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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

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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

**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, $\lambda$, 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 $\lambda$. 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

| | | 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 | |
| Sex | WHO region | 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]

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