standardised and comprehensive HSV systematic reviews, meta-analyses, and meta-regressions covering all global regions, published over the last few years.[9–12 27 28 34–40]

METHODS

Model input

The model input was provided by the databases of the published systematic reviews.[9–12 27 28 34–40] Since the reviews were published over several years,[9–12 27 28 34–40] and considering the lag of a few years between sample collection and data publication,[9–12 27 28 34–40] an update was done up to 30 March 2022, to ensure completeness and inclusion of the most recent data for each WHO region. However, only data based on samples collected up to 2020 were used for the modelling input. Since the regional groupings of countries in the published reviews were not WHO region groupings, country-level data were re-grouped into the six WHO regions. While the details of the standardised methodology of the reviews have been published previously,[9–12 27 28 34–40] a summary is provided in online supplemental box S1 of the supplementary material for inclusiveness.

The validity of each HSV diagnostic assay for each data point was investigated, considering the known limitations of HSV serology and potential cross-reactivity between HSV-1 and HSV-2 antibodies.[41 42] This assessment was conducted in consultation with Professor Rhoda Ashley-Morrow of the University of Washington, an expert in HSV diagnostic methods. Only studies with valid and reliable laboratory methods were included in the systematic reviews. Common reasons for excluding an assay included potential issues related to sensitivity, specificity, and particularly the risk of cross-reactivity between HSV-1 and HSV-2 antibodies.[41–43] To ensure validity, the assay used had to detect antibodies specific to the HSV type, such as glycoprotein G-2 for HSV-2 infection.[44 45] The issue of cross-reactivity with HSV-1 antibodies was particularly important in regions with high HSV-1 prevalence but low HSV-2 prevalence.[46–48] Since measured prevalence can be affected by the choice of ELISA optical density cut-off for positivity,[42 46 49] studies were excluded if an inappropriate cut-off was clearly used. Flowcharts outlining the selection process for prevalence measures and excluded studies due to laboratory methods have been reported previously.[9–12 27 28 34–40]

Data were synthesised based on methods used to generate the 2016 WHO HSV estimates,[1] but with adjustments to improve on study methodology, to incorporate recent findings on HSV-1 and HSV-2 epidemiology, and to account for limitations in available data for specific regions (online supplemental box S1). These adjustments are summarised in online supplemental box S2. Inclusion criteria for HSV-1 was an antibody prevalence (seroprevalence) measure in a general population aged 0–49 years with a midpoint of 2004 up to 2020 for the year of data collection (and 1995 up to 2020 for the African and South-East Asia regions due to poor data availability). Inclusion criteria for HSV-2 was an antibody prevalence measure among a general population aged 15–49 years with a midpoint of 2004 up to 2020 for the year of data collection.

Meta-analyses were conducted using the DerSimonian-Laird random-effects models[50] with the Freeman-Tukey double arcsine transformation.[51] Pooled mean HSV-1 and HSV-2 prevalences were calculated by sex (when possible) and by age. In this simplified representation of populations, we stratified populations into two groups, 'females' and 'males'; however, we recognise that a range of gender identities are possible. The meta package[52] was used to perform the meta-analyses in R, version 4.0.4[53] (online supplemental box S1). The pooled prevalence estimates for each region were subsequently used to calibrate the mathematical model[1 32 33] that generated the HSV estimations.

Model calibrations

HSV-1 and HSV-2 incidence estimates were calibrated to the pooled mean prevalences using maximum likelihood, as per the previously published WHO HSV estimation model.[1] Any prevalence values of 0% and 100% were recoded as 0.1% and 99.9%, respectively, before taking logs for the likelihood equations. For the calibration, a constant force of infection, λ, was assumed; that is, assuming a constant incidence rate model. An additional term, k, representing the maximum proportion of individuals that can be infected, was also included and simultaneously calibrated along with λ. It was assumed that individuals can be

infected with HSV-1 from age 0 years, and with HSV-2 from age 15 years. Calibration was done using the Solver function in Microsoft Excel. Since the model estimation was conducted over a 1 year time frame, vital dynamics were not incorporated, as the risk of death within such a short horizon is minimal. Further details and the model equations can be found in online supplemental box S3.

For HSV-1, single data points were included in the calibrations for the WHO South-East Asia region, due to particularly poor data availability. Sex-specific estimates were produced for the Americas and European regions as conducted previously,[1] but for children (<15 years), all of female, male, and mixed data for a given age band were pooled and used for calibration for each of the females and males, to avoid skewing the model calibrations by sex. For the Western Pacific, African, Eastern Mediterranean, and South-East Asia regions all of female, male, and mixed data were pooled for a given age band. Previous meta-regressions on all prevalence data for these regions showed no difference in prevalence by sex whether for Africa,[38] Eastern Mediterranean,[36] and Asia (combining South-East Asia and Western Pacific regions).[39] For HSV-2, single data points were included in the calibration for the Eastern Mediterranean region, again due to poor data availability.

Despite the steps taken to maximise the use of available data, data were still sparse for some calibrations. The model fit for the Eastern Mediterranean region was very skewed due to low availability of HSV-1 related data among children. A better fit for this region was produced by using the data for children from the Western Pacific region, due to close similarity in pooled prevalence for HSV-1 among adults in these two regions.

Prevalence and incidence estimates

Smoothed prevalence estimates by sex and 5-year age group and calibrated incidence obtained from the model fitting were then applied to demographic data by sex and 5-year age group for 2020 obtained from the United Nations Population Division.[54]

Genital infections with HSV-1 were assumed to occur only in individuals over the age of 15 years. All individuals under 15 years of age were assumed to have acquired the infection orally. Among individuals over 15 years of age, we used the same pooled values as in the 2016 estimates: 72.4% of new infections over 15 years of age were assumed to be genital, and 36.4% oral infections (percentages add up to more than 100% due to dual oral and genital infections).[1]

Estimates for genital HSV-1 and HSV-2 infections were generated for individuals aged 15–49 years. The percentage of individuals with genital infection due to either HSV-1 or HSV-2 was calculated by summing the separate estimates for genital HSV-1 and HSV-2, and then applying a correction factor for the estimated percentage with dual HSV-1 and HSV-2 infection (online supplemental box S3). Estimates for oral HSV-1 infection were generated for individuals aged 0–49 years.

As in the 2016 estimation round,[1] a secondary exploratory analysis was conducted where the number of individuals with HSV-1 and HSV-2 infections in each WHO region for those aged 50–99 years was estimated by applying the prevalence of each infection in individuals aged 45–49 years to the population aged 50–99 years.

Uncertainty analysis was conducted to estimate the 95% uncertainty intervals (95% UI) (online supplemental box S2). Calculation of all estimates was done in Excel.

GUD estimates

GUD due to HSV-2 or genital HSV-1 infection was estimated using two measures following our published method[2]: (1) the percentage and the number of people aged 15–49 years with any HSV GUD in 2020; and (2) the total number of person-days with HSV GUD among individuals aged 15–49 years in 2020. GUD estimates were calculated by applying natural history estimates for HSV-2 and genital HSV-1 infections, that is, the probability and duration of a first episode, the probability of a recurrence, and the length and frequency of recurrences, to the HSV-2 and HSV-1 infection estimates for 2020. These natural history estimates were derived by pooling study-level estimates obtained from a comprehensive literature review.[2] It was assumed that the total HSV-related GUD burden was equal to the sum of the burden for each of HSV-2 and genital HSV-1. Calculation of all estimates was done in Excel. Further details of how to obtain these estimates have been previously published.[2]

The 95% UI for the percentage and number of individuals aged 15–49 years with any GUD and the total number of person-days with GUD among individuals aged 15–49 years were derived as for 2016.[2] In brief, all natural history parameters, and the calibrated force of infection, were sampled 1000 times in Excel. The 95% UIs were then derived from these 1000 runs.

Compliance with guidelines

This study complies with the Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER) recommendation.[55] The complete GATHER checklist can be found in online supplemental table S1.

RESULTS

Given that HSV-2 is the primary contributor to genital infection and recurrent GUD, the results are presented first for HSV-2.

Model input and fitting

In the published reviews[9–12 27 28 34–40] and their update to complete the database of HSV data used for the model input, titles and abstracts of 76 972 citations were screened for relevant HSV-2 and HSV-1 data for all WHO regions. Of these, 1228 articles reported an HSV-2 and/or HSV-1 epidemiological outcome measure (online supplemental table S2). A total of 134 articles included data that met the specific inclusion criteria for the 2020 HSV-2 estimates (list of articles in online supplemental box S4) and 82 articles included data that met the specific inclusion criteria for the 2020 HSV-1 estimates (list of articles in online supplemental box S5).

In comparison to the 2016 estimates,[1] the number of available data points improved for most of the regions (online supplemental tables S3, S4 and S5). Globally, the number of articles in 2020 surpassed that of 2016. Specifically, the number of articles on HSV-2 increased from 88 to 134, and for HSV-1, it rose from 44 to 82 (online supplemental table S5). However, this increased availability did not necessarily translate into a larger number of represented countries in some of the regions.

Online supplemental figure S1 shows the model fits for HSV-2 prevalence versus age for each WHO region. Overall, the model fitted well available data. These model fits were subsequently used to generate HSV-2 incidence and prevalence estimates.

Online supplemental figure S2 shows the model fits for HSV-1 prevalence versus age for each WHO region. Overall, the model fitted well available data. These model fits were subsequently used to generate HSV-1 incidence and prevalence estimates.

Table 1 Global and regional estimates of the number and percentage of the population aged 15–49 years with incident HSV-2 infection in 2020, by age and sex

		Number of people with incident HSV-2 infection in millions (population incidence, %) by age group								
		15–19 years	20–24 years	25–29 years	30–34 years	35–39 years	40–44 years	45–49 years	All ages	
Sex	WHO region	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (95% UI*)	% (95% UI†)
Females	AFR	1.9 (3.2)	1.3 (2.6)	0.9 (2.2)	0.7 (1.8)	0.5 (1.5)	0.3 (1.2)	0.2 (1.0)	5.8 (5.1–6.5)	2.2 (1.9–2.4)
	AMR	0.5 (1.3)	0.5 (1.2)	0.4 (1.1)	0.4 (1.0)	0.4 (1.0)	0.3 (0.9)	0.3 (0.8)	2.7 (2.0–3.5)	1.1 (0.8–1.4)
	EMR	0.1 (0.2)	0.1 (0.2)	<0.1‡ (0.2)	0.1‡ (0.2)	<0.1‡ (0.2)	<0.1‡ (0.2)	<0.1‡ (0.2)	0.3 (0.1–1.0)	0.2 (0.0–0.6)
	EUR	0.1 (0.6)	0.1 (0.6)	0.2 (0.6)	0.2 (0.5)	0.2 (0.5)	0.2 (0.5)	0.2 (0.5)	1.1 (0.7–1.7)	0.5 (0.3–0.8)
	SEAR	0.5 (0.6)	0.5 (0.5)	0.4 (0.5)	0.4 (0.5)	0.4 (0.5)	0.3 (0.5)	0.3 (0.5)	2.7 (2.1–3.5)	0.5 (0.4–0.7)
	WPR	0.4 (0.7)	0.4 (0.7)	0.4 (0.7)	0.5 (0.6)	0.4 (0.6)	0.4 (0.6)	0.4 (0.6)	2.9 (1.7–5.0)	0.6 (0.4–1.1)
	Overall	3.4 (1.2)	2.8 (1.0)	2.4 (0.9)	2.2 (0.7)	1.8 (0.7)	1.5 (0.6)	1.4 (0.6)	15.6 (13.8–18.0)	0.8 (0.7–0.9)
Males	AFR	1.1 (1.9)	0.9 (1.7)	0.7 (1.5)	0.5 (1.4)	0.4 (1.2)	0.3 (1.1)	0.2 (1.0)	4.0 (3.3–5.0)	1.5 (1.2–1.9)
	AMR	0.3 (0.7)	0.3 (0.6)	0.3 (0.6)	0.2 (0.6)	0.2 (0.6)	0.2 (0.6)	0.2 (0.5)	1.6 (1.1–2.1)	0.6 (0.4–0.8)
	EMR	0.1 (0.2)	0.1 (0.2)	0.1 (0.2)	0.1 (0.2)	0.1 (0.2)	<0.1‡ (0.2)	<0.1‡ (0.2)	0.4 (0.2–0.8)	0.2 (0.1–0.4)
	EUR	0.1 (0.3)	0.1 (0.3)	0.1 (0.3)	0.1 (0.3)	0.1 (0.3)	0.1 (0.3)	0.1 (0.3)	0.7 (0.4–1.2)	0.3 (0.2–0.5)
	SEAR	0.3 (0.3)	0.3 (0.3)	0.3 (0.3)	0.2 (0.3)	0.2 (0.3)	0.2 (0.3)	0.2 (0.3)	1.6 (1.0–2.4)	0.3 (0.2–0.4)
	WPR	0.2 (0.4)	0.2 (0.4)	0.3 (0.4)	0.3 (0.4)	0.2 (0.3)	0.2 (0.3)	0.3 (0.3)	1.7 (0.7–4.2)	0.4 (0.1–0.9)
	Overall	2.0 (0.6)	1.8 (0.6)	1.6 (0.5)	1.4 (0.5)	1.2 (0.4)	1.0 (0.4)	0.9 (0.4)	10.0 (8.4–12.9)	0.5 (0.4–0.6)
Both	Global	5.5 (0.9)	4.6 (0.8)	4.0 (0.7)	3.6 (0.6)	3.0 (0.6)	2.5 (0.5)	2.3 (0.5)	25.6 (23.1–29.4)	0.7 (0.6–0.8)

Numbers (N) are the estimated number of people newly infected with HSV-2 during 2020. Numbers do not always sum exactly to the totals due to rounding.
Incidences (%) are the percentage of infected people in the age-, sex-, and region-specific population.
Regions are per WHO definitions.
*95% UI of the total number of infected people in millions.
†95% UI of percentage incidence.
‡Numbers are <50 000 but ≥10 000.
AFR, African Region; AMR, Region of the Americas; EMR, Eastern Mediterranean Region; EUR, European Region; HSV, herpes simplex virus; SEAR, South East Asia Region; UI, uncertainty interval; WPR, Western Pacific Region.

HSV-2 infection

The number of incident HSV-2 infections globally in 2020 among individuals aged 15–49 years was estimated at 25.6 million (95% UI 23.1–29.4 million) (table 1). Of these, 15.6 million (95% UI 13.8–18.0 million) infections were among females and 10.0 million (95% UI 8.4–12.9 million) among males. The African region had the highest HSV-2 incidence for both females and males at nearly 10 million infections, accounting for 38.3% of all infections. The HSV-2 incidence rate decreased with age for all regions and was notably high among young adults in the African and Americas regions.

The number of people with prevalent HSV-2 infections globally in 2020 among individuals aged 15–49 years was estimated at 519.5 million (95% UI 464.3–611.3 million), an HSV-2 prevalence of 13.3% (95% UI 11.9–15.6%) (table 2). HSV-2 prevalence was higher in females (17.0%, 95% UI 14.9–20.1%) than in males (9.7%, 95% UI 8.0–13.0%). The African region exhibited both the highest prevalence and the largest number of infected persons. In the secondary analysis, among individuals aged 50–99 years, an additional 389.1 million people were estimated to be infected worldwide (online supplemental table S6).

Genital HSV-1 infection

The number of incident genital HSV-1 infections globally in 2020 among individuals aged 15–49 years was estimated at 16.8 million (95% UI 10.6–22.4 million) (table 3). Of these, 8.4 million (95% UI 5.1–11.5 million) infections were among females and 8.4 million (95% UI 5.0–11.8 million) among males. The Western Pacific region had the highest incidence of genital HSV-1, with 4.8 million infections combining females and males. The genital HSV-1 incidence rate decreased with age for all regions and was notably high among young adults in the Americas and European regions.

The number of people with prevalent genital HSV-1 infections globally in 2020 among individuals aged 15–49 years was estimated at 376.2 million (95% UI 235.6–483.5 million), a genital HSV-1 prevalence of 10.2% (95% UI 6.4–13.1%) (table 4). Globally, genital HSV-1 prevalence was slightly higher in females (10.5%, 95% UI 6.4–13.8%) than in males (9.9%, 95% UI 5.9–13.4%). The Americas region had the highest genital HSV-1 prevalence, but the Western Pacific region had the largest number of infected persons among those aged 15–49 years.

All genital HSV infections

The number of incident genital HSV infections (HSV-2 and/or HSV-1) globally in 2020 among individuals aged 15–49 years was estimated at 42.4 million (95% UI 33.7–51.8 million). The number of people with prevalent genital HSV infections (HSV-2 and/or HSV-1) globally in 2020 among individuals aged 15–49 years was estimated at 846.1 million (95% UI 661.1–1034.2 million).

HSV-2 and HSV-1 GUD

The number of individuals aged 15–49 years with at least one HSV-2 GUD episode in 2020 was estimated at 187.9 million (95% UI 116.0–291.8 million), a prevalence of 4.8% (95% UI 3.0–7.5%) (table 5). Globally, HSV-2 GUD prevalence was considerably higher in females (6.2%, 95% UI 3.8–9.6%) than in males (3.5%, 95% UI 2.2–5.8%). The total sum of GUD person-days was estimated at 8675 million (95% UI 5632–15 068 million) (online supplemental table S7). The African region

Table 2 Global and regional estimates of the number and percentage of the population aged 15–49 years with prevalent HSV-2 infection in 2020, by age and sex

		Number of people with prevalent HSV-2 infection in millions (population prevalence, %) by age group								
		15–19 years	20–24 years	25–29 years	30–34 years	35–39 years	40–44 years	45–49 years	All ages	
Sex	WHO region	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (95% UI*)	% (95% UI†)
Females	AFR	10.3 (19.3)	16.2 (33.6)	19.2 (45.3)	20.4 (55.0)	20.0 (63.0)	18.0 (69.5)	15.7 (74.9)	119.8 (99.8–141.8)	44.4 (37.0–52.5)
	AMR	2.5 (7.2)	4.9 (13.4)	7.3 (19.1)	9.1 (24.4)	10.6 (29.4)	11.4 (34.1)	12.0 (38.4)	57.8 (42.2–77.4)	22.6 (16.5–30.2)
	EMR	0.3 (0.9)	0.5 (1.8)	0.7 (2.6)	0.9 (3.4)	1.0 (4.2)	1.0 (5.0)	1.0 (5.8)	5.5 (1.4–19.1)	3.0 (0.8–10.5)
	EUR	0.8 (3.3)	1.5 (6.1)	2.5 (8.9)	3.8 (11.6)	4.7 (14.3)	5.4 (16.8)	6.1 (19.3)	24.7 (15.2–39.3)	11.7 (7.2–18.6)
	SEAR	2.4 (3.1)	4.7 (5.8)	6.6 (8.4)	8.4 (11.0)	9.8 (13.5)	10.4 (15.9)	10.8 (18.3)	53.1 (40.2–69.1)	10.0 (7.6–13.0)
	WPR	2.0 (4.0)	4.1 (7.5)	6.7 (10.8)	10.9 (14.0)	11.1 (17.2)	12.5 (20.2)	17.1 (23.1)	64.5 (35.8–116.4)	14.0 (7.8–25.3)
	Overall	18.2 (6.2)	32.0 (11.1)	43.2 (15.0)	53.5 (18.2)	57.1 (21.4)	58.7 (24.2)	62.7 (26.5)	325.5 (284.9–383.0)	17.0 (14.9–20.1)
Males	AFR	5.8 (10.7)	9.5 (19.5)	11.6 (27.4)	12.7 (34.5)	12.7 (41.0)	11.8 (46.8)	10.6 (52.0)	74.8 (59.0–97.0)	27.7 (21.9–36.0)
	AMR	1.3 (3.7)	2.7 (7.0)	4.0 (10.2)	4.9 (13.2)	5.7 (16.2)	6.2 (19.0)	6.5 (21.8)	31.3 (22.1–43.3)	12.2 (8.6–16.9)
	EMR	0.3 (1.1)	0.6 (2.0)	0.9 (3.0)	1.2 (4.0)	1.3 (4.9)	1.3 (5.8)	1.2 (6.8)	7.0 (3.0–16.0)	3.5 (1.5–8.1)
	EUR	0.4 (1.8)	0.9 (3.4)	1.5 (5.0)	2.2 (6.5)	2.6 (8.0)	3.0 (9.5)	3.4 (11.0)	14.0 (7.6–24.9)	6.5 (3.5–11.6)
	SEAR	1.4 (1.6)	2.7 (3.1)	3.9 (4.6)	4.8 (6.0)	5.6 (7.4)	5.9 (8.8)	6.2 (10.2)	30.6 (19.7–46.3)	5.4 (3.5–8.2)
	WPR	1.1 (2.1)	2.4 (3.9)	3.9 (5.7)	6.1 (7.5)	6.2 (9.2)	7.0 (10.9)	9.6 (12.6)	36.5 (13.8–93.3)	7.4 (2.8–18.9)
	Overall	10.5 (3.3)	18.8 (6.1)	25.8 (8.5)	32.0 (10.4)	34.3 (12.5)	35.3 (14.2)	37.5 (15.6)	194.1 (160.0–260.5)	9.7 (8.0–13.0)
Both	Global	28.7 (4.7)	50.8 (8.5)	69.0 (11.7)	85.5 (14.2)	91.4 (16.9)	94.0 (19.2)	100.2 (21.0)	519.5 (464.3–611.3)	13.3 (11.9–15.6)

Numbers (N) are the year 2020 estimated number of people living with HSV-2 infection. Numbers do not always sum exactly to the totals due to rounding.
Prevalences (%) are the percentage of infected people in the age-, sex-, and region-specific population.
Regions are per WHO definitions.
*95% UI of the total number of infected people in millions.
†95% UI of percentage prevalence.
AFR, African Region; AMR, Region of the Americas; EMR, Eastern Mediterranean Region; EUR, European Region; HSV, herpes simplex virus; SEAR, South East Asia Region; UI, uncertainty interval; WPR, Western Pacific Region.

Table 3 Global and regional estimates of the number and percentage of the population aged 15–49 years with incident genital HSV-1 infection in 2020, by age and sex

		Number of people with incident genital HSV-1 infection in millions (population incidence, %) by age group								
		15–19 years	20–24 years	25–29 years	30–34 years	35–39 years	40–44 years	45–49 years	All ages	
Sex	WHO region	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (95% UI*)	% (95% UI†)
Females	AFR	<0.1‡ (0.1)	<0.1§ (0.0)	<0.1§ (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0–0.5)	0.0 (0.0–0.3)
	AMR	0.5 (1.4)	0.4 (1.1)	0.4 (0.9)	0.3 (0.8)	0.2 (0.6)	0.2 (0.5)	0.1 (0.4)	2.1 (1.4–2.6)	0.9 (0.6–1.0)
	EMR	0.2 (0.7)	0.1 (0.3)	<0.1‡ (0.2)	<0.1‡ (0.1)	<0.1‡ (0.0)	<0.1§ (0.0)	<0.1§ (0.0)	0.4 (0.0–1.2)	0.3 (0.0–0.8)
	EUR	0.4 (1.4)	0.3 (1.1)	0.2 (0.8)	0.2 (0.6)	0.2 (0.5)	0.1 (0.4)	0.1 (0.3)	1.5 (0.9–1.9)	0.7 (0.4–0.8)
	SEAR	0.9 (1.0)	0.5 (0.6)	0.3 (0.4)	0.2 (0.2)	0.1 (0.1)	0.1 (0.1)	<0.1‡ (0.1)	2.1 (0.2–3.9)	0.4 (0.0–0.8)
	WPR	0.7 (1.3)	0.5 (0.9)	0.4 (0.6)	0.3 (0.4)	0.2 (0.2)	0.1 (0.2)	0.1 (0.1)	2.3 (1.3–3.3)	0.5 (0.3–0.7)
	Overall	2.7 (0.9)	1.9 (0.6)	1.3 (0.5)	1.0 (0.3)	0.7 (0.3)	0.5 (0.2)	0.3 (0.1)	8.4 (5.1–11.5)	0.5 (0.3–0.6)
Males	AFR	<0.1‡ (0.1)	<0.1§ (0.0)	<0.1§ (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0–0.5)	0.0 (0.0–0.3)
	AMR	0.5 (1.3)	0.4 (1.0)	0.3 (0.8)	0.3 (0.7)	0.2 (0.6)	0.2 (0.5)	0.1 (0.4)	2.0 (1.3–2.4)	0.8 (0.5–1.0)
	EMR	0.2 (0.7)	0.1 (0.3)	0.1 (0.2)	<0.1‡ (0.1)	<0.1‡ (0.0)	<0.1§ (0.0)	<0.1§ (0.0)	0.4 (0.0–1.3)	0.3 (0.0–0.8)
	EUR	0.3 (1.2)	0.2 (0.9)	0.2 (0.6)	0.2 (0.5)	0.1 (0.4)	0.1 (0.3)	0.1 (0.2)	1.2 (0.7–1.5)	0.5 (0.3–0.7)
	SEAR	1.0 (1.0)	0.6 (0.6)	0.3 (0.4)	0.2 (0.2)	0.1 (0.1)	0.1 (0.1)	<0.1‡ (0.1)	2.3 (0.2–4.2)	0.4 (0.0–0.8)
	WPR	0.8 (1.3)	0.8 (0.9)	0.4 (0.6)	0.3 (0.4)	0.2 (0.2)	0.1 (0.2)	0.1 (0.1)	2.5 (1.4–3.5)	0.5 (0.3–0.7)
	Overall	2.9 (0.9)	1.9 (0.6)	1.3 (0.4)	1.0 (0.3)	0.6 (0.2)	0.4 (0.2)	0.3 (0.1)	8.4 (5.0–11.8)	0.4 (0.3–0.6)
Both	Global	5.6 (0.9)	3.8 (0.6)	2.7 (0.5)	2.0 (0.3)	1.3 (0.2)	0.9 (0.2)	0.6 (0.1)	16.8 (10.6–22.4)	0.3 (0.2–0.4)

Numbers (N) are the estimated number of people newly infected with HSV-1 during 2020. Numbers do not always sum exactly to the totals due to rounding.
Incidences (%) are the percentage of infected people in the age-, sex-, and region-specific population.
Regions are per WHO definitions.
*95% UI of the total number of infected people in millions.
†95% UI of percentage incidence.
‡Numbers are <50 000 but ≥10 000.
§Numbers are <5000 but ≥1000.
AFR, African Region; AMR, Region of the Americas; EMR, Eastern Mediterranean Region; EUR, European Region; HSV, herpes simplex virus; SEAR, South East Asia Region; UI, uncertainty interval; WPR, Western Pacific Region.

Table 4 Global and regional estimates of the number and percentage of the population aged 15–49 years with prevalent genital HSV-1 infection in 2020, by age and sex

Sex	WHO region	Number of people with prevalent genital HSV-1 infection in millions (population prevalence, %) by age group								
		15–19 years	20–24 years	25–29 years	30–34 years	35–39 years	40–44 years	45–49 years	All ages	
		N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (95% UI*)	% (95% UI†)
Females	AFR	0.1 (0.2)	0.1 (0.2)	0.1 (0.2)	0.1 (0.3)	0.1 (0.3)	0.1 (0.3)	0.1 (0.3)	0.6 (0.0–9.4)	0.3 (0.0–4.4)
	AMR	1.0 (3.5)	3.5 (9.6)	5.6 (14.6)	7.0 (18.6)	7.9 (22.0)	8.3 (24.7)	8.5 (26.9)	41.7 (27.5–50.6)	17.0 (11.2–20.6)
	EMR	0.5 (1.9)	1.2 (4.3)	1.6 (5.4)	1.7 (5.9)	1.5 (6.2)	1.3 (6.3)	1.1 (6.4)	8.8 (0.4–22.5)	5.7 (0.3–14.5)
	EUR	0.7 (3.8)	2.4 (9.9)	4.1 (14.5)	5.9 (18.1)	6.8 (20.8)	7.3 (22.8)	7.7 (24.4)	35.1 (22.8–43.0)	15.9 (10.3–19.5)
	SEAR	1.8 (2.7)	5.1 (6.5)	6.9 (8.8)	7.8 (10.2)	8.1 (11.1)	7.7 (11.7)	7.2 (12.0)	44.7 (4.4–74.2)	9.3 (0.9–15.4)
	WPR	1.5 (3.6)	4.8 (8.8)	7.6 (12.2)	11.3 (14.4)	10.4 (15.9)	10.6 (16.9)	13.1 (17.5)	59.3 (35.1–80.1)	12.0 (7.1–16.2)
	Overall	5.7 (1.9)	17.2 (6.0)	25.9 (9.0)	33.8 (11.5)	34.9 (13.1)	35.3 (14.5)	37.6 (15.9)	190.3 (115.2–249.7)	10.5 (6.4–13.8)
Males	AFR	0.1 (0.2)	0.1 (0.2)	0.1 (0.2)	0.1 (0.3)	0.1 (0.3)	0.1 (0.3)	0.1 (0.3)	0.6 (0.0–9.2)	0.3 (0.0–4.3)
	AMR	1.0 (3.3)	3.3 (8.9)	5.2 (13.5)	6.5 (17.2)	7.2 (20.3)	7.4 (22.8)	7.4 (24.8)	38.0 (24.8–45.8)	15.6 (10.2–18.9)
	EMR	0.5 (1.9)	1.3 (4.3)	1.7 (5.4)	1.8 (5.9)	1.7 (6.2)	1.4 (6.3)	1.2 (6.4)	9.7 (0.6–25.0)	5.8 (0.3–14.9)
	EUR	0.6 (3.0)	2.0 (7.9)	3.4 (11.5)	4.7 (14.2)	5.3 (16.1)	5.6 (17.6)	5.8 (18.7)	27.5 (16.8–34.0)	12.4 (7.5–15.3)
	SEAR	2.0 (2.7)	5.6 (6.5)	7.5 (8.8)	8.3 (10.2)	8.5 (11.1)	8.0 (11.7)	7.3 (12.0)	47.3 (3.7–78.6)	9.3 (0.7–15.5)
	WPR	1.7 (3.6)	5.3 (8.8)	8.3 (12.2)	12.0 (14.4)	10.9 (15.9)	11.0 (16.9)	13.6 (17.5)	62.9 (38.4–84.3)	12.0 (7.3–16.1)
	Overall	5.9 (1.9)	17.7 (5.8)	26.3 (8.6)	33.4 (10.9)	33.7 (12.3)	33.5 (13.5)	35.4 (14.8)	186.0 (111.4–250.7)	9.9 (5.9–13.4)
Both	Global	11.6 (1.9)	34.9 (5.9)	52.2 (8.8)	67.2 (11.2)	68.6 (12.7)	68.8 (14.0)	73.0 (15.3)	376.2 (235.6–483.5)	10.2 (6.4–13.1)

Numbers (N) are the year 2020 estimated number of people living with HSV-1 infection. Numbers do not always sum exactly to the totals due to rounding.
Prevalences (%) are the percentage of infected people in the age-, sex-, and region-specific population.
Regions are per WHO definitions.
*95% UI of the total number of infected people in millions.
†95% UI of percentage prevalence.
AFR, African Region; AMR, Region of the Americas; EMR, Eastern Mediterranean Region; EUR, European Region; HSV, herpes simplex virus; SEAR, South East Asia Region; UI, uncertainty interval; WPR, Western Pacific Region.

had both the highest HSV-2 GUD prevalence and the largest number of HSV-2 GUD person-days.

The number of individuals aged 15–49 years with at least one HSV-1 GUD episode in 2020 was estimated at 16.7 million (95% UI 9.3–25.2 million), a prevalence of 0.5% (95% UI 0.3–0.7%) (table 5). The total sum of GUD person-days was estimated at 166 million (95% UI 98–562 million) (online supplemental table S7). The Americas region had the highest HSV-1 GUD prevalence and the Western Pacific region had the largest number of HSV-1 GUD person-days.

The number of individuals aged 15–49 years with at least one HSV-2 or HSV-1 GUD episode in 2020 was estimated to be 204.6 million (95% UI 132.3–306.5 million) (table 5). The total number of person-days with GUD was estimated at 8841 million (95% UI 5795–15 425 million) (online supplemental table S7).

All and only oral HSV-1 infections

The number of new (incident) HSV-1 infections globally in 2020 at any site (oral and genital) among individuals aged 0–49 years was estimated at 122.2 million (95% UI 116.2–128.6 million) (online supplemental table S8). The African region had the highest HSV-1 incidence at nearly 40 million infections. The HSV-1 incidence rate decreased with age, most notably in regions where prevalence reached saturation at younger ages such as the African and Eastern Mediterranean regions (online supplemental table S8 and figure S1).

The number of people with prevalent HSV-1 infections globally in 2020 at any site (oral and genital) among individuals aged 0–49 years was estimated at 3779.1 million (95% UI 3510.3–3921.6 million), a prevalence of 64.2% (95% UI 59.7–66.7%) (online supplemental table S9). The African region had the highest prevalence, but the Western Pacific region had the largest number of HSV-1 infected persons. In the secondary analysis among individuals aged 50–99 years, an additional 1523.6 million people were estimated to be infected worldwide (online supplemental table S6).

The global prevalence of oral HSV-1 infection in 2020 among individuals aged 0–49 years was estimated at 58.6% (95% UI 53.5–62.1%) (online supplemental table S10). A total of 3448.9 million (95% UI 3144.9–3655.2 million) people aged 0–49 years were estimated to be orally infected worldwide. The African region had the highest oral HSV-1 prevalence.

DISCUSSION

In 2020, we estimated that 26 million people aged 15–49 years acquired a new HSV-2 infection, 520 million people were living with an HSV-2 infection, and 188 million people had at least one episode of GUD caused by HSV-2. Additionally, in 2020, 17 million people aged 15–49 years acquired a new genital HSV-1 infection through sexual transmission, 376 million people were living with genital HSV-1 infection, and 17 million people had at least one episode of GUD caused by HSV-1. Notably, sexual transmission accounted for only a portion of all HSV-1 infections. In total, two-thirds of the global population aged 0–49 years, or nearly 4 billion people, were infected (mostly orally) with HSV-1 in 2020, with over 120 million individuals newly infected in this year.

The estimates for genital infection, and particularly for GUD, are higher for HSV-2 than for HSV-1. Almost all HSV-2 acquisitions are sexually transmitted and occur genitally, while the majority of HSV-1 acquisitions are not genitally acquired. Most HSV-1 infections are acquired orally in childhood, although an increasing number are being acquired through sexual activity in adolescence and adulthood.[26–28 35] In addition, HSV-1 genital

Table 5 Global and regional estimates of number and percentage of the population aged 15–49 years with at least one episode of GUD due to HSV-2 or HSV-1 in 2020, by age and sex

Sex	WHO region	Number of people with HSV GUD in millions (population prevalence, %) by age group								
		15–19 years	20–24 years	25–29 years	30–34 years	35–39 years	40–44 years	45–49 years	All ages	
		N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (95% UI*)	% (95% UI†)
		HSV-2								
Females	AFR	4.0 (6.8)	6.0 (11.9)	7.0 (16.0)	7.3 (19.4)	7.1 (22.2)	6.4 (24.4)	5.6 (26.3)	43.3 (26.3–67.4)	16.1 (9.8–25.0)
	AMR	1.0 (2.6)	1.8 (4.7)	2.7 (6.7)	3.3 (8.6)	3.8 (10.4)	4.1 (12.0)	4.3 (13.5)	20.9 (12.2–33.9)	8.2 (4.7–13.2)
	EMR	0.1 (0.3)	0.2 (0.6)	0.3 (0.9)	0.3 (1.2)	0.4 (1.5)	0.4 (1.8)	0.3 (2.1)	2.0 (0.5–7.6)	1.1 (0.3–4.1)
	EUR	0.3 (1.2)	0.6 (2.2)	0.9 (3.2)	1.4 (4.1)	1.7 (5.0)	1.9 (5.9)	2.2 (6.8)	8.9 (4.5–16.6)	4.2 (2.1–7.9)
	SEAR	1.0 (1.1)	1.7 (2.1)	2.4 (3.0)	3.0 (3.9)	3.5 (4.8)	3.7 (5.6)	3.9 (6.4)	19.2 (11.2–32.0)	3.6 (2.1–6.0)
	WPR	0.8 (1.4)	1.5 (2.6)	2.5 (3.8)	3.9 (5.0)	4.0 (6.0)	4.5 (7.1)	6.1 (8.1)	23.3 (10.6–46.6)	5.1 (2.3–10.1)
	Overall	7.1 (2.4)	11.8 (4.1)	15.7 (5.5)	19.3 (6.5)	20.4 (7.7)	21.0 (8.6)	22.3 (9.4)	117.6 (72.0–184.1)	6.2 (3.8–9.6)
Males	AFR	2.3 (3.8)	3.5 (6.9)	4.2 (9.7)	4.6 (12.2)	4.6 (14.4)	4.2 (16.5)	3.8 (18.3)	27.1 (15.9–43.1)	10.1 (5.9–16.0)
	AMR	0.5 (1.3)	1.0 (2.5)	1.4 (3.6)	1.8 (4.7)	2.1 (5.7)	2.2 (6.7)	2.3 (7.7)	11.3 (6.2–19.0)	4.4 (2.4–7.4)
	EMR	0.1 (0.4)	0.2 (0.7)	0.3 (1.1)	0.4 (1.4)	0.5 (1.7)	0.5 (2.1)	0.4 (2.4)	2.5 (1.0–6.3)	1.3 (0.5–3.2)
	EUR	0.2 (0.6)	0.3 (1.2)	0.5 (1.8)	0.8 (2.3)	0.9 (2.8)	1.1 (3.4)	1.2 (3.9)	5.0 (2.3–10.2)	2.3 (1.0–4.7)
	SEAR	0.6 (0.6)	1.0 (1.1)	1.4 (1.6)	1.7 (2.1)	2.0 (2.6)	2.1 (3.1)	2.2 (3.6)	11.1 (5.5–20.2)	2.0 (1.0–3.6)
	WPR	0.5 (0.7)	0.9 (1.4)	1.4 (2.0)	2.2 (2.6)	2.2 (3.2)	2.5 (3.8)	3.4 (4.4)	13.2 (4.4–36.2)	2.7 (0.9–7.4)
	Overall	4.1 (1.3)	7.0 (2.3)	9.4 (3.1)	11.5 (3.7)	12.3 (4.5)	12.6 (5.1)	13.4 (5.6)	70.3 (43.0–116.7)	3.5 (2.2–5.8)
Both	Global	11.2 (1.8)	18.8 (3.2)	25.1 (4.2)	30.8 (5.1)	32.7 (6.0)	33.6 (6.8)	35.7 (7.5)	187.9 (116.0–291.8)	4.8 (3.0–7.5)
		HSV-1								
Females	AFR	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0–0.5)	0.0 (0.0–0.3)
	AMR	0.4 (0.9)	0.5 (1.2)	0.4 (1.0)	0.3 (0.8)	0.2 (0.7)	0.2 (0.5)	0.1 (0.4)	2.1 (1.2–3.0)	0.8 (0.5–1.2)
	EMR	0.2 (0.5)	0.1 (0.5)	0.1 (0.2)	0.0 (0.1)	0.0 (0.1)	0.0 (0.0)	0.0 (0.0)	0.4 (0.0–1.2)	0.3 (0.0–0.8)
	EUR	0.3 (1.0)	0.3 (1.2)	0.3 (0.9)	0.2 (0.7)	0.2 (0.5)	0.1 (0.4)	0.1 (0.3)	1.5 (0.8–2.2)	0.7 (0.4–1.0)
	SEAR	0.6 (0.7)	0.6 (0.7)	0.4 (0.5)	0.2 (0.3)	0.1 (0.2)	0.1 (0.1)	0.0 (0.1)	2.1 (0.2–4.1)	0.4 (0.0–0.8)
	WPR	0.5 (0.9)	0.6 (1.0)	0.4 (0.7)	0.4 (0.4)	0.2 (0.3)	0.1 (0.2)	0.1 (0.1)	2.3 (1.2–3.6)	0.5 (0.2–0.7)
	Overall	1.9 (0.7)	2.1 (0.7)	1.5 (0.5)	1.1 (0.4)	0.8 (0.3)	0.5 (0.2)	0.4 (0.2)	8.4 (4.7–12.5)	0.5 (0.3–0.7)
Males	AFR	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0–0.6)	0.0 (0.0–0.3)
	AMR	0.3 (0.9)	0.4 (1.1)	0.4 (0.9)	0.3 (0.7)	0.2 (0.6)	0.2 (0.5)	0.1 (0.4)	1.9 (1.1–2.8)	0.8 (0.5–1.1)
	EMR	0.2 (0.5)	0.1 (0.5)	0.1 (0.2)	0.0 (0.1)	0.0 (0.1)	0.0 (0.0)	0.0 (0.0)	0.4 (0.0–1.4)	0.3 (0.0–0.8)
	EUR	0.2 (0.8)	0.3 (1.0)	0.2 (0.7)	0.2 (0.5)	0.1 (0.4)	0.1 (0.3)	0.1 (0.2)	1.2 (0.6–1.7)	0.5 (0.3–0.8)
	SEAR	0.7 (0.7)	0.7 (0.7)	0.4 (0.5)	0.2 (0.3)	0.1 (0.2)	0.1 (0.1)	0.0 (0.1)	2.2 (0.2–4.4)	0.4 (0.0–0.9)
	WPR	0.6 (0.9)	0.7 (1.0)	0.5 (0.7)	0.4 (0.4)	0.2 (0.3)	0.1 (0.2)	0.1 (0.1)	2.5 (1.3–4.0)	0.5 (0.2–0.8)
	Overall	2.0 (0.6)	2.2 (0.7)	1.5 (0.5)	1.1 (0.4)	0.7 (0.3)	0.5 (0.2)	0.3 (0.1)	8.3 (4.5–12.7)	0.4 (0.2–0.7)
Both	Global	3.9 (0.6)	4.3 (0.7)	3.1 (0.5)	2.2 (0.4)	1.4 (0.3)	1.0 (0.2)	0.7 (0.1)	16.7 (9.3–25.2)	0.5 (0.3–0.7)
		HSV-2 and HSV-1								
Overall GUD	Females	9.0 (3.1)	14.0 (4.9)	17.2 (6.0)	20.4 (6.9)	21.2 (8.0)	21.5 (8.8)	22.7 (9.6)	126.0 (80.3–191.4)	6.6 (4.2–10.1)
	Males	6.1 (1.9)	9.2 (3.0)	10.9 (3.6)	12.6 (4.1)	13.0 (4.7)	13.1 (5.3)	13.7 (5.7)	78.6 (50.2–125.2)	4.0 (2.5–6.3)
	Both	15.2 (2.5)	23.2 (3.9)	28.1 (4.8)	33.0 (5.5)	34.2 (6.3)	34.5 (7.0)	36.4 (7.6)	204.6 (132.3–306.5)	5.3 (3.4–7.9)

Numbers (N) are the year 2020 estimated number of people living with genital ulcer disease caused by HSV-1 and/or HSV-2. Numbers do not always sum exactly to the totals due to rounding.
Prevalences (%) are the percentage of infected people in the age-, sex-, and region-specific population.
Regions are per WHO definitions.
*95% UI of the total number of infected people in millions.
†95% UI of percentage prevalence.
AFR, African Region; AMR, Region of the Americas; EMR, Eastern Mediterranean Region; EUR, European Region; GUD, genital ulcer disease; HSV, herpes simplex virus; SEAR, South East Asia Region; UI, uncertainty interval; WPR, Western Pacific Region.

tract infection is much less likely to recur compared with HSV-2 infection,[4] further reducing the relative contribution of HSV-1 to GUD, even in the presence of numerous genital HSV-1 infections.

HSV-2 global prevalence was virtually equal in the 2016 and 2020 estimation rounds (online supplemental table S5). Considering the shifts in the underlying demography during this time (increase in global average age and the changing proportion of the global population in each region[54]), HSV-2 prevalence, adjusted for the demographic trends, appears to be slowly declining, as indicated also by meta-regression and modelling analyses applied on prevalence data.[10–12 34 56] This decline may reflect less risky sexual behaviour following the HIV epidemic,[57–60] improved sexually transmitted infection (STI) awareness,[61] increasing access to HIV/STI services,[62 63] and/or changes in the structure of sexual networks following changes in socioeconomic conditions.[10]

The estimated number of prevalent genital HSV-1 infections is nearly twofold higher in 2020 compared with 2016 (376 vs 192 million) (online supplemental table S5). Meta-regression

analyses on the data extracted through the regional systematic reviews as well as modelling analyses have also indicated increasing rates of genital HSV-1 infection and decreasing rates of oral infections in several regions,[26–28 35] suggesting an epidemiological transition for this infection from an oral to increasingly genital acquisition.[26 64 65] The increase in the global adult population and its average age[54] has also contributed to the higher number of prevalent genital HSV-1 cases.

Differences in the global or regional estimates between 2016 and 2020 for both infections may also be attributed to improved data availability, specifically for capturing HSV-1 genital infections. In 2020, we had considerably more data from children in the South-East Asia region and the Western Pacific region, potentially presenting a more realistic pattern of HSV-1 prevalence by age in these regions. Although there was some overlap in the data used for the 2016 and 2020 rounds, these inputs were sourced from different countries and diverse general populations. Caution is warranted in interpreting differences or similarity in time trends of all estimates considering the changes in input data.

This study has limitations. The primary challenge in estimating HSV-1 and HSV-2 outcomes lies in the availability and representativeness of the data. However, the enhancement in the 2020 round of calibrating the model based on the series of HSV-1 and HSV-2 systematic reviews covering all global regions[9–12 27 28 34–40] has improved on this limitation, with more data available than were used in previous rounds (although this was also partly due to an expanded time frame for including data in the 2020 estimates). The challenges associated with input data underscore the need for more substantial, high quality, and representative HSV epidemiological data.

Some of the estimates, particularly those relating to HSV-1 genital infection, had wide 95% UIs due to limited input data. HSV-1 prevalence data among children remain very limited, but these data are critical for accurate and precise estimates of HSV-1 genital infection rates. Adults can be infected genitally only if they were not infected orally during childhood.[26] The proportion of incident HSV-1 infections that were estimated to be genital versus oral in adulthood was based on pooled data from only four available longitudinal studies, all of which were from the USA and based only on symptomatic infection incidence.[1 64 66–68] The estimate for this proportion may not be representative of its value in other countries or of asymptomatic infection.

The force of infection was assumed to be constant across age, but it was applied only to those still susceptible to infection, thereby allowing the incidence rate to decrease effectively with age. The model was calibrated to account for the maximum proportion of the population that can be infected, in addition to the force of infection. This ensured that prevalence saturates below 100% where indicated by the prevalence data. The scarcity of prevalence data for older age groups precluded the use of more complex models to account directly for a diminishing risk of infection at older ages.

The model was designed to provide estimates only for those aged under 50 years, as this age group is the focus of WHO programmes for sexual transmission of infection and reproductive health outcomes, and to align HSV estimates with WHO estimates for other STIs.[69–71] Prevalence estimates were additionally calculated in a secondary exploratory analysis for those aged above 50 years. However, these estimates were based on simplifying assumptions due to very limited prevalence data for those aged above 50 years. No incidence estimates could be generated, and no uncertainty bounds were incorporated for these prevalence estimates due to the simplifying assumptions in generating them.

In conclusion, HSV infections are widely prevalent in all global regions, leading to a significant burden of GUD with repercussions on psychosocial, sexual, and reproductive health, neonatal transmission, and HIV transmission. However, hardly any specific programmes for HSV prevention and control exist, even in resource-rich countries,[72 73] partly due to the lack of tools to address such highly prevalent, often asymptomatic, and incurable infections on a population level. Available prevention modalities, including condoms and antiviral therapy, are insufficient to control infection transmission and have, at best, had a modest population impact in reducing incidence rates. There is a need for HSV prophylactic and therapeutic vaccines as a strategic approach to control transmission and to curb the disease and economic burdens of these infections.[74–76]

Author affiliations
[1]Infectious Disease Epidemiology Group, Weill Cornell Medicine - Qatar, Doha, Qatar
[2]World Health Organization Collaborating Centre for Disease Epidemiology Analytics on HIV/AIDS, Sexually Transmitted Infections, and Viral Hepatitis, Weill Cornell Medicine–Qatar, Cornell University, Qatar Foundation - Education City, Doha, Qatar
[3]Department of Sexual and Reproductive Health and Research, World Health Organization, Geneva, GE, Switzerland
[4]Global HIV, Hepatitis and Sexually Transmitted Infections Programmes, World Health Organization, Geneva, Switzerland
[5]Department of Population Health Sciences, Weill Cornell Medicine, Cornell University, Ithaca, New York, USA
[6]Department of Public Health, College of Health Sciences, QU Health, Qatar University, Doha, Qatar
[7]College of Health and Life Sciences, Hamad bin Khalifa University, Doha, Qatar
[8]Population Health Sciences, University of Bristol, Bristol, UK

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ORCID iD

Laith J Abu-Raddad http://orcid.org/0000-0003-0790-0506

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Supplementary Material

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Box S1. Summary of the standardized methodology used in updating the previously conducted systematic reviews for Asia,[1 2] Europe,[3 4] Latin America and the Caribbean,[5 6] Middle East and North Africa,[7 8] sub-Saharan Africa,[9 10] and for Canada, Australia, New Zealand, and Pacific Island nations.[11-13]

Methodology	Detailed description
Data source and search strategy	- Searches were conducted up to March 30, 2022 in PubMed and Embase as well as in regional and country level databases for each of Asia, Europe, Latin America and the Caribbean, Middle East and North Africa, sub-Saharan Africa, and Canada, Australia, New Zealand, and Pacific Island nations. - Search strategies included exploded MeSH/Emtree terms and broad terms with no language or time restrictions.
Study selection and inclusion and exclusion criteria	- Search results were imported into the reference manager Endnote (Thomson Reuters, USA). - New citations were identified and screened. - Screening was performed in three stages: 1. Duplicate publications were identified and excluded. 2. Titles and abstracts were screened for relevant and potentially relevant publications. 3. Full texts of relevant and potentially relevant publications were retrieved and screened for relevance. - Inclusion criteria were any publication, including a study with a minimum sample size of 10, reporting primary data on HSV-1 and/or HSV-2 outcome measures (seroprevalence, seroincidence, proportion of HSV detection in clinically diagnosed genital ulcer disease, and proportion of HSV detection in laboratory-confirmed genital herpes). - Exclusion criteria were: o Case reports, case series, reviews, editorials, commentaries, and qualitative studies. o Measures reporting seroprevalence in infants aged <6 months as their antibodies can be maternal in origin.
Data extraction and data synthesis	- Extracted variables included: author(s), publication title, year(s) of data collection, year of publication, country of origin, country of survey, city, study site, study design, study sampling procedure, study population and its characteristics (e.g., sex and age), sample size, HSV outcome measures, and diagnostic assay. - Overall outcome measures and their stratified measures were extracted, provided the sample size in each stratum is ≥10. - For studies including overall sample size, but no individual strata sample sizes, the sample size of each stratum was assumed equal to overall sample size divided by the number of strata in the study. - Missing data points for year of data collection were imputed by adjusting the year of publication using the median difference with the year of data collection in studies that reported year of data collection. - Age was converted into a numeric variable using the mean or the median when reported or the midpoint of the age range reported. If a range is not fully defined (i.e. <25) we assumed that the range covered 10 years (i.e. 15-24) and calculated its midpoint accordingly. - Stratification hierarchy for HSV-1 seroprevalence in descending order of preference was: o Age o Sex - Stratification hierarchy for HSV-2 seroprevalence in descending order of preference was: o Sex o Age - Measures reporting any HSV-2 outcome among children <15 years old were not included in the analyses. - Data synthesis for HSV-1 infection: o HSV-1 seroprevalence measures among general populations* were included in the analysis, up to the year 2020. o Data with a midpoint of 2004 or thereafter for the year of data collection were included due to low data availability. o Data with a midpoint of 1995 or thereafter for the year of data collection were included only for Africa and South-East Asia, due to particularly poor data availability. o Studies with undefined age range were assumed to have an age range between 15-49 years and were included for Africa, Eastern Mediterranean, South-East Asia, and Western Pacific. o Studies among pregnant women with undefined age range were assumed to have an age range between 18-49. - Data synthesis for HSV-2 infection: o HSV-2 seroprevalence measures among general populations* were included in the analysis, up to the year 2020. o Data with a midpoint of 2004 or thereafter for the year of data collection were included due to low data availability. o Studies with undefined age range were assumed to have an age range between 15-49 years and were included for the Eastern Mediterranean and South-East Asia. o Studies among pregnant women with undefined age range were assumed to have an age range between 18-49. o One study among construction workers with an age range identified as ≥36 years was assumed to have an age range between 36-45 years.
Meta-analyses	- Meta-analyses were conducted using DerSimonian-Laird random-effects models with inverse variance weighting. The variance of each outcome measure was stabilized using the Freeman-Tukey arcsine square-root transformation. - For each WHO region, pooled mean HSV-1 seroprevalence and pooled mean HSV-2 seroprevalence were estimated by sex (when possible) and by 5-year age group when three or more data points were available. If only two data points were available, an average weighted by sample size was calculated. - Heterogeneity assessment was based on three complementary metrics: o Cochran's Q statistic to assess existence of heterogeneity in effect size (p-value<0.1 indicated heterogeneity). o I^2 heterogeneity measure to assess the percentage of between-study variation in effect size that is due to actual differences in effect size rather than chance. o Prediction interval to describe the distribution of true outcome measures around the pooled mean.

Abbreviations: HSV = Herpes simplex virus, WHO = World Health Organization

*General populations include populations at average exposure to HSV infections in the population, such as persons included in population-based surveys, antenatal clinic attendees, and pregnant women, among others.

Preparation of the seroprevalence data for pooling

1. Equivocal samples were included in the denominator of seroprevalence data points, rather than being excluded from both numerator and denominator, to avoid bias as such equivocal samples are likely to be sero-negative.
2. Adjustment for sensitivity and specificity for each assay type was not conducted since only studies using a robust assay were included. Moreover, assay type showed no association with HSV seroprevalence based on the series of conducted regional systematic reviews and meta-regressions for HSV-1 and HSV-2 seroprevalence.[1-13]
3. Meta-analyses were conducted when three or more data points were available. Average seroprevalence (weighted by sample size) was calculated when only two data points were available.
4. Missing data points for year of data collection were imputed by adjusting the year of publication using the median difference with the year of data collection in studies that reported year of data collection.
5. For studies of pregnant women where data on age were not available, we assumed an age range of 18-49 years.

Decisions on pooling criteria

HSV-1 estimates

1. Data with a midpoint of 2004 or thereafter for the year of data collection were included due to low data availability.
2. Data with a midpoint of 1995 or thereafter for the year of data collection were included only for Africa and South-East Asia, due to particularly poor data availability.
3. Studies with undefined age range were assumed to have an age range between 15-49 years and were included for Africa, Eastern Mediterranean, South-East Asia, and Western Pacific.
4. Single data points were included in the fitting for South-East Asia, due to particularly poor data availability.
5. Sex-specific estimates were produced for the Americas and Europe as per previous estimation round (with mixed-sex estimates for the other regions), except for children (<15 years), where mixed-sex pooled mean estimates were calculated for a given age band. These combined estimates were used in the fitting for each of females and males, to avoid the few data points for children by sex skewing the model fits by sex.
6. No sex specific estimates were calculated for Africa, Eastern Mediterranean region, South-East Asia, and Western Pacific since previous systematic reviews and meta-regressions showed no difference in seroprevalence by sex for these regions.[2 7 10 13]

HSV-2 estimates

1. Data with a midpoint of 2004 or thereafter for the year of data collection were included due to low data availability.
2. Studies with undefined age range were assumed to have an age range between 15-49 years and were included for Eastern Mediterranean and South-East Asia.
3. Single data points were included in the fitting for Eastern Mediterranean, due to particularly poor data availability.

Box S2. List of changes and methodological enhancements on the 2016 WHO HSV estimation round.[14]

Abbreviations: HSV = Herpes simplex virus, WHO = World Health Organization

Box S3. Calculation of prevalence and incidence estimates.

Pooled mean herpes simplex virus (HSV) seroprevalence values were used to calibrate HSV-1 and HSV-2 incidence using a constant incidence rate model. This model additionally accommodates a term representing the maximum proportion of individuals that can be infected which was simultaneously calibrated. This term allows seroprevalence to saturate at a low or moderate value if this is indicated by the pooled seroprevalence values. The model equation was as follows:

$$F(a) = k * (1 - e^{(-\lambda * a)})$$

where *F(a)* is the proportion of individuals (sero)positive at age *a* in years (i.e., with prevalent HSV-1 or HSV-2 infection), *k* is the maximum proportion of individuals that can be infected and λ is the force of infection per year. Both *k* and λ are sex-specific and region-specific parameters derived through model fitting.

The parameter *k* accounts for the fact that not all individuals in the population are at risk of infection. For example, someone who has never had sex, or had sex within a closed sexual network where no HSV-2 is circulating, is not at risk of HSV-2 infection regardless of the force of infection. The inclusion of this parameter in the equation, indirectly through the model fitting, also accounts for the possibility of lower incidence at older ages due to a diminishing risk of infection.

The force of infection (λ) represents the hazard rate of infection, which is the instantaneous rate at which susceptible individuals in a population become infected at a specific point in time, given that they have not yet been infected. It reflects the likelihood of infection occurring per unit of time and can be interpreted as the risk of infection for an individual who remains susceptible.

Interventions can affect one or both of these parameters. For instance, a vaccine that reduces susceptibility to infection can lower the values of both *k* and λ. However, the extent of this effect depends on the vaccine's mechanism of action and whether the protection it provides is sterilizing immunity or partial immunity. Although several vaccines are under development, no vaccine is currently available against HSV-2 or HSV-1 infections.

The model was applied for a specific year, 2020. Since the model estimation was conducted over a one-year time frame, vital dynamics were not incorporated, as the risk of death within such a short horizon is minimal.

We assumed that individuals can be infected with HSV-1 from age 0 years, and with HSV-2 from age 12 years, and adjusted the above equation as follows for HSV-2:

$$F(a) = k * (1 - e^{(-\lambda * (a-12))})$$

Fitting was done by using the Solver function in Excel to find those values of *k* and λ which maximized the (Bernoulli likelihood) value of:

$$ln \prod_{a} \left[F(a)^{S(a) * P(a)} * (1 - F(a))^{S(a) * (1 - P(a))} \right]$$

where *a* is the mid-point of each 5-year age group, *S(a)* is the total sample size (from summing across all studies), and *P(a)* is the pooled seroprevalence.

From the model fits we obtained smoothed seroprevalence estimates by sex and 5-year age group. Using demographic data for 2020 by sex and 5-year age group obtained from the United Nations Population Division,[15] and assuming a uniform distribution for population size within each 5-year age group, we multiplied seroprevalence estimates at each single year of age by regional population sizes to obtain estimates for the number of people with prevalent HSV-1 and HSV-2 infection by World Health Organization (WHO) region in 2020. The estimated number of new (incident) cases of infection at each single year of age, *I(a)*, was calculated as:

$$I(a) = \left(k - F(a)\right) * \lambda * N(a)$$

where *N(a)* is the total number of individuals (i.e., regional population size) at age *a*.

The percentage of people with genital infection due to either HSV-1 or HSV-2 was calculated using the following formula to correct for the estimated percentage with both HSV-2 and genital HSV-1 infection:

% with any genital HSV infection = [(% with HSV-2 infection + % with genital HSV-1 infection)] – (% with HSV-2 infection * % with genital HSV-1 infection)

Calculations were done for each single year of age separately by WHO region and sex. These percentages were then applied to demographic data for 2020[15] and summed.

Uncertainty bounds

We computed 95% uncertainty intervals (UI) on the number of individuals with prevalent HSV-1 and HSV-2 infection in 2020, as a function of the uncertainty in the underlying seroprevalence data. First, we recalibrated the force of infection, λ, to the upper confidence bounds of each region-, age-, and sex-specific pooled HSV-1 or HSV-2 seroprevalence value, keeping k constant. We then repeated this for the lower confidence

bounds of each pooled seroprevalence value. Next, we sampled the log force of infection using the log fitted force of infection and the standard error of the log fitted force of infection by sex and WHO region, assuming a normal distribution. The proportion of individuals from age 15 years that are infected orally and the proportion that are infected genitally among those with incident HSV-1 infection were also simultaneously sampled, again using the log odds and standard error of the log odds from the results of the meta-analysis for these proportions.[15] Repeating this 1000 times, the resulting set of 1000 estimates was then sorted from low to high for each estimate, sex, and region of interest and the 2.5 and 97.5 percentiles taken to represent the lower and upper uncertainty bounds.

Parameter values

The following inserts provide the values of the k and λ parameters for HSV-2 and HSV-1 as estimated through model fitting for the 2020 round reported in this study, along with the parameter values estimated in the prior 2016 round. The parameter values were generally similar across both rounds in most regions, reflecting the consistency in the estimated outcomes. However, more variation was observed in regions with sparse data, primarily due to changes in the input data.

HSV-2 parameters

	2020				**2016**			
	Females		**Males**		**Females**		**Males**	
	k	λ	k	λ	k	λ	k	λ
Americas	1.000000	0.013654	1.000000	0.006929	1.000000	0.014785	1.000000	0.006582
Africa	1.000000	0.038944	1.000000	0.020674	0.759723	0.061039	1.000000	0.018679
Eastern Mediterranean	1.000000	0.001693	1.000000	0.001969	1.000000	0.004516	1.000000	0.001584
Europe	1.000000	0.006041	1.000000	0.003282	1.000000	0.005556	1.000000	0.002686
South-East Asia	1.000000	0.005694	1.000000	0.003018	1.000000	0.005526	1.000000	0.004134
Western Pacific	1.000000	0.007384	1.000000	0.003782	1.000000	0.007731	1.000000	0.003633

All figures to 6 decimal places.

HSV-1 parameters

	2020				**2016**			
	Females		**Males**		**Females**		**Males**	
	k	λ	k	λ	k	λ	k	λ
Americas	0.931595	0.039927	0.860120	0.040899	0.980463	0.032228	1.000000	0.025174
Africa	0.952743*	0.374496*	0.952743*	0.374496*	0.973413*	0.439394*	0.973413*	0.439394*
Eastern Mediterranean	0.766483*	0.143536*	0.766483*	0.143536*	0.927792*	0.101961*	0.927792*	0.101961*
Europe	0.920377	0.054858	0.740170	0.059997	0.875067	0.087355	1.000000	0.033077
South-East Asia	0.735303*	0.096413*	0.735303*	0.096413*	0.679605*	0.321209*	0.679605*	0.321209*
Western Pacific	0.914719*	0.084245*	0.914719*	0.084245*	0.836954	0.216385	0.723833	0.261755

All figures to 6 decimal places.
*Sex-specific estimates not done.

Table S1. Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER) checklist.[16]

Item #	Checklist item	Reported on page #
Objectives and funding		
1	Define the indicator(s), populations (including age, sex, and geographic entities), and time period(s) for which estimates were made.	Introduction section, Page 7
2	List the funding sources for the work.	Title page, Page 1
Data Inputs		
For all data inputs from multiple sources that are synthesized as part of the study:		
3	Describe how the data were identified and how the data were accessed.	Methods: Model input, Page 8; Box S1, Page 3 of Supplementary Material
4	Specify the inclusion and exclusion criteria. Identify all ad-hoc exclusions.	Methods: Model input, Page 8; Box S1, Page 3 of Supplementary Material
5	Provide information on all included data sources and their main characteristics. For each data source used, report reference information or contact name/institution, population represented, data collection method, year(s) of data collection, sex and age range, diagnostic criteria or measurement method, and sample size, as relevant.	Table S1, Page 6, Table S2, Page 7, and Table S3, Page 16; Box S4, Page 8 and Box S5, Page 13. All in Supplementary Material
6	Identify and describe any categories of input data that have potentially important biases (e.g., based on characteristics listed in item 5).	Box S2, Page 4 of Supplementary Material
For data inputs that contribute to the analysis but were not synthesized as part of the study:		
7	Describe and give sources for any other data inputs.	Box S3, Page 5 of Supplementary Material
For all data inputs:		
8	Provide all data inputs in a file format from which data can be efficiently extracted (e.g., a spreadsheet rather than a PDF), including all relevant meta-data listed in item 5. For any data inputs that cannot be shared because of ethical or legal reasons, such as third-party ownership, provide a contact name or the name of the institution that retains the right to the data.	Table S1, Page 6, Table S2, Page 7, and Table S3, Page 16; Box S4, Page 8 and Box S5, Page 13. All in Supplementary Material
Data analysis		
9	Provide a conceptual overview of the data analysis method. A diagram may be helpful.	Methods: Starting in Model calibrations, Page 9; Box S3, Page 5 of Supplementary Material
10	Provide a detailed description of all steps of the analysis, including mathematical formulae. This description should cover, as relevant, data cleaning, data pre-processing, data adjustments and weighting of data sources, and mathematical or statistical model(s).	Methods: Starting in Model calibrations, Page 9; Box S3, Page 5 of Supplementary Material
11	Describe how candidate models were evaluated and how the final model(s) were selected.	NA
12	Provide the results of an evaluation of model performance, if done, as well as the results of any relevant sensitivity analysis.	NA
13	Describe methods for calculating uncertainty of the estimates. State which sources of uncertainty were, and were not, accounted for in the uncertainty analysis.	Methods: Starting in Model calibrations, Page 9; Box S3, Page 5 of Supplementary Material
14	State how analytic or statistical source code used to generate estimates can be accessed.	Box S3, Page 5 of Supplementary Material
Results and Discussion		
15	Provide published estimates in a file format from which data can be efficiently extracted.	Tables 1-5, Pages 24-28; Tables S5-S10, Pages 18, 21-25
16	Report a quantitative measure of the uncertainty of the estimates (e.g. uncertainty intervals).	Tables 1-5, Pages 24-28; Tables S5-S10, Pages 18, 21-25
17	Interpret results in light of existing evidence. If updating a previous set of estimates, describe the reasons for changes in estimates.	Results: starting in Page 12; Discussion: starting in Page 17
18	Discuss limitations of the estimates. Include a discussion of any modelling assumptions or data limitations that affect interpretation of the estimates.	Discussion: starting in Page 17

Abbreviations: HSV = Herpes simplex virus, NA: Not Applicable.

Table S2. Summary of the extracted HSV-1 and HSV-2 epidemiological outcome measures in the series of regional systematic reviews and their updates.

Region	Screened citations for HSV-1 and HSV-2	Previously extracted relevant publications in the regional systematic reviews	Newly extracted relevant publications in the updates of the systematic reviews	Extracted epidemiological outcome measures
Asia	16,375	222	20	• 26 overall HSV-2 seroincidence measures • 66 overall HSV-1 seroprevalence measures yielding 204 stratified measures • 283 overall HSV-2 seroprevalence measures yielding 697 stratified measures • 9 overall proportions of HSV-1 detection in GUD cases • 15 overall proportions of HSV-2 detection in GUD cases yielding 16 stratified proportions • 26 overall proportions of HSV-1 detection in genital herpes cases yielding 27 stratified proportions • 43 overall proportions of HSV-2 detection in genital herpes cases yielding 46 stratified proportions
Africa	24,474	255	19	• 95 overall HSV-2 seroincidence measures • 49 overall HSV-1 seroprevalence measures yielding 76 stratified measures • 352 overall HSV-2 seroprevalence measures yielding 811 stratified measures • 19 overall proportions of HSV-1 detection in GUD cases yielding 32 stratified proportions • 26 overall proportions of HSV-2 detection in GUD cases • 8 overall proportions of HSV-1 detection in genital herpes cases • 9 overall proportions of HSV-2 detection in genital herpes cases yielding 11 stratified proportions
Canada, Australia, New Zealand, and Pacific Islands	3,173	90	55	• 2 overall HSV-1 seroincidence measures • 7 overall HSV-2 seroincidence measures • 61 overall HSV-1 seroprevalence measures yielding 106 stratified seroprevalence measures • 37 overall HSV-2 seroprevalence measures yielding 99 stratified seroprevalence measures • 5 overall proportions of HSV-1 detection in GUD cases • 5 overall proportions of HSV-2 detection in GUD cases • 17 overall proportions of HSV-1 detection in genital herpes cases yielding 52 stratified proportions • 16 overall proportions of HSV-2 detection in genital herpes cases yielding 46 stratified proportions
Europe	19,153	353	15	• 1 overall HSV-1 seroincidence measure • 14 overall HSV-2 seroincidence measures • 198 overall HSV-1 seroprevalence measures yielding 648 stratified measures • 302 overall HSV-2 seroprevalence measures yielding 822 stratified measures • 8 overall proportions of HSV-1 detection in GUD cases • 17 overall proportions of HSV-2 detection in GUD cases yielding 19 stratified proportions • 70 overall proportions of HSV-1 detection in genital herpes cases yielding 180 stratified proportions • 76 overall proportions of HSV-2 detection in genital herpes cases yielding 201 stratified proportions
Middle East and North Africa	5,320	52	8	• 62 overall HSV-1 seroprevalence measures yielding 112 stratified measures • 60 overall HSV-2 seroprevalence measures yielding 131 stratified measures • 1 overall proportion of HSV-1 detection in GUD cases • 1 overall proportion of HSV-2 detection in GUD cases • 1 overall proportion of HSV-1 detection in genital herpes cases • 3 overall proportions of HSV-2 detection in genital herpes cases yielding 6 stratified proportions
Latin America and the Caribbean	8,477	133	6	• 13 overall HSV-2 seroincidence measures • 47 overall HSV-1 seroprevalence measures yielding 73 stratified measures • 167 overall HSV-2 seroprevalence measures yielding 410 stratified measures • 18 overall proportions of HSV-1 detection in GUD cases • 7 overall proportions of HSV-2 detection in GUD cases • 8 overall proportions of HSV-1 detection in genital herpes cases • 10 overall proportion of HSV-2 detection in genital herpes cases

Abbreviations: HSV = Herpes simplex virus, GUD = Genital ulcer disease.

Box S4. List of articles on the general population from which an HSV-2 prevalence measure was extracted and included in the meta-analyses.

1. Abbai NS, Govender S, Nyirenda M. Herpes simplex virus-2 infections in pregnant women from Durban, South Africa: prevalence, risk factors and co-infection with HIV-1. Southern African Journal of Infectious Diseases 2018.
2. Abdool Karim Q, Kharsany AB, Leask K, et al. Prevalence of HIV, HSV-2 and pregnancy among high school students in rural KwaZulu-Natal, South Africa: a bio-behavioural cross-sectional survey. Sex Transm Infect 2014; 90(8): 620-6.
3. Abul-Razak SHH, Abbas AA-D, Hwaid AH, Wasan AM, Fadeel ZG. Seroprevalence of Anti- Herpes Simplex Virus Type2 IgG, IgM Antibodies Among Pregnant Women in Diyala Province. Diyala Journal of Medicine 2013; 5(1): 36-43.
4. Achilles SL, Mhlanga F, Dezzutti CS, et al. Differences in genital tract immune cell populations and innate cervicovaginal fluid anti-HIV activity among women from Zimbabwe and the United States. AIDS Research and Human Retroviruses 2016; 32(Supplement 1): 78.
5. Adamson PC, Krupp K, Freeman AH, Klausner JD, Reingold AL, Madhivanan P. Prevalence & correlates of primary infertility among young women in Mysore, India. Indian Journal of Medical Research 2011; 134(10): 440-6.
6. Akinyi B, Odhiambo C, Otieno F, et al. Prevalence, incidence, and correlates of HSV-2 infection in an HIV incidence adolescent and adult cohort study in western Kenya. PloS one 2017; 12(6): e0178907.
7. Al-Hakami AM, Paul E, Al-Abed F, et al. Prevalence of toxoplasmosis, rubella, cytomegalovirus, and herpes (TORCH) infections among women attending the antenatal care clinic, maternity hospital in Abha, Southwestern Saudi Arabia. Saudi Med J 2020; 41(7): 757-62.
8. Alberts CJ, Schim van der Loeff MF, Papenfuss MR, et al. Association of Chlamydia trachomatis infection and herpes simplex virus type 2 serostatus with genital human papillomavirus infection in men: the HPV in men study. Sex Transm Dis 2013; 40(6): 508-15.
9. Ali MK, Hathal HD, Almoayed HA. Prevalence and diagnosis of genital herpes by immunological and molecular study Iraqi Journal of Medical Sciences 2018; 16(1): 4-7.
10. Alshareef SA, Eltom AM, Nasr AM, Hamdan HZ, Adam I. Rubella, herpes simplex virus type 2 and preeclampsia. Virol J 2017; 14(1): 142.
11. Anaedobe CG, Ajani TA. Co-infection of herpes simplex virus type 2 and HIV infections among pregnant women in Ibadan, Nigeria. Journal of Global Infectious Diseases 2019; 11(1): 19-24.
12. Anjulo AA, Abebe T, Hailemichael F, Mihret A. Seroprevalence and risk factors of herpes simplex virus-2 among pregnant women attending antenatal care at health facilities in Wolaita zone, Ethiopia. Virol J 2016; 13: 43.
13. Arama V, Cercel AS, Vladareanu R, et al. Type-specific herpes simplex virus-1 and herpes simplex virus-2 seroprevalence in Romania: comparison of prevalence and risk factors in women and men. International journal of infectious diseases: IJID: official publication of the International Society for Infectious Diseases 2010; 14 Suppl 3: e25-31.
14. Asgari S, Chamani-Tabriz L, Asadi S, et al. HSV-2 seroepidemiology and risk factors among Iranian women: A time to new thinking. Iranian Red Crescent Medical Journal 2011; 13(11): 818-23.
15. Austrian K, Hewett PC, Soler-Hampejsek E, Bozzani F, Behrman JR, Digitale J. Adolescent Girls Empowerment Programme: research and evaluation mid-term technical report, 2016.
16. Baird SJ, Garfein RS, McIntosh CT, Ozler B. Effect of a cash transfer programme for schooling on prevalence of HIV and herpes simplex type 2 in Malawi: a cluster randomised trial. Lancet (London, England) 2012; 379(9823): 1320-9.
17. Balaeva T, Grjibovski AM, Sidorenkov O, et al. Seroprevalence and correlates of herpes simplex virus type 2 infection among young adults in Arkhangelsk, Northwest Russia: a population-based cross-sectional study. 2016; 16(1): 616.
18. Behanzin L, Diabate S, Minani I, et al. Decline in HIV Prevalence among Young Men in the General Population of Cotonou, Benin, 1998-2008. PloS one 2012; 7(8): e43818.
19. Benjamin RJ, Busch MP, Fang CT, et al. Human immunodeficiency virus-1 infection correlates strongly with herpes simplex virus-2 (genital herpes) seropositivity in South African and United States blood donations. Transfusion 2008; 48(2): 295-303.
20. Biraro S, Kamali A, White R, et al. Effect of HSV-2 on population-level trends in HIV incidence in Uganda between 1990 and 2007. Tropical medicine & international health: TM & IH 2013; 18(10): 1257-66.
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22. Biswas D, Borkakoty B, Mahanta J, et al. Seroprevalence and risk factors of herpes simplex virus type-2 infection among pregnant women in Northeast India. BMC Infect Dis 2011; 11: 325.
23. Bjerke SE, Holter E, Vangen S, Stray-Pedersen B. Sexually transmitted infections among Pakistani pregnant women and their husbands in Norway. International journal of women's health 2010; 2: 303-9.
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35. Chen L, Liu J, Shi L, et al. Seasonal influence on TORCH infection and analysis of multi-positive samples with indirect immunofluorescence assay. J Clin Lab Anal 2019; 33(4): e22828.
36. Cheslack-Postava K, Brown AS, Chudal R, et al. Maternal exposure to sexually transmitted infections and schizophrenia among offspring. Schizophrenia research 2015; 166(1-3): 255-60.
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Abbreviations: HSV = Herpes simplex virus.

Box S5. List of articles on the general population from which an HSV-1 prevalence measure was extracted and included in the meta-analyses.

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Abbreviations: HSV = Herpes simplex virus.

Table S3. HSV-2 prevalence measures among general populations included in the WHO HSV estimations, by region, sex, and age group.

WHO Region	Sex	Number of data points that contributed to the estimation by age group (in years)							Countries with data
		15-19	20-24	25-29	30-34	35-39	40-44	45-49	
African	Females	45	33	27	19	9	8	4	Benin, Côte d'Ivoire, Ethiopia, Kenya, Malawi, Namibia, Nigeria, Rwanda, Senegal, South Africa, Tanzania, Uganda, Zambia, Zimbabwe
	Males	17	22	10	11	5	10	4	Benin, Kenya, Malawi, Namibia, Nigeria, Rwanda, South Africa, Tanzania, Uganda, Zambia
Americas	Females	7	8	11	11	7	8	7	Bolivia, Brazil, Canada, Haiti, Honduras, Mexico, Panama, USA
	Males	6	6	6	6	6	11	6	Brazil, Canada, Honduras, Mexico, Panama, USA
Eastern Mediterranean	Females	1	1	4	6	1	-	-	Iran, Iraq, Pakistan, Saudi Arabia, Sudan
	Males	4	2	10	5	8	5	5	Afghanistan, Egypt, Iraq, Jordan, Lebanon, Pakistan, Palestine, Qatar, Saudi Arabia, Syria
European	Females	6	11	15	16	10	7	6	Croatia, Finland, France, Germany, Greece, Italy, Netherlands, Norway, Poland, Romania, Russia, Serbia, Sweden, Switzerland, Turkey
	Males	3	9	7	10	8	6	5	Croatia, Germany, Greece, Italy, Netherlands, Norway, Romania, Russia, Serbia, Sweden, Turkey
South-East Asia	Females	4	6	8	4	4	3	1	India
	Males	1	3	4	6	3	4	2	India
Western Pacific	Females	2	7	12	12	6	5	7	Australia, China, Korea, Papua New Guinea, Vietnam
	Males	2	5	6	8	4	5	4	Australia, China, Korea, Papua New Guinea, Philippines

Abbreviations: HSV= Herpes simplex virus, USA = United States of America, WHO = World Health Organization.
Regions are per World Health Organization definitions.

Table S4. HSV-1 prevalence measures among general populations included in the WHO HSV estimations, by region, sex, and age group.

WHO Region	Sex	Number of data points that contributed to the estimation by age group (in years)										Countries with data
		0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	
African	Females, males, and mixed sexes	3	2	3	4	-	6	7	2	2	-	Central African Republic, Mali, South Africa, Uganda, Zimbabwe
Americas	Females	-	2[a]	10[a]	6	6	8	9	6	5	5	Brazil, Canada, Mexico, USA
	Males				6	5	6	6	6	5	5	Mexico, USA
Eastern Mediterranean	Females, males, and mixed sexes	-	-	-	3	4	8	7	17	7	5	Egypt, Iran, Iraq, Jordan, Lebanon, Morocco, Pakistan, Palestine, Qatar, Sudan, Syria, Tunisia, Yemen
European	Females	7[a]	6[a]	5[a]	4	6	10	10	5	5	2	Croatia, Finland, France, Germany, Greece, Netherland, Poland, Romania, Serbia, Sweden, Switzerland, Turkey
	Males				2	3	4	3	3	3	2	Germany, Greece, Netherland, Romania, Sweden
South-East Asia	Females, males, and mixed sexes	-	1	-	4	2	3	8	2	4	1	India, Indonesia
Western Pacific	Females, males, and mixed sexes	2	12	5	2	5	4	15	3	6	5	Australia, China, Philippines

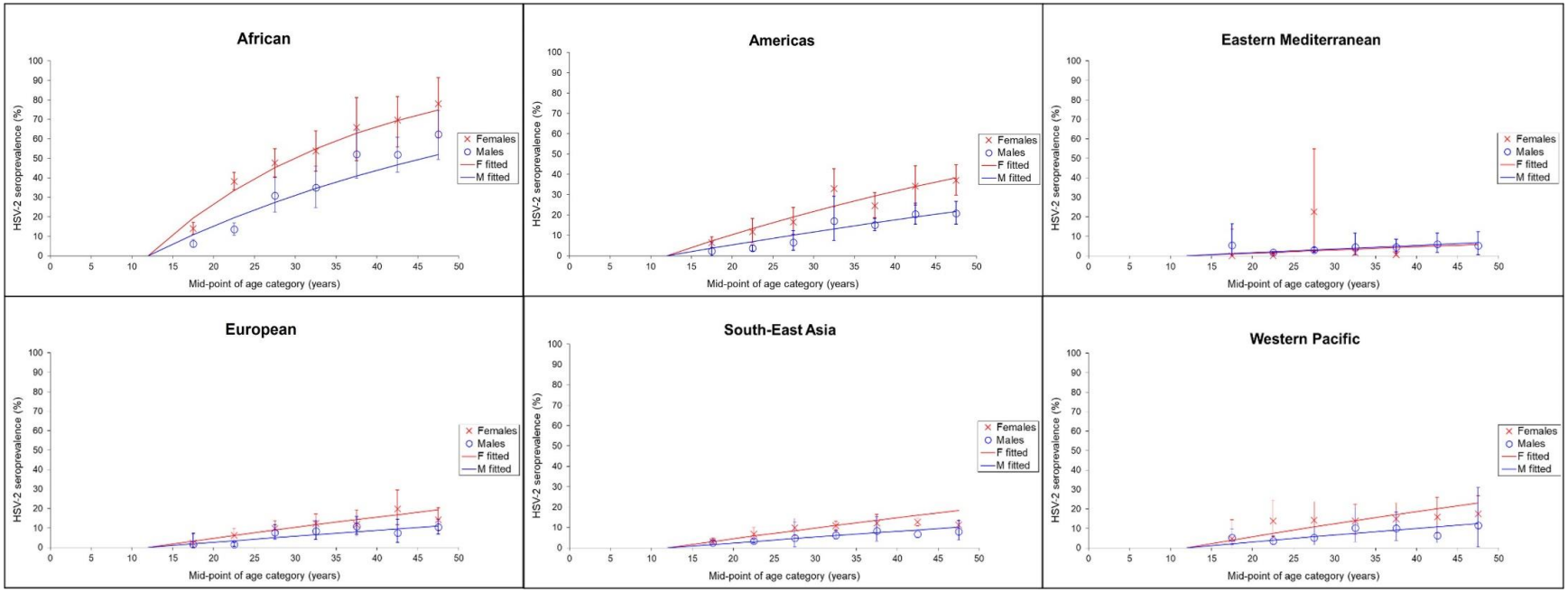
Abbreviations: HSV = Herpes simplex virus, USA = United States of America, WHO = World Health Organization.
[a] These measures included females, males, and mixed sexes for given age bands.
Regions are per World Health Organization definitions.

Table S5. Comparison of HSV estimates over the WHO HSV estimation rounds.[14 17-19]

2012 global estimates	2016 global estimates	2020 global estimates
• 37 articles were used as modelling input for HSV-1 • 111 articles were used as modelling input for HSV-2	• 44 articles were used as modelling input for HSV-1 • 88 articles were used as modelling input for HSV-2	• 82 articles were used as modelling input for HSV-1 • 134 articles were used as modelling input for HSV-2
HSV-1 incidence at any site (oral and genital): • 118.0 million new HSV-1 infections among individuals aged 0-49 years • HSV-1 incidence rate of 2.0%	**HSV-1 incidence at any site (oral and genital):** • 120.4 million new HSV-1 infections among individuals aged 0-49 years • HSV-1 incidence rate of 2.1%	**HSV-1 incidence at any site (oral and genital):** • 122.2 million new HSV-1 infections among individuals aged 0-49 years • HSV-1 incidence rate of 2.1%
HSV-1 prevalence at any site (oral and genital): • 3,709.0 million HSV-1 prevalent infections among individuals aged 0-49 years • HSV-1 prevalence of 67.0%	**HSV-1 prevalence at any site (oral and genital):** • 3,752.0 million HSV-1 prevalent infections among individuals aged 0-49 years • HSV-1 prevalence of 66.6%	**HSV-1 prevalence at any site (oral and genital):** • 3,779.1 million HSV-1 prevalent infections among individuals aged 0-49 years • HSV-1 prevalence of 64.2%
Oral HSV-1 prevalence: No estimates were produced	**Oral HSV-1 prevalence:** • 3,583.5 million oral HSV-1 prevalent infections among individuals aged 0-49 years • Oral HSV-1 prevalence of 63.6%	**Oral HSV-1 prevalence:** • 3,448.9 million oral HSV-1 prevalent infections among individuals aged 0-49 years • Oral HSV-1 prevalence of 58.6%
Genital HSV-1 prevalence: • 140.0 million genital HSV-1 prevalent infections among individuals aged 15-49 years • Genital HSV-1 prevalence of 4.0%	**Genital HSV-1 prevalence:** • 192.0 million genital HSV-1 prevalent infections among individuals aged 15-49 years • Genital HSV-1 prevalence of 5.2%	**Genital HSV-1 prevalence:** • 376.2 million genital HSV-1 prevalent infections among individuals aged 15-49 years • Genital HSV-1 prevalence of 10.2%
HSV-2 Incidence: • 19.2 million new HSV-2 infections among individuals aged 15-49 years • HSV-2 incidence rate of 0.5%	**HSV-2 Incidence:** • 23.9 million new HSV-2 infections among individuals aged 15-49 years • HSV-2 incidence rate of 0.6%	**HSV-2 Incidence:** • 25.6 million new HSV-2 infections among individuals aged 15-49 years • HSV-2 incidence rate of 0.7%
HSV-2 prevalence: • 417.3 million HSV-2 prevalent infections among individuals aged 15-49 years • HSV-2 prevalence of 11.3%	**HSV-2 prevalence:** • 491.5 million HSV-2 prevalent infections among individuals aged 15-49 years • HSV-2 prevalence of 13.2%	**HSV-2 prevalence:** • 519.5 million HSV-2 prevalent infections among individuals aged 15-49 years • HSV-2 prevalence of 13.3%
GUD caused by HSV-1: No estimates were produced	**GUD caused by HSV-1:** • 9.2 million individuals living with GUD due to HSV-1 infection among individuals aged 15-49 years • Prevalence of GUD caused by HSV-1 of 0.2%	**GUD caused by HSV-1:** • 16.7 million individuals living with GUD due to HSV-1 infection among individuals aged 15-49 years • Prevalence of GUD caused by HSV-1 of 0.5%
GUD caused by HSV-2: No estimates were produced	**GUD caused by HSV-2:** • 177.7 million individuals living with GUD due to HSV-2 infection among individuals aged 15-49 years • Prevalence of GUD caused by HSV-2 of 4.8%	**GUD caused by HSV-2:** • 187.9 million individuals living with GUD due to HSV-2 infection among individuals aged 15-49 years • Prevalence of GUD caused by HSV-2 of 4.8%

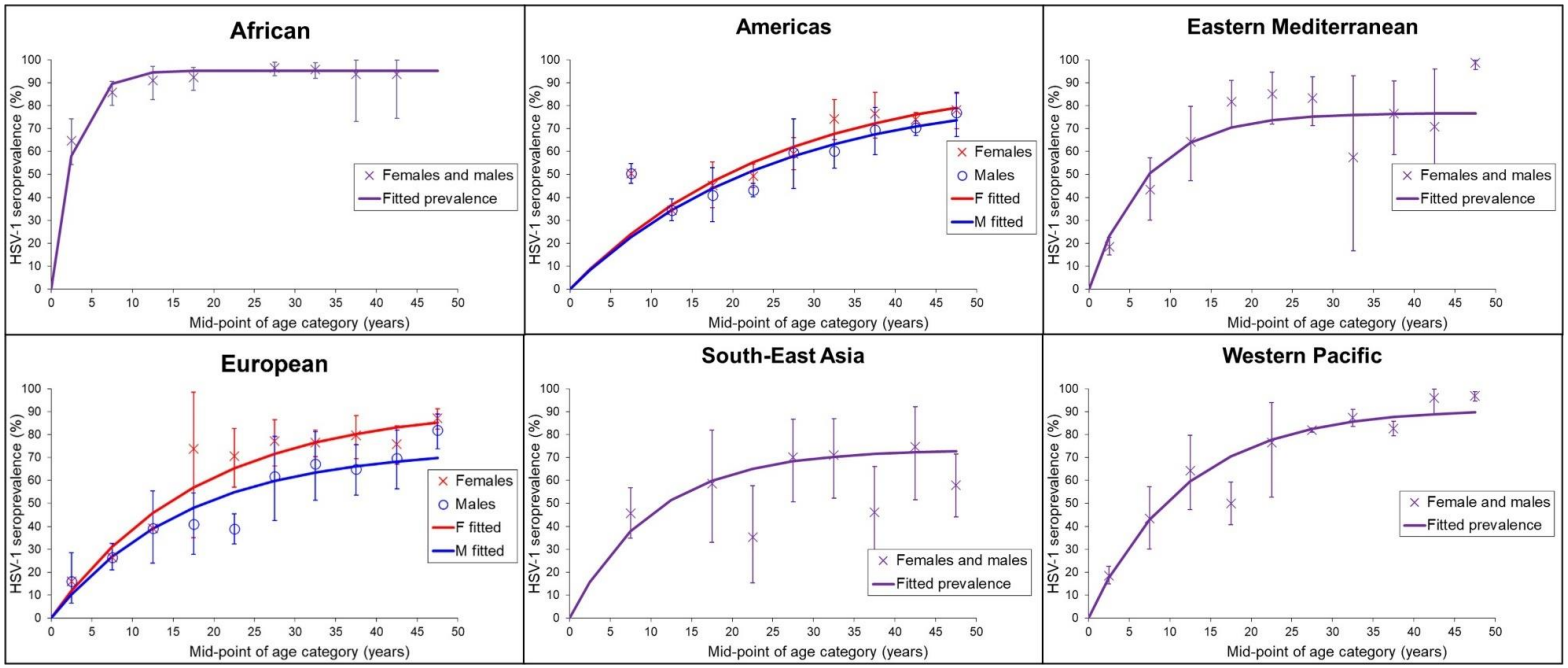
Abbreviations: GUD = Genital ulcer disease, HSV = Herpes simplex virus, WHO = World Health Organization.

Figure S1. Model fits for HSV-2 prevalence for each WHO region. Data are presented as pooled mean point estimates and corresponding 95% confidence intervals. Error bars represent the 95% confidence intervals of the pooled estimates.



Abbreviations: HSV = Herpes simplex virus, WHO = World Health Organization.
Regions are per World Health Organization definitions.

Figure S2. Model fits for HSV-1 prevalence (any site; oral and genital) for each WHO region. Data are presented as pooled mean point estimates and corresponding 95% confidence intervals. Error bars represent the 95% confidence intervals of the pooled estimates.



Abbreviations: HSV = Herpes simplex virus, WHO = World Health Organization.
Regions are per World Health Organization definitions.

Table S6. Global and regional estimates of the number of people aged 50-99 years with prevalent HSV-1 or HSV-2 infection in 2020, by sex.

WHO Region	Number of people with prevalent infection in millions by sex					
	HSV-1 (any site, oral or genital)			HSV-2		
	Female	Male	Both	Female	Male	Both
AFR	58.2	51.3	**109.4**	45.7	28.0	**73.7**
AMR	119.6	97.7	**217.3**	58.0	28.9	**86.9**
EMR	40.4	41.2	**81.5**	3.1	3.6	**6.7**
EUR	158.8	104.9	**263.6**	36.0	16.5	**52.5**
SEAR	150.1	145.7	**295.7**	37.7	20.3	**58.1**
WPR	286.0	270.0	**555.9**	73.4	37.8	**111.2**
Global	**813.0**	**710.6**	**1,523.6**	**254.0**	**135.2**	**389.1**

Abbreviations: AFR = African Region, AMR = Region of the Americas, EMR = Eastern Mediterranean Region, EUR = European Region, HSV = Herpes simplex virus, SEAR = South-East Asia region, WHO = World Health Organization, WPR = Western Pacific Region.
Numbers are the year 2020 estimated number of people living with HSV-1 and HSV-2 infections. Numbers do not always sum exactly to the totals due to rounding.
Regions are per World Health Organization definitions.

Table S7. Global and regional estimates of GUD person-days due to HSV-2 or HSV-1 among the population aged 15-49 years in 2020, by age and sex.

Sex	WHO region	Number of GUD person-days in millions by age group								
		15-19 years	20-24 years	25-29 years	30-34 years	35-39 years	40-44 years	45-49 years	All ages	95% UI[a]
						HSV-2				
Females	AFR	187	269	321	341	335	303	264	2,019	1,270-3,365
	AMR	45	82	121	151	175	190	200	964	574-1,674
	EMR	5	8	12	16	17	17	16	91	26-415
	EUR	14	25	42	63	77	89	101	411	221-767
	SEAR	44	77	110	138	162	173	179	883	535-1,505
	WPR	36	68	112	181	184	208	283	1,072	538-2,315
	Overall	330	530	717	890	951	978	1,044	5,440	3,581-9,436
Males	AFR	106	157	193	211	212	197	176	1,253	767-2,157
	AMR	24	44	66	82	95	102	108	520	307-932
	EMR	6	10	15	20	22	22	21	116	46-291
	EUR	8	15	24	36	44	50	56	232	110-498
	SEAR	26	46	64	80	93	98	102	509	274-985
	WPR	21	39	64	102	103	117	160	606	196-1,813
	Overall	190	311	427	530	568	586	622	3,235	2,038-5,508
Both	Global	520	841	1,144	1,421	1,519	1,564	1,666	8,675	5,632-15,068
						HSV-1				
Females	AFR	0.3	0.0	0.0	0.0	0.0	0.0	0.0	0.3	0-7
	AMR	5	4	4	3	2	2	1	21	13-66
	EMR	2	1	0.5	0.2	0.1	0.0	0.0	4	0-16
	EUR	4	3	2	2	2	1	0.9	15	9-50
	SEAR	9	5	3	2	1	0.6	0.3	20.6	2-72
	WPR	7	5	4	3	2	1	0.8	22	12-82
	Overall	27	18	13	10	7	5	3	83	50-275
Males	AFR	0.3	0.0	0.0	0.0	0.0	0.0	0.0	0.3	0-7
	AMR	5	4	3	3	2	1	1	19	12-62
	EMR	2	1	0.5	0.3	0.0	0.0	0.0	4	0-18
	EUR	3	2	2	2	1	1	1	11	6-37
	SEAR	9	6	3	2	1	0.6	0.3	22.4	2-78
	WPR	8	6	4	3	2	1	0.8	24	13-87
	Overall	28	19	13	10	6	4	3	83	48-264
Both	Global	55	37	26	19	13	9	6	166	98-562
						HSV-2 and HSV-1				
Global	Females	357	548	730	900	958	983	1,047	5,523	3,676-9,539
	Males	218	330	440	540	574	590	625	3,318	2,120-5,805
	Both	575	878	1,170	1,440	1,532	1,573	1,672	8,841	5,795-15,425

Abbreviations: AFR = African Region, AMR = Region of the Americas, EMR = Eastern Mediterranean Region, EUR = European Region, GUD = Genital ulcer disease, HSV = Herpes simplex virus, SEAR = South-East Asia region, UI = Uncertainty interval, WHO = World Health Organization, WPR = Western Pacific Region.

Abbreviations: AFR = Africa, AMR = Americas, EMR = Eastern Mediterranean, EUR = Europe, GUD = Genital ulcer disease, HSV = Herpes simplex virus, SEAR = South-East Asia, UI = Uncertainty interval, WHO = World Health Organization, WPR = Western Pacific.

[a] 95% UI of the total number of GUD person-days in millions.

Numbers (N) are the year 2020 estimated person-days of GUD caused by HSV-1 and/or HSV-2 infection. Numbers do not always sum exactly to the totals due to rounding.

Regions are per World Health Organization definitions.

Table S8. Global and regional estimates of the number and percentage of the population aged 0-49 years with incident HSV-1 infection (any site, oral or genital) in 2020, by age and sex.

Sex	WHO region	Number of people with incident HSV-1 infection in millions (population incidence, %) by age group											
		0-4 years	5-9 years	10-14 years	15-19 years	20-24 years	25-29 years	30-34 years	35-39 years	40-44 years	45-49 years	All ages	
		N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (95% UI[a])	% (95% UI[b])
Females	AFR	16.5 (19.3)	2.3 (3.0)	0.3 (0.5)	<0.1[c] (0.1)	<0.1[d] (0.0)	<0.1[d] (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	19.1 (16.4-23.5)	3.8 (3.3-4.7)
	AMR	1.2 (3.4)	1.0 (2.8)	0.8 (2.3)	0.7 (1.9)	0.6 (1.5)	0.5 (1.3)	0.4 (1.0)	0.3 (0.9)	0.2 (0.7)	0.2 (0.6)	6.0 (5.5-6.4)	1.7 (1.5-1.8)
	EMR	3.5 (8.4)	1.6 (4.1)	0.7 (2.0)	0.3 (1.0)	0.1 (0.5)	0.1 (0.2)	<0.1[c] (0.1)	<0.1[c] (0.1)	<0.1[d] (0.0)	<0.1[d] (0.0)	6.4 (5.2-7.4)	2.1 (1.8-2.5)
	EUR	1.2 (4.5)	1.0 (3.4)	0.7 (2.6)	0.5 (2.0)	0.4 (1.5)	0.3 (1.2)	0.3 (0.9)	0.2 (0.7)	0.2 (0.5)	0.1 (0.4)	4.9 (4.5-5.2)	1.7 (1.5-1.8)
	SEAR	4.8 (5.9)	3.0 (3.6)	1.9 (2.2)	1.2 (1.4)	0.7 (0.9)	0.4 (0.5)	0.3 (0.3)	0.1 (0.2)	0.1 (0.1)	<0.1[c] (0.1)	12.6 (10.0-13.7)	1.6 (1.3-1.8)
	WPR	3.7 (6.6)	2.5 (4.3)	1.6 (2.8)	1.0 (1.9)	0.7 (1.2)	0.5 (0.8)	0.4 (0.5)	0.2 (0.3)	0.1 (0.2)	0.1 (0.1)	10.9 (10.5-11.0)	1.7 (1.7-1.7)
	Overall	30.9 (9.4)	11.4 (3.5)	6.1 (1.8)	3.8 (1.3)	2.6 (0.9)	1.9 (0.6)	1.4 (0.5)	0.9 (0.3)	0.6 (0.3)	0.5 (0.2)	60.0 (56.1-64.6)	2.1 (2.0-2.3)
Males	AFR	16.9 (19.3)	2.3 (3.0)	0.3 (0.5)	<0.1[c] (0.1)	<0.1[d] (0.0)	<0.1[d] (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	19.7 (17.0-24.0)	3.9 (3.3-4.7)
	AMR	1.2 (3.2)	1.0 (2.6)	0.8 (2.2)	0.7 (1.8)	0.6 (1.4)	0.5 (1.2)	0.4 (1.0)	0.3 (0.8)	0.2 (0.6)	0.2 (0.5)	5.8 (5.2-6.3)	1.6 (1.4-1.7)
	EMR	3.7 (8.4)	1.7 (4.1)	0.7 (2.0)	0.3 (1.0)	0.2 (0.5)	0.1 (0.2)	<0.1[c] (0.1)	<0.1[c] (0.1)	<0.1[d] (0.0)	<0.1[d] (0.0)	6.8 (5.5-7.8)	2.1 (1.7-2.4)
	EUR	1.1 (4.0)	0.9 (2.9)	0.6 (2.2)	0.4 (1.6)	0.3 (1.2)	0.3 (0.9)	0.2 (0.7)	0.2 (0.5)	0.1 (0.4)	0.1 (0.3)	4.2 (3.8-4.4)	1.4 (1.2-1.5)
	SEAR	5.2 (5.9)	3.3 (3.6)	2.1 (2.2)	1.3 (1.4)	0.8 (0.9)	0.5 (0.5)	0.3 (0.3)	0.2 (0.2)	0.1 (0.1)	<0.1[c] (0.1)	13.7 (10.7-14.9)	1.6 (1.3-1.8)
	WPR	4.1 (6.6)	2.8 (4.3)	1.8 (2.8)	1.1 (1.9)	0.8 (1.2)	0.6 (0.8)	0.4 (0.5)	0.2 (0.3)	0.2 (0.2)	0.1 (0.1)	12.1 (11.7-12.3)	1.8 (1.7-1.8)
	Overall	32.4 (9.3)	11.9 (3.5)	6.4 (1.9)	3.9 (1.2)	2.6 (0.9)	1.8 (0.6)	1.3 (0.4)	0.9 (0.3)	0.6 (0.2)	0.4 (0.2)	62.2 (57.9-66.6)	2.1 (1.9-2.2)
Both	Global	63.2 (9.4)	23.3 (3.5)	12.5 (2.0)	7.7 (1.3)	5.2 (0.9)	3.7 (0.6)	2.7 (0.5)	1.8 (0.3)	1.2 (0.2)	0.9 (0.2)	122.2 (116.2-128.6)	2.1 (2.0-2.2)

Abbreviations: AFR = African Region, AMR = Region of the Americas, EMR = Eastern Mediterranean Region, EUR = European Region, HSV = Herpes simplex virus, SEAR = South-East Asia region, UI = Uncertainty interval, WHO = World Health Organization, WPR = Western Pacific Region.

[a] 95% UI of the total number of infected people in millions.

[b] 95% UI of percentage incidence.

[c] Numbers are <50,000 but ≥10,000.

[d] Number are <10,000 but ≥1,000.

Numbers (N) are the estimated number of people newly infected with HSV-1 during 2020. Numbers do not always sum exactly to the totals due to rounding.

Incidences (%) are the percentage of infected people in the age-, sex-, and region-specific population.

Regions are per World Health Organization definitions.

Table S9. Global and regional estimates of the number and percentage of the population aged 0-49 years with prevalent HSV-1 infection (any site, oral or genital) in 2020, by age and sex.

Sex	WHO region	Number of people with prevalent HSV-1 infection in millions (population prevalence, %) by age group											
		0-4 years	5-9 years	10-14 years	15-19 years	20-24 years	25-29 years	30-34 years	35-39 years	40-44 years	45-49 years	All ages	
		N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (95% UI[a])	% (95% UI[b])
Females	AFR	37.2 (57.9)	67.1 (89.5)	63.9 (94.4)	55.8 (95.1)	48.1 (95.3)	41.5 (95.3)	35.9 (95.3)	30.6 (95.3)	24.9 (95.3)	20.1 (95.3)	425.2 (381.9-446.7)	85.1 (76.4-89.4)
	AMR	2.5 (8.8)	8.2 (24.1)	13.0 (36.6)	17.2 (46.8)	21.1 (55.2)	24.2 (62.1)	25.6 (67.7)	26.3 (72.3)	25.7 (76.1)	25.0 (79.2)	188.9 (165.2-210.9)	51.7 (45.3-57.8)
	EMR	7.5 (23.1)	18.8 (50.5)	22.0 (63.9)	22.3 (70.4)	22.2 (73.6)	22.1 (75.2)	21.4 (75.9)	19.0 (76.3)	15.9 (76.5)	13.0 (76.6)	184.0 (137.9-207.1)	61.7 (46.2-69.4)
	EUR	2.5 (11.8)	8.2 (31.0)	12.0 (45.7)	14.1 (56.8)	16.7 (65.3)	20.9 (71.7)	25.4 (76.6)	26.5 (80.3)	26.9 (83.1)	27.1 (85.2)	180.3 (153.4-203.9)	61.4 (52.2-69.4)
	SEAR	10.0 (15.7)	29.5 (37.8)	43.2 (51.5)	51.1 (59.9)	54.6 (65.1)	55.0 (68.3)	54.5 (70.3)	52.7 (71.6)	47.9 (72.3)	43.5 (72.8)	442.0 (288.6-520.7)	56.7 (37.0-66.8)
	WPR	7.7 (17.4)	23.3 (42.8)	32.2 (59.6)	37.8 (70.5)	44.5 (77.7)	52.8 (82.5)	67.9 (85.6)	57.7 (87.6)	55.9 (88.9)	67.3 (89.8)	447.0 (404.2-479.9)	71.0 (64.2-76.2)
	Overall	67.4 (20.6)	155.0 (48.4)	186.3 (60.4)	198.3 (67.4)	207.2 (72.0)	216.5 (75.4)	230.7 (78.3)	212.8 (79.8)	197.2 (81.3)	196.0 (82.9)	1,867.4 (1,695.3-1,969.7)	65.2 (59.2-68.7)
Males	AFR	38.3 (57.9)	68.8 (89.5)	65.3 (94.4)	56.8 (95.1)	48.6 (95.3)	41.6 (95.3)	35.7 (95.3)	30.1 (95.3)	24.4 (95.3)	19.5 (95.3)	429.1 (388.5-450.8)	84.9 (76.9-89.2)
	AMR	2.5 (8.4)	8.0 (22.7)	12.7 (34.4)	16.7 (44.0)	20.2 (51.7)	23.1 (58.1)	24.0 (63.2)	24.1 (67.5)	23.1 (70.9)	22.2 (73.7)	176.7 (150.9-204.5)	47.8 (40.8-55.4)
	EMR	7.9 (23.1)	19.9 (50.5)	23.2 (63.9)	23.6 (70.4)	23.6 (73.6)	24.1 (75.2)	23.6 (75.9)	20.9 (76.3)	17.6 (76.5)	14.3 (76.6)	198.8 (145.8-222.6)	61.9 (45.4-69.4)
	EUR	2.3 (10.3)	7.5 (26.8)	10.8 (39.1)	12.6 (48.1)	14.8 (54.8)	18.2 (59.8)	21.5 (63.5)	22.0 (66.2)	21.8 (68.2)	21.7 (69.7)	153.2 (123.7-175.4)	50.7 (40.9-58.0)
	SEAR	10.9 (15.7)	31.9 (37.8)	47.0 (51.5)	56.1 (59.9)	59.8 (65.1)	59.5 (68.3)	57.7 (70.3)	55.3 (71.6)	49.6 (72.3)	44.6 (72.8)	472.5 (303.0-560.2)	56.5 (36.3-67.0)
	WPR	8.5 (17.4)	26.1 (42.8)	36.6 (59.6)	42.6 (70.5)	49.5 (77.7)	57.6 (82.5)	72.0 (85.6)	60.4 (87.6)	58.3 (88.9)	69.8 (89.8)	481.4 (437.8-517.0)	70.5 (64.1-75.7)
	Overall	70.3 (20.2)	162.3 (47.5)	195.7 (59.3)	208.4 (66.1)	216.4 (70.5)	224.2 (73.6)	234.6 (76.2)	212.8 (77.4)	194.8 (78.6)	192.2 (80.1)	1,911.7 (1,722.8-2,023.9)	63.4 (57.1-67.1)
Both	Global	137.7 (20.4)	317.2 (47.9)	382.1 (59.8)	406.7 (66.7)	423.6 (71.2)	440.7 (74.5)	465.3 (77.2)	425.6 (78.6)	392.0 (79.9)	388.2 (81.5)	3,779.1 (3,510.3-3,921.6)	64.2 (59.7-66.7)

Abbreviations: AFR = African Region, AMR = Region of the Americas, EMR = Eastern Mediterranean Region, EUR = European Region, HSV = Herpes simplex virus, SEAR = South-East Asia region, UI = Uncertainty interval, WHO = World Health Organization, WPR = Western Pacific Region.
[a] 95% UI of the total number of infected people in millions.
[b] 95% UI of percentage prevalence.
Numbers (N) are the year 2020 estimated number of people living with HSV-1 infection. Numbers do not always sum exactly to the totals due to rounding.
Prevalences (%) are the percentage of infected people in the age-, sex-, and region-specific population.
Regions are per World Health Organization definitions.

Table S10. Global and regional estimates of the number and percentage of the population aged 0-49 years with prevalent oral HSV-1 infection in 2020, by age and sex.

Sex	WHO region	Number of people with prevalent oral HSV-1 infection in millions (population prevalence, %) by age group											
		0-4 years	5-9 years	10-14 years	15-19 years	20-24 years	25-29 years	30-34 years	35-39 years	40-44 years	45-49 years	All ages	
		N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (95% UI[a])	% (95% UI[b])
Females	AFR	37.2 (57.9)	67.1 (89.5)	63.9 (94.4)	55.8 (95.0)	48.0 (95.0)	41.4 (95.1)	35.9 (95.1)	30.5 (95.1)	24.9 (95.1)	20.1 (95.1)	424.7 (372.9-446.7)	85.0 (74.6-89.4)
	AMR	2.5 (8.8)	8.2 (24.1)	13.0 (36.6)	16.3 (43.7)	18.0 (46.8)	19.4 (49.3)	19.5 (51.3)	19.3 (53.0)	18.4 (54.4)	17.6 (55.5)	152.2 (129.8-174.7)	41.7 (35.6-47.9)
	EMR	7.5 (23.1)	18.8 (50.5)	22.0 (63.9)	21.8 (68.7)	21.1 (69.9)	20.7 (70.5)	19.9 (70.7)	17.7 (70.9)	14.7 (70.9)	12.1 (71.0)	176.3 (118.5-206.7)	59.1 (39.7-69.3)
	EUR	2.5 (11.8)	8.2 (31.0)	12.0 (45.7)	13.4 (53.5)	14.6 (56.6)	17.3 (58.9)	20.2 (60.7)	20.6 (62.1)	20.4 (63.1)	20.3 (63.9)	149.5 (121.4-178.2)	50.9 (41.3-60.6)
	SEAR	10.0 (15.7)	29.5 (37.8)	43.2 (51.5)	49.5 (57.6)	50.0 (59.5)	49.0 (60.6)	47.6 (61.4)	45.6 (61.8)	41.2 (62.1)	37.2 (62.2)	402.8 (231.3-516.6)	51.7 (29.7-66.3)
	WPR	7.7 (17.4)	23.3 (42.8)	32.2 (59.6)	36.5 (67.4)	40.3 (70.0)	46.1 (71.8)	57.9 (72.9)	48.5 (73.6)	46.7 (74.1)	55.8 (74.4)	395.0 (340.5-443.3)	62.7 (54.1-70.4)
	Overall	67.4 (20.6)	155.0 (48.4)	186.3 (60.4)	193.3 (65.7)	192.1 (66.8)	193.8 (67.5)	201.0 (68.2)	182.2 (68.3)	166.2 (68.5)	163.1 (18.9)	1,700.4 (1,501.7-1,841.0)	59.3 (52.4-64.2)
Males	AFR	38.3 (57.9)	68.8 (89.5)	65.3 (94.4)	56.7 (95.0)	48.5 (95.0)	41.5 (95.1)	35.6 (95.1)	30.0 (95.1)	24.4 (95.1)	19.5 (95.1)	428.6 (380.5-450.8)	84.8 (75.3-89.2)
	AMR	2.5 (8.4)	8.0 (22.7)	12.7 (34.4)	15.8 (41.1)	17.3 (43.9)	18.5 (46.2)	18.3 (48.1)	17.8 (49.6)	16.6 (50.9)	15.7 (51.9)	143.3 (118.8-172.3)	38.8 (32.2-46.6)
	EMR	7.9 (23.1)	19.9 (50.5)	23.2 (63.9)	23.1 (68.7)	22.5 (69.9)	22.7 (70.5)	22.0 (70.7)	19.4 (70.9)	16.3 (70.9)	13.3 (71.0)	190.3 (124.3-222.1)	59.3 (38.7-69.2)
	EUR	2.3 (10.3)	7.5 (26.8)	10.8 (39.1)	12.0 (45.4)	13.0 (47.9)	15.2 (49.7)	17.4 (51.0)	17.4 (52.0)	16.9 (52.8)	16.6 (53.3)	129.0 (97.9-157.3)	42.7 (32.4-52.1)
	SEAR	10.9 (15.7)	31.9 (37.8)	47.0 (51.5)	54.4 (57.6)	54.8 (59.5)	53.0 (60.6)	50.5 (61.4)	47.8 (61.8)	42.6 (62.1)	38.2 (62.2)	431.0 (242.9-556.4)	51.6 (29.1-66.6)
	WPR	8.5 (17.4)	26.1 (42.8)	36.6 (59.6)	41.1 (67.4)	44.8 (70.0)	50.3 (71.8)	61.4 (72.9)	50.8 (73.6)	48.7 (74.1)	57.9 (74.4)	426.2 (371.0-477.7)	62.4 (54.3-70.0)
	Overall	70.3 (20.2)	162.3 (47.5)	195.7 (59.3)	203.2 (64.4)	200.9 (65.5)	201.1 (66.1)	205.2 (66.7)	183.2 (66.7)	165.4 (66.8)	161.1 (67.2)	1,748.5 (1,531.6-1,905.2)	58.0 (50.8-63.2)
Both	Global	137.7 (20.4)	317.2 (47.9)	382.1 (59.8)	396.5 (65.0)	393.0 (66.1)	394.9 (66.8)	406.3 (67.4)	365.4 (67.5)	331.7 (67.6)	324.2 (68.1)	3,448.9 (3,144.9-3,655.2)	58.6 (53.5-62.1)

Abbreviations: AFR = African Region, AMR = Region of the Americas, EMR = Eastern Mediterranean Region, EUR = European Region, HSV = Herpes simplex virus, SEAR = South-East Asia region, UI = Uncertainty interval, WHO = World Health Organization, WPR = Western Pacific Region.

[a] 95% UI of the total number of infected people in millions.

[b] 95% UI of percentage prevalence.

Numbers (N) are the year 2020 estimated number of people living with oral HSV-1 infection. Numbers do not always sum exactly to the totals due to rounding.

Prevalences (%) are the percentage of infected people in the age-, sex-, and region-specific population.

Regions are per World Health Organization definitions.

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