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

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.2,12–15

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 multisectoral 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 Africa29 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,11 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
This methodology was adapted from a previously conducted systematic review characterising the epidemiology of HSV-1 in Europe.88

Exclusion criteria

Study selection and inclusion and exclusion criteria

Data extraction and data synthesis

Meta-analyses

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 regression 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,


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.
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 models37 with the variance stabilised using the Freeman-Tukey double arcsine transformation.38 These analyses were conducted in R V.3.4.139 using the ‘meta’ package40 (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.1341 using the ‘metareg’ package42 (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.

![Flowchart of article selection for the systematic review of HSV-2 infection in Latin America and the Caribbean, per the PRISMA guidelines.](http://sti.bmj.com/fig.png)

**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 da Saúde, 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

<table>
<thead>
<tr>
<th>Population type</th>
<th>Total N</th>
<th>Total N</th>
<th>Range</th>
<th>Median</th>
<th>Mean (%)</th>
<th>Q* (P value)</th>
<th>I² (%)</th>
<th>Prediction interval (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General populations</td>
<td>236</td>
<td>56457</td>
<td>0.0–71.4</td>
<td>19.6</td>
<td>20.6 (18.7 to 22.5)</td>
<td>6495.1 (&lt;0.001)</td>
<td>96.91 to 96.6</td>
<td>1.4–52.5</td>
</tr>
<tr>
<td>Women</td>
<td>139</td>
<td>22959</td>
<td>0.0–71.4</td>
<td>23.9</td>
<td>25.3 (22.5 to 28.0)</td>
<td>2940.6 (&lt;0.001)</td>
<td>95.3 (94.8 to 95.8)</td>
<td>2.7–59.2</td>
</tr>
<tr>
<td>Men</td>
<td>85</td>
<td>16446</td>
<td>0.0–64.3</td>
<td>10.9</td>
<td>14.2 (11.6 to 17.0)</td>
<td>1914.1 (&lt;0.001)</td>
<td>95.6 (95.0 to 96.1)</td>
<td>0.0–44.8</td>
</tr>
<tr>
<td>Mixed sexes</td>
<td>12</td>
<td>16052</td>
<td>2.2–35.8</td>
<td>15.0</td>
<td>16.5 (11.7 to 22.6)</td>
<td>6892.1 (&lt;0.001)</td>
<td>98.4 (98.0 to 98.8)</td>
<td>1.8–47.7</td>
</tr>
<tr>
<td>Intermediate-risk populations</td>
<td>24</td>
<td>6775</td>
<td>3.4–79.2</td>
<td>32.2</td>
<td>33.3 (26.0 to 41.0)</td>
<td>817.4 (&lt;0.001)</td>
<td>97.2 (96.5 to 97.7)</td>
<td>4.1–72.6</td>
</tr>
<tr>
<td>Women</td>
<td>9</td>
<td>1255</td>
<td>22.2–79.2</td>
<td>43.5</td>
<td>49.3 (38.9 to 60.8)</td>
<td>102.5 (&lt;0.001)</td>
<td>92.2 (87.4 to 95.2)</td>
<td>13.4–85.6</td>
</tr>
<tr>
<td>Men</td>
<td>15</td>
<td>5520</td>
<td>3.4–51.1</td>
<td>26.8</td>
<td>25.6 (19.3 to 32.5)</td>
<td>331.0 (&lt;0.001)</td>
<td>95.8 (94.3 to 96.9)</td>
<td>4.6–55.6</td>
</tr>
<tr>
<td>High-risk populations</td>
<td>93</td>
<td>25344</td>
<td>9.0–100</td>
<td>71.2</td>
<td>66.2 (61.0 to 71.2)</td>
<td>6206.7 (&lt;0.001)</td>
<td>98.5 (98.4 to 98.6)</td>
<td>18.0–99.3</td>
</tr>
<tr>
<td>FSWs</td>
<td>56</td>
<td>9023</td>
<td>9.0–100</td>
<td>75.0</td>
<td>74.8 (70.6 to 78.8)</td>
<td>901.6 (&lt;0.001)</td>
<td>93.9 (92.8 to 94.9)</td>
<td>43.2–96.7</td>
</tr>
<tr>
<td>MSWs, MSM and transgender people</td>
<td>37</td>
<td>16321</td>
<td>13.0–39.9</td>
<td>50.9</td>
<td>54.6 (47.4 to 61.7)</td>
<td>2851.4 (&lt;0.001)</td>
<td>98.7 (98.6 to 98.9)</td>
<td>13.9–91.9</td>
</tr>
<tr>
<td>STI clinic attendees and symptomatic populations</td>
<td>6</td>
<td>432</td>
<td>38.9–95.0</td>
<td>47.0</td>
<td>49.2 (41.9 to 56.5)</td>
<td>8.2 (0.146)</td>
<td>39.0 (0.0 to 75.8)</td>
<td>31.3–67.1</td>
</tr>
<tr>
<td>Mixed sexes</td>
<td>6</td>
<td>432</td>
<td>38.9–95.0</td>
<td>47.0</td>
<td>49.2 (41.9 to 56.5)</td>
<td>8.2 (0.146)</td>
<td>39.0 (0.0 to 75.8)</td>
<td>31.3–67.1</td>
</tr>
<tr>
<td>HIV-positive individuals and individuals in HIV discordant couples</td>
<td>19</td>
<td>2840</td>
<td>20.0–88.0</td>
<td>65.6</td>
<td>67.3 (60.0 to 74.2)</td>
<td>264.1 (&lt;0.001)</td>
<td>93.2 (90.7 to 95.0)</td>
<td>33.8–93.2</td>
</tr>
<tr>
<td>Women</td>
<td>9</td>
<td>1354</td>
<td>20.0–88.0</td>
<td>65.6</td>
<td>68.9 (56.2 to 78.6)</td>
<td>133.4 (&lt;0.001)</td>
<td>94.0 (90.7 to 96.1)</td>
<td>25.6–97.7</td>
</tr>
<tr>
<td>Men</td>
<td>5</td>
<td>1066</td>
<td>42.3–81.1</td>
<td>73.0</td>
<td>60.6 (45.6 to 74.7)</td>
<td>83.9 (&lt;0.001)</td>
<td>95.2 (91.5 to 97.3)</td>
<td>9.4–99.3</td>
</tr>
<tr>
<td>Mixed sexes</td>
<td>5</td>
<td>420</td>
<td>61.4–87.0</td>
<td>73.0</td>
<td>71.9 (62.9 to 80.2)</td>
<td>13.9 (0.007)</td>
<td>71.3 (27.4 to 88.7)</td>
<td>40.0–94.0</td>
</tr>
<tr>
<td>Other populations§</td>
<td>24</td>
<td>3497</td>
<td>15.1–82.0</td>
<td>56.8</td>
<td>51.1 (43.7 to 58.5)</td>
<td>422.6 (&lt;0.001)</td>
<td>94.6 (93.0 to 95.8)</td>
<td>16.5–85.2</td>
</tr>
<tr>
<td>Women</td>
<td>21</td>
<td>3225</td>
<td>45.1–82.0</td>
<td>56.6</td>
<td>52.0 (44.2 to 59.8)</td>
<td>368.7 (&lt;0.001)</td>
<td>94.6 (92.9 to 95.9)</td>
<td>17.4–85.5</td>
</tr>
<tr>
<td>Men</td>
<td>2¶</td>
<td>172</td>
<td>59.6–60.8</td>
<td>60.2</td>
<td>60.5 (53.0 to 67.8)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Mixed sexes</td>
<td>1¶</td>
<td>100</td>
<td>–</td>
<td>–</td>
<td>18.0 (11.0 to 26.2)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

*Q*: the Cochran’s Q statistic is a measure assessing the existence of heterogeneity in seroprevalence.

I²: 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, 102 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 54. 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, 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 43.8–54.6).
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% to 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 table 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

<table>
<thead>
<tr>
<th>Outcome measures</th>
<th>Sample size</th>
<th>Univariable analysis</th>
<th>Multivariable analysis*</th>
<th>Model 1†</th>
<th>Model 2‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total n</td>
<td>Total N RR (95% CI)</td>
<td>p value</td>
<td>Adjusted $R^2$ (%)</td>
<td>ARR (95% CI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Population type</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General populations</td>
<td>236</td>
<td>56,457</td>
<td>1.00</td>
<td>--</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Intermediate-risk populations</td>
<td>24</td>
<td>6,775</td>
<td>1.52 (1.16 to 2.00)</td>
<td>0.002</td>
<td>1.55 (1.22 to 1.96)</td>
</tr>
<tr>
<td>High-risk populations</td>
<td>93</td>
<td>25,344</td>
<td>3.09 (2.64 to 3.61)</td>
<td>&lt;0.001</td>
<td>3.09 (2.67 to 3.57)</td>
</tr>
<tr>
<td>STI clinic attendees and symptomatic populations</td>
<td>6</td>
<td>432</td>
<td>2.49 (1.47 to 4.22)</td>
<td>0.001</td>
<td>2.40 (1.48 to 3.90)</td>
</tr>
<tr>
<td>HIV-positive individuals and individuals in HIV discordant couples</td>
<td>19</td>
<td>2,840</td>
<td>3.21 (2.38 to 4.32)</td>
<td>&lt;0.001</td>
<td>3.06 (2.37 to 3.95)</td>
</tr>
<tr>
<td>Other populations§</td>
<td>24</td>
<td>3,497</td>
<td>2.42 (1.85 to 3.16)</td>
<td>&lt;0.001</td>
<td>1.56 (1.24 to 1.97)</td>
</tr>
<tr>
<td>Age group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20 years</td>
<td>35</td>
<td>6,538</td>
<td>1.00</td>
<td>--</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>20–30 years</td>
<td>47</td>
<td>7,751</td>
<td>2.05 (1.40 to 3.00)</td>
<td>&lt;0.001</td>
<td>1.63 (1.27 to 2.09)</td>
</tr>
<tr>
<td>30–40 years</td>
<td>22</td>
<td>2,933</td>
<td>2.58 (1.64 to 4.04)</td>
<td>&lt;0.001</td>
<td>2.24 (1.68 to 2.99)</td>
</tr>
<tr>
<td>&gt;40 years</td>
<td>39</td>
<td>5,940</td>
<td>2.84 (1.92 to 4.18)</td>
<td>&lt;0.001</td>
<td>3.22 (2.50 to 4.14)</td>
</tr>
<tr>
<td>Mixed ages</td>
<td>259</td>
<td>7,183</td>
<td>2.49 (1.82 to 3.41)</td>
<td>&lt;0.001</td>
<td>1.79 (1.44 to 2.21)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>234</td>
<td>38,816</td>
<td>1.00</td>
<td>--</td>
<td>0.001</td>
</tr>
<tr>
<td>Men</td>
<td>144</td>
<td>39,525</td>
<td>0.67 (0.56 to 0.80)</td>
<td>&lt;0.001</td>
<td>0.68 (0.60 to 0.76)</td>
</tr>
<tr>
<td>Mixed sexes</td>
<td>24</td>
<td>17,004</td>
<td>0.81 (0.57 to 1.16)</td>
<td>0.267</td>
<td>0.59 (0.46 to 0.77)</td>
</tr>
<tr>
<td>Countries</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brazil</td>
<td>106</td>
<td>25,766</td>
<td>1.00</td>
<td>--</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Colombia</td>
<td>19</td>
<td>2,247</td>
<td>1.36 (0.91 to 2.01)</td>
<td>0.125</td>
<td>--</td>
</tr>
<tr>
<td>Costa Rica</td>
<td>13</td>
<td>2,364</td>
<td>1.46 (0.92 to 2.30)</td>
<td>0.102</td>
<td>--</td>
</tr>
<tr>
<td>Mexico</td>
<td>76</td>
<td>23,437</td>
<td>0.71 (0.56 to 0.91)</td>
<td>0.008</td>
<td>--</td>
</tr>
<tr>
<td>Panama</td>
<td>15</td>
<td>3,334</td>
<td>1.81 (1.18 to 2.78)</td>
<td>0.006</td>
<td>--</td>
</tr>
<tr>
<td>Peru</td>
<td>131</td>
<td>24,976</td>
<td>0.92 (0.74 to 1.14)</td>
<td>0.476</td>
<td>--</td>
</tr>
<tr>
<td>Other¶</td>
<td>42</td>
<td>13,221</td>
<td>1.84 (1.39 to 2.45)</td>
<td>&lt;0.001</td>
<td>--</td>
</tr>
<tr>
<td>Subregions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central America</td>
<td>124</td>
<td>38,103</td>
<td>1.00</td>
<td>--</td>
<td>0.065</td>
</tr>
<tr>
<td>South America</td>
<td>264</td>
<td>54,798</td>
<td>0.95 (0.79 to 1.14)</td>
<td>0.606</td>
<td>1.13 (1.00 to 1.27)</td>
</tr>
<tr>
<td>Caribbean</td>
<td>14</td>
<td>2,444</td>
<td>1.62 (1.02 to 2.58)</td>
<td>0.040</td>
<td>1.17 (0.87 to 1.57)</td>
</tr>
<tr>
<td>Country's income</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LIC and LMIC</td>
<td>29</td>
<td>9,846</td>
<td>1.00</td>
<td>--</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>UMIC</td>
<td>354</td>
<td>81,539</td>
<td>0.45 (0.33 to 0.62)</td>
<td>&lt;0.001</td>
<td>--</td>
</tr>
<tr>
<td>HIC</td>
<td>19</td>
<td>3,960</td>
<td>0.86 (0.54 to 1.36)</td>
<td>0.528</td>
<td>--</td>
</tr>
</tbody>
</table>

Continued
<table>
<thead>
<tr>
<th>Study methodology characteristics</th>
<th>Outcome measures</th>
<th>Sample size</th>
<th>Univariable analysis</th>
<th>Multivariable analysis*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Total n</td>
<td>Total N</td>
<td>RR (95% CI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study methodology characteristics</td>
<td>As assay type</td>
<td>Western blot</td>
<td>94</td>
<td>11 898</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ELISA</td>
<td>304</td>
<td>82 744</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Monoclonal antibody</td>
<td>4</td>
<td>703</td>
</tr>
<tr>
<td></td>
<td>Sample size**</td>
<td>&lt;200</td>
<td>81</td>
<td>7 542</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;200</td>
<td>321</td>
<td>87 803</td>
</tr>
<tr>
<td></td>
<td>Sampling method</td>
<td>Probability-based</td>
<td>151</td>
<td>47 471</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-probability-based</td>
<td>251</td>
<td>47 874</td>
</tr>
<tr>
<td></td>
<td>Response rate</td>
<td>≥80%</td>
<td>194</td>
<td>48 220</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;80%</td>
<td>32</td>
<td>60 62</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unclear</td>
<td>176</td>
<td>41 063</td>
</tr>
<tr>
<td>Temporal variables</td>
<td>Year of publication category</td>
<td>&lt;2000</td>
<td>49</td>
<td>7 244</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2000–2010</td>
<td>206</td>
<td>51 983</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;2010</td>
<td>147</td>
<td>31 118</td>
</tr>
<tr>
<td></td>
<td>Year of publication</td>
<td>2000–2010</td>
<td>321</td>
<td>87 803</td>
</tr>
</tbody>
</table>

*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 R²)=68.85%.
‡Variance explained by multivariable model 2 (adjusted R²)=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, and Dominican Republic.
**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.
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. 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,67^68 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,17^64 STI awareness that encouraged engagement in safer sexual practices67 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 HIV66 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,9^52^72 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

---

### 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

<table>
<thead>
<tr>
<th>Population type</th>
<th>Outcome measures</th>
<th>Samples</th>
<th>Proportion of HSV-2 isolation (%)</th>
<th>Pooled proportion of HSV-2 isolation (%)</th>
<th>Heterogeneity measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with GUD</td>
<td>Total N</td>
<td>Total N</td>
<td>Range</td>
<td>Median</td>
<td>Mean (95% CI)</td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>------------------</td>
<td>---------</td>
<td>---------</td>
<td>--------</td>
<td>---------------</td>
</tr>
<tr>
<td>Patients with genital herpes</td>
<td>7</td>
<td>603</td>
<td>0.0–77.7</td>
<td>50.9</td>
<td>41.4 (18.9 to 67.0)</td>
</tr>
<tr>
<td>Patients with genital herpes</td>
<td>10</td>
<td>278</td>
<td>71.5–90.0</td>
<td>90.1</td>
<td>91.1 (82.7 to 97.2)</td>
</tr>
</tbody>
</table>

*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.

P*: 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.
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,77 78 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.30–88

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

Handling editor Jason Ong

Acknowledgements The authors gratefully acknowledge Professor Emeritus Rhodes Ashley Morrow from the University of Washington, for her support in assessing the quality of study diagnostic methods. The authors are also grateful for Ms Adona Canlas for administrative support. This publication was made possible by NPRP grant number 9-040-3-008 from the Qatar National Research Fund (a member of Qatar Foundation). The findings achieved herein are solely the responsibility of the authors. The authors are also grateful for pilot funding by the Biomedical Research Program and infrastructure support provided by the Biostatistics, Epidemiology, and Biometrics Research Core, both at Weill Cornell Medicine in Qatar.

Contributors MH and HM conducted the systematic search, data extraction and data analysis. MH wrote the first draft of the paper. LJA-R conceived the study and led the data extraction and analyses and interpretation of the results. All authors contributed to drafting and revising the manuscript.

Funding This work was supported by the Qatar National Research Fund (NPRP 9-040-3-008) and through pilot funding by the Biomedical Research Program at Weill Cornell Medicine in Qatar.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

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

REFERENCES
Review


66 Awad SF, Abu-Raddad L. Could there have been substantial declines in sexual risk behavior across sub-Saharan Africa in the mid-1990s? Epidemics 2014;8:9–17.


84 Samra Z, Scherf E, Dan M. Herpes simplex virus type 1 is the prevailing cause of genital herpes in the Tel Aviv area, Israel. Sex Transm Dis 2003;30:784–6.


86 Roberts CM, Pfister JR, Spear SJ. Increasing proportion of herpes simplex virus type 1 as a cause of genital herpes infection in college students. Sex Transm Dis 2003;30:797–800.


