Herpes simplex virus type 1 epidemiology in Latin America and the Caribbean: Systematic review and meta-analytics

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Abstract

Objectives

To investigate the epidemiology of herpes simplex virus type 1 (HSV-1) in Latin America and the Caribbean.

Methods

Systematic review and meta-analytics guided by the Cochrane Collaboration Handbook and reported following the PRISMA guidelines.

Results

Thirty-three relevant reports were identified including 35 overall (and 95 stratified) seroprevalence measures, and five and nine proportions of virus isolation in genital ulcer disease (GUD) and in genital herpes, respectively. Pooled mean seroprevalence was 57.2% (95% CI: 49.7–64.6%) among children and 88.4% (95% CI: 85.2–91.2%) among adults. Pooled mean seroprevalence was lowest at 49.7% (95% CI: 42.8–56.6%) in those aged \(<10\), followed by 77.8% (95% CI: 67.9–84.8%) in those aged 10–20, 82.8% (95% CI: 73.1–90.8%) in those aged 20–30, 92.5% (95% CI: 89.4–95.1%) in those aged 30–40, and 94.2% (95% CI: 92.7–95.5%) in those aged \(\geq40\). Age was the strongest source of heterogeneity in seroprevalence, explaining 54% of variation. Evidence was found for seroprevalence decline over time. Pooled mean proportion of HSV-1 isolation was 0.9% (95% CI: 0.0–3.6%) in GUD and 10.9% (95% CI: 4.4–19.4%) in genital herpes.

Conclusions

HSV-1 is a widely prevalent infection in this region, but its epidemiology may be slowly transitioning, with still limited contribution for HSV-1 in genital herpes.
Introduction

Infection with herpes simplex virus type 1 (HSV-1) is prevalent globally [1]. HSV-1 is responsible for a range of mild to serious morbidities [2, 3], with its typical clinical manifestation being orolabial herpes lesions [2, 4]. The infection, lifelong and mostly asymptomatic, is usually acquired orally and in childhood [3]. However, mounting evidence suggests an HSV-1 epidemiological transition in Europe and North America [4–7] and in Asia [8], associated with decreasing oral acquisition in childhood and increasing sexual acquisition (through oral sex) in adulthood [4–6]. In multiple Western countries, HSV-1 is already the primary cause of first episode genital herpes, surpassing the role of that of HSV-2 [4, 5, 7, 9–11]. An epidemiological transition is defined here as a significant change in the occurrence of the infection and/or its mode of transmission patterns.

HSV-1 infection is of growing interest and a focus of an international multi-sectorial effort, guided by the World Health Organization, to develop a vaccine to control infection transmission [12, 13]. To inform these global health efforts, we aimed in the present study to provide a detailed investigation of the epidemiology of HSV-1 in Latin America and the Caribbean, by conducting a comprehensive systematic review and a range of meta-analytics. Importantly, we estimated HSV-1 antibody prevalence (seroprevalence), its associations and temporal trend, and assessed the role of HSV-1 as a cause of clinically-diagnosed genital ulcer disease (GUD) and clinically-diagnosed genital herpes.

Material and methods

The methodology of this study was adapted from that of a study investigating HSV-1 epidemiology in Asia [8].

Data sources and search strategy

The systematic review and meta-analyses were guided by the Cochrane collaboration Handbook [14], and were reported following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (checklist in S1 Table) [15]. PubMed, Embase, and LILACS databases were systematically searched up to September 12, 2018. The search strategies included MeSH/Emtree and broad terms with no language or year restrictions (S2 Table). The definition for the Latin America and the Caribbean region included 46 countries, as listed in S1 Box.

Study selection and inclusion and exclusion criteria

Search results were de-duplicated using a reference manager, Endnote (Thomson Reuters, USA). Titles and abstracts were screened for relevant and potentially relevant reports, and the full-texts of these relevant or potentially relevant reports were retrieved for further screening. Bibliographies of identified relevant reports and reviews were also screened for additional potentially relevant reports. Initial screening was conducted by LS and MA, and double screening was conducted by MH.

Reports met the inclusion criteria if they reported primary data on any of three outcome measures: 1) HSV-1 seroprevalence based on a valid diagnostic method (i.e. strictly type-specific glycoprotein-G based assays), 2) proportion of HSV-1 virus isolation in clinically-diagnosed GUD, or 3) proportion of HSV-1 virus isolation in clinically-diagnosed genital herpes. Only measures with a sample size ≥10 were included. Case reports, editorials, letters to editors, commentaries, and reviews were excluded. HSV-1 seroprevalence measures among...
newborns <3 months of age were excluded, as they may reflect maternal antibodies as opposed to current infection.

In this systematic review, a “report” denotes a publication reporting a relevant outcome measure, while a “study” denotes the extracted details of an outcome measure.

Data extraction and synthesis

Relevant reports were extracted by LS and MA, and double-extracted by MH. Extracted data included publication details, population characteristics, study methodology characteristics, and outcome measures. The extracted variables are listed in S2 Box. Extracted overall outcome measures for the full sample were replaced by stratified measures (if available), based on a pre-defined protocol for the stratification hierarchy, provided that the sample size in each stratum was ≥10.

For HSV-1 seroprevalence measures, extracted strata were prioritized for population type (Fig 1), followed by age bracket (children (≤15 years of age) versus adults (>15 years of age)), and age group (≤10, 10–20, 20–30, 30–40, and >40 years of age). These age ranges were informed by the actually available age strata in extracted studies. For the proportions of HSV-1 virus isolation in GUD or in genital herpes, the stratification hierarchy included primary versus recurrent episode, followed by study site (hospital versus sexually transmitted infection clinic).

Quality assessment

Given the documented limitations in the sensitivity and specificity of HSV-1 serology diagnostic assays [16, 17], the validity of the type-specific diagnostic method of each study was investigated and determined in consultation with an expert advisor in HSV-1 serology, Professor Rhoda Ashley-Morrow, University of Washington, Seattle. Studies where the validity of the diagnostic method could not be confirmed, were excluded from the systematic review and meta-analytics.

Informed by the Cochrane approach [14], studies with valid assays were further classified into low versus high precision based on the number of individuals tested for HSV-1 in that study (<100 versus ≥100). Moreover, studies were classified into low versus high risk of bias (ROB) using two quality domains: sampling method (probability-based versus non-
probability-based sampling) and response rate (≥80% versus <80%). Studies with no information on a quality domain were classified as having an “unclear” ROB for that domain.

Precision and ROB domains were included in the meta-regression analyses (as described below), to examine their associations with seroprevalence, that is the influence of the characteristics of the study methodology on observed HSV-1 seroprevalence.

**Meta-analyses**

Pooled means were estimated for HSV-1 seroprevalence and its relevant strata by population type, age bracket, age group, and year of publication category (<2000, 2000–2009, and 2010–2018), as well as for the proportions of HSV-1 virus isolation in GUD and in genital herpes, whenever ≥3 measures were available. The estimates were calculated in R version 3.4.1 [18] using a DerSimonian-Laird random-effects model [19], as applied in the meta package [20]. The Freeman-Tukey type arcsine square-root transformation [21] was utilized to stabilize the variance of each included measure. Forest plots were produced to visualise estimates and their 95% confidence intervals (CIs).

Heterogeneity was assessed using three complementary metrics: 1) Cochrane Q statistics to test for existence of heterogeneity [19, 22], 2) I² to provide the magnitude of heterogeneity that is explained by true differences in the outcome measures across studies (as opposed to being due to sampling variation) [19, 23], and 3) prediction interval to provide the range of true effect sizes of the outcome measures around the pooled mean [19, 23].

**Meta-regressions**

Associations with HSV-1 seroprevalence and sources of between-study heterogeneity were investigated using univariable and multivariable random-effects meta-regression analyses. Independent variables with a p-value ≤0.1 in univariable analysis were included in the multivariable analyses. In the multivariable models, a p-value of ≤0.05 for any given independent variable indicated strong evidence for an association with HSV-1 seroprevalence.

The included independent variables were set a priori and consisted of: age bracket, age group, sex, population type, country’s income, assay type (Western blot, enzyme-linked immunosorbent assay, and others), sample size (<100 versus ≥100), sampling method (non-probability-based versus probability-based), response rate (≥80 versus otherwise), year of publication category, year of data collection, and year of publication.

The variable of country’s income (for countries with available data and per World Bank classification [24]) categorized the countries into upper-middle-income countries (Brazil, Colombia, Costa Rica, Jamaica, Mexico, and Peru), high-income countries (Barbados, Chile, and Argentina), and “mixed” for studies including different countries in the study sample.

Missing values for the year of data collection were imputed utilizing data for the year of publication as adjusted by the median difference between year of publication and year of data collection (for studies with non-missing data).

The meta-regressions were conducted on the log-transformed proportions (with inverse-variance weighting) in Stata/SE version 13 [25], using the metareg package [26].

**Results**

**Search results and scope of evidence**

Fig 2 details the study selection process per PRISMA guidelines [15]. The search identified 4,023 citations (PubMed: 847, Embase: 1,329, and LILACS 1,847) of which duplicates were
removed. Title and abstract screening yielded 367 relevant and potentially relevant reports. Full-text screening of these latter reports identified 29 reports that met the inclusion criteria. Four additional relevant reports [27–30] were identified through bibliography screening of reviews and relevant reports.
Extracted measures included: 35 overall HSV-1 seroprevalence measures yielding 95 stratified seroprevalence measures, five proportions of viral HSV-1 isolation in GUD, and nine proportions of viral HSV-1 isolation in genital herpes. No HSV-1 seroprevalence measure was identified among clinical children populations.

Overview of HSV-1 seroprevalence

Table 1 lists the extracted stratified HSV-1 seroprevalence measures and their characteristics (number of measures (n) = 95). Most measures were from studies conducted prior to 2010 (n = 76; 80.0%), and were based on convenience samples (n = 68; 71.0%). Seroprevalence across all measures ranged between 7.7–100% with a median of 86.0% (n = 95; Table 2).

HSV-1 seroprevalence ranged between 7.7–92.0% with a median of 55.1% among healthy children populations (n = 19), between 38.3–98.9% with a median of 87.6% among healthy adult populations (n = 51), and between 74.4–100% with a median of 91.5% among clinical adult populations (n = 7). Table 2 lists summaries for other population categories.

Pooled mean estimates for HSV-1 seroprevalence

Table 2 displays the results of the meta-analyses. The overall pooled mean HSV-1 seroprevalence (n = 95) was 83.1% (95% CI: 79.2–86.5%).

The pooled mean HSV-1 seroprevalence was 57.2% (95% CI: 49.7–64.6%) among healthy children populations, 84.5% (95% CI: 79.9–88.5%) among healthy adult populations, and 90.9% (95% CI: 84.2–95.9%) among clinical adult populations.

The pooled mean seroprevalence increased with age. It was lowest at 49.7% (n = 14; 95% CI: 42.8–56.6%) in those aged ≤10, followed by 77.8% (n = 17; 95% CI: 67.9–84.8%) in those aged 10–20, 82.8% (n = 12; 95% CI: 73.1–90.8%) in those aged 20–30, 92.5% (n = 9; 95% CI: 89.4–95.1%) in those aged 30–40, and 94.2% (n = 11; 95% CI: 92.7–95.5%) in those aged ≥40.

The pooled mean seroprevalence decreased with time. It was highest at 90.8% (95% CI: 85.8–94.9%) before the year 2000, followed by 80.7% (95% CI: 73.6–87.0%) in 2000–2009, and 78.8% (95% CI: 72.7–84.3) in 2010–2018.

Forest plots for all adult populations and all children populations can be found in S1 Fig. All meta-analyses showed evidence of heterogeneity (Table 2). Heterogeneity was attributed to true variability in seroprevalence across studies rather than chance (Table 2). The heterogeneity was affirmed by the wide prediction intervals (Table 2).

Predictors of HSV-1 seroprevalence

Table 3 and S3 Table display the results of the univariable and multivariable analyses. In the univariable analyses, age bracket, age group, sex, population type, year of publication category, year of data collection, and year of publication qualified to be included in the multivariable analysis (p < 0.1). Country’s income, assay type, response rate, sample size, and sampling method all had a p-value >0.1, and hence, were not included in the multivariable analyses.

Since age bracket and age group are variables that are not independent of each other, two multivariable models were analyzed, each using one of these variables. For a similar consideration, the year of publication was included in the multivariable analyses, instead of year of data collection, given its more complete data. As for the multivariable analyses including the year of publication category, instead of the linear year of publication term, the results can be found in S3 Table.

The first model included age bracket, sex, population type, and year of publication. It explained 42.82% of the seroprevalence variation. In adults, seroprevalence was 1.39-fold (95% CI: 1.24–1.57) higher than that in children.
Table 1. Studies reporting HSV-1 seroprevalence in Latin America and the Caribbean.

| Author, year | Year(s) of data collection | Country          | Study site | Study design | Sampling method | Population            | HSV-1 serological assay | Sample size | HSV-1 seroprevalence (%) |
|--------------|----------------------------|------------------|------------|--------------|-----------------|------------------------|------------------------|--------------|--------------------------|
| Healthy children populations (n = 19) |
| Clemens, 2010 [43] | 1996–97 | Brazil | Community | CS RS | 1–5 years old boys | ELISA | 52 | 44.2 |
| Clemens, 2010 [43] | 1996–97 | Brazil | Community | CS RS | 6–10 years old boys | ELISA | 49 | 55.1 |
| Clemens, 2010 [43] | 1996–97 | Brazil | Community | CS RS | 11–15 years old boys | ELISA | 125 | 65.6 |
| Clemens, 2010 [43] | 1996–97 | Brazil | Community | CS RS | 1–5 years old girls | ELISA | 47 | 38.3 |
| Clemens, 2010 [43] | 1996–97 | Brazil | Community | CS RS | 6–10 years old girls | ELISA | 50 | 58.0 |
| Clemens, 2010 [43] | 1996–97 | Brazil | Community | CS RS | 11–15 years old girls | ELISA | 126 | 74.6 |
| Conde-Glez, 2013 [44] | 2005–06 | Mexico | Community | CS RS | 1–9 years old girls | ELISA | 252 | 51.0 |
| Conde-Glez, 2013 [44] | 2005–06 | Mexico | Community | CS RS | 1–9 years old boys | ELISA | 264 | 50.0 |
| Cowan, 2003 [45] | - | Brazil | Outpatient clinic | CS Conv | 1–4 years old children | ELISA | 232* | 36.0 |
| Cowan, 2003 [45] | - | Brazil | Outpatient clinic | CS Conv | 5–9 years old children | ELISA | 232* | 52.4 |
| Cowan, 2003 [45] | - | Brazil | Outpatient clinic | CS Conv | 10–14 years old children | ELISA | 233* | 68.1 |
| De Salles-Gomes, 1981 [46] | 1980 | Brazil | Outpatient clinic | CS Conv | 7–11 month babies | IF | 13 | 7.7 |
| De Salles-Gomes, 1981 [46] | 1980 | Brazil | Outpatient clinic | CS Conv | 1–4 years old children | IF | 50 | 38.0 |
| De Salles-Gomes, 1981 [46] | 1980 | Brazil | Outpatient clinic | CS Conv | 5–9 years old children | IF | 50 | 64.0 |
| De Salles-Gomes, 1981 [46] | 1980 | Brazil | Outpatient clinic | CS Conv | 10–14 years old children | IF | 50 | 92.0 |
| Robinson, 2002 [47] | - | Multiple countries in South America | Community | CS Conv | ≤3 years old children | WB | 23 | 29.0 |
| Robinson, 2002 [47] | - | Multiple countries in South America | Community | CS Conv | 4–6 years old children | WB | 56 | 72.0 |
| Robinson, 2002 [47] | - | Multiple countries in South America | Community | CS Conv | 7–9 years old children | WB | 68 | 76.0 |
| Robinson, 2002 [47] | - | Multiple countries in South America | Community | CS Conv | 10–13 years old children | WB | 54 | 81.0 |
| Healthy adult populations (n = 51) |
| Arriaga-Demeza, 2008 [48] | 2002–03 | Mexico | Community | CS Conv | 18–20 years old females | WB | 195 | 50.3 |

(Continued)
| Author, year                      | Year(s) of data collection | Country | Study site | Study design | Sampling method | Population | HSV-1 serological assay | Sample size | HSV-1 seroprevalence (%) |
|----------------------------------|-----------------------------|---------|------------|--------------|----------------|------------|------------------------|-------------|--------------------------|
| Arriaga-Demeza, 2008 [48]        | 2002–03                     | Mexico  | Community  | CS           | Conv           | 21–25 years old females | WB          | 153                      | 53.6         |
| Arriaga-Demeza, 2008 [48]        | 2002–03                     | Mexico  | Community  | CS           | Conv           | ≥26 years old females   | WB          | 31                       | 74.2         |
| Arriaga-Demeza, 2008 [48]        | 2002–03                     | Mexico  | Community  | CS           | Conv           | 18–20 years old males   | WB          | 103                      | 46.6         |
| Arriaga-Demeza, 2008 [48]        | 2002–03                     | Mexico  | Community  | CS           | Conv           | 21–25 years old males   | WB          | 102                      | 61.8         |
| Morrow, 2014 [16]                | 2000–01                     | Argentina | Community | CS           | Conv           | Argentinian women      | WB          | 99                       | 98.9         |
| Morrow, 2014 [16]                | 2000–01                     | Costa Rica | Community | CS           | Conv           | Costa Rican women      | WB          | 98                       | 92.9         |
| Morrow, 2014 [16]                | 2000–01                     | Mexico   | Community  | CS           | Conv           | Mexican women          | WB          | 100                      | 98.0         |
| Clemens, 2010 [43]               | 1996–97                     | Brazil   | Community  | CS           | RS             | 16–20 years old males   | ELISA       | 119                      | 69.8         |
| Clemens, 2010 [43]               | 1996–97                     | Brazil   | Community  | CS           | RS             | 21–30 years old males   | ELISA       | 107                      | 76.6         |
| Clemens, 2010 [43]               | 1996–97                     | Brazil   | Community  | CS           | RS             | 31–40 years old males   | ELISA       | 78                       | 85.9         |
| Clemens, 2010 [43]               | 1996–97                     | Brazil   | Community  | CS           | RS             | 16–20 years old females | ELISA       | 128                      | 75.8         |
| Clemens, 2010 [43]               | 1996–97                     | Brazil   | Community  | CS           | RS             | 21–30 years old females | ELISA       | 126                      | 81.0         |
| Clemens, 2010 [43]               | 1996–97                     | Brazil   | Community  | CS           | RS             | 31–40 years old females | ELISA       | 82                       | 81.7         |
| Conde-Glez, 2013 [44]            | 2005–06                     | Mexico   | Community  | CS           | RS             | 20–29 years old females | ELISA       | 252*                     | 78.0         |
| Conde-Glez, 2013 [44]            | 2005–06                     | Mexico   | Community  | CS           | RS             | 30–39 years old females | ELISA       | 252*                     | 96.0         |
| Conde-Glez, 2013 [44]            | 2005–06                     | Mexico   | Community  | CS           | RS             | 40–49 years old female  | ELISA       | 252*                     | 91.0         |
| Conde-Glez, 2013 [44]            | 2005–06                     | Mexico   | Community  | CS           | RS             | 50–59 years old females | ELISA       | 252*                     | 98.0         |
| Conde-Glez, 2013 [44]            | 2005–06                     | Mexico   | Community  | CS           | RS             | ≥60 years old females   | ELISA       | 252*                     | 95.0         |
| Conde-Glez, 2013 [44]            | 2005–06                     | Mexico   | Community  | CS           | RS             | 20–29 years old males   | ELISA       | 264*                     | 91.0         |
| Conde-Glez, 2013 [44]            | 2005–06                     | Mexico   | Community  | CS           | RS             | 30–39 years old males   | ELISA       | 264*                     | 91.0         |
| Conde-Glez, 2013 [44]            | 2005–06                     | Mexico   | Community  | CS           | RS             | 40–49 years old male    | ELISA       | 264*                     | 93.0         |
| Conde-Glez, 2013 [44]            | 2005–06                     | Mexico   | Community  | CS           | RS             | 50–59 years old males   | ELISA       | 264*                     | 95.0         |
| Conde-Glez, 2013 [44]            | 2005–06                     | Mexico   | Community  | CS           | RS             | ≥60 years old males     | ELISA       | 264*                     | 94.0         |

(Continued)
| Author, year | Year(s) of data collection | Country | Study site | Study design | Sampling method | Population | HSV-1 serological assay | Sample size | HSV-1 seroprevalence (%) |
|--------------|-----------------------------|---------|------------|--------------|----------------|------------|------------------------|-------------|--------------------------|
| Corona, 2010 [28] | 2002–05 Mexico | Community | CS | Conv | ≥ 26 years old students | ELISA | 59 | 72.9 |
| Corona, 2010 [28] | 2002–05 Mexico | Community | CS | Conv | 21–25 years old students | ELISA | 412 | 59.7 |
| Corona, 2010 [28] | 2002–05 Mexico | Community | CS | Conv | 18–20 years old students | ELISA | 335 | 50.1 |
| Cowan, 2003 [45] | - Brazil | Outpatient clinic | CS | Conv | 15–19 years old adults | ELISA | 146 | 83.3 |
| Cowan, 2003 [45] | - Brazil | Outpatient clinic | CS | Conv | 20–29 years old adults | ELISA | 147 | 83.6 |
| Cowan, 2003 [45] | - Brazil | Outpatient clinic | CS | Conv | 30–34 years old adults | ELISA | 147 | 95.2 |
| Cowan, 2003 [45] | - Brazil | Outpatient clinic | CS | Conv | 35–39 years old adults | ELISA | 147 | 92.9 |
| Cowan, 2003 [45] | - Brazil | Outpatient clinic | CS | Conv | 40–44 years old adults | ELISA | 147 | 96.0 |
| Cowan, 2003 [45] | - Brazil | Outpatient clinic | CS | Conv | ≥45 years old adults | ELISA | 147 | 94.6 |
| De Salles-Gomes, 1981 [46] | 1980 Brazil | Outpatient clinic | CS | Conv | 15–19 years old adults | IF | 50 | 90.0 |
| De Salles-Gomes, 1981 [46] | 1980 Brazil | Outpatient clinic | CS | Conv | 20–24 years old adults | IF | 50 | 84.0 |
| De Salles-Gomes, 1981 [46] | 1980 Brazil | Outpatient clinic | CS | Conv | 25–29 years old adults | IF | 50 | 86.0 |
| De Salles-Gomes, 1981 [46] | 1980 Brazil | Outpatient clinic | CS | Conv | 30–34 years old adults | IF | 60 | 98.3 |
| De Salles-Gomes, 1981 [46] | 1980 Brazil | Outpatient clinic | CS | Conv | 35–39 years old adults | IF | 50 | 90.0 |
| De Salles-Gomes, 1981 [46] | 1980 Brazil | Outpatient clinic | CS | Conv | ≥40 years old adults | IF | 50 | 96.0 |
| Evans, 1974 [49] | - Brazil | Outpatient clinic | CC | Conv | Healthy adults | IF | 26 | 87.5 |
| Jimenez, 1979 [50] | - Costa Rica | Outpatient clinic | CS | Conv | ≥18 years old students | NAb | 16 | 50.0 |
| Levett, 2005 [51] | - Barbados | Outpatient clinic | CS | Conv | Blood donors | ELISA | 184 | 81.0 |
| Levett, 2005 [51] | - Barbados | Outpatient clinic | CS | Conv | Ante-natal clinic attendees | ELISA | 122 | 83.6 |
| Lupi, 2011 [52] | 1996–97 Brazil | Outpatient clinic | Cohort | Conv | Blood donors | ELISA | 155 | 68.0 |
| Oberle, 1989 [53] | 1984–85 Costa Rica | Community | CS | MCS | ≥25 years old females | MAb | 766 | 97.1 |
| Patnaik, 2007 [54] | 1985–97 Peru | Community | CS | Conv | Peruvian women | WB | 171 | 91.8 |
| Patnaik, 2007 [54] | 1985–97 Colombia | Community | CS | Conv | Colombian women | WB | 65 | 89.2 |

(Continued)
### Table 1. (Continued)

| Author, year | Year(s) of data collection | Country   | Study site   | Study design | Sampling method | Population                                      | HSV-1 serological assay | Sample size | HSV-1 seroprevalence (%) |
|--------------|----------------------------|-----------|--------------|--------------|-----------------|------------------------------------------------|------------------------|-------------|--------------------------|
| Prabhakar, 1984 [55] | [55]          | Jamaica   | Hospital CC  | Conv         | Healthy Jamaican women | NAb                | 60          | 38.3                     |
| Smith, 2002 [29] | 1996–97        | Peru      | Hospital CC  | Conv         | Healthy Peruvian women | WB                 | 171         | 91.8                     |
| Smith, 2002 [29] | 1985–88        | Colombia  | Community CC | Conv         | Healthy Colombian women | WB                 | 65          | 89.2                     |
| Healthy age-mixed populations (n = 2) |
| Conde-Glez, 2013 [44] | 2005–06       | Mexico    | Community CS | RS           | 10–19 years old females | ELISA              | 252         | 70.0                     |
| Conde-Glez, 2013 [44] | 2005–06       | Mexico    | Community CS | RS           | 10–19 years old males | ELISA              | 264         | 71.0                     |
| Clinical adult populations (n = 7) |
| Calderon, 2018 [56] | 2014–15       | Peru      | Outpatient clinic CS | Conv | Women with breast cancer | ELISA              | 44          | 88.6                     |
| Evans, 1974 [49] | [49]          | Brazil    | Outpatient clinic CC | Conv | Patients with Hodgkin’s disease | IF                  | 26          | 84.4                     |
| Moreira, 2018 [57] | 2015–16       | Brazil    | Outpatient clinic CC | Conv | Women from a highly ZIKV-affected region | WB                  | 32          | 93.8                     |
| Moreira, 2018 [57] | 2015–16       | Brazil    | Outpatient clinic CC | Conv | Women from a highly ZIKV-affected region | WB                  | 160         | 95.0                     |
| Smith, 2002 [29] | 1996–97       | Peru      | Hospital CC  | Conv         | Women with squamous-cell carcinoma | WB                 | 166         | 91.5                     |
| Smith, 2002 [29] | 1996–97       | Peru      | Hospital CC  | Conv         | Women with adenousquamous carcinoma | WB                 | 24          | 100                      |
| Smith, 2002 [29] | 1985–88       | Colombia  | Hospital CC  | Conv         | Women with squamous-cell carcinoma | WB                 | 78          | 74.4                     |
| Other populations (n = 16) |
| Levett, 2005 [51] | [51]          | Barbados  | Outpatient clinic CS | Conv | HIV-positive adults | ELISA              | 120         | 89.2                     |
| Luchsinger, 2010 [58] | 2005–06       | Chile     | Outpatient clinic CS | Conv | HIV-positive adults | ELISA              | 400         | 92.2                     |
| Boullos, 1992 [59] | [59]          | Haiti     | Outpatient clinic CS | Conv | Healthy/clinical women | ELISA              | 228         | 96.9                     |
| Conde-Glez, 1999 [60] | 1992          | Mexico    | Outpatient clinic CS | Conv | 16–22 years old FSWs | WB                  | 302         | 92.7                     |
| Conde-Glez, 1999 [60] | 1992          | Mexico    | Outpatient clinic CS | Conv | 23–27 years old FSWs | WB                  | 330         | 93.1                     |
| Conde-Glez, 1999 [60] | 1992          | Mexico    | Outpatient clinic CS | Conv | 28–32 years old FSWs | WB                  | 187         | 94.7                     |
| Conde-Glez, 1999 [60] | 1992          | Mexico    | Outpatient clinic CS | Conv | 33–37 years old FSWs | WB                  | 101         | 94.1                     |
| Conde-Glez, 1999 [60] | 1992          | Mexico    | Outpatient clinic CS | Conv | >37 years old FSWs | WB                  | 77          | 100                      |
| Duenas, 1972 [61] | [61]          | Colombia  | Outpatient clinic CS | Conv | 14–15 years old FSWs | NAb                 | 15          | 100                      |

(Continued)
The second model included age group, sex, population type, and year of publication. It explained 69.57% of the seroprevalence variation. Compared to those aged ≤10, seroprevalence was 1.36-fold (95% CI: 1.19–1.56) higher in those aged 10–20, 1.44-fold (95% CI: 1.25–1.65) higher in those aged 20–30, 1.70-fold (95% CI: 1.47–1.97) higher in those aged 30–40, and 1.81-fold (95% CI: 1.58–2.08) higher in those aged ≥40. There was evidence here for a statistically-significant declining seroprevalence over time by 0.99-fold (95% CI: 0.99–0.99) per year, in contrast to the first model analysis (Table 3) and the analyses including the year of publication as a category (S3 Table), where the evidence for the decline in sero-prevalence did not reach statistical significance.

HSV-1 virus isolation in genital ulcer disease and in genital herpes

Tables 4 and 5 summarize the extracted proportions of HSV-1 virus isolation in GUD (n = 5) and in genital herpes (n = 9), as well as their pooled mean estimates.

In GUD cases, the virus isolation proportion ranged between 0.0–6.6%, with a median of 1.1% and a pooled mean of 0.9% (95% CI: 0.0–3.6%). In genital herpes cases, the proportion ranged between 0.0–28.5%, with a median of 10.0% and a pooled mean of 10.9% (95% CI: 4.4–19.4%). Both meta-analyses of proportions showed strong evidence of heterogeneity (Table 5). Forest plots can be found in S2 Fig.

Quality assessment

A total of 31 reports were included in the systematic review, while an additional 12 reports were excluded due to potential issues in their diagnostic method (Fig 2).
Table 2. Pooled mean estimates for HSV-1 seroprevalence in Latin America and the Caribbean.

| Population type                  | Outcome measures | Samples | HSV-1 seroprevalence | Pooled mean HSV-1 seroprevalence | Heterogeneity measures |
|----------------------------------|------------------|---------|----------------------|-----------------------------------|------------------------|
|                                  |                  | Total n | Total N | Range     | Median   | Mean (95% CI) | Q* (p-value) | I²b (%) (95% CI) | Prediction Interval (%) |
| Healthy general populations      |                  |         |         |           |          |              |             |                |                         |
| Children                         |                  | 19      | 2,026   | 7.7–92.0  | 55.1     | 57.2 (49.7–64.6) | 190.8 (p<0.001) | 90.6 (86.8–93.3) | 24.7–86.7               |
| Adults                           |                  | 51      | 7,917   | 38.3–98.9 | 87.6     | 84.5 (79.9–88.5) | 1,323.5 (p<0.001) | 96.2 (95.7–96.8) | 46.1–100                |
| Age-mixed                        |                  | 2       | 516     | 70.0–71.0 | 70.5     | 70.3 (66.2–74.2) |              |          |                         |
| All healthy general populations  |                  | 72      | 10,459  | 7.7–98.9  | 81.0     | 77.7 (72.9–82.2) | 2,269.1 (p<0.001) | 96.9 (96.5–97.3) | 32.6–100                |
| Clinical populations             |                  |         |         |           |          |              |             |                |                         |
| Adults                           |                  | 7       | 530     | 74.4–100  | 91.5     | 90.9 (84.2–95.9) | 25.9 (p<0.001) | 76.8 (51.5–88.9) | 65.5–100                |
| All clinical populations         |                  | 7       | 530     | 74.4–100  | 91.5     | 90.9 (84.2–95.9) | 25.9 (p<0.001) | 76.8 (51.5–88.9) | 65.5–100                |
| Other populations                |                  |         |         |           |          |              |             |                |                         |
| HIV positive patients             |                  | 2       | 520     | 89.2–92.2 | 90.7     | 91.5 (88.8–93.7) |              |          |                         |
| Female sex workers               |                  | 12      | 1,340   | 93.1–100  | 100      | 98.5 (96.4–99.8) | 46.3 (p<0.001) | 76.2 (58.4–96.4) | 88.4–100                |
| Men who have sex with men        |                  | 1       | 170     | -         | -        | 85.3 (79.1–90.2) |              |          |                         |
| Mixed healthy clinical adults    |                  | 1       | 228     | -         | -        | 96.9 (93.8–98.7) |              |          |                         |
| Mixed age-mixed healthy/clinical |                  |         |         |           |          |              |             |                |                         |
| age groups                       |                  |         |         |           |          |              |             |                |                         |
| <10 years                        |                  | 14      | 1,438   | 7.7–76.0  | 50.5     | 49.7 (42.8–56.6) | 76.4 (p<0.001) | 83.0 (72.7–89.4) | 24.8–74.7               |
| 10–20 years                      |                  | 17      | 2,294   | 46.6–100  | 74.6     | 77.8 (67.9–84.8) | 280.8 (p<0.001) | 94.3 (92.2–95.8) | 40.0–99.5               |
| 20–30 years                      |                  | 12      | 1,926   | 53.6–100  | 82.5     | 82.8 (73.1–90.8) | 276.9 (p<0.001) | 96.0 (94.5–97.2) | 39.1–100                |
| 30–40 years                      |                  | 9       | 1,181   | 81.7–88.3 | 92.9     | 92.5 (89.4–95.1) | 24.6 (p = 0.002) | 67.4 (34.3–83.8) | 81.4–99.0               |
| ≥40 years                        |                  | 11      | 2,128   | 89.2–98.0 | 94.6     | 94.2 (92.7–95.5) | 17.5 (p = 0.064) | 42.9 (0.0–71.8) | 89.9–97.4               |
| Mixed                            |                  | 32      | 4,280   | 38.3–100  | 90.3     | 89.6 (85.7–93.9) | 405.7 (p<0.001) | 92.4 (90.2–94.0) | 62.9–100                |
| Age bracket                      |                  |         |         |           |          |              |             |                |                         |
| All children                     |                  | 19      | 2,026   | 7.7–92.0  | 55.1     | 57.2 (49.7–64.6) | 190.8 (p<0.001) | 90.6 (86.8–93.3) | 24.7–86.7               |
| All adults                       |                  | 73      | 10,690  | 38.3–100  | 91.0     | 88.4 (85.2–91.2) | 1,588.2 (p<0.001) | 95.5 (94.8–96.0) | 54.8–100                |
| All age-mixed                    |                  | 3       | 531     | 70.0–100  | 71.0     | 77.5 (65.8–87.5) | 12.3 (p = 0.002) | 83.7 (50.8–94.6) | 0.0–100                 |
| Year of publication category     |                  |         |         |           |          |              |             |                |                         |
| <2000                            |                  | 28      | 2,935   | 7.7–100   | 93.6     | 90.8 (85.8–94.9) | 394.7 (p<0.001) | 93.2 (91.2–94.7) | 57.1–100                |
| 2000–2009                        |                  | 32      | 3,844   | 29.0–100  | 83.0     | 80.7 (73.6–87.0) | 847.7 (p<0.001) | 96.3 (95.6–97.0) | 34.0–100                |
| 2010–2018                        |                  | 35      | 6,468   | 38.3–98.0 | 78.0     | 78.8 (72.7–84.3) | 1,113.4 (p<0.001) | 96.9 (96.4–97.4) | 37.4–100                |
| All studies                      |                  | 95      | 13,335  | 7.7–100   | 86.0     | 83.1 (79.3–86.5) | 2,772.4 (p<0.001) | 96.6 (96.2–97.0) | 40.2–100                |

* Q: The Cochran’s Q statistic is a measure assessing the existence of heterogeneity in pooled outcome measures, here HSV-1 seroprevalence.
* I²: A measure assessing the magnitude of between-study variation that is due to true differences in HSV-1 seroprevalence across studies rather than sampling variation.
* Prediction interval: A measure quantifying the distribution 95% interval of true HSV-1 seroprevalence around the estimated pooled mean.
* No meta-analysis was done as number of studies was <3. If there was only one study, the reported 95% CI is the 95% CI of this study. If there were two studies, both samples were merged to yield one sample size, for which the 95% CI was calculated.

Abbreviations: CI = Confidence interval, HIV = Human immunodeficiency virus, HSV-1 = Herpes simplex virus type 1.

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Summary of the precision and ROB assessments are in S4 Table. High precision was found in the majority of studies (62.9%). High ROB in the sampling method domain was found in the vast majority of studies (94.3%). Low ROB in the response rate domain was found in 25.7% of studies, while the remaining studies had a high ROB (2.9%), or an unclear ROB (71.4%).
Since none of the study characteristics of sample size, sampling method, and response rate were found associated with HSV-1 seroprevalence (Table 3), it is not likely that precision nor ROB have affected the results of the present study.

**Discussion**

The systematic review and meta-analytics reported here indicate that HSV-1 infection is widely prevalent in Latin America and the Caribbean, at a seroprevalence level that is higher than that of the global population at 67% [1]. Nearly 60% of children and 90% of adults are infected, a higher seroprevalence than that in Western Countries [31] and Asia [8], though lower than that in Africa [32] and the Middle East and North Africa (MENA) [33]. Seroprevalence increased steadily with age, but most HSV-1 acquisitions still occurred in childhood (Tables 2 and 3).
Age was by far the strongest predictor of infection, explaining alone >50% of the seroprevalence variation (Table 3). Meanwhile, sex, clinical condition, and country’s income did not affect HSV-1 seroprevalence (Table 3), in broad agreement with the results of similar studies for Africa [32], Asia [8], and MENA [33]. These findings affirm the notion that HSV-1 is a truly general population infection, with largely homogenous exposure risk in the population.

There was evidence for a declining seroprevalence over the last three decades, but the exact effect size of the decline and nature of the decline (linear or not) are not yet certain with currently available data (Tables 2 and 3 and S3 Table). While seroprevalence declines have been also observed in North America and Europe [31, 34–41], no evidence for such declines was found in Africa [32], Asia [8], and MENA [33]. The large gap in HSV-1 seroprevalence between children and adults (Tables 2 and 3), supports also the interpretation of recent declines in seroprevalence, with the currently older cohorts experiencing higher infection risk in earlier times. As observed in North America [31], improvements in hygiene and standard of living may have driven the seroprevalence declines.

With this evidence for a possible slow transition in HSV-1 epidemiology in Latin America and the Caribbean, there is a cause for concern for genital herpes, as increasingly a larger fraction of adolescents may initiate sexual activity with no antibodies to protect them against acquiring HSV-1 sexually, and thus at risk of genital herpes. Indeed, we found evidence supporting a role for HSV-1 as the etiological cause of genital herpes (Tables 4 and 5), though at rates much lower than those observed in Western countries [4, 5, 7–11] and Asia [8].

This study has limitations. Data were available only for 14 mostly populous countries (Tables 1 and 4), with no data found for the remaining 32 smaller countries. Studies varied in methods and quality and used different diagnostic assays, with potentially different sensitivity and specificity profiles [16, 17]. However, no effect was found on seroprevalence for assay type, sample size, sampling method, and response rate (Table 3), indicating that the variability in study methods may not have impacted the results and findings of the present study.

Conclusions

As in North America, Europe, and Asia [5, 7–11, 31, 35, 42], there is evidence for a possible transitioning HSV-1 epidemiology in Latin America and the Caribbean, though at a slower rate and with still limited contribution for HSV-1 in genital herpes and as a sexually transmitted infection. HSV-1 seroprevalence appears to be declining, with the younger cohorts
experiencing lower infection risk than those experienced by the younger cohorts in earlier times. Yet, HSV-1 persists as a widely prevalent infection in this region, with 60% of children and 90% of adults being infected. These findings support the need for surveillance to monitor trends in seroprevalence and genital herpes etiology, and highlight the need for a vaccine to prevent infection and associated disease burden.

Supporting information

S1 Table. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) checklist. (DOCX)

S2 Table. Data sources and search criteria for systematically reviewing HSV-1 epidemiology in Latin America and the Caribbean. (DOCX)

S3 Table. Multivariable meta-regression models for HSV-1 seroprevalence in Latin America and the Caribbean including the categorical stratification by year of publication. (DOCX)

S4 Table. Summary of the precision assessment and risk of bias (ROB) assessment for the studies reporting HSV-1 seroprevalence in Latin America and the Caribbean. (DOCX)

S1 Box. List of the 46 countries included in our definition for the Latin America and the Caribbean region. (DOCX)

S2 Box. List of variables extracted from the relevant reports meeting the inclusion criteria. (DOCX)

S1 Fig. Forest plots presenting the outcomes of the pooled mean HSV-1 seroprevalence among children and adult populations in Latin America and the Caribbean. (DOCX)

S2 Fig. Forest plots presenting the outcomes of the pooled mean proportions of HSV-1 virus isolation in clinically-diagnosed genital ulcer disease and in clinically-diagnosed genital herpes in Latin America and the Caribbean. (DOCX)

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