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Epidemiology of herpes simplex virus type 2 in Latin America and the Caribbean: systematic review, meta-analyses and metaregressions

Manale Harfouche,[1,2] Haifa Maalmi,[3] Laith J Abu-Raddad [1,2,4]

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For numbered affiliations see end of article.

Correspondence to
Professor Laith J Abu-Raddad, WHO 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; lja2002@qatar-med.cornell.edu

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ABSTRACT

Objective To characterise epidemiology of herpes simplex virus type 2 (HSV-2) in Latin America and the Caribbean.

Methods HSV-2 reports were systematically reviewed and synthesised, and findings were reported following Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Meta-analyses and metaregressions were conducted.

Finding 102 relevant reports were identified including 13 overall incidence measures, 163 overall (and 402 stratified) seroprevalence measures, and 7 and 10 proportions of virus detection in genital ulcer disease and in genital herpes, respectively. Pooled mean seroprevalence was 20.6% (95% CI 18.7% to 22.5%) in general populations, 33.3% (95% CI 26.0% to 41.0%) in intermediate-risk populations, 74.8% (95% CI 70.6% to 78.8%) in female sex workers, and 54.6% (95% CI 47.4% to 61.7%) in male sex workers, men who have sex with men and transgender people. In general populations, seroprevalence increased from 9.6% (95% CI 7.1% to 12.4%) in those aged <20 years to 17.9% (95% CI 13.6% to 22.5%) in those aged 20–30, 27.6% (95% CI 21.4% to 34.2%) in those aged 30–40 and 38.4% (95% CI 32.8% to 44.2%) in those aged >40. Compared with women, men had lower seroprevalence with an adjusted risk ratio (ARR) of 0.68 (95% CI 0.60 to 0.76). Seroprevalence declined by 2% per year over the last three decades (ARR of 0.98, 95% CI 0.97 to 0.99). Pooled mean proportions of HSV-2 detection in GUD and genital herpes were 41.4% (95% CI 18.9% to 67.0%) and 91.1% (95% CI 82.7% to 97.2%), respectively.

Conclusions One in five adults is HSV-2 infected, a higher level than other world regions, but seroprevalence is declining. Despite this decline, HSV-2 persists as the aetiological cause of nearly half of GUD cases and almost all of genital herpes cases.

INTRODUCTION

With an estimated 24 million incident infections every year, herpes simplex virus type 2 (HSV-2) is an STI of global concern.[1] Unlike common bacterial STIs, HSV-2 is a chronic and incurable infection that is characterised by frequent subclinical shedding and reactivation.[2–6] When symptomatic, HSV-2 infection manifests in the form of painful recurrent genital ulcers that are associated with sexual and psychosocial morbidities and adverse impact on quality of life.[7–10] HSV-2 can also be passed vertically from mother to child, thus causing neonatal herpes, a rare but highly disabling and sometimes fatal outcome in newborns.[9 11] Though with some debate,[12] evidence suggests that HSV-2 increases the risk of HIV acquisition and transmission and may have contributed to driving larger HIV epidemics especially in Africa.[2 13–15]

With the disease burden of STIs, and per the United Nations Sustainable Development Goals,[16] the WHO formulated the 'Global Health Sector Strategy on STIs',[17] which focused on integrating preventive and control measures aimed at eliminating STIs as a main public health concern by 2030. While controlling HSV-2 infection is a main pillar of the global effort to address the population's sexual and reproductive health needs,[18 19] current prevention modalities are inadequate to control transmission and there are no specific programmes for HSV-2 prevention and control even in high-income countries.[20–22] This highlights the critical need for HSV-2 vaccination as a strategic approach to control transmission and to reduce if not eliminate the clinical, psychosexual and economic burden of this infection.[18 23–26]

Against this context, the WHO is spearheading a multisectorial effort to establish the business case and return on investment for HSV-2 vaccines.[18 19 27 28] To inform this effort, this study aims to characterise HSV-2 epidemiology in Latin America and the Caribbean by delineating HSV-2 incidence and antibody prevalence (seroprevalence) levels, estimating pooled mean HSV-2 seroprevalence in the different at-risk populations, identifying predictors of high seroprevalence, and estimating the pooled means for the proportion of HSV-2 detection in genital ulcer disease (GUD) and the proportion of HSV-2 detection in genital herpes.

METHODS

The methods for this study were adapted from our previous systematic reviews characterising HSV-2 epidemiology in Africa[29] and HSV-1 epidemiology in Latin America and the Caribbean.[30] The study methods are described in table 1.

Data sources and search strategy

This systematic review was informed by the *Cochrane Collaboration Handbook*,[31] and its findings were reported per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (online supplemental table S1).[32] Forty-seven countries were included in the study and classified into subregions based on the

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Table 1 Description of the methodology for this study

Methodology	Detailed description
Data source and search strategy	► Search conducted on 12 March 2020 in PubMed, Embase and Literatura Latino Americana em Ciências daSaúde (LILACS). ► Search strategies included exploded MeSH/Emtree terms and broad terms with no language or time restrictions. ► The definition of Latin America and the Caribbean included 47 countries classified into three subregions: – Central America: Belize, Costa Rica, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama. – South America: Argentina, Bolivia, Brazil, Chile, Colombia, Ecuador, French Guiana, Guyana, Paraguay, Peru, Surinam, Uruguay, Venezuela. – Caribbean: Anguilla, Antigua and Barbuda, Aruba, Bahamas, Barbados, Bermuda, British Virgin Islands, Cayman Islands, Cuba, Curacao, Dominica, Dominican Republic, Grenada, Guadeloupe, Haiti, Jamaica, Martinique, Montserrat, Puerto Rico, Saint Kitts and Nevis, Saint Lucia, Saint Vincent and the Grenadines, St. Barthelemy, St. Martin, Trinidad and Tobago, Turks and Caicos.
Study selection and inclusion and exclusion criteria	► Search results were imported into the reference manager EndNote (Thomson Reuters, USA). ► Screening was performed in four 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. 4. Bibliographies of relevant publications and reviews were checked for additional potentially relevant publications. ► Inclusion criteria were any publication, including a study with a minimum sample size of 10, reporting primary data on any of the following outcome measures: 1. HSV-2 antibody incidence as detected by a type-specific diagnostic assay. 2. HSV-2 antibody prevalence (seroprevalence) as detected by a type-specific diagnostic assay. 3. Proportion of HSV-2 in GUD as detected by standard viral detection and subtyping methods. 4. Proportion of HSV-2 in genital herpes (as opposed to HSV-1), as detected by standard viral detection and subtyping methods. ► Exclusion criteria were – Case reports, case series, reviews, editorials, commentaries and qualitative studies. – Measures reporting seroprevalence in infants <6 months old as their antibodies can be maternal in origin. ► In this study, the term 'publication' refers to a document reporting one or several outcome measures. 'Study' or 'measure' refers to a specific outcome measure and its details.
Data extraction and data synthesis	► Extracted variables included author(s), publication title, year(s) of data collection, publication year, country of origin, country of survey, city, study site, study design, study sampling procedure, study population and its characteristics (eg, sex and age), sample size, HSV-2 outcome measures, and diagnostic assay. ► Overall outcome measure 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. ► Stratification hierarchy for incidence and seroprevalence in descending order of preference were 1. Population type as defined in online supplemental box S1. 2. Sex. 3. Age group classified as (groups optimised to best fit reported data): – <20 years old. – 20–30 years old. – 30–40 years old. – >40 years old. ► Stratification hierarchy for GUD and genital herpes included genital herpes episode status and study site: 1. Genital herpes episode status classified as – First episode genital herpes. – Recurrent genital herpes. 2. Study site stratification classified as – Hospital. – STD clinic. ► Measures reporting any HSV-2 outcome among children <15 years old were only reported but not included in the analyses.
Quality assessment	The Cochrane's approach for ROB assessment included ► Study's precision classification into low versus high based on the sample size (<200 vs ≥200). ► Study's appraisal into low vs high ROB was determined using two quality domains: – Sampling method: probability-based *vs* non-probability based. – Response rate: ≥80% vs <80% or unclear.
Meta-analyses	► Meta-analyses were conducted using DerSimonian-Laird random-effects models with inverse variance weighting. The variance of each outcome measure was stabilised using the Freeman-Tukey arcsine square-root transformation. ► Pooled mean HSV-2 seroprevalence was estimated for each population type by sex, and for general populations by country, subregion, year of data collection range and year of publication range. ► Pooled proportions of HSV-2 detection in GUD and in genital herpes cases were estimated. ► Heterogeneity assessment was based on three complementary metrics: – Cochran's Q statistic to assess existence of heterogeneity in effect size (p value of <0.1 indicated heterogeneity). – 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. – Prediction interval to describe the distribution of true outcome measures around the pooled mean.
Metaregressions	► Univariable and multivariable random-effects meta-regression analyses using log-transformed proportions were carried out to identify predictors of HSV-2 seroprevalence. ► Factors in the univariable model with a p value of <0.1 were included in the multivariable analysis. ► Factors in the multivariable model with a p value of ≤0.05 were deemed to be significant predictors. ► Variables included in the univariable metaregression model for HSV-2 seroprevalence were – Population type. – Age group. – Sex. – Country. – Subregion. – Country's income: LIC, LMIC, UMIC, and HIC according the World Bank classification. – Assay type (western blot, ELISA, and monoclonal antibody). – Sample size. – Sampling method. – Response rate. – Year of data collection. – Year of publication. – Year of data collection category (<2000, 2000–2010, >2010). – Year of publication category (<2000, 2000–2010, >2010). ► The year of data collection had a few missing variables that were imputed by adjusting the year of publication using the median difference with the year of data collection.

This methodology was adapted from a previously conducted systematic review characterising the epidemiology of HSV-1 in Europe.[88]
GUD, genital ulcer disease; HIC, high-income country; HSV-1, herpes simplex virus type 1; HSV-2, herpes simplex virus type 2; LIC, low-income country; LMIC, lower-income to middle-income country; ROB, risk of bias; UMIC, upper-income to middle-income country.

WHO and United Nations definitions for Latin America and the Caribbean (table 1).[33 34] Search strategies are in online supplemental table S2.

Study selection and inclusion and exclusion criteria

Screening and double screening were conducted by HM and MH, respectively. Screening steps and eligibility criteria are detailed in table 1.

Data extraction and synthesis

Extraction and double extraction of relevant publications were performed by MH and HM. The list of extracted variables is found in table 1.

Quality assessment

Given documented limitations in HSV-2 assays,[35 36] assessment of assays' reliability and validity was conducted with the assistance of Professor Rhoda Ashley-Morrow of the University of Washington, a leading expert in HSV-2 serology. Only studies with reliable and valid assays were included in the systematic review, and each study was subsequently assessed for precision and risk of bias (ROB) as informed by the Cochrane approach.[31] Details of the quality assessment are in table 1.

Meta-analyses

To account for sampling variation and heterogeneity in effect sizes, meta-analyses were conducted using DerSimonian-Laird random-effects models[37] with the variance stabilised using the Freeman-Tukey double arcsine transformation.[38] These analyses were conducted in R V.3.4.1[39] using the 'meta' package[40] (table 1).

Metaregressions

To identify possible predictors of HSV-2 seroprevalence and sources of between-study heterogeneity, log-transformed seroprevalence measures were regressed in STATA/SE V.13[41] using the 'metareg' package[42] (table 1).

RESULTS

Search results and scope of evidence

Study selection process following the PRISMA guidelines is detailed in figure 1. Overall, 4371 citations were identified. After deduplication and title and abstract screening, full text of 631 unique citations were retrieved for further screening. This step identified 95 relevant publications, and their bibliography

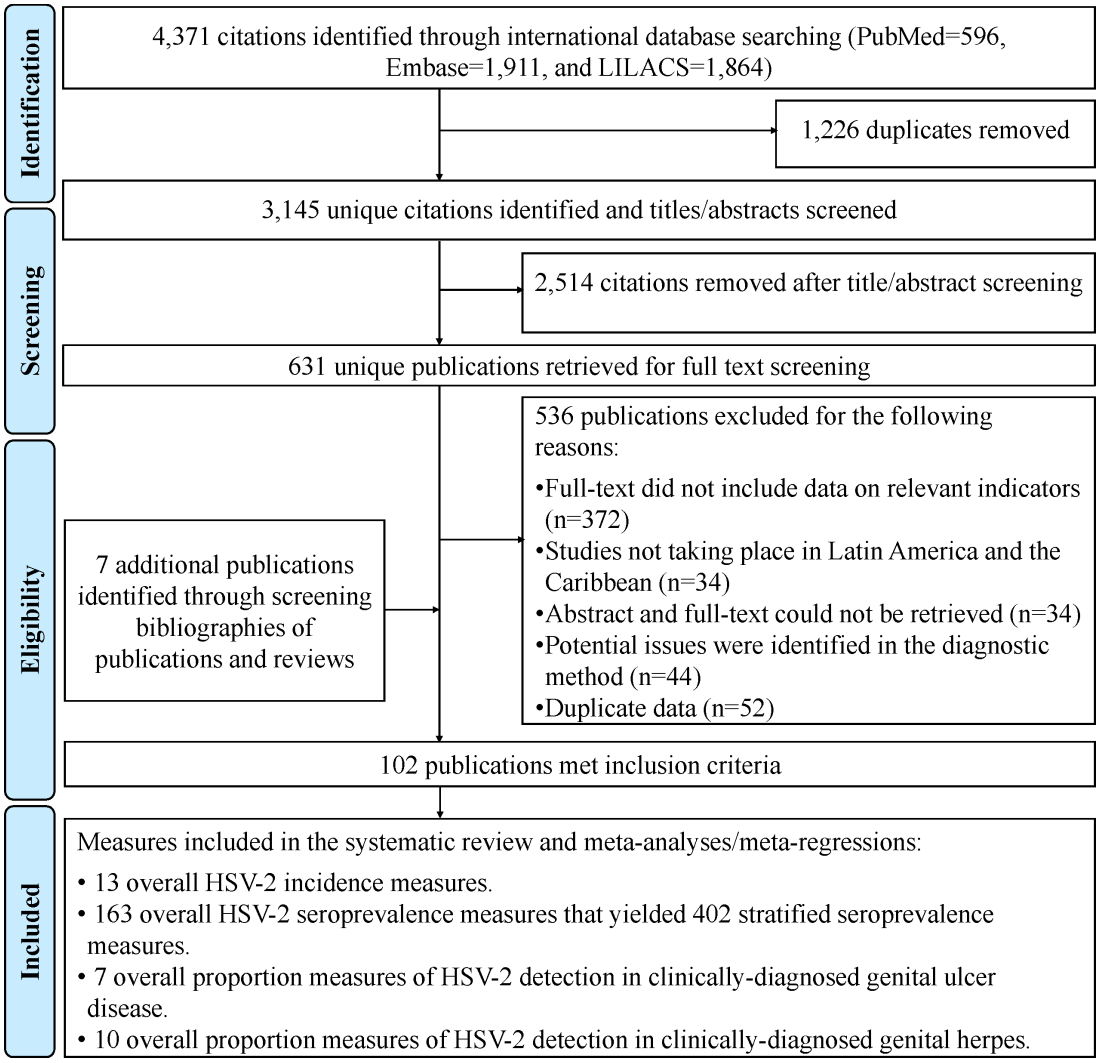

Figure 1 Flowchart of article selection for the systematic review of HSV-2 infection in Latin America and the Caribbean, per the PRISMA guidelines.[32] HSV-2, herpes simplex virus type 2; LILACS, Literatura Latino Americana em Ciências daSaúde, PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Table 2 Pooled mean estimates for HSV-2 seroprevalence among the different at-risk populations in Latin America and the Caribbean

	Outcome measures	Samples	HSV-2 seroprevalence (%)		Pooled mean HSV-2 seroprevalence	Heterogeneity measures		
Population type	Total N	Total N	Range	Median	Mean (%) (95% CI)	Q* (P value)	I²† (%) (95% CI)	Prediction interval‡ (%)
General populations	236	56 457	0.0–71.4	19.6	20.6 (18.7 to 22.5)	6495.1 (<0.001)	96.(96.1 to 96.6)	1.4–52.5
Women	139	23 959	0.0–71.4	23.9	25.2 (22.5 to 28.0)	2940.6 (<0.001)	95.3 (94.8 to 95.8)	2.7–59.2
Men	85	16 446	0.0–64.3	10.9	14.2 (11.6 to 17.0)	1914.1 (<0.001)	95.6 (95.0 to 96.1)	0.0–44.8
Mixed sexes	12	16 052	2.2–35.8	15.0	16.8 (11.7 to 22.6)	689.2 (<0.001)	98.4 (98.0 to 98.8)	1.7–42.4
Intermediate-risk populations	24	6775	3.4–79.2	32.2	33.3 (26.0 to 41.0)	817.4 (<0.001)	97.2 (96.5 to 97.7)	4.1–72.6
Women	9	1255	22.2–79.2	43.5	49.3 (38.9 to 60.8)	102.5 (<0.001)	92.2 (87.4 to 95.2)	13.4–85.6
Men	15	5520	3.4–51.1	26.8	25.6 (19.5 to 32.2)	331.0 (<0.001)	95.8 (94.3 to 96.9)	4.6–55.6
High-risk populations	93	25 344	9.0–100	71.2	66.2 (61.0 to 71.2)	6206.7 (<0.001)	98.5 (98.4 to 98.6)	18.0–99.3
FSWs	56	9023	9.0–100	75.0	74.8 (70.6 to 78.8)	901.6 (<0.001)	93.9 (92.8 to 94.9)	43.2–96.7
MSWs, MSM and transgender people	37	16 321	13.0–39.9	50.9	54.6 (47.4 to 61.7)	2851.4 (<0.001)	98.7 (98.6 to 98.9)	13.9–91.9
STI clinic attendees and symptomatic populations	6	432	38.9–95.0	47.0	49.2 (41.9 to 56.5)	8.2 (0.146)	39.0 (0.0 to 75.8)	31.3–67.1
Mixed sexes	6	432	38.9–95.0	47.0	49.2 (41.9 to 56.5)	8.2 (0.146)	39.0 (0.0 to 75.8)	31.3–67.1
HIV-positive individuals and individuals in HIV discordant couples	19	2840	20.0–88.0	65.6	67.3 (60.0 to 74.2)	264.1 (<0.001)	93.2 (90.7 to 95.0)	33.8–93.2
Women	9	1354	20.0–88.0	65.6	68.9 (56.2 to 78.6)	133.4 (<0.001)	94.0 (90.7 to 96.1)	25.6–97.7
Men	5	1066	42.3–81.1	53.0	60.6 (45.6 to 74.7)	83.9 (<0.001)	95.2 (91.5 to 97.3)	9.4–99.3
Mixed sexes	5	420	61.4–87.0	73.0	71.9 (62.9 to 80.2)	13.9 (0.007)	71.3 (27.4 to 88.7)	40.0–95.0
Other populations§	24	3497	15.1–82.0	56.8	51.1 (43.7 to 58.5)	422.6 (<0.001)	94.6 (93.0 to 95.8)	16.5–85.2
Women	21	3225	45.1–82.0	56.6	52.0 (44.2 to 59.8)	368.7 (<0.001)	94.6 (92.9 to 95.9)	17.4–85.5
Men	2¶	172	59.6–60.8	60.2	60.5 (53.0 to 67.8)	–	–	–
Mixed sexes	1¶	100	–	–	18.0 (11.0 to 26.2)	–	–	–

*Q: the Cochran's Q statistic is a measure assessing the existence of heterogeneity in seroprevalence.
†I^2: a measure that assesses the magnitude of between-study variation that is due to actual differences in seroprevalence across studies rather than chance.
‡Prediction interval: a measure that estimates the distribution (95% interval) of true seroprevalence around the estimated mean.
§Other populations include populations with an undetermined risk of acquiring HSV-2 infection such as patients with cervical cancer or their spouses.
¶No meta-analysis was done due to the small number of studies (n<3).
FSW, female sex worker; HSV-2, herpes simplex virus type 2; MSM, men who have sex with men; MSW, male sex worker.;

screening identified seven additional relevant publications, including conference posters and abstracts.[43–49]

In total, 102 publications were deemed relevant and extracted. This extraction yielded 13 HSV-2 overall incidence measures, 163 overall (402 stratified) seroprevalence measures, 7 overall proportion measures of HSV-2 detection in GUD and 10 overall proportion measures of HSV-2 detection in genital herpes.

HSV-2 incidence overview

Online supplemental table 3 summarises the extracted seroconversion rates (number of measures (n)=10) and incidence rates (n=6). Study design was either longitudinal cohort (n=8, 61.5%) or randomised controlled trial (n=5, 38.4%), with follow-up durations ranging between 335 days and 2 years. Across all populations, seroconversion rate ranged between 2.0% and 51.1%, and incidence rate ranged between 4.5 and 38.5 per 100 person-years.

HSV-2 seroprevalence overview

Overall extracted seroprevalence measures (n=163) are listed in online supplemental table S4. The earliest study was published in 1989 and the most recent study was published in 2020. Majority of studies were based on convenience sampling (n=96, 58.9%).

Stratified seroprevalence measures varied by population type classification (table 2), with seroprevalence ranging between 0.0% and 71.4% with a median of 19.6% among general populations (n=236), between 3.4% and 79.2% with a median of 32.2% among intermediate-risk populations (n=24), between 9.0% and 100% with a median of 71.2% among high-risk populations (n=93), between 38.9% and 95.0% with a median of 47.0% among STI clinic attendees and symptomatic populations (n=6), and between 20.0% and 88.0% with a median of 65.6% among HIV-positive individuals and individuals in HIV discordant couples (n=19). A detailed summary of seroprevalence measures by sex across the population type classifications is in table 2.

Pooled mean HSV-2 seroprevalence

Table 2 summarises the pooled mean HSV-2 seroprevalence by sex across populations. In general populations, the pooled mean was 25.2% (95% CI 22.5% to 28.0%) among women and 14.2% (95% CI 11.6% to 17.0%) among men. In intermediate-risk populations, the pooled mean was 49.3% (95% CI 38.9% to 60.8%) among women and 25.6% (95% CI 19.5% to 32.2%) among men. In high-risk populations, the pooled mean was 74.8% (95% CI 70.6% to 78.8%) among female sex workers and 54.6% (95% CI 47.4% to 61.7%) among male sex workers, men who have sex with men and transgender people. In STI clinic attendees and symptomatic populations (mixed population of women and men), the pooled mean was 49.2% (95% CI

Table 3 Pooled mean estimates for HSV-2 seroprevalence among the general population in Latin America and the Caribbean

	Outcome measures	Sample size	HSV-2 seroprevalence (%)		Pooled mean HSV-2 seroprevalence	Heterogeneity measures		
Population classification	Total N	Total N	Range	Median	Mean (%) (95% CI)	Q* (P value)	I^2† (%) (95% CI)	Prediction interval‡ (%)
Countries								
Brazil	79	22 671	0.0–71.4	28.0	25.5 (22.2 to 28.9)	2049.9 (<0.001)	96.2 (95.7 to 96.6)	3.8–56.9
Colombia	14	1633	1.7–67.3	37.7	35.9 (23.9 to 48.7)	351.6 (<0.001)	96.3 (95.0 to 97.3)	0.5–86.6
Costa Rica	11	1800	17.7–58.8	44.6	41.7 (34.2 to 49.4)	108.8 (<0.001)	90.8 (85.6 to 94.1)	15.7–70.4
Mexico	53	19 574	0.0–45.0	10.9	13.4 (10.8 to 16.2)	1392.9 (<0.001)	96.3 (95.7 to 96.8)	0.6–37.1
Peru	65	6896	0.0–38.0	9.0	11.7 (9.5 to 14.1)	500.3 (<0.001)	87.2 (84.4 to 89.5)	0.0–33.1
Other countries§	14	3883	11.8–65.0	39.6	41.2 (32.6 to 50.1)	378.4 (<0.001)	96.6 (95.4 to 97.4)	10.0–77.0
Subregions								
Central America	68	22 688	0.0–59.9	14.9	18.4 (15.1 to 21.9)	2694.7 (<0.001)	97.5 (97.2 to 97.8)	0.5–51.4
South America	164	32 590	0.0–71.4	21.3	21.1 (18.8 to 23.4)	3632.7 (<0.001)	95.5 (95.1 to 95.9)	1.5–53.3
Caribbean	4	1179	30.5–54.0	37.2	38.7 (29.9 to 47.9)	20.9 (0.001)	85.7 (64.9 to 94.2)	5.9–79.0
Age group								
<20 years	28	5194	0.0–29.0	9.0	9.6 (7.1 to 12.4)	229.1 (<0.001)	88.2 (84.1 to 91.2)	0.5–26.4
20–30 years	30	4453	0.0–47.4	20.8	17.9 (13.6 to 22.5)	379.7 (<0.001)	92.4 (90.2 to 94.1)	1.1–46.4
30–40 years	17	1983	9.6–56.0	28.3	27.6 (21.4 to 34.2)	157.2 (<0.001)	89.8 (95.3 to 93.1)	5.6–57.8
>40 years	34	5029	10.9–71.4	40.3	38.4 (32.8 to 44.2)	561.6 (<0.001)	94.1 (92.7 to 95.3)	10.0–72.0
Mixed	127	39 798	0.0–67.3	17.0	18.7 (16.4 to 21.2)	4188.3 (<0.001)	997.0 (96.7 to 97.3)	0.9–49.5
Year of publication category								
<2000	21	2901	5.0–67.3	36.0	34.1 (26.2 to 42.5)	406.4 (<0.001)	95.1 (93.6 to 96.2)	4.0–74.2
2000–2010	132	28 618	0.0–71.4	23.1	22.8 (20.3 to 25.5)	3336.4 (<0.001)	96.1 (95.7 to 96.4)	2.1–55.6
>2010	83	24 938	0.0–65.0	10.9	14.3 (12.1 to 16.8)	1812.0 (<0.001)	94.9 (94.9 to 96.0)	0.7–39.1
Year of data collection category								
<2000	83	9229	0.0–71.4	30.8	31.1 (27.4 to 34.9)	1173.1 (<0.001)	93.0 (91.9 to 94.0)	5.3–65.7
2000–2010	143	33 565	0.0–59.9	12.0	15.0 (13.1 to 17.1)	3450.4 (<0.001)	95.9 (95.5 to 96.3)	0.3–43.4
>2010	12	13 835	10.4–65.0	29.3	30.7 (24.5 to 38.4)	649.0 (<0.001)	98.3 (97.8 to 98.7)	6.9–61.9
All studies	238	56 628	0.0–71.4	20.0	20.8 (19.0 to 22.8)	6630.7 (<0.001)	96.4 (96.2 to 96.7)	1.4–53.1

*Q: the Cochran's Q statistic is a measure assessing the existence of heterogeneity in seroprevalence.
†I^2: a measure that assesses the magnitude of between-study variation that is due to actual differences in seroprevalence across studies rather than chance.
‡Prediction interval: a measure that estimates the distribution (95% interval) of true seroprevalence around the estimated mean.
§Other countries include Argentina, Barbados, Bolivia, Haiti, Honduras and Panama.
HSV-2, herpes simplex virus type 2.

41.9% to 56.5%). In HIV-positive individuals and individuals in HIV discordant couples, the pooled mean was 68.9% (95% CI 56.2% to 78.6%) among women and 60.6% (95% CI 45.6% to 74.7%) among men. Forest plots of these meta-analyses are in online supplemental figure S1.

Table 3 summarises pooled mean seroprevalence estimates in general populations for different subpopulation categorisations. By country, the pooled mean was lowest at 11.7% (95% CI 9.5% to 14.1%) in Peru and was higher at 13.4% (95% CI 10.8% to 16.2%) in Mexico, 25.5% (95% CI 22.2% to 28.9%) in Brazil, 35.9% (95% CI 23.9% to 48.7%) in Colombia and 41.7% (95% CI 34.2%–49.4%) in Costa Rica. Across age groups, pooled mean seroprevalence increased steadily starting at 9.6% (95% CI 7.1% to 12.4%) in <20-year-old individuals, then at 17.9% (95% CI 13.6% to 22.5%) in individuals aged 20–30 years, 27.6% (95% CI 21.4% to 34.2%) in individuals aged 30–40 years and reaching 38.4% (95% CI 32.8% to 44.2%) in >40-year-old individuals.

Predictors of HSV-2 seroprevalence

Results of the metaregression analyses are shown in table 4 (online supplemental tables S5 and S6). In the univariable analysis, 12 variables were found eligible for inclusion in the multivariable model ($p<0.1$). Two sets of multivariable models were conducted to account for the collinearity between the year of publication and the year of data collection.

Each conducted multivariable model explained about 69% of seroprevalence variation and included population type, age group, sex, subregion, country's income, sample size, sampling method and response rate, in addition to year of publication or year of data collection. The 'country' and 'country's income' variables were not included in the multivariable models due to collinearity with subregion. However, they did not add notable new results when they were included in sensitivity analyses instead of subregion (online supplemental table S5).

In the model including year of publication as a categorical variable (table 4) and compared with the general populations, HSV-2 seroprevalence was higher by 1.55-fold (95% CI 1.22 to 1.96) in intermediate-risk populations, 3.09-fold (95% CI 2.67 to 3.57) in high-risk populations, 2.40-fold (95% CI 1.48 to 3.90) in STI clinic attendees and symptomatic populations, and 3.06-fold (95% CI:2.37 to 3.95) in HIV-positive individuals and individuals in HIV discordant couples.

Compared with women, men had a 0.68-fold (95% CI 0.60 to 0.76) lower seroprevalence. Compared with those <20 years old, seroprevalence was higher by 1.63-fold (95% CI 1.27 to 2.09) in individuals aged 20–30 years old, 2.24-fold (95% CI 1.68 to 2.99) in individuals aged 30–40 years old individuals,

Table 4 Univariable and multivariable metaregression analyses for HSV-2 seroprevalence among different at-risk populations in Latin America and the Caribbean using the year of publication as the temporal variable

			Outcome measures	Sample size	Univariable analysis				Multivariable analysis*			
									Model 1†		Model 2 ‡	
			Total n	Total N	RR (95% CI)	p value	LR test P value	Adjusted R^2 (%)	ARR (95% CI)	P value	ARR (95% CI)	P value
Population characteristics	Population type	General populations	236	56 457	1.00	–	<0.001	45.98	1.00	–	1.00	–
		Intermediate-risk populations	24	6775	1.52 (1.16 to 2.00)	0.002			1.55 (1.22 to 1.96)	<0.001	1.54 (1.22 to 1.96)	<0.001
		High-risk populations	93	25 344	3.09 (2.64 to 3.61)	<0.001			3.09 (2.67 to 3.57)	<0.001	3.08 (2.66 to 3.57)	<0.001
		STI clinic attendees and symptomatic populations	6	432	2.49 (1.47 to 4.22)	0.001			2.40 (1.48 to 3.90)	<0.001	2.35 (1.45 to 3.81)	0.001
		HIV-positive individuals and individuals in HIV discordant couples	19	2840	3.21 (2.38 to 4.32)	<0.001			3.06 (2.37 to 3.95)	<0.001	3.02 (2.34 to 3.89)	<0.001
		Other populations§	24	3497	2.42 (1.85 to 3.16)	<0.001			1.56 (1.24 to 1.97)	<0.001	1.53 (1.21 to 1.94)	<0.001
	Age group	<20 years	35	6538	1.00	–	<0.001	10.26	1.00	–	1.00	–
		20–30 years	47	7751	2.05 (1.40 to 3.00)	<0.001			1.63 (1.27 to 2.09)	<0.001	1.62 (1.26 to 2.09)	<0.001
		30–40 years	22	2933	2.58 (1.64 to 4.04)	<0.001			2.24 (1.68 to 2.99)	<0.001	2.22 (1.66 to 2.97)	<0.001
		>40 years	39	5940	2.84 (1.92 to 4.18)	<0.001			3.22 (2.50 to 4.14)	<0.001	3.08 (2.40 to 3.96)	<0.001
		Mixed ages	259	72 183	2.49 (1.82 to 3.41)	<0.001			1.79 (1.44 to 2.21)	<0.001	1.71 (1.39 to 2.11)	<0.001
	Sex	Women	234	38 816	1.00	–	0.001	4.82	1.00	–	1.00	–
		Men	144	39 525	0.67 (0.56 to 0.80)	<0.001			0.68 (0.60 to 0.76)	<0.001	0.69 (0.61 to 0.77)	<0.001
		Mixed sexes	24	17 004	0.81 (0.57 to 1.16)	0.267			0.59 (0.46 to 0.77)	<0.001	0.62 (0.48 to 0.80)	<0.001
	Countries	Brazil	106	25 766	1.00	–	<0.001‡	12.58	–	–	–	–
		Colombia	19	2247	1.36 (0.91 to 2.01)	0.125			–	–	–	–
		Costa Rica	13	2364	1.46 (0.92 to 2.30)	0.102			–	–	–	–
		Mexico	76	23 437	0.71 (0.56 to 0.91)	0.008			–	–	–	–
		Panama	15	3334	1.81 (1.18 to 2.78)	0.006			–	–	–	–
		Peru	131	24 976	0.92 (0.74 to 1.14)	0.476			–	–	–	–
		Other¶	42	13 221	1.84 (1.39 to 2.45)	<0.001			–	–	–	–
	Subregions	Central America	124	38 103	1.00	–	0.065	0.82	1.00	–	1.00	–
		South America	264	54 798	0.95 (0.79 to 1.14)	0.606			1.13 (1.00 to 1.27)	0.047	1.12 (0.99 to 1.27)	0.053
		Caribbean	14	2444	1.62 (1.02 to 2.58)	0.040			1.17 (0.87 to 1.57)	0.281	1.17 (0.87 to 1.56)	0.287
	Country's income	LIC and LMIC	29	9846	1.00	–	<0.001‡	9.07	–	–	–	–
		UMIC	354	81 539	0.45 (0.33 to 0.62)	<0.001			–	–	–	–
		HIC	19	3960	0.86 (0.54 to 1.36)	0.528			–	–	–	–

Continued

Table 4 Continued

			Outcome measures	Sample size	Univariable analysis				Multivariable analysis*			
									Model 1†		Model 2 ‡	
			Total n	Total N	RR (95% CI)	p value	LR test P value	Adjusted R^2 (%)	ARR (95% CI)	P value	ARR (95% CI)	P value
Study methodology characteristics	Assay type	Western blot	94	11 898	1.00	–	0.432	0.00	–	–	–	–
		ELISA	304	82 744	0.89 (0.73 to 1.09)	0.280			–	–	–	–
		Monoclonal antibody	4	703	1.24 (0.53 to 2.87)	0.614			–	–	–	–
	Sample size**	<200	81	7542	1.00	–	<0.001	7.27	1.00	–	1.00	–
		>200	321	87 803	0.58 (0.47 to 0.71)	<0.001			0.75 (0.64 to 0.87)	<0.001	0.74 (0.64 to 0.87)	<0.001
	Sampling method	Probability-based	151	47 471	1.00	–	<0.001	18.05	1.00	–	1.00	–
		Non-probability-based	251	47 874	2.08 (1.76 to 2.44)	<0.001			1.16 (1.00 to 1.35)	0.037	1.17 (1.01 to 1.35)	0.033
	Response rate	≥80%	194	48 220	1.00	–	0.002	5.52	1.00	–	1.00	–
		<80%	32	6062	0.59 (0.42 to 0.82)	0.002			0.79 (0.63 to 0.99)	0.044	0.77 (0.62 to 0.96)	0.025
		Unclear	176	41 063	1.25 (1.05 to 1.49)	0.010			1.07 (0.94 to 1.22)	0.262	1.09 (0.96 to 1.24)	0.169
Temporal variables	Year of publication category	<2000	49	7244	1.00	–	<0.001	4.39	1.00	–	–	–
		2000–2010	206	51 983	0.61 (0.47 to 0.79)	<0.001			0.88 (0.75 to 1.05)	0.166	–	–
		>2010	147	31 118	0.56 (0.42 to 0.73)	<0.001			0.74 (0.61 to 0.89)	0.002	–	–
	Year of publication		402	95 345	0.97 (0.96 to 0.98)	<0.001	<0.001	2.98	–	–	0.98 (0.97 to 0.99)	0.002

The analysis using year of data collection as the temporal variable is found in online supplemental table S6.
*Countries and country's income were not included in the multivariable models due to collinearity with the variable subregions.
†Variance explained by multivariable model 1 (adjusted R^2)=68.85%.
‡Variance explained by multivariable model 2 (adjusted R^2)=68.99%.
§Other populations include populations with an undetermined risk of acquiring HSV-2 infection such as patients with cervical cancer or their spouses.
¶Other countries include Argentina, Barbados, Bolivia, Chile, Dominican Republic, El Salvador, Guatemala, Haiti, Honduras, Jamaica and Nicaragua.
**Sample size denotes the sample size of each study population found in the original publication.
ARR, adjusted risk ratio; HIC, high-income country; HSV-2, herpes simplex virus type 2; LIC, low-income country; LMIC, lower-income to middle-income country; LR, likelihood ratio; RR, risk ratio; UMIC, upper-income to middle-income country.

Table 5 Pooled mean proportions of HSV-2 virus isolation in clinically diagnosed GUD and in clinically diagnosed genital herpes in Latin America and the Caribbean

	Outcome measures	Samples	Proportion of HSV-2 isolation (%)		Pooled proportion of HSV-2 isolation (%)	Heterogeneity measures		
Population type	Total N	Total N	Range	Median	Mean (95% CI)	Q*(P value)	I²† (%) (95% CI)	Prediction interval‡ (%)
Patients with GUD	7	603	0.0–77.7	50.9	41.4 (18.9 to 67.0)	184.5 (<0.001)	96.7 (95.0 to 97.9)	0.0–100
Patients with genital herpes	10	278	71.5–100	90.1	91.1 (82.7 to 97.2)	31.3 (<0.001)	71.2 (45.2 to 84.9)	58.3–100

*Q: the Cochran's Q statistic is a measure assessing the existence of heterogeneity in pooled outcome measures, here proportions of HSV-2 virus isolation in GUD and in genital herpes.
†I² a measure assessing the magnitude of between-study variation that is due to true differences in proportions of HSV-2 virus isolation across studies rather than sampling variation.
‡Prediction interval: a measure quantifying the distribution 95% interval of true proportions of HSV-2 virus isolation around the estimated pooled mean.
GUD, genital ulcer disease; HSV-2, herpes simplex virus type 2.

and 3.22-fold (95% CI 2.50 to 4.14) in >40-year-old individuals. Seroprevalence was 1.13-fold (95% CI 1.00 to 1.27) higher in South America compared with Central America.

Small-study effect was identified—seroprevalence was 0.75-fold (95% CI 0.64 to 0.87) lower in studies with a sample size of >200 compared with those with a sample size of <200. Seroprevalence was 1.16-fold (95% CI 1.00 to 1.35) higher in studies using non-probability-based sampling compared with studies using probability-based sampling. Seroprevalence was 0.79-fold (95% CI 0.63 to 0.99) lower in studies with low response rate (<80%) compared with studies with high response rate (>80%). No effect was found for assay type on observed seroprevalence.

Compared with studies published before the year 2000, those published after 2010 had 0.74-fold (95% CI 0.61 to 0.89) lower seroprevalence. When year of publication was included as a linear term instead of a categorical variable, seroprevalence was found declining by 0.98-fold (95% CI 0.97 to 0.99) per year. Similar results were found when the year of data collection was used in the metaregressions instead of the year of publication (online supplemental table S6). Year of publication was used in the main analysis as its data were more complete than those for year of data collection.

HSV-2 isolation in GUD and in genital herpes

Online supplemental table S7 summarises the studies reporting proportions of HSV-2 detection in GUD or in genital herpes, while table 5 shows the pooled means for these proportions. Proportion of HSV-2 detection in GUD (n=7) ranged between 0.0% and 77.7% with a median of 50.9% and a pooled proportion of 41.4% (95% CI 18.9% to 67.0%). The proportion of HSV-2 detection in genital herpes (n=10) ranged between 71.5% and 100% with a median of 90.1% and a pooled proportion of 91.1% (95% CI 82.7% to 97.2%). Forest plots of the meta-analyses are in online supplemental figure S2.

Quality assessment

The results of the quality assessment are summarised in online supplemental table S8. In total, 82.2% of studies had high precision; 28.8% had low ROB in the sampling method domain; and 35.6% had low ROB in the response rate domain. Only 2.4% of studies had high ROB in both quality domains.

DISCUSSION

Based on a large volume of data that powered a variety of analyses, the epidemiology of HSV-2 infection in Latin America and the Caribbean was comprehensively investigated. With about 20% of adults being seropositive (table 2), this region harbours one of the highest seroprevalence levels worldwide,[1 50–52] second only to sub-Saharan Africa.[1] Nonetheless and remarkably, this region is witnessing a rapidly declining seroprevalence at a rate of about 2% per year (table 4), for reasons that are not yet clear. Curiously, such declines have been also observed in the USA[26 53–56] and more recently in sub-Saharan Africa.[29] Since HSV-2 seroprevalence has been shown to be an objective biomarker of a population's sexual risk behaviour and risk of HIV infection,[57–62] seroprevalence declines could be suggestive of declines in risky sex, possibly in response to the threat of HIV infection.[63–66] Other factors may have also contributed, such as the global expansion of HIV/STI response, including primary prevention interventions,[67 68] STI awareness that encouraged engagement in safer sexual practices[69] and, possibly, socioeconomic development that has changed the structure of sexual networks towards a structure that is less conducive for STI transmission. In concordance with these declines for HSV-2 seroprevalence, evidence suggests declines in the prevalence of other STIs across world regions, such as of HIV[66 70] and syphilis.[71] It remains to be seen whether these declines are localised to some regions or subregions, or global in nature.

The results of the present study confirmed key classic attributes of HSV-2 epidemiology, and importantly established *effect sizes* for these attributes (table 4), thereby providing parameter inputs and adjustment cofactors for future STI burden estimations using mathematical modelling. There was strong hierarchy in seroprevalence based on sexual risk behaviour classification that explained alone 44% of the seroprevalence variation (table 4). This hierarchy was also consistent with that found recently for sub-Saharan Africa.[29] Seroprevalence reached high levels that exceeded 60% in populations at high risk, such as female sex workers and men who have sex with men (table 2).

Compared with women, men had 0.68-fold lower HSV-2 seroprevalence (table 4), providing further support for a higher bioanatomical susceptibility to the infection among women.[9 52 72] Consistent with existing evidence,[1 52 72 73] age played a critical role in exposure to this infection. Seroprevalence grew steadily with age right after sexual debut (tables 3 and 4). However, unlike in sub-Saharan Africa where it plateaued by mid-30s,[29] seroprevalence continued to grow with age in Latin America and the Caribbean even for those >40 years of age.

The results have shown some evidence for subregion and country variability in HSV-2 seroprevalence (tables 3 and 4). There was also evidence for higher seroprevalence in countries

with lower income (tables 3 and 4) that are suggestive of lower socioeconomic status being conducive to higher risk of exposure to this infection, as observed elsewhere.[50 74 75]

The results further show that HSV-2 infection is the aetiological cause of nearly half of GUD cases in this region (table 5), confirming the disproportional role for this infection in this disease outcome. The role of HSV-2 in GUD may continue at this high level for decades to come despite the declining seroprevalence, as other causes of GUD, such as syphilis,[71 76] could also be declining at the same time. HSV-2 infection (as opposed to HSV-1 infection) was also the aetiological cause of >90% of genital herpes cases (table 5). This finding is in line with a recent assessment of HSV-1 infection in Latin America and the Caribbean, indicating that HSV-1 is still mainly acquired orally in a context of slow transitioning epidemiology and limited contribution for HSV-1 in genital herpes.[30] While this finding is consistent with what is observed in sub-Saharan Africa and possibly the Middle East and North Africa,[77–79] it contrasts with what is observed in North America, Europe, and Asia, where the role of HSV-1 in genital herpes has been increasing, and in some settings and populations even reaching the point of being the leading cause of this disease outcome.[80–88]

This study has limitations. HSV-2 epidemiological data were mainly available for the large countries of Latin America and the Caribbean region that constitute most of its population, but there were no data available for 27 out of the 47 (mostly small) countries constituting this part of the world. There were also less data for GUD and genital herpes than for seroprevalence. There was evidence for a small-study effect and somewhat varying seroprevalence by sampling method and response rate (table 4), which may have biased assessed seroprevalence. Studies differed in the employed diagnostic assays (online supplemental table S4), with possibly different sensitivity and specificity profiles.[35 36 89] However, no effect was found for assay type on estimated seroprevalence (table 4). Measured seroprevalence can be affected by the choice of ELISA optical density cut-off for positivity.[35 51 90 91] Studies were excluded if clearly an inappropriate cut-off was used. Still, variation in the use of optical density cutoffs across studies could have influenced estimated seroprevalence.[35 51 90 91] There was high heterogeneity in seroprevalence (tables 2 and 3), but strikingly most of this heterogeneity was subsequently explained by the 'classic' attributes driving variation in HSV-2 seroprevalence, including sexual risk behaviour, sex and age (table 4). On balance, these limitations may have had inconsequential impact on the results and findings of the present study.

CONCLUSIONS

One in five adults in Latin America and the Caribbean is chronically infected with HSV-2, a higher level than that found in most other world regions, but seroprevalence is rapidly declining at a rate of about 2% per year, possibly reflecting changes in sexual behaviour and patterns, sexual networks or use of protective measures, such as condoms, over the last three decades. Despite this decline, HSV-2 infection persists as the aetiological cause of nearly half of GUD cases in this region, and almost all of genital herpes cases. These findings highlight the importance of HSV-2 seroprevalence monitoring and surveillance and demonstrate the need for prophylactic and therapeutic vaccines to alleviate this disease burden. They also advocate for increased momentum and support to the slowly progressing efforts of vaccine development.

Key messages

- Herpes simplex virus type 2 (HSV-2) infection is a highly prevalent STI worldwide, and results in a sizeable disease burden.
- One in five adults in Latin America and the Caribbean is chronically infected with HSV-2, a higher level than in other regions.
- However, this region is witnessing a rapidly declining seroprevalence at a rate of 2% per year.
- HSV-2 is the aetiological cause of nearly half of GUD cases and almost all of genital herpes cases in this region.
- The findings highlights the need for seroprevalence monitoring, GUD/genital herpes aetiological surveillance, and an HSV-2 vaccine to control transmission and alleviate the disease burden.

Author affiliations
[1]Infectious Disease Epidemiology Group, Weill Cornell Medicine—Qatar, Cornell University, Qatar Foundation—Education City, Doha, Qatar
[2]WHO 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]Institute for Clinical Diabetology, German Diabetes Center, Leibniz Center for Diabetes Research, Heinrich Heine University Düsseldorf, Dusseldorf, Germany
[4]Department of Population Health Sciences, Weill Cornell Medicine, Cornell University, New York, New York, USA

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

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