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Global and regional estimates of herpes simplex virus infection prevalence and incidence in 2016

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Abstract

Objective: Herpes simplex virus (HSV) types 1 and 2 are common viruses globally. HSV-2 infection is almost exclusively genital, while HSV-1 infection is mostly oral but can be genital. The World Health Organization last produced global and regional HSV-1 and HSV-2 infection estimates for 2012. Here we present updated estimates for 2016.

Methods: We conducted a literature review to August 2018 to update studies able to contribute data to the estimates. Adjustments were made to account for test sensitivity and specificity. For each WHO region, we applied a constant incidence model to pooled prevalence by age and sex to estimate HSV-1 and HSV-2 prevalence and incidence. For HSV-1, we apportioned infection by anatomic site using pooled estimates of the proportions that are oral and genital.

Findings: In 2016, an estimated 491 million (95% uncertainty interval, UI, 430-611 million) had HSV-2 infection, equivalent to 13.2% (95%UI 11.5%-16.3%) of the world's population aged 15-49 years. An estimated 3.8 billion (95%UI 3.6-3.9 billion) had HSV-1 infection at any site (the vast majority oral), equivalent to 67% (95%UI 63%-68%) global prevalence in those up to 49 years of age. Differing patterns were observed by age, sex and geographic region, with HSV-2 prevalence highest among women and in WHO Africa region.

Conclusion: We estimated that, in 2016, over half a billion people had genital infection with either HSV-2 or HSV-1, and several billion had oral HSV-1 infection. This leaves millions at risk of disease sequelae, such as genital ulcer disease, orolabial herpes, ocular disease, and encephalitis. Since HSV-2 infection likely increases HIV susceptibility, millions may also be at elevated risk of acquiring HIV, particularly women in WHO Africa region who have highest HSV-2 prevalence and exposure to HIV.

Introduction

Herpes simplex virus (HSV) infections are widespread among humans globally(1, 2). They are lifelong, characterized by periodic reactivations at the infection site. HSV-1 is primarily transmitted by oral-oral contact and commonly causes orolabial herpes (“cold sores”)(3). It also causes rarer conditions such as keratitis and other ocular sequelae, and encephalitis(4). HSV-1 genital infection from oral-genital contact is becoming increasingly common, although has less frequent reactivations than HSV-2(5-10). HSV-2 is almost entirely sexually transmitted, causing genital herpes(11). Genital HSV infection may be unrecognized or result in painful genital ulcer disease (GUD) in a proportion of those infected. Neonates can acquire HSV infection from genitally-infected mothers during birth and through oral contact from caregivers postnatally(12). Although rare, neonatal infection has a high fatality rate, and high disability rate in surviving infants(12). Evidence also suggests that HSV-2 infection increases the risk of acquiring HIV(13). For both HSV-1 and HSV-2, symptomatic and asymptomatic viral shedding are common(14, 15). Thus, individuals can be asymptomatic yet infectious, allowing these viruses to be unknowingly transmitted, which contributes to their large global prevalence.

Global and World Health Organization (WHO) regional estimates of HSV-2 infection prevalence and (derived) incidence among 15-49 year-olds have been produced by WHO twice before: for 2005 and for 2012(2, 16). The first estimates of HSV-1 infection (any site) in those aged 0-49 years, and of genital HSV-1 infection in those aged 15-49 years, were done for 2012(1). The Global Burden of Disease (GBD) study has also produced estimates for HSV-2 infection (deriving incidence from estimated prevalence similarly to the WHO estimates), most recently for 2017(17). GBD estimates are not directly comparable as they are not adjusted for assay performance, extend to age 99 years, and use different regional groupings to the WHO estimates. The GBD study does not produce any estimates for HSV-1 infection, an increasingly important cause of genital infection.

HSV-1 and HSV-2 infection estimates are important for understanding the total number of infections and their distribution across populations by geographical region, age, sex, HSV type, and infection site (oral vs genital). This information is needed for advocacy and resource planning. In 2016 the World Health Assembly adopted the Global Health Sector Strategy on Sexually Transmitted Infections, 2016–2021(18), which aims to end sexually transmitted infections (STIs) as a public health concern by 2030. The Strategy sets out reduction targets, which in turn depend on reliable baseline estimates for each STI. Quantifying HSV infection and disease is also necessary to guide new product development, such as vaccines(19-21). Infection estimates can be used as a starting point for estimating the HSV-related disease burden where direct incidence data are lacking (by applying risks of particular outcomes to infection numbers), as has been done for neonatal herpes(22). Previous estimates were not done for oral HSV-1 infection specifically, precluding the use of this methodology for orolabial herpes. Furthermore, the 2012 infection estimates are becoming out-of-date as new studies and surveys of HSV infection are published. Here we present global and WHO regional estimates of HSV-2 and genital HSV-1 infection for 2016, incorporating newly-available data, and first estimates specifically for oral HSV-1 infection.

Methods

Calculation of estimates

All estimates were done for 2016 by applying 2016 population data. The methods used were similar to those used for our previous estimates(1, 2, 16). Firstly, we conducted a literature search for studies (in any language) of HSV-1 and HSV-2 infection prevalence and incidence (as measured by the detection of type-specific IgG antibodies) published since the last reviews(1, 2, 16). The 2012 estimates used literature reviews to 2014 and incorporated data from 2000 onwards. Our current review was intended to identify newly-published studies with publication date between 2013 and 2018. Data from any study from year 2004 or later were eligible for inclusion in the estimates. Thus, there was a

large overlap in the studies included between the current and previous set of estimates. We applied broad inclusion and exclusion criteria to studies for the purposes of extracting HSV-1 or HSV-2 infection prevalence and incidence data (“data extraction”). We then applied additional inclusion and exclusion criteria for using the extracted data in the estimates calculation (“data synthesis”), which was based on prevalence data (incidence data were used solely for comparison/validation purposes) from general populations (as defined in **Appendix**) only.

For each WHO region (the Americas, Africa, Eastern Mediterranean, Europe, South-East Asia and Western Pacific), and separately for HSV-1 and HSV-2, prevalence values were pooled by sex (where possible) and 5-year age group. The force of infection for HSV-1 and HSV-2 was then calibrated to pooled prevalence using a constant incidence model. Prevalence values were adjusted for test sensitivity and specificity prior to pooling (**Tables S1 and S2, Appendix**). Smoothed prevalence, and calibrated incidence, were applied to population data for 2016(23), to obtain estimates of the number of people with prevalent (existing) and incident (acquired in the current year) HSV-1 and HSV-2 infection by WHO region in 2016. Estimates for oral HSV-1 infection were done for 0-49 year-olds, and estimates for genital HSV-1 and HSV-2 infection were done for 15-49 year-olds. For full details on the methods see **Appendix**.

We also carried out a speculative analysis to estimate infection numbers in older individuals by applying the prevalence in those aged 45-49 years to population numbers for those aged 50-99 years.

Estimation of the contribution of oral versus genital HSV-1 infection

To estimate the proportion of individuals (from age 15 years) infected orally and the proportion infected genitally among those with incident HSV-1 infection, we first pooled values from longitudinal studies of the proportions of symptomatic HSV-1 seroconversions in adults that are oral (pooled estimate 36.4%) and genital (pooled estimate 72.4%)(24-27). Pooling was done using the metan command in Stata and assuming a random effects model. We then applied these proportions to HSV-1 incidence in those aged 15 years and older to separately estimate the numbers with oral and genital HSV-1 infection. This was slightly different to the method of estimating genital HSV-1 infection for 2012, where values from two studies of the proportion of symptomatic HSV-1 seroconversions in adults that are genital were used to generate two separate sets of estimates(1). HSV-1 infection in those aged under 15 years was assumed to be all oral. In a separate sensitivity analysis, we limited those able to be infected with genital HSV-1 to the proportion of individuals by age who engaged in oral sex in the last 12 months (data for females and males combined) according to the National Health and Nutrition Evaluation Survey (NHANES; the largest, national population-based survey in the USA) 2015-16(28).

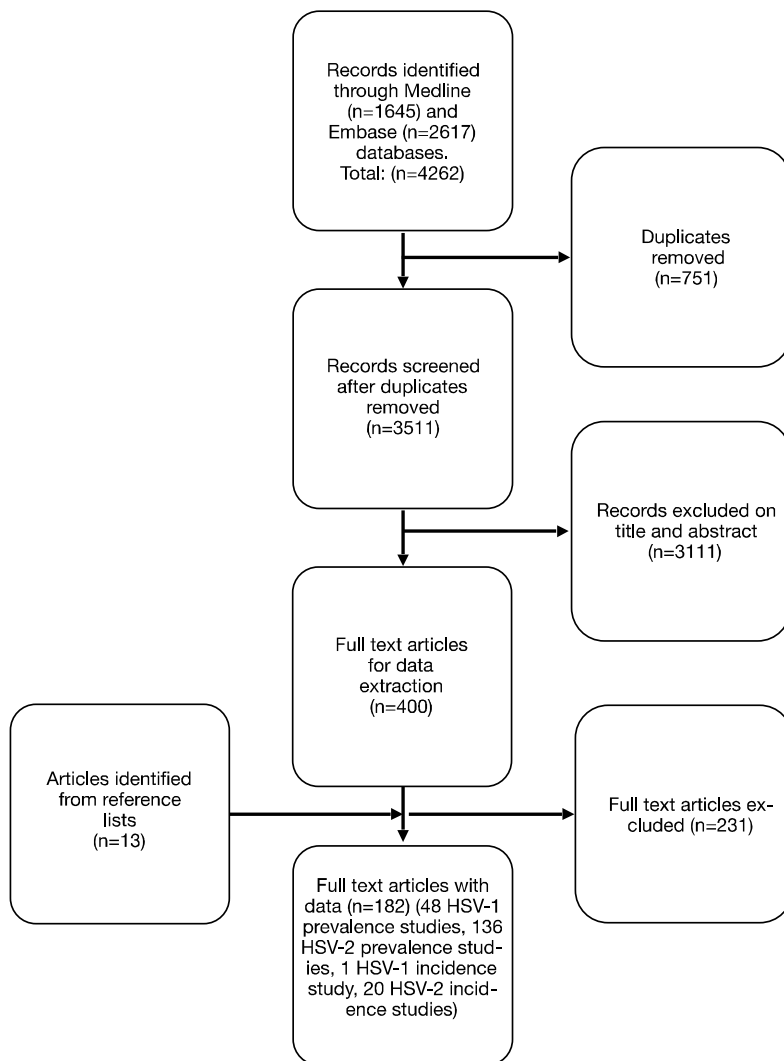


FIGURE 1: FLOWCHART SUMMARISING THE RESULTS OF THE LITERATURE SEARCH

Results

Literature search

In total, 4262 publications were identified in the literature search (**Figure 1**). After removal of duplicates, 3511 records were screened on the basis of title and abstract, of which a further 3111 were excluded due to non-relevance. Full texts were obtained for the remaining 400 records along with an additional 13 publications identified from reference lists(8, 29, 30). Of these 413 publications, 182 contained relevant data and were subsequently included in the data extraction: 48 HSV-1 prevalence studies, 136 HSV-2 prevalence studies, 1 HSV-1 incidence study and 20 HSV-2 incidence studies (some studies contributed data in more than one category). However, not all of these studies met our criteria for inclusion in the estimates, while some studies identified in previous reviews were still sufficiently recent. When added together with studies identified previously that were still sufficiently recent, 474 HSV-2 prevalence data points (262 from newly-identified studies) and 223 HSV-1 prevalence data points (128 from newly-identified studies) were able to contribute to the estimates. For tables of the number of available data points

by age and sex, list of countries with data, and inclusion criteria applied, see **Tables S3 and S4 (Appendix)**. **Figures S1 and S2 (Appendix)** show the pooled prevalence values and model fits.

In comparison to the 2012 estimates, the number of available prevalence data points improved for both HSV-1 and HSV-2 (**Tables S3 and S4, Appendix**). However, this did not generally follow from an increase in the number of countries represented, as the number of contributing countries mostly declined between the 2012 and 2016 estimates. This was particularly apparent for WHO Americas region where male HSV-1 estimates were based solely on data from individuals from the USA. HSV-1 and HSV-2 prevalence and incidence data from general populations newly-extracted for this review (i.e., from the literature search using publication dates August 2013–August 2018) are given in the **Supplementary File(31-121)**.

Prevalent HSV infection in 2016

The global prevalence of HSV-2 among 15-49 year-olds in 2016 was estimated to be 13.2% (95%UI 11.5%-16.3%) (**Table 1**). Prevalence was highest in WHO Africa region, followed by WHO Americas region, and among women (**Table 1; Figure 2; Figure S1, Appendix**). Prevalence increased with age since HSV-2 infection is lifelong, which was largely reflected in the numbers infected, although underlying demography contributed to observed patterns. The corresponding number of people with prevalent HSV-2 infection was estimated to be 491 million (95%UI 430-611 million) (**Table 1**). More women (313 million; 95%UI 266-389 million) than men (178 million; 95%UI 141-270 million) were infected. The number infected was highest in WHO Africa region: 103 million (95%UI 85-120 million) infections in women and 59 million (95%UI 44-77 million) infections in men (**Table 1; Figure 2**). This was followed by WHO Western Pacific region and WHO Americas region.

Globally, 67% (95%UI 63%-68%) of the world's population aged 0-49 years were estimated to have HSV-1 infection at any site, equivalent to 3.8 billion (95%UI 3.6-3.9 billion) people (**Table S5, Appendix**). Global oral HSV-1 prevalence among 0-49 year-olds in 2016 was estimated to be 64% (95%UI 59%-66%), or 3.6 billion (95%UI 3.3-3.7 billion) people (**Table 2**). The number infected was largest for WHO Western Pacific region, followed by WHO South-East Asia region (**Table 2**), although prevalence was highest in WHO Africa region (**Table 2; Figure S2, Appendix**). Worldwide, 5.2% (95%UI 3.3%-8.0%) of 15-49 year-olds were estimated to have prevalent genital HSV-1 infection in 2016: 192 million (95%UI 123-294 million) people (**Table 3**). The number of genitally HSV-1 infected individuals was highest for WHO Americas region, followed by WHO Europe region (**Table 3**). (Note that the numbers with oral and genital HSV-1 infection do not sum exactly to the number with HSV-1 infection at any site, as we assume a small proportion can be infected at both sites simultaneously.) However, the estimates were highly sensitive to the assumptions made around genital HSV-1 acquisition. If only those individuals who engaged in oral sex in the last year are at risk of acquiring genital HSV-1 infection (rather than simply assuming anyone aged 15 years and over who does not have existing HSV-1 infection can acquire genital HSV-1), then 3.3% (122 million) of 15-49 year-olds were estimated to have prevalent genital HSV-1 infection in 2016 (**Table S6, Appendix**). Prevalence of both oral and genital HSV-1 infection increased with age as HSV-1 infection is lifelong, meaning there was a general trend of increasing numbers infected with age. Taken together, an estimated 596-656 million people (16.0-17.6% of the world's population) aged 15-49 years had either genital HSV-1 or HSV-2 infection or both in 2016, based on 122-192 million genital HSV-1 infections.

Applying prevalence in those aged 45-49 years to population numbers for those aged 50-99 years, we estimated that globally in 2016, 1.3 billion people and 344 million people aged 50-99 years were infected with HSV-1 (any site) and HSV-2, respectively, bringing the totals to 5.0 billion and 836 million (**Table S7, Appendix**).

TABLE 1: GLOBAL AND REGIONAL ESTIMATES FOR THE NUMBER (IN MILLIONS) AND PERCENTAGE OF THE POPULATION WITH PREVALENT HSV-2 INFECTION IN 2016 BY AGE AND SEX

Both									
Global Total (All)	Age Group (years)								
	15-19	20-24	25-29	30-34	35-39	40-44	45-49	All ages	95%UI
	27.8	49.6	68.6	78.9	83.3	89.6	93.7	491.5	430.4-610.6
4.8%	8.5%	11.4%	14.3%	16.8%	18.8%	20.8%	13.2%	11.5%-16.3%	
Females									
WHO Region	Age Group (years)								
	15-19	20-24	25-29	30-34	35-39	40-44	45-49	All ages	95%UI
Americas	2.6	5.1	7.3	9.1	10.3	11.3	12.0	57.7	46.4-71.6
	7.8%	14.4%	20.5%	26.1%	31.4%	36.3%	40.8%	24.0%	19.3%-29.7%
Africa	10.1	15.3	17.5	17.8	16.3	14.1	11.9	102.9	85.0-120.0
	21.7%	35.9%	46.5%	54.2%	60.0%	64.2%	67.3%	43.9%	36.3%-51.2%
Eastern Mediter-ranean	0.7	1.3	1.9	2.3	2.3	2.2	2.2	12.8	5.7-29.4
	2.5%	4.6%	6.8%	8.8%	10.9%	12.9%	14.8%	7.6%	3.4%-17.6%
Europe	0.7	1.5	2.5	3.4	4.0	4.8	5.4	22.2	10.4-45.2
	3.0%	5.7%	8.3%	10.8%	13.2%	15.6%	17.9%	10.7%	5.0%-21.7%
South-East Asia	2.3	4.4	6.3	7.8	8.7	9.3	9.5	48.4	20.2-105.2
	3.0%	5.6%	8.2%	10.7%	13.1%	15.5%	17.8%	9.6%	4.0%-20.9%
Western Pacific	2.0	4.7	8.7	10.0	10.9	14.9	18.3	69.5	43.8-106.3
	4.2%	7.8%	11.3%	14.7%	17.9%	21.0%	24.0%	14.6%	9.2%-22.3%
Global Total (Female)	18.4	32.2	44.1	50.3	52.7	56.5	59.2	313.5	265.7-389.1
	6.6%	11.4%	15.0%	18.5%	21.6%	24.1%	26.4%	17.1%	14.5%-21.3%
Males									
WHO Region	Age Group (years)								
	15-19	20-24	25-29	30-34	35-39	40-44	45-49	All ages	95%UI
Americas	1.2	2.5	3.5	4.4	5.0	5.5	5.9	28.0	18.2-42.0
	3.6%	6.7%	9.7%	12.6%	15.5%	18.2%	20.8%	11.6%	7.5%-17.3%
Africa	4.6	7.6	9.4	10.3	10.1	9.3	8.1	59.3	44.1-77.1
	9.8%	17.8%	25.1%	31.8%	37.9%	43.4%	48.5%	25.4%	18.9%-33.0%
Eastern Mediter-ranean	0.2	0.5	0.7	0.9	0.9	0.9	0.9	5.1	1.1-23.9
	0.9%	1.6%	2.4%	3.2%	4.0%	4.7%	5.5%	2.8%	0.6%-13.2%
Europe	0.3	0.8	1.3	1.7	2.0	2.4	2.7	11.1	5.1-23.1
	1.5%	2.8%	4.1%	5.4%	6.6%	7.9%	9.1%	5.3%	2.4%-11.0%
South-East Asia	1.9	3.6	5.0	6.2	6.9	7.3	7.5	38.5	12.2-117.6
	2.2%	4.2%	6.2%	8.1%	10.0%	11.8%	13.7%	7.2%	2.3%-22.1%
Western Pacific	1.1	2.5	4.5	5.1	5.6	7.8	9.4	36.0	15.8-79.7
	2.0%	3.7%	5.5%	7.2%	8.8%	10.5%	12.1%	7.1%	3.1%-15.7%
Global Total (Male)	9.4	17.3	24.4	28.6	30.6	33.1	34.5	178.0	140.6-270.1
	3.1%	5.8%	7.9%	10.2%	12.2%	13.8%	15.2%	9.3%	7.4%-14.2%

FIGURE 2: HSV-2 PREVALENCE (%; SHOWN BY COLOUR GRADIENT) AND NUMBERS (IN MILLIONS) IN 2016 BY WHO REGION FOR (A) FEMALES AND (B) MALES

NUMBERS DO NOT ALWAYS SUM EXACTLY TO TOTALS DUE TO ROUNDING

TABLE 2: GLOBAL AND REGIONAL ESTIMATES FOR THE NUMBER (IN MILLIONS) AND PERCENTAGE OF THE POPULATION WITH PREVALENT ORAL HSV-1 INFECTION IN 2016 BY AGE AND SEX

Both												
Global Total (All)	Age Group (years)											
	0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	All ages	95%UI
	181.0	371.4	404.3	404.0	407.7	423.3	389.2	348.0	335.9	318.6	3583.5	3322.2-3715.8
	27.4%	58.5%	67.1%	69.7%	70.0%	70.5%	70.5%	70.4%	70.6%	70.7%	63.6%	59.0%-66.0%
Females												
WHO Region	Age Group (years)											
	0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	All ages	95%UI
Americas	2.1	6.9	11.2	14.3	15.7	16.4	16.7	16.3	15.8	15.4	130.8	121.8-140.6
	7.6%	21.1%	32.5%	39.3%	42.3%	44.9%	47.1%	48.9%	50.5%	51.9%	37.8%	35.2%-40.6%
Africa	37.9	62.9	57.4	49.8	43.0	37.4	32.3	26.7	21.5	17.3	386.2	354.8-400.9
	64.9%	93.7%	96.9%	97.2%	97.3%	97.3%	97.3%	97.3%	97.3%	97.3%	87.8%	80.6%-91.1%
Eastern Mediterranean	6.4	16.7	20.6	21.8	21.9	22.2	20.6	17.4	14.0	11.8	173.5	112.0-220.9
	20.9%	49.6%	66.8%	74.3%	76.6%	78.0%	78.8%	79.3%	79.6%	79.7%	63.3%	40.9%-80.7%
Europe	3.6	10.4	13.9	15.9	18.5	21.8	22.5	22.2	22.2	22.0	173.1	126.6-210.8
	17.2%	42.1%	58.1%	65.6%	68.0%	69.6%	70.6%	71.3%	71.7%	72.0%	60.6%	44.4%-73.9%
South-East Asia	23.5	51.4	57.5	57.3	55.2	53.3	50.7	45.9	41.0	36.6	472.5	449.4-485.5
	37.5%	61.9%	66.7%	67.5%	67.6%	67.6%	67.6%	67.6%	67.6%	67.6%	62.3%	59.3%-64.0%
Western Pacific	15.3	35.6	40.9	43.4	51.3	64.6	56.8	50.7	58.9	62.9	480.4	332.7-517.9
	35.0%	67.2%	78.1%	80.9%	81.4%	81.5%	81.6%	81.6%	81.6%	81.6%	74.8%	51.8%-80.6%
Global Total (Female)	88.9	184.0	201.5	202.4	205.6	215.8	199.7	179.1	173.4	165.9	1816.5	1641.5-1899.6
	27.9%	60.0%	69.3%	72.2%	72.8%	73.6%	73.5%	73.4%	73.8%	74.1%	66.1%	59.8%-69.2%
Males												
WHO Region	Age Group (years)											
	0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	All ages	95%UI
Americas	1.7	5.9	9.7	12.4	13.7	14.3	14.3	13.9	13.4	13.0	112.3	103.8-120.4
	6.1%	17.2%	27.0%	33.0%	35.7%	38.2%	40.3%	42.2%	43.9%	45.4%	31.9%	29.5%-34.2%
Africa	39.0	64.4	58.5	50.5	43.3	37.3	32.0	26.4	21.1	16.5	389.0	356.9-404.1
	64.9%	93.7%	96.9%	97.2%	97.3%	97.3%	97.3%	97.3%	97.3%	97.3%	87.6%	80.4%-91.0%
Eastern Mediterranean	6.8	17.6	21.8	23.2	23.3	23.8	22.1	19.0	15.8	13.2	186.6	120.6-237.3
	20.9%	49.6%	66.8%	74.3%	76.6%	78.0%	78.8%	79.3%	79.6%	79.7%	63.5%	41.1%-80.8%
Europe	1.8	5.7	8.4	10.4	12.5	15.0	15.8	15.7	16.0	15.9	117.1	102.2-134.7
	7.9%	22.0%	33.9%	40.9%	44.0%	46.6%	48.9%	50.8%	52.4%	53.7%	40.1%	35.0%-46.1%
South-East Asia	25.6	56.2	63.1	62.6	59.7	56.5	53.0	47.5	42.5	37.7	504.3	479.3-518.4
	37.5%	61.9%	66.7%	67.5%	67.6%	67.6%	67.6%	67.6%	67.6%	67.6%	62.2%	59.1%-63.9%
Western Pacific	17.1	37.7	41.3	42.6	49.5	60.5	52.3	46.4	53.8	56.5	457.6	301.0-488.0
	34.8%	62.2%	69.6%	71.2%	71.4%	71.5%	71.5%	71.5%	71.5%	71.5%	66.0%	43.4%-70.4%
Global Total (Male)	92.1	187.4	202.8	201.6	202.1	207.4	189.5	168.9	162.5	152.7	1767.0	1594.7-1837.6
	27.0%	57.1%	65.0%	67.3%	67.4%	67.5%	67.5%	67.4%	67.5%	67.4%	61.2%	55.2%-63.7%

TABLE 3: GLOBAL AND REGIONAL ESTIMATES FOR THE NUMBER (IN MILLIONS) AND PERCENTAGE OF THE POPULATION WITH PREVALENT GENITAL HSV-1 INFECTION IN 2016 BY AGE AND SEX

Both									
Global Total (All)	Age Group (years)								
	15-19	20-24	25-29	30-34	35-39	40-44	45-49	All ages	95%UI
	5.8	17.9	27.5	32.6	34.7	36.3	37.2	192.0	123.0-294.0
1.0%	3.1%	4.6%	5.9%	7.0%	7.6%	8.2%	5.2%	3.3%-8.0%	
Females									
WHO Region	Age Group (years)								
	15-19	20-24	25-29	30-34	35-39	40-44	45-49	All ages	95%UI
Americas	1.0	3.3	5.2	6.6	7.4	8.0	8.4	39.8	25.7-48.1
	3.4%	9.4%	14.5%	18.9%	22.6%	25.7%	28.4%	16.2%	10.5%-19.6%
Africa	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.2	0.0-3.8
	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.0%-1.8%
Eastern Mediterranean	0.8	2.1	2.9	3.1	2.9	2.4	2.1	16.2	1.9-27.7
	3.3%	7.8%	10.5%	12.1%	13.1%	13.7%	14.0%	10.5%	1.2%-17.8%
Europe	0.6	2.1	3.5	4.2	4.5	4.8	4.9	24.7	8.2-36.4
	3.4%	8.2%	11.4%	13.4%	14.7%	15.5%	16.1%	11.2%	3.7%-16.5%
South-East Asia	0.1	0.3	0.3	0.3	0.3	0.2	0.2	1.8	0.1-8.3
	0.2%	0.4%	0.4%	0.4%	0.4%	0.4%	0.4%	0.4%	0.0%-1.7%
Western Pacific	0.4	1.1	1.7	1.6	1.5	1.7	1.8	9.8	0.0-66.9
	1.0%	1.9%	2.2%	2.3%	2.3%	2.4%	2.4%	2.0%	0.0%-13.5%
Global Total (Female)	3.0	9.0	13.6	15.8	16.6	17.1	17.4	92.5	54.6-154.6
	1.1%	3.2%	4.6%	5.8%	6.8%	7.3%	7.8%	5.1%	3.0%-8.5%
Males									
WHO Region	Age Group (years)								
	15-19	20-24	25-29	30-34	35-39	40-44	45-49	All ages	95%UI
Americas	0.9	3.1	4.9	6.2	7.0	7.5	7.9	37.4	23.8-45.4
	3.0%	8.5%	13.4%	17.7%	21.5%	24.8%	27.7%	15.4%	9.8%-18.7%
Africa	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.2	0.0-3.7
	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.0%-1.7%
Eastern Mediterranean	0.8	2.2	3.1	3.4	3.1	2.7	2.3	17.7	2.1-30.2
	3.3%	7.8%	10.5%	12.1%	13.1%	13.7%	14.0%	10.5%	1.2%-18.0%
Europe	0.7	2.6	4.7	6.1	7.1	8.0	8.5	37.7	24.3-45.7
	3.5%	9.7%	14.9%	19.4%	23.1%	26.3%	29.0%	16.9%	10.9%-20.5%
South-East Asia	0.2	0.3	0.3	0.3	0.3	0.3	0.2	1.9	0.2-8.8
	0.2%	0.4%	0.4%	0.4%	0.4%	0.4%	0.4%	0.4%	0.0%-1.7%
Western Pacific	0.2	0.6	0.8	0.7	0.7	0.8	0.8	4.7	0.0-59.7
	0.5%	0.9%	1.0%	1.0%	1.0%	1.0%	1.0%	0.9%	0.0%-11.4%
Global Total (Male)	2.8	8.9	13.9	16.8	18.1	19.2	19.8	99.4	64.2-167.6
	0.9%	3.0%	4.5%	6.0%	7.2%	8.0%	8.7%	5.3%	3.4%-8.9%

Incident HSV infection in 2016

The total number of people aged 15-49 years with incident HSV-2 infection in 2016 was estimated to be 24 million (95%UI 21-29 million) (Table 4). Of these, 15 million (95%UI 12-18 million) infections were in women and 9 million (95%UI 7-14 million) were in men. The number was highest in WHO Africa region, and there was an overall trend of decreasing incidence with age, as prevalence increased. However, this was less marked for those settings where prevalence did not saturate at younger ages (Figures S1 and S2, Appendix). We estimated that 120 million (95%UI 114-130 million) people aged 0-49 years had incident HSV-1 infection at any site in 2016 (Table 5). The number was highest for WHO Africa region, and decreased with age, most notably in regions where prevalence

saturated at younger ages (**Figures S1 and S2, Appendix**). Available empirical incidence data suggested that force of infection may vary with age, but were too limited to draw further conclusions (**Figure S3, Appendix**).

TABLE 4: GLOBAL AND REGIONAL ESTIMATES FOR THE NUMBER (IN MILLIONS) AND PERCENTAGE OF THE POPULATION WITH INCIDENT HSV-2 INFECTION IN 2016 BY AGE AND SEX

Both									
Global Total (All)	Age Group (years)								
	15-19	20-24	25-29	30-34	35-39	40-44	45-49	All ages	95%UI
	5.2	4.4	3.9	3.2	2.7	2.4	2.1	23.9	21.0-29.5
0.9%	0.8%	0.6%	0.6%	0.5%	0.5%	0.5%	0.6%	0.6%-0.8%	
Females									
WHO Region	Age Group (years)								
	15-19	20-24	25-29	30-34	35-39	40-44	45-49	All ages	95%UI
Americas	0.503	0.477	0.436	0.392	0.342	0.298	0.262	2.7	2.2-3.3
	1.4%	1.3%	1.2%	1.1%	1.0%	0.9%	0.9%	1.1%	0.9%-1.4%
Africa	1.8	1.1	0.717	0.456	0.277	0.165	0.098	4.6	4.1-4.9
	3.4%	2.5%	1.9%	1.4%	1.0%	0.7%	0.5%	2.0%	1.7%-2.1%
Eastern Mediterranean	0.130	0.124	0.120	0.108	0.088	0.069	0.057	0.698	0.315-1.5
	0.4%	0.4%	0.4%	0.4%	0.4%	0.4%	0.4%	0.4%	0.2%-0.9%
Europe	0.132	0.143	0.161	0.159	0.151	0.146	0.140	1.0	0.496-2.0
	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%	0.2%-1.0%
South-East Asia	0.456	0.427	0.401	0.371	0.326	0.284	0.247	2.5	1.1-5.2
	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%	0.2%-1.0%
Western Pacific	0.399	0.451	0.546	0.461	0.396	0.442	0.454	3.1	2.0-4.6
	0.7%	0.7%	0.7%	0.7%	0.6%	0.6%	0.6%	0.7%	0.4%-1.0%
Global Total (Female)	3.4	2.7	2.4	1.9	1.6	1.4	1.3	14.7	12.4-18.1
	1.2%	1.0%	0.8%	0.7%	0.6%	0.6%	0.6%	0.8%	0.7%-1.0%
Males									
WHO Region	Age Group (years)								
	15-19	20-24	25-29	30-34	35-39	40-44	45-49	All ages	95%UI
Americas	0.242	0.238	0.225	0.206	0.184	0.165	0.150	1.4	0.930-2.1
	0.6%	0.6%	0.6%	0.6%	0.6%	0.5%	0.5%	0.6%	0.4%-0.9%
Africa	0.884	0.690	0.542	0.424	0.318	0.231	0.164	3.3	2.5-4.1
	1.7%	1.6%	1.4%	1.3%	1.2%	1.1%	1.0%	1.4%	1.1%-1.7%
Eastern Mediterranean	0.049	0.048	0.047	0.043	0.036	0.030	0.025	0.279	0.059-1.3
	0.2%	0.2%	0.2%	0.2%	0.2%	0.2%	0.1%	0.2%	0.0%-0.7%
Europe	0.068	0.075	0.083	0.083	0.078	0.076	0.072	0.535	0.246-1.1
	0.3%	0.3%	0.3%	0.3%	0.3%	0.2%	0.2%	0.3%	0.1%-0.5%
South-East Asia	0.376	0.351	0.325	0.298	0.262	0.230	0.200	2.0	0.659-5.9
	0.4%	0.4%	0.4%	0.4%	0.4%	0.4%	0.4%	0.4%	0.1%-1.1%
Western Pacific	0.213	0.243	0.291	0.247	0.215	0.245	0.253	1.7	0.761-3.6
	0.4%	0.4%	0.3%	0.3%	0.3%	0.3%	0.3%	0.3%	0.2%-0.7%
Global Total (Male)	1.8	1.6	1.5	1.3	1.1	1.0	0.864	9.2	7.4-13.6
	0.6%	0.5%	0.5%	0.5%	0.4%	0.4%	0.4%	0.5%	0.4%-0.7%

NUMBERS LESS THAN 1 MILLION SHOWN TO 3 D.P. FOR COMPARATIVE PURPOSES, BUT THIS IS NOT NECESSARILY INDICATIVE OF ACCURACY.

TABLE 5: GLOBAL AND REGIONAL ESTIMATES FOR THE NUMBER (IN MILLIONS) AND PERCENTAGE OF THE POPULATION WITH INCIDENT HSV-1 INFECTION (ANY SITE) IN 2016 BY AGE AND SEX

Both												
Global Total (All)	Age Group (years)											
	0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	All ages	95%UI
	81.4	19.1	7.0	3.8	2.7	2.1	1.5	1.2	0.9	0.7	120.4	114.3-130.1
	12.3%	3.0%	1.2%	0.7%	0.5%	0.3%	0.3%	0.2%	0.2%	0.2%	2.1%	2.0%-2.3%
Females												
WHO Region	Age Group (years)											
	0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	All ages	95%UI
Americas	1.0	0.885	0.766	0.670	0.583	0.488	0.401	0.321	0.257	0.206	5.6	5.4-5.8
	3.0%	2.5%	2.1%	1.8%	1.6%	1.3%	1.1%	1.0%	0.8%	0.7%	1.6%	1.5%-1.7%
Africa	16.7	1.6	0.157	0.015	0.001	0.000	0.000	0.000	0.000	0.000	18.5	16.1-22.0
	21.4%	2.4%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	4.2%	3.6%-5.0%
Eastern Medi- terranean	3.1	1.7	0.889	0.497	0.291	0.174	0.096	0.048	0.023	0.012	6.8	5.3-8.0
	7.8%	4.7%	2.8%	1.7%	1.0%	0.6%	0.4%	0.2%	0.1%	0.1%	2.5%	1.9%-2.9%
Europe	1.7	1.1	0.661	0.425	0.308	0.229	0.150	0.095	0.061	0.039	4.8	4.4-5.0
	6.5%	4.2%	2.7%	1.7%	1.1%	0.7%	0.5%	0.3%	0.2%	0.1%	1.7%	1.5%-1.8%
South-East Asia	10.5	2.2	0.444	0.087	0.017	0.003	0.001	0.000	0.000	0.000	13.2	12.6-14.2
	12.7%	2.5%	0.5%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	1.7%	1.7%-1.9%
Western Pacif- ic	7.0	2.3	0.749	0.257	0.102	0.044	0.013	0.004	0.002	0.001	10.5	9.8-13.1
	12.3%	4.2%	1.4%	0.5%	0.2%	0.1%	0.0%	0.0%	0.0%	0.0%	1.6%	1.5%-2.0%
Global Total (Female)	40.0	9.8	3.7	2.0	1.3	0.938	0.661	0.468	0.342	0.257	59.4	56.3-63.9
	12.6%	3.2%	1.3%	0.7%	0.5%	0.3%	0.2%	0.2%	0.1%	0.1%	2.2%	2.0%-2.3%
Males												
WHO Region	Age Group (years)											
	0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	All ages	95%UI
Americas	0.864	0.773	0.692	0.624	0.560	0.481	0.402	0.328	0.267	0.222	5.2	4.9-5.5
	2.4%	2.1%	1.9%	1.6%	1.4%	1.3%	1.1%	1.0%	0.9%	0.8%	1.5%	1.4%-1.6%
Africa	17.2	1.7	0.160	0.015	0.001	0.000	0.000	0.000	0.000	0.000	19.0	16.5-22.6
	21.4%	2.4%	0.3%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	4.3%	3.7%-5.1%
Eastern Medi- terranean	3.3	1.8	0.941	0.529	0.310	0.187	0.103	0.053	0.026	0.013	7.2	5.7-8.4
	7.8%	4.7%	2.8%	1.7%	1.0%	0.6%	0.4%	0.2%	0.1%	0.1%	2.4%	1.9%-2.9%
Europe	0.880	0.729	0.574	0.484	0.456	0.438	0.372	0.303	0.252	0.207	4.7	4.3-5.1
	3.1%	2.6%	2.2%	1.9%	1.6%	1.4%	1.1%	1.0%	0.8%	0.7%	1.6%	1.5%-1.7%
South-East Asia	11.4	2.4	0.486	0.095	0.018	0.003	0.001	0.000	0.000	0.000	14.4	13.8-15.5
	12.7%	2.5%	0.5%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	1.8%	1.7%-1.9%
Western Pacif- ic	7.7	2.0	0.525	0.142	0.044	0.015	0.003	0.001	0.000	0.000	10.5	9.4-15.5
	12.0%	3.2%	0.9%	0.2%	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	1.5%	1.3%-2.2%
Global Total (Male)	41.3	9.3	3.4	1.9	1.4	1.1	0.882	0.685	0.546	0.442	61.0	57.6-66.8
	12.1%	2.8%	1.1%	0.6%	0.5%	0.4%	0.3%	0.3%	0.2%	0.2%	2.1%	2.0%-2.3%

NUMBERS LESS THAN 1 MILLION SHOWN TO 3 D.P. FOR COMPARATIVE PURPOSES, BUT THIS IS NOT NECESSARILY INDICATIVE OF ACCURACY.

Discussion

An estimated 491 million people were living with HSV-2 infection, 3.6 billion with oral HSV-1 infection, and 122-192 million with genital HSV-1 infection, in those up to 49 years of age in 2016. An estimated 596-656 million people were genitally-infected with either HSV-1 or HSV-2 globally, meaning HSV has a substantial effect on the sexual and reproductive health of millions of people worldwide. HSV-2 infection disproportionately affected women and the WHO Africa region. This is particularly concerning, as young women in this region are at particular risk of acquiring HIV(122).

Strengths and Limitations

These latest HSV-1 and HSV-2 infection estimates for 2016 are informed by extensive literature reviews, with 474 and 223 prevalence data points for HSV-2 and HSV-1, respectively, contributing to the estimates. For the first time we estimated the numbers with oral HSV-1 infection separately. Our estimates provide a global picture of the overall numbers with HSV infection, and can be built upon to better understand the global burden of HSV-associated disease.

These estimates have some limitations. Firstly, they rely on accurate data to inform them, and assume contributing studies are representative of their respective regions. We found evidence that despite an increased number of studies contributing data compared with previous estimates, the number of contributing countries is generally declining. To help mitigate these issues, our literature search used broad search terms and was not restricted by language. We adjusted reported prevalence for assay sensitivity and specificity, since lack of adjustment tends to inflate HSV prevalence, and generated estimate bounds to reflect uncertainty in prevalence reported by publications. We also assumed a constant force of infection by age. However, this was applied only to those susceptible, allowing the number infected to decrease with age, and the fitting process also allowed prevalence to saturate below 100% where suggested by the data. Nonetheless, future modelling analyses would be useful to explore how the limited available empirical incidence data could further inform infection estimates. In the meantime, these estimates provide a “snapshot” of prevalence, and project ahead by a single year to estimate the incidence that could achieve that prevalence pattern.

Secondly, our estimates for genital HSV-1 infection are particularly uncertain, as reflected in the wide uncertainty bounds. HSV-1 prevalence data are lacking among children for all regions, and across all ages for WHO Africa and South-East Asia regions. Accurate fitting to prevalence is important for predicting the potential for genital infection upon commencing sexual activity. Our model fits suggest that in some regions, few HSV-1 infections are acquired in adulthood, resulting in low estimates of genital HSV-1 infection. However, since the model fits are poorly informed by data, the numbers could be higher than estimated. Conversely, we applied a relatively high value to the proportion of incident HSV-1 infections that are genital during adulthood. While pooled across contributing studies, this value was only informed by four longitudinal studies, all from the US and in sexually-active populations that may not be representative everywhere. It was also calculated by assuming that oral and genital HSV-1 infections are equally likely to be symptomatic. The proportion may vary between regions due to variation in the frequency of oral sex, the main route of transmission of HSV-1 genital herpes, as well as variation in background HSV-1 prevalence(5). Thus, there is also potential for overestimation of the contribution of genital HSV-1 infection. A sensitivity analysis showed how genital HSV-1 infection estimates might change if fewer people were able to acquire infection.

Thirdly, our infection estimates do not translate into direct estimates of symptoms or disease. Of the 596-656 million people estimated to be genitally-infected with either HSV-1 or HSV-2 for example, many infections will be asymptomatic (or at least, not recognized as genital herpes), particularly those due to genital HSV-1. However, the potential for HSV transmission to sex partners or neonates, and for augmentation of HIV acquisition risk which has been documented for HSV-2, remain even in the absence of symptoms.

Fourthly, time trends between estimate years should be cautiously interpreted. Global HSV-2 prevalence in 2016 (13.2%) was estimated to be somewhat higher than that estimated for 2012 (11.3%) although the 95%UI overlapped. However, while the estimates used population data for a single year, there was a large overlap in the informing data between estimate years. At the same time, there was a change in the countries and types of populations contributing data. Furthermore, both overall prevalence and numbers infected are a function of underlying demography, and there has been a global shift towards an ageing population, which will increase overall prevalence even in the absence of a change in the force of infection, since infection is lifelong. Applying equal population numbers by age, sex, WHO region and estimate year, the observed increase in global HSV-2 prevalence between 2016 and 2012 remained but was somewhat diminished (15.2% versus 13.7%; data not shown), and 95%UI continued to overlap. This pattern was seen across all regions and especially for females, except for WHO Eastern Mediterranean region where a decrease was observed. Time trends can be investigated in future work through analyses of study-level data.

Lastly, older age groups contribute an important burden of infection (and likely also disease in terms of continuing recurrences(123)), which is not captured by restricting the estimates to those aged under 50 years. This was done because the 15-49 year old age group is the most important in terms of sexual transmission and sexual and reproductive health outcomes, prevalence in those of older age is not well informed by data, and this allows alignment with other STI estimates produced by WHO, which are done for 15-49 year olds(124). However, we speculated on the potential for underestimation, estimating that globally in 2016, 5.0 billion and 836 million people aged up to 99 years had HSV-1 and HSV-2 infection, respectively. Our HSV-2 estimate is similar to the 956 million (95%UI 847-1087 million) estimated by the 2017 GBD study, which includes older ages(17). The GBD study uses a Bayesian model with HSV-2 prevalence data identified by a basic search string supplemented by data from our earlier reviews(2, 16) not found by the search. GBD HSV-2 infection estimates are not adjusted for test underperformance, which tends to overestimate prevalence(2). Differences in regional groupings will also influence global totals.

Implications and Future Directions

The global number of HSV-1 and HSV-2 infections is huge and more than half a billion people are estimated to have genital infection with either HSV type. HSV disease sequelae range from the very common (orolabial herpes, genital ulcer disease), to the rarer but potentially life-changing and even life-threatening (eye disease, encephalitis, neonatal herpes), and HSV-2 infection also likely contributes to the spread of HIV. Although not all infections lead to symptoms, because billions of people have HSV infection, this translates into a large burden of disease worldwide. Current prevention methods against HSV infection are inadequate(19). The most effective intervention against HSV, given its frequently asymptomatic presentation, may be a vaccine(19). These estimates provide up-to-date information on infection rates and their distribution by age, sex and geographical region to inform the development and subsequent targeting of interventions. They also provide the basis to estimate the burden of all the possible disease consequences of HSV infection, to stimulate new product development and inform the use of interventions to maximize impact on morbidity and mortality, especially in low- and middle-income countries.

Contributors

SLG commissioned the study. CJ conducted the literature searches, data extraction, and data synthesis, and wrote the first draft of the manuscript. KJL checked a subset of the literature searches, the data extraction for WHO Africa region, the data standardization, and stages of the estimates calculation, provided input and guidance at all stages, and revised the manuscript. MH and LJA-R provided additional references. NJW gave statistical advice. KMET supervised KJL and co-supervised CJ with KJL. All authors gave input on the direction of the study and commented on the manuscript drafts.

Conflict of interest

KJL reports grants from WHO during the conduct of the study and outside the submitted work. KJL and KMET report a grant from GSK outside the submitted work. NJW reports grants from the National Institute for Health Research during the conduct of the study and grants from Pfizer Ltd outside the submitted work. SLG reports grants from National Institute of Allergy and Infectious Diseases during the conduct of the study.

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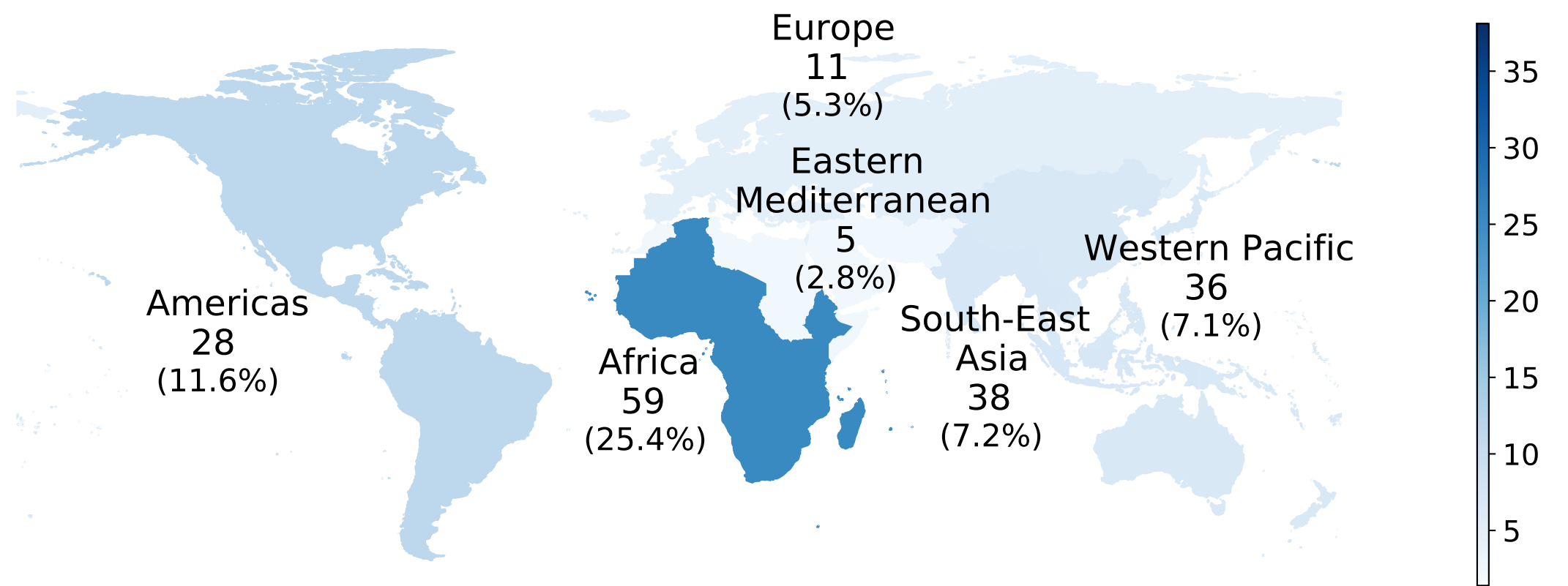
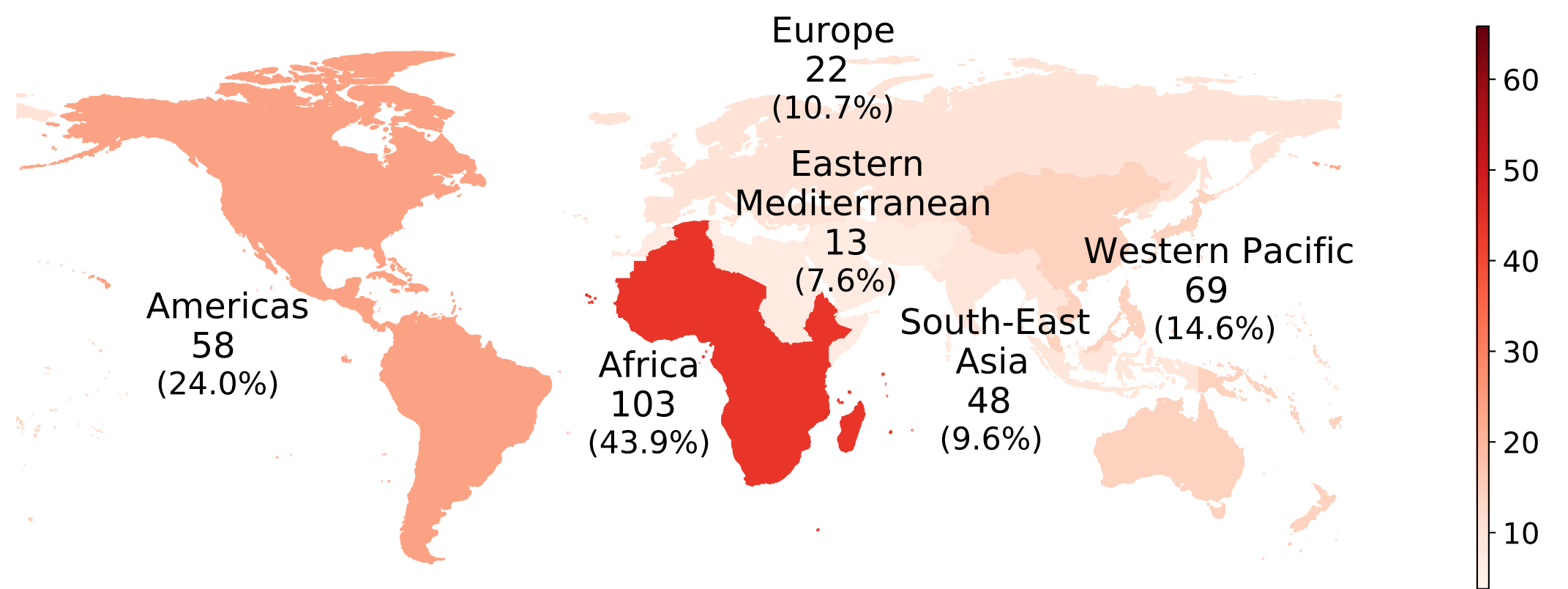
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	Global Total Female	Global Total Male	Global Total All
Prevalence %	17.1	9.3	13.2
Number (millions)	313	178	491