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# The Epidemiology of Herpes Simplex Virus Type 1 in Asia: Systematic Review, Meta-analyses, and Meta-regressions

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***Background.*** Herpes simplex virus type 1 (HSV-1) epidemiology in Asia was characterized by assessing seroprevalence levels and extent to which HSV-1 is isolated from clinically diagnosed genital ulcer disease (GUD) and genital herpes.

***Methods.*** HSV-1 reports in Asia were systematically reviewed and synthesized, following PRISMA guidelines. Random-effects meta-analyses estimated pooled mean seroprevalence and proportion of HSV-1 detection in GUD and genital herpes. Random-effects meta-regressions identified predictors of seroprevalence and sources of between-study heterogeneity.

***Results.*** Forty-nine relevant publications were identified. Fifty-four overall seroprevalence measures (182 stratified measures), and 8 and 24 proportions of HSV-1 detection in GUD and in genital herpes, respectively, were extracted. The pooled mean seroprevalence was 50.0% (n = 26; 95% confidence interval [CI], 41.3%–58.7%) for children and 76.5% (n = 151; 73.3%–79.6%) for adults. By age group, the pooled mean was lowest at 55.5% (n = 37; 95% CI, 47.5%–63.4%) in individuals aged <20 years, followed by 67.9% (n = 48; 62.4%–73.3%) in those aged 20–39 and 87.5% (n = 44; 83.4%–91.1%) in those aged ≥40 years. In meta-regression, age was the major predictor of seroprevalence. The mean proportion of HSV-1 detection was 5.6% (n = 8; 95% CI, 0.8%–13.6%) in GUD and 18.8% (n = 24; 12.0%–26.7%) in genital herpes.

***Conclusions.*** HSV-1 epidemiology is transitioning in Asia. HSV-1 is probably playing a significant role as a sexually transmitted infection, explaining one-fifth of genital herpes cases. There is a need for expanded seroprevalence monitoring and GUD/genital herpes etiological surveillance.

**Keywords.** seroprevalence; genital ulcer disease; genital herpes; synthesis; region.

Herpes simplex virus (HSV) type 1 (HSV-1) infection is widely prevalent [1, 2]. With its persistent shedding [3, 4], HSV-1 is infectious for lifetime, but mostly subclinically and asymptomatically [5–7]. When symptomatic, HSV-1 can cause mild to severe disease [5, 8]. Although infection is often manifested as orolabial herpes [5, 8], the virus can cause a spectrum of diseases such as herpetic whitlow, gingivostomatitis, meningitis, encephalitis, corneal blindness, and neonatal herpes [8, 9].

HSV-1 clinical manifestations are determined by the virus's initial portal of entry [5, 8]. Although it is predominantly transmitted through oral shedding [5–7], leading to oral manifestations [5, 8], HSV-1 can be transmitted sexually, leading to genital herpes, given the portal of entry [5, 6, 10].

HSV-1 antibody prevalence (seroprevalence) seems to be very high globally, with the majority of affected persons seroconverting by the time they reach puberty [2, 11, 12]. However, with continuing improvement in hygiene and living conditions, seroprevalence seems to have declined, at least in Western countries [11, 13–20]. About half of youth there reach sexual debut before being exposed (nonsexually) to HSV-1 and thus are at risk of acquiring the infection genitally [5, 21]. Evidence indicates a growing role for HSV-1 as a sexually transmitted infection (STI) and as a leading, if not *the* leading, cause of initial episodes of genital herpes in Western countries [5, 21–25].

Although this striking transition in HSV-1 epidemiology in the West is well documented [5, 7, 26], the extent to which it is occurring elsewhere is unknown. Understanding HSV-1 epidemiology in different regions will help characterize the HSV-1 burden, oral and genital, and target the most affected populations with interventions. To this end, the World Health Organization and global partners are spearheading efforts to accelerate the development of HSV vaccines [27, 28]. A business case is being developed that factors public health needs,

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pathways of vaccine rollout, impact and cost-effectiveness, and return on investment [27]. To inform this effort, it is critical to establish current infection levels and trends.

Our overarching goals were to assess HSV-1 seroprevalence levels and trends in Asia and the extent to which HSV-1 is the cause of genital ulcer disease (GUD) and genital herpes. We specifically aimed to (1) methodologically review and synthesize available studies on seroprevalence; (2) estimate seroprevalence in different populations and ages by pooling existing measures; (3) assess seroprevalence temporal trend, population-level associations with seroprevalence, and sources of between-study heterogeneity; (4) assess the proportion of HSV-1 viral detection in clinically diagnosed GUD; and (5) assess the proportion of HSV-1 viral detection in clinically diagnosed genital herpes. The distinction between the last 2 aims lies in the denominator—the etiology of GUD includes several indications other than HSV-1 infection (diagnosis of any GUD) [29], and the etiology of genital herpes includes only HSV-1 and HSV type 2 (HSV-2) infections (virological diagnosis of herpes) [30].

## MATERIALS AND METHODS

### Data Sources and Search Strategy

This systematic review was informed by the Cochrane Collaboration Handbook [31] and followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [32]. The PRISMA checklist is in Supplementary Table 1.

Available HSV-1 publications in PubMed (from 1950) and Embase (from 1974) databases were systematically reviewed until 22 April 2018. For inclusiveness, broad search criteria were used, with MeSH/Emtree terms exploded to cover all subheadings and with no language or year restrictions (Supplementary Box 1). Articles in Chinese, English, French, and Japanese were reviewed in their original language. Articles in other languages were translated. Asia region definition was informed by the World Health Organizations definitions for South-East Asia and Western Pacific regions [33]. The list of included countries/territories is in Supplementary Box 2.

### Study Selection and Inclusion/Exclusion Criteria

Search results were imported into Endnote (a reference manager), where duplicate publications were identified and excluded. Titles and abstracts of remaining records were screened for relevance, and full texts of relevant and potentially relevant publications were retrieved for additional screening. References of articles and reviews were also checked to identify further publications that could have been missed.

The inclusion criteria were met for any publication that reported HSV-1 seroprevalence measure(s), based on primary data using type-specific diagnostic assays such as Western blot or type-specific (glycoprotein-G-based) enzyme-linked immunosorbent assays (ELISAs). The inclusion criteria were also met for any publication that reported a proportion of HSV-1 detection by standard viral detection and subtyping methods in GUD or genital herpes—to estimate the "etiological" (or "associative") fraction for HSV-1 in these clinical conditions. Included studies had to have a sample size of ≥10, regardless of outcome measure.

Exclusion criteria included case reports, case series, reviews, editorials, letters to editors, commentaries, and qualitative studies. Measures reporting seroprevalence in <3-month-old infants were excluded because of maternal antibodies.

For terminology, a "publication" is a document containing a relevant outcome measure, and a "study" or a "measure" indicates all details pertaining to a specific outcome measure—a single publication may contribute multiple measures, and multiple publications of the same data set are deemed a single study.

### 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-1 outcome measures, and diagnostic assay. Data from relevant publications were double extracted by L. K. and M. H., with input from R. O.

Extracted overall outcome measures were substituted with stratified measures, provided the sample size requirement was fulfilled for each stratum. The stratification hierarchy for seroprevalence included population type, age bracket, and age group, for epidemiological relevance and analysis. In age-bracket stratification, we aimed to assess seroprevalence in adults (≥15 years of age) versus children (<15 years). In age-group stratification, we aimed to assess seroprevalence growth with age (<20, 20–39, or ≥40 years); these strata were optimal given reported age-stratified data. Stratification hierarchy for GUD and genital herpes proportions included ethnicity, study site (eg, hospital or STI clinic), and genital herpes episode (first vs recurrent).

Extracted seroprevalence measures were stratified by population type into (1) healthy general populations, consisting of healthy populations such as blood donors, pregnant women, and outpatients with minor health conditions; (2) clinical populations, consisting of any population with a major clinical condition, or a condition related (potentially) to HSV-1 infection; and (3) other populations, consisting of the remaining populations not satisfying the above definitions or populations with an undetermined risk of acquiring HSV-1, such as persons with human immunodeficiency virus infection, sex workers, and men who have sex with men.

### Meta-analyses

Meta-analyses were conducted to estimate pooled mean HSV-1 seroprevalence by population type and by age bracket or group and to estimate the pooled mean proportions of HSV-1 detection in GUD and genital herpes.

Pooled means were estimated using DerSimonian-Laird random-effects models [34], provided that ≥3 measures were available. This method accounts for sampling variation and heterogeneity in effect size (seroprevalence or GUD/genital herpes proportion) [34]. The Freeman-Tukey double-arcsine transformation was used for variance stabilization [35].

The Cochran *Q* statistic was calculated to assess existence of heterogeneity in effect size ($P < .10$ indicated heterogeneity) [36, 37]. The $I^2$ heterogeneity measure was estimated to assess the percentage of between-study variation in effect size that is due to actual differences in effect size rather than chance [37]. Prediction intervals were calculated to describe the heterogeneity in meta-analyses [36, 37]. Meta-analyses were performed in R software, version 3.4.1 [38] using the meta package [39].

### Meta-regression Analyses

Univariable and multivariable random-effects meta-regression analyses were conducted to identify predictors of HSV-1 seroprevalence (including temporal trend) and sources of between-study heterogeneity. The log-transformed proportions were regressed to estimate risk ratios.

Relevant independent variables were specified a priori: age bracket, age group, assay type (Western blot, ELISA, or other), country's income, population type, sample size (<100 vs ≥100 subjects), sampling method (probability-based vs non–probability-based sampling), sex, year of data collection, and year of publication. Factors associated with seroprevalence at $P \leq .10$ in univariable analysis were included in the final multivariable analysis. Factors associated with seroprevalence at $P \leq .05$ in the final multivariable analysis were deemed statistically significant.

For the country's income variable, countries with available data were grouped according to the World Bank classification [40]. For measures that did not include a year of data collection, missing values were imputed using the median of the values calculated by subtracting the year of data collection (when available) from the year of publication. Meta-regression analyses were conducted with Stata/SE software, version 13 [41], using the metareg package [42].

### Quality Assessment

For diagnostic methods, diversity, and potential issues of sensitivity or specificity [43, 44], we performed quality assessment with the support of an expert advisor, Rhoda Ashley-Morrow, University of Washington, Seattle. Only publications with sufficiently reliable assays were eligible for inclusion. Study quality was further assessed by conducting risk of bias (ROB) assessment (as informed by the Cochrane approach [31]) and precision assessment.

Studies were categorized as low versus high ROB using 2 quality domains assessing the rigor of sampling method (probability based vs otherwise) and response rate (≥80% vs otherwise). A study was considered to have high (vs low) precision if the sample size was ≥100.

## RESULTS

### Search Results and Scope of Evidence

Figure 1 describes the study-selection process based on PRISMA guidelines [32]. A total of 3517 citations were identified (988 through PubMed and 2529 through Embase). Of these, 528 were relevant or potentially relevant after removal of duplicates and screening of titles and abstracts. Eventually, 45 publications were eligible for inclusion after full-text screening. Four additional publications were identified through screening of bibliographies of publications and reviews [45–48].

A total of 54 overall seroprevalence measures (distinct overall measures in different populations) were extracted, and these yielded 182 stratified seroprevalence measures. Eight proportions of HSV-1 detection in GUD and 24 proportions in genital herpes were further extracted. Extracted measures originated from 13 of 26 Asian countries/territories.

### Seroprevalence Overview

Table 1 summarizes the stratified seroprevalence measures. The earliest measure was published in 1986. Most measures were based on cross-sectional study design (n = 152 measures; 83.5%), and convenience sampling (n = 150; 82.4%).

Extracted stratified seroprevalence measures varied across and within populations, with a range of 11.1%–100% and a median of 74.1% (Table 2). The range and median for seroprevalence were 11.1%–78.3% and 46.8%, respectively, in populations of healthy children (n = 19), 16.7%–75.9% and 53.1% in clinical populations of children (n = 7), 14.1%–100% and 78.5% in healthy adult populations (n = 103), and 32.1%–95.8% and 67.5% in clinical adult populations (n = 23). Table 2 also includes the ranges and medians for further populations.

### Pooled Seroprevalence Estimates

Table 2 shows the results of the seroprevalence meta-analyses. Among children, the pooled mean seroprevalence was 48.5% (n = 19; 95% confidence interval [CI], 37.8%–59.3%) for those who were healthy and 54.2% (n = 7; 40.5%–67.6%) for those with clinical conditions. Among adults, the pooled mean was 77.4% (n = 103; 95% CI, 73.4%–81.1%) for healthy adults and 67.1% (n = 23; 56.7%–76.8%) for those with clinical conditions. Table 2 includes pooled results for further populations. By age group, the pooled mean was lowest, at 55.5% (n = 37; 95% CI,

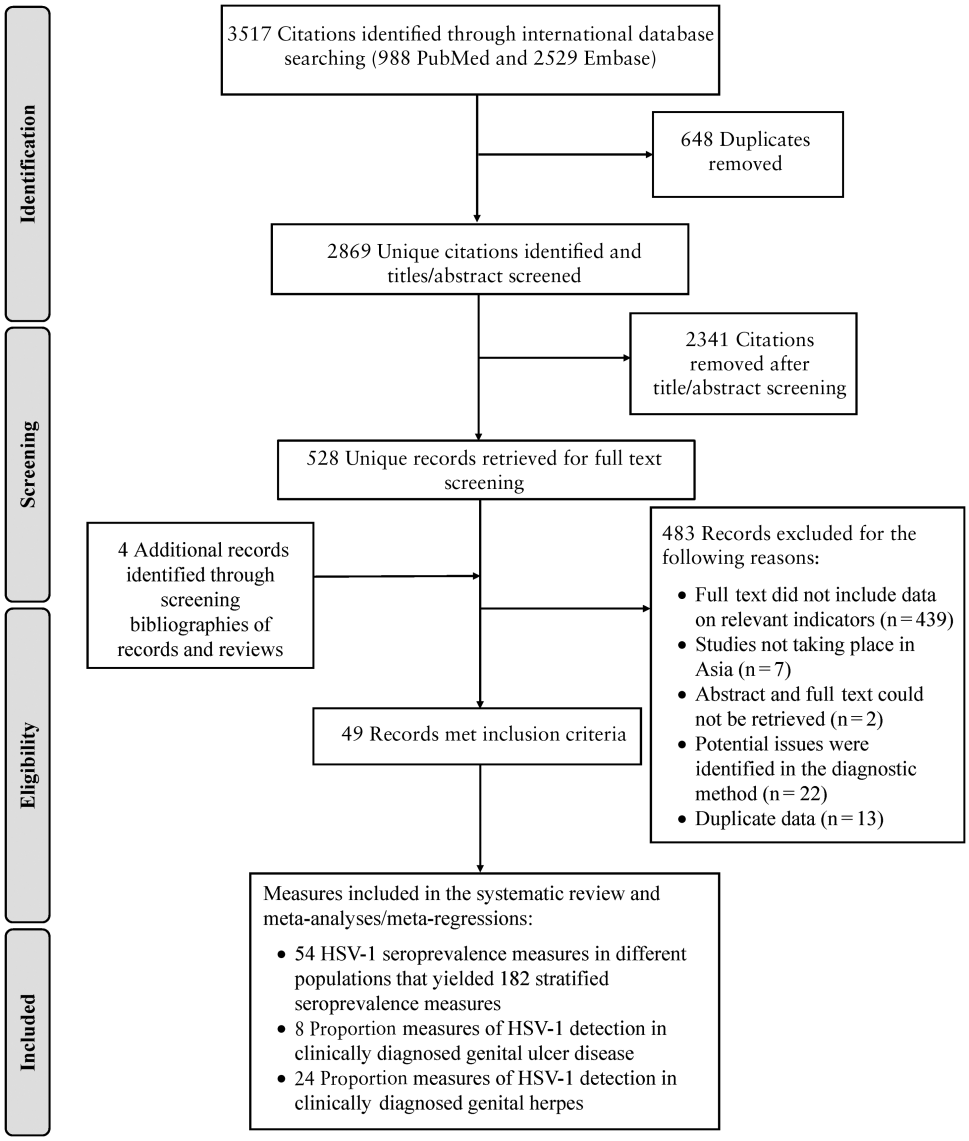


**Figure 1.** Flow chart of article selection for the systematic review of herpes simplex virus type 1 (HSV-1) in Asia, as adapted from the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) 2009 guidelines [32].

47.5%–63.4%), in individuals aged <20 years, followed by 67.9% (n = 48; 62.4%–73.3%) in those aged 20–39 and 87.5% (n = 44; 83%.4–91.1%) in those aged ≥40 years.

Country-specific meta-analyses were conducted for countries with ≥5 measures for healthy children or adults. For China, the pooled means were 61.3% (n = 12; 95% CI, 53.1%–69.2%) in children and 93.1% (n = 23; 90.0%–95.6%) in adults. For India and Japan, the pooled means were 66.8% (n = 21; 95% CI, 58.6%–74.6%) and 68.1% (n = 34; 61.5%–74.6%), respectively, in healthy adults.

There was strong evidence for heterogeneity in seroprevalence in all meta-analyses ($P < .003$; Table 2). Most variation was due to true variation in seroprevalence rather than sampling variation ($I^2 > 50\%$). The prediction intervals affirmed substantial variation in seroprevalence. Forest plots are shown in Supplementary Figure 1.

#### Predictors of Seroprevalence and Sources of Between-study Heterogeneity

Table 3 shows the results of the regression analyses. In univariable analyses, age bracket, age group, assay type, country's income, population type, and sampling method had $P$ values of <.10 and were included in the final multivariable analyses. Age group best explained the seroprevalence variation (adjusted $R^2 = 21.1\%$).

Sample size and sex were not statistically significant. Year of data collection and year of publication were also not statistically significant; strikingly, both risk ratios were 1.0 (95% CI, 1.0–1.0) supporting a flat seroprevalence over time.

**Table 1. Studies Reporting Herpes Simplex Virus Type 1 Seroprevalence Among Different Populations in Asia**

| Authors (Year) | Year(s) of Data Collection | Country | Study Site | Study Design | Sampling Method | Population | HSV-1 Serological Assay | Sample Size, No. | HSV-1 Seroprevalence, % |
|---|---|---|---|---|---|---|---|---|---|
| **Healthy Children Populations (n = 19)** | | | | | | | | | |
| Bogaerts et al (2001) [49] | 1996–1998 | Bangladesh | Outpatient clinic | CS | Conv | 1–12-y-old children | WB | 79 | 46.0 |
| Chang (1986) [50] | 1984–1986 | China | Hospital | CS | Conv | 7–12-mo-old infants | CFT | 31 | 41.9 |
| Chang (1986) [50] | 1984–1987 | China | Hospital | CS | Conv | 13–24-mo-old children | CFT | 31 | 51.6 |
| Chang (1986) [50] | 1984–1988 | China | Hospital | CS | Conv | 24–35-mo-old children | CFT | 30 | 43.3 |
| Chang (1986) [50] | 1984–1989 | China | Hospital | CS | Conv | 3–4-y-old children | CFT | 31 | 67.7 |
| Chang (1986) [50] | 1984–1990 | China | Hospital | CS | Conv | 5–6-y-old children | CFT | 31 | 48.4 |
| Chang (1986) [50] | 1984–1991 | China | Hospital | CS | Conv | 7–8-y-old children | CFT | 31 | 71.0 |
| Chang (1986) [50] | 1984–1992 | China | Hospital | CS | Conv | 9–14-y-old children | CFT | 31 | 74.2 |
| Chen et al (2013) [51] | 2007 | Taiwan | Community | CS | Conv | 1-y-old children | ELISA | 90 | 11.1 |
| Chen et al (2013) [51] | 2007 | Taiwan | Community | CS | Conv | 2-y-old children | ELISA | 127 | 14.2 |
| Chen et al (2013) [51] | 2007 | Taiwan | Community | CS | Conv | 3-y-old children | ELISA | 92 | 31.5 |
| Chen et al (2013) [51] | 2007 | Taiwan | Community | CS | Conv | 4-y-old children | ELISA | 84 | 23.8 |
| Chen et al (2013) [51] | 2007 | Taiwan | Community | CS | Conv | 5–9-y-old children | ELISA | 111 | 46.8 |
| Chen et al (2013) [51] | 2007 | Taiwan | Community | CS | Conv | 10–14-y-old children | ELISA | 92 | 46.7 |
| Li et al (1990) [52] | 1988–1989 | China | Community | CS | Conv | 1–10-y-old Koreans | PHA | 16 | 38.0 |
| Lin et al (2011) [53] | 2006 | China | Community | CS | RS | 5–9-y-old girls | ELISA | 40 | 64.9 |
| Lin et al (2011) [53] | 2006 | China | Community | CS | RS | 10–14-y-old girls | ELISA | 45 | 78.3 |
| Lin et al (2011) [53] | 2006 | China | Community | CS | RS | 5–9-y-old boys | ELISA | 75 | 59.8 |
| Lin et al (2011) [53] | 2006 | China | Community | CS | RS | 10–14-y-old boys | ELISA | 64 | 78.0 |
| **Healthy Adult Populations (n = 103)** | | | | | | | | | |
| Armelia et al (2012) [54] | 2010–2011 | Indonesia | Hospital | CS[a] | Conv | Kidney donors | Anti-HSV-1 IgG | 23 | 72.7 |
| Ashley et al (2004) [55] | 2000–2001 | Thailand | Community | CS | Conv | ≥15-y-old women in Lampang | WB | 98 | 92.9 |
| Ashley et al (2004) [55] | 2000–2001 | Thailand | Community | CS | Conv | ≥15-y-old women in Songkla | WB | 90 | 61.1 |
| Ashley et al (2004) [55] | 2000–2001 | Vietnam | Community | CS | Conv | ≥15-y-old women in Hanoi | WB | 99 | 100.0 |
| Ashley et al (2004) [55] | 2000–2001 | Vietnam | Community | CS | Conv | ≥15-y-old women in Ho Chi Minh | WB | 100 | 98.0 |
| Bogaerts et al (2001) [49] | 1996–1998 | Bangladesh | Outpatient clinic | CS | Conv | Healthy women | ELISA | 183 | 97.0 |
| Bu et al (2015) [45] | 2012–2013 | China | Hospital | CC | Conv | Healthy individuals | ELISA | 135 | 78.5 |
| Chang (1986) [50] | 1984–1986 | China | Hospital | CS | Conv | >14-y-old adults | CFT | 30 | 93.3 |
| Cowan et al (2003) [56] | 1998–2000 | India | Community | CS | Conv | 15–20-y-old adults | ELISA | 239[b] | 85.7 |
| Chen et al (2013) [51] | 2007 | Taiwan | Community | CS | Conv | 15–19-y-old adults | ELISA | 115 | 53.0 |
| Chen et al (2013) [51] | 2007 | Taiwan | Community | CS | Conv | 20–29-y-old adults | ELISA | 123 | 69.9 |
| Chen et al (2013) [51] | 2007 | Taiwan | Community | CS | Conv | 30–39-y-old adults | ELISA | 129 | 84.5 |
| Chen et al (2013) [51] | 2007 | Taiwan | Community | CS | Conv | 40–49-y-old adults | ELISA | 100 | 94.0 |
| Chen et al (2013) [51] | 2007 | Taiwan | Community | CS | Conv | 50–59-y-old adults | ELISA | 91 | 98.9 |
| Chen et al (2013) [51] | 2007 | Taiwan | Community | CS | Conv | 60–69-y-old adult | ELISA | 122 | 100 |
| Chen et al (2013) [51] | 2007 | Taiwan | Community | CS | Conv | >70-y-old adults | ELISA | 96 | 100 |
| Cowan et al (2003) [56] | 1998–2000 | India | Community | CS | Conv | 20–30-y-old adults | ELISA | 239[b] | 79.9 |
| Cowan et al (2003) [56] | 1998–2000 | India | Community | CS | Conv | 30–35-y-old adults | ELISA | 239[b] | 80.0 |
| Cowan et al (2003) [56] | 1998–2000 | India | Community | CS | Conv | 25–40-y-old adults | ELISA | 239[b] | 84.8 |
| Cowan et al (2003) [56] | 1998–2000 | India | Community | CS | Conv | 40–45-y-old adults | ELISA | 239[b] | 86.2 |
| Cowan et al (2003) [56] | 1998–2000 | India | Community | CS | Conv | >45-y-old adults | ELISA | 239[b] | 92.5 |
| Doi et al (2009) [57] | 2002 | Japan | Community | CS[a] | RS | 18–29-y-old women | ELISA | 83 | 45.8 |
| Doi et al (2009) [57] | 2002 | Japan | Community | CS[a] | RS | 30–39-y-old women | ELISA | 184 | 50.5 |
| Doi et al (2009) [57] | 2002 | Japan | Community | CS[a] | RS | 40–49-y-old women | ELISA | 198 | 66.7 |
| Doi et al (2009) [57] | 2002 | Japan | Community | CS[a] | RS | 50–59-y-old women | ELISA | 200 | 79.0 |
| Doi et al (2009) [57] | 2002 | Japan | Community | CS[a] | RS | 18–29-y-old men | ELISA | 45 | 44.4 |
| Doi et al (2009) [57] | 2002 | Japan | Community | CS[a] | RS | 30–39-y-old men | ELISA | 129 | 44.2 |
| Doi et al (2009) [57] | 2002 | Japan | Community | CS[a] | RS | 40–49-y-old men | ELISA | 198 | 49.0 |

**Table 1. Continued**

| Authors (Year) | Year(s) of Data Collection | Country | Study Site | Study Design | Sampling Method | Population | HSV-1 Serological Assay | Sample Size, No. | HSV-1 Seroprevalence, % |
|---|---|---|---|---|---|---|---|---|---|
| Doi et al (2009) [57] | 2002 | Japan | Community | CS[a] | RS | 50–59-y-old men | ELISA | 198 | 71.7 |
| Hashido et al (1998) [58] | NA | Japan | Community | CS | Conv | <30-y-old men blood donors | EIA | 12 | 33.0 |
| Hashido et al (1998) [58] | NA | Japan | Community | CS | Conv | 30–50-y-old men blood donors | EIA | 17 | 70.0 |
| Hashido et al (1998) [58] | NA | Japan | Community | CS | Conv | >50-y-old men blood donors | EIA | 12 | 92.0 |
| Hashido et al (1998) [58] | NA | Japan | Community | CS | Conv | 20–39-y-old healthy women | EIA | 20 | 65.0 |
| Hashido et al (1998) [58] | NA | Japan | Community | CS | Conv | 40–99-y-old healthy women | EIA | 28 | 89.0 |
| Hashido et al (1998) [58] | NA | Japan | Community | CS | Conv | >50-y-old healthy women | EIA | 27 | 92.5 |
| Hashido et al (1998) [58] | NA | Japan | Community | CS | Conv | Pregnant women from Tokyo | EIA | 58 | 47.0 |
| Hashido et al (1998) [58] | NA | Japan | Community | CS | Conv | Pregnant women from Kagoshima | EIA | 100 | 61.0 |
| Hashido et al (1999) [59] | 1973–1993 | Japan | Community | CS | Conv | 20–29-y-old men in 1973 | ELISA | 31 | 64.5 |
| Hashido et al (1999) [59] | 1973–1993 | Japan | Community | CS | Conv | 30–39-y-old men in 1973 | ELISA | 25 | 76.0 |
| Hashido et al (1999) [59] | 1973–1993 | Japan | Community | CS | Conv | 40–49-y-old men in 1973 | ELISA | 15 | 86.7 |
| Hashido et al (1999) [59] | 1973–1993 | Japan | Community | CS | Conv | 20–29-y-old men in 1983 | ELISA | 24 | 37.5 |
| Hashido et al (1999) [59] | 1973–1993 | Japan | Community | CS | Conv | 30–39-y-old men in 1983 | ELISA | 30 | 76.7 |
| Hashido et al (1999) [59] | 1973–1993 | Japan | Community | CS | Conv | 40–49-y-old men in 1983 | ELISA | 33 | 90.9 |
| Hashido et al (1999) [59] | 1973–1993 | Japan | Community | CS | Conv | 20–29-y-old men in 1993 | ELISA | 30 | 33.3 |
| Hashido et al (1999) [59] | 1973–1993 | Japan | Community | CS | Conv | 30–39-y-old men in 1993 | ELISA | 30 | 56.7 |
| Hashido et al (1999) [59] | 1973–1993 | Japan | Community | CS | Conv | 40–49-y-old men in 1993 | ELISA | 45 | 75.6 |
| Hashido et al (1999) [59] | 1973–1993 | Japan | Community | CS | Conv | 20–29-y-old women in 1973 | ELISA | 32 | 59.4 |
| Hashido et al (1999) [59] | 1973–1993 | Japan | Community | CS | Conv | 30–39-y-old women in 1973 | ELISA | 33 | 84.8 |
| Hashido et al (1999) [59] | 1973–1993 | Japan | Community | CS | Conv | 40–49-y-old women in 1973 | ELISA | 23 | 100.0 |
| Hashido et al (1999) [59] | 1973–1993 | Japan | Community | CS | Conv | 20–29-y-old women in 1983 | ELISA | 35 | 51.4 |
| Hashido et al (1999) [59] | 1973–1993 | Japan | Community | CS | Conv | 30–39-y-old women in 1983 | ELISA | 36 | 77.8 |
| Hashido et al (1999) [59] | 1973–1993 | Japan | Community | CS | Conv | 40–49-y-old women in 1983 | ELISA | 34 | 97.1 |
| Hashido et al (1999) [59] | 1973–1993 | Japan | Community | CS | Conv | 20–29-y-old women in 1993 | ELISA | 63 | 31.7 |
| Hashido et al (1999) [59] | 1973–1993 | Japan | Community | CS | Conv | 30–39-y-old women in 1993 | ELISA | 54 | 69.1 |
| Hashido et al (1999) [59] | 1973–1993 | Japan | Community | CS | Conv | 40–49-y-old women in 1993 | ELISA | 41 | 80.5 |
| Kaur et al (1999) [60] | NA | India | Outpatient clinic | CS | Conv | 16–20-y-old pregnant women | EIA | 24 | 50.0 |
| Kaur et al (1999) [60] | NA | India | Outpatient clinic | CS | Conv | 21–25-y-old pregnant women | EIA | 36 | 44.4 |
| Kaur et al (1999) [60] | NA | India | Outpatient clinic | CS | Conv | 26–30-y-old pregnant women | EIA | 34 | 55.8 |
| Kaur et al (1999) [60] | NA | India | Outpatient clinic | CS | Conv | 31–35-y-old pregnant women | EIA | 14 | 14.1 |

**Table 1. Continued**

| Authors (Year) | Year(s) of Data Collection | Country | Study Site | Study Design | Sampling Method | Population | HSV-1 Serological Assay | Sample Size, No. | HSV-1 Seroprevalence, % |
|---|---|---|---|---|---|---|---|---|---|
| Kaur et al (1999) [60] | NA | India | Outpatient clinic | CS | Conv | >36-y-old pregnant women | EIA | 12 | 83.3 |
| Kaur et al (2005) [61] | NA | India | Outpatient clinic | CS | Conv | 16–20-y-old women | ELISA | 12 | 50.0 |
| Kaur et al (2005) [61] | NA | India | Outpatient clinic | CS | Conv | 21–25-y-old women | ELISA | 17 | 47.1 |
| Kaur et al (2005) [61] | NA | India | Outpatient clinic | CS | Conv | 26–30-y-old women | ELISA | 18 | 50.0 |
| Kaur et al (2005) [61] | NA | India | Outpatient clinic | CS | Conv | 31–40-y-old women | ELISA | 13 | 46.1 |
| Kaur et al (2005) [61] | NA | India | Outpatient clinic | CS | Conv | 16–20-y-old men | ELISA | 13 | 46.1 |
| Kaur et al (2005) [61] | NA | India | Outpatient clinic | CS | Conv | 21–25-y-old men | ELISA | 20 | 25.0 |
| Kaur et al (2005) [61] | NA | India | Outpatient clinic | CS | Conv | 26–30-y-old men | ELISA | 14 | 71.4 |
| Kaur et al (2005) [61] | NA | India | Outpatient clinic | CS | Conv | 31–40-y-old men | ELISA | 13 | 46.1 |
| Li et al (1990) [52] | 1988–1989 | China | Community | CS | Conv | >21-y-old Hans Chinese | PHA | 78 | 99.0 |
| Li et al (1990) [52] | 1988–1989 | China | Community | CS | Conv | >21-y-old Koreans | PHA | 34 | 97.0 |
| Lin et al (2011) [53] | 2006 | China | Community | CS | RS | 15–19-y-old women | ELISA | 78 | 87.5 |
| Lin et al (2011) [53] | 2006 | China | Community | CS | RS | 20–24-y-old women | ELISA | 101 | 86.1 |
| Lin et al (2011) [53] | 2006 | China | Community | CS | RS | 25–29-y-old women | ELISA | 135 | 93.3 |
| Lin et al (2011) [53] | 2006 | China | Community | CS | RS | 30–34-y-old women | ELISA | 152 | 96.7 |
| Lin et al (2011) [53] | 2006 | China | Community | CS | RS | 35–39-y-old women | ELISA | 154 | 95.5 |
| Lin et al (2011) [53] | 2006 | China | Community | CS | RS | 40–44-y-old women | ELISA | 129 | 98.4 |
| Lin et al (2011) [53] | 2006 | China | Community | CS | RS | 45–49-y-old women | ELISA | 97 | 98.0 |
| Lin et al (2011) [53] | 2006 | China | Community | CS | RS | 50–54-y-old women | ELISA | 101 | 98.1 |
| Lin et al (2011) [53] | 2006 | China | Community | CS | RS | 55–60-y-old women | ELISA | 44 | 97.8 |
| Lin et al (2011) [53] | 2006 | China | Community | CS | RS | 15–19-y-old men | ELISA | 89 | 76.5 |
| Lin et al (2011) [53] | 2006 | China | Community | CS | RS | 20–24-y-old men | ELISA | 93 | 81.9 |
| Lin et al (2011) [53] | 2006 | China | Community | CS | RS | 25–29-y-old men | ELISA | 112 | 86.5 |
| Lin et al (2011) [53] | 2006 | China | Community | CS | RS | 30–34-y-old men | ELISA | 137 | 90.4 |
| Lin et al (2011) [53] | 2006 | China | Community | CS | RS | 35–39-y-old men | ELISA | 144 | 93.7 |
| Lin et al (2011) [53] | 2006 | China | Community | CS | RS | 40–44-y-old men | ELISA | 118 | 97.4 |
| Lin et al (2011) [53] | 2006 | China | Community | CS | RS | 45–49-y-old men | ELISA | 89 | 96.7 |
| Lin et al (2011) [53] | 2006 | China | Community | CS | RS | 50–54-y-old men | ELISA | 82 | 98.7 |
| Lin et al (2011) [53] | 2006 | China | Community | CS | RS | 55–60-y-old men | ELISA | 62 | 98.4 |
| Nasrallah GK, Dargham SR, Harfouche M, and Abu-Raddad LJ (2018, unpublished data) | 2013–2016 | India | Community | CS | Conv | <24-y-old Indian men | ELISA | 40 | 40.0 |
| Nasrallah GK, Dargham SR, Harfouche M, and Abu-Raddad LJ (2018, unpublished data) | 2013–2016 | India | Community | CS | Conv | 25–29-y-old Indian men | ELISA | 49 | 34.0 |
| Nasrallah GK, Dargham SR, Harfouche M, and Abu-Raddad LJ (2018, unpublished data) | 2013–2016 | India | Community | CS | Conv | 30–34-y-old Indian men | ELISA | 50 | 60.0 |
| Nasrallah GK, Dargham SR, Harfouche M, and Abu-Raddad LJ (2018, unpublished data) | 2013–2016 | India | Community | CS | Conv | 35–39-y-old Indian men | ELISA | 50 | 36.0 |
| Nasrallah GK, Dargham SR, Harfouche M, and Abu-Raddad LJ (2018, unpublished data) | 2013–2016 | India | Community | CS | Conv | 40–44-y-old Indian men | ELISA | 50 | 48.0 |
| Nasrallah GK, Dargham SR, Harfouche M, and Abu-Raddad LJ (2018, unpublished data) | 2013–2016 | India | Community | CS | Conv | 45–49-y-old Indian men | ELISA | 50 | 58.0 |
| Nasrallah GK, Dargham SR, Harfouche M, and Abu-Raddad LJ (2018, unpublished data) | 2013–2016 | India | Community | CS | Conv | >50-y-old Indian men | ELISA | 35 | 62.0 |

**Table 1. Continued**

| Authors (Year) | Year(s) of Data Collection | Country | Study Site | Study Design | Sampling Method | Population | HSV-1 Serological Assay | Sample Size, No. | HSV-1 Seroprevalence, % |
|---|---|---|---|---|---|---|---|---|---|
| Nasrallah GK, Dargham SR, Harfouche M, and Abu-Raddad LJ (2018, unpublished data) | 2013–2016 | Philippines | Community | CS | Conv | <34-y-old Filipino men | ELISA | 52 | 84.6 |
| Nasrallah GK, Dargham SR, Harfouche M, and Abu-Raddad LJ (2018, unpublished data) | 2013–2016 | Philippines | Community | CS | Conv | 35–44-y-old Filipino men | ELISA | 40 | 82.5 |
| Nasrallah GK, Dargham SR, Harfouche M, and Abu-Raddad LJ (2018, unpublished data) | 2013–2016 | Philippines | Community | CS | Conv | >45-y-old Filipino men | ELISA | 28 | 85.7 |
| Patnaik et al (2007) [62] | 1985–2007 | Thailand | Hospital | CC | Conv | Healthy women | WB | 78 | 51.3 |
| Schmid et al (1999) [63] | 1991–1993 | Thailand | Hospital | CS | Conv | >21-y-old army men | WB | 1158 | 77.9 |
| Shivaswamy et al (2005) [64] | 2001–2003 | India | Outpatient clinic | CC | Conv | Healthy individuals | ELISA | 135 | 91.8 |
| Yue (1990) [65] | 1987–1989 | China | Outpatient clinic | CS | Conv | Pregnant women | ELISA | 295 | 82.0 |
| Zegans et al (1999) [66] | 1997 | India | Hospital | CC | Conv | Controls for a study of Mooren ulcer | ELISA | 44 | 64.0 |
| **Healthy Mixed-Age Populations (n = 4)** | | | | | | | | | |
| Li et al (1990) [52] | 1988–1989 | China | Community | CS | Conv | 11–20-y-old Hans Chinese | PHA | 17 | 94.1 |
| Li et al (1990) [52] | 1988–1989 | China | Community | CS | Conv | 11–20-y-old Koreans | PHA | 13 | 85.0 |
| Shen et al (2015) [67] | 2007 | Taiwan | Community | CS | RS | Healthy women | ELISA | 830 | 64.5 |
| Shen et al (2015) [67] | 2007 | Taiwan | Community | CS | RS | Healthy men | ELISA | 581 | 52.0 |
| **Clinical Children Populations (n = 7)** | | | | | | | | | |
| Cowan et al (2003) [56] | 1998–2000 | India | Hospital | CS | Conv | 1–5-y-old children | ELISA | 90[b] | 40.2 |
| Cowan et al (2003) [56] | 1998–2000 | India | Hospital | CS | Conv | 5–10-y-old children | ELISA | 90[b] | 68.4 |
| Cowan et al (2003) [56] | 1998–2000 | India | Hospital | CS | Conv | 10–15-y-old children | ELISA | 90[b] | 75.9 |
| Cowan et al (2003) [56] | 1998–2000 | Sri Lanka | Hospital | CS | Conv | 1–5-y-old children | ELISA | 144[b] | 40.5 |
| Cowan et al (2003) [56] | 1998–2000 | Sri Lanka | Hospital | CS | Conv | 5–10-y-old children | ELISA | 144[b] | 53.1 |
| Cowan et al (2003) [56] | 1998–2000 | Sri Lanka | Hospital | CS | Conv | 10–15-y-old children | ELISA | 144[b] | 74.0 |
| Shymala et al (2008) [68] | 2005–2006 | India | Outpatient clinic | CS | Conv | Infants with congenital cataract | ELISA | 18 | 16.7 |
| **Clinical Adult Populations (n = 23)** | | | | | | | | | |
| Armelia et al (2012) [54] | 2010–2011 | Indonesia | Hospital | CS[a] | Conv | Pre–kidney transplant patients | Anti-HSV-1 IgG | 23 | 68.2 |
| Bu et al (2015) [45] | 2012–2013 | China | Hospital | CC | Conv | Patients with Alzheimer disease | ELISA | 128 | 85.2 |
| Hashido et al (1998) [58] | NA | Japan | Community | CS | Conv | <39-y-old patients with STD | EIA | 10 | 60.0 |
| Hashido et al (1998) [58] | NA | Japan | Community | CS | Conv | >40-y-old patients with STD | EIA | 16 | 81.2 |
| Hashido et al (1998) [58] | NA | Japan | Community | CS | Conv | Pregnant Tokyo women with HTLV-1 | EIA | 32 | 56.0 |
| Hashido et al (1998) [58] | NA | Japan | Community | CS | Conv | Pregnant Kagoshima women with HTLV-1 | EIA | 100 | 83.0 |
| Kaur et al (2006) [69] | NA | India | Outpatient clinic | CS | Conv | Women attending an STD clinic | ELISA | 52 | 82.7 |
| Kaur et al (2006) [69] | NA | India | Outpatient clinic | CS | Conv | Women attending an STD clinic | ELISA | 76 | 73.7 |
| Patwardhan and Bhalla (2016) [70] | NA | India | Hospital | CS | Conv | Patients with first genital herpes | ELISA | 21 | 42.8 |
| Patwardhan and Bhalla (2016) [70] | NA | India | Hospital | CS | Conv | Patients with recurrent genital herpes | ELISA | 23 | 65.2 |
| Shivaswamy et al (2005) [64] | 2001–2003 | India | Outpatient clinic | CC | Conv | <40-y-old patients in an STI clinic | ELISA | 111 | 90.1 |

**Table 1. Continued**

| Authors (Year) | Year(s) of Data Collection | Country | Study Site | Study Design | Sampling Method | Population | HSV-1 Serological Assay | Sample Size, No. | HSV-1 Seroprevalence, % |
|---|---|---|---|---|---|---|---|---|---|
| Shivaswamy et al (2005) [64] | 2001–2003 | India | Outpatient clinic | CC | Conv | ≥40-y-old patients in an STI clinic | ELISA | 24 | 95.8 |
| Sun et al (2005) [48] | NA | China | Hospital | CS | Conv | Diabetic inpatients | ELISA | 206 | 46.1 |
| Sun et al (2005) [48] | NA | China | Hospital | CS | Conv | Nondiabetic inpatients | ELISA | 1360 | 36.3 |
| Theng et al (2006) [71] | 2003–2004 | Singapore | Outpatient clinic | CS | Conv | <29-y-old men | ELISA | 72 | 47.2 |
| Theng et al (2006) [71] | 2003–2004 | Singapore | Outpatient clinic | CS | Conv | 30–39-y-old men | ELISA | 50 | 52.0 |
| Theng et al (2006) [71] | 2003–2004 | Singapore | Outpatient clinic | CS | Conv | 40–49-y-old men | ELISA | 41 | 58.8 |
| Theng et al (2006) [71] | 2003–2004 | Singapore | Outpatient clinic | CS | Conv | >50-y-old men | ELISA | 37 | 78.4 |
| Theng et al (2006) [71] | 2003–2004 | Singapore | Outpatient clinic | CS | Conv | <20-y-old female patients | ELISA | 28 | 32.1 |
| Theng et al (2006) [71] | 2003–2004 | Singapore | Outpatient clinic | CS | Conv | 20–29-y-old women | ELISA | 98 | 49.0 |
| Theng et al (2006) [71] | 2003–2004 | Singapore | Outpatient clinic | CS | Conv | 30–39-y-old women | ELISA | 40 | 67.5 |
| Theng et al (2006) [71] | 2003–2004 | Singapore | Outpatient clinic | CS | Conv | >40-y-old women | ELISA | 32 | 78.2 |
| Zegans et al (1999) [66] | 1999 | India | Hospital | CS | Conv | Patients with Mooren ulcers | ELISA | 21 | 86.0 |
| **Clinical Mixed-Age Population (n = 1)** | | | | | | | | | |
| Lee and Lee (2015) [72] | NA | South Korea | Community | CS[a] | Conv | >11-y-old patients | Multiplex immu-noassay | 2317 | 73.8 |
| **Other Populations (n = 25)** | | | | | | | | | |
| Chu et al (2006) [73] | NA | Thailand | Hospital | CS | Conv | HIV-infected men | ELISA | 66 | 53.0 |
| Chu et al (2006) [73] | NA | Thailand | Hospital | CS | Conv | HIV-infected women | ELISA | 70 | 73.0 |
| Cowan et al (2003) [56] | 1998–2000 | Sri Lanka | Outpatient clinic | CS | Conv | 15–20-y-old healthy/clinical patients | ELISA | 622[b] | 74.3 |
| Cowan et al (2003) [56] | 1998–2000 | Sri Lanka | Outpatient clinic | CS | Conv | 20–30-y-old healthy/clinical patients | ELISA | 622[b] | 79.2 |
| Cowan et al (2003) [56] | 1998–2000 | Sri Lanka | Outpatient clinic | CS | Conv | 30–35-y-old health/clinical patients | ELISA | 622[b] | 74.6 |
| Cowan et al (2003) [56] | 1998–2000 | Sri Lanka | Outpatient clinic | CS | Conv | 25–40-y-old healthy/clinical patients | ELISA | 622[b] | 74.5 |
| Cowan et al (2003) [56] | 1998–2000 | Sri Lanka | Outpatient clinic | CS | Conv | 40–45-y-old healthy/clinical patients | ELISA | 622[b] | 77.1 |
| Cowan et al (2003) [56] | 1998–2000 | Sri Lanka | Outpatient clinic | CS | Conv | >45-y-old healthy/clinical patients | ELISA | 622[b] | 82.0 |
| Hashido et al (1998) [58] | NA | Japan | Community | CS | Conv | Female sex workers | EIA | 70 | 75.7 |
| Hashido et al (1998) [58] | NA | Japan | Community | CS | Conv | <39-y-old MSM | EIA | 15 | 53.3 |
| Hashido et al (1998) [58] | NA | Japan | Community | CS | Conv | >40-y-old MSM | EIA | 19 | 97.4 |
| Lin et al (2011) [53] | NA | China | Community | CS | Conv | 18–29-y-old HIV-infected patients | ELISA | 191 | 94.3 |
| Lin et al (2011) [53] | NA | China | Community | CS | Conv | 30–39-y-old HIV-infected patients | ELISA | 503 | 92.6 |
| Lin et al (2011) [53] | NA | China | Community | CS | Conv | 40–49-y-old HIV-infected patients | ELISA | 290 | 89.7 |
| Lin et al (2011) [53] | NA | China | Community | CS | Conv | 50–59-y-old HIV-infected patients | ELISA | 96 | 85.4 |
| Lin et al (2011) [53] | NA | China | Community | CS | Conv | 60–94-y-old HIV-infected patients | ELISA | 30 | 93.3 |
| Limpakarnjanara et al (1999) [74] | 1994 | Thailand | Community | CS | Conv | >16-y-old female sex workers | WB | 500 | 91.0 |
| Neal et al (2011) [75] | NA | China | Community | CS | Conv | Sex workers | WB | 273 | 91.9 |
| Qutub and Akhter (2003) [76] | NA | Bangladesh | Community | CS[a] | Conv | Female sex workers | WB | 463 | 92.7 |
| Theng et al (2006) [77] | 2003–2004 | Singapore | Outpatient clinic | CS | Conv | 20–29-y-old sex workers | ELISA | 146 | 80.1 |
| Theng et al (2006) [77] | 2003–2004 | Singapore | Outpatient clinic | CS | Conv | 30–39-y-old sex workers | ELISA | 56 | 67.9 |
| Theng et al (2006) [77] | 2003–2004 | Singapore | Outpatient clinic | CS | Conv | 40–49-y-old sex workers | ELISA | 60 | 68.3 |

**Table 1. Continued**

| Authors (Year) | Year(s) of Data Collection | Country | Study Site | Study Design | Sampling Method | Population | HSV-1 Serological Assay | Sample Size, No. | HSV-1 Seroprevalence, % |
|---|---|---|---|---|---|---|---|---|---|
| Theng et al (2006) [77] | 2003–2004 | Singapore | Outpatient clinic | CS | Conv | >50-y-old sex workers | ELISA | 38 | 89.5 |
| Van Griensven et al (2013) [78] | 2006–2010 | Thailand | Community | CS | Conv | >18-y-old MSM | ELISA | 1740 | 56.5 |
| Yap et al (2017) [79] | NA | Malaysia | Hospital | CS | Conv | HIV-infected patients | ELISA | 232 | 70.7 |

Abbreviations: CC, case-control; CFT, complement fixation test; Conv, convenience; CS, cross-sectional; EIA, enzyme immunoassay; ELISA, enzyme-linked immunosorbent assay; HIV, human immunodeficiency virus; HSV-1, herpes simplex virus type 1; HTLV-1, human T-lymphotropic virus 1; MSM, men who have sex with men; NA, not available; PHA, passive hemagglutination assay; RS, random sampling; STD, sexually transmitted disease; STI, sexually transmitted infection; WB, Western blot.

[a]The actual study design was cohort, but the extracted seroprevalence measure was for the baseline measurement.

[b]The study included overall sample size but no sample sizes for individual strata. Each stratum sample size was assumed to be equal to the overall sample size divided by the number of strata in the study.

**Table 2. Pooled Mean Estimates for Herpes Simplex Virus Type 1 Seroprevalence Among Different Populations in Asia**

| Population Type | Outcome Measures, Total No. | Samples, Total No. | HSV-1 Seroprevalence | | Pooled Mean HSV-1 Seroprevalence, Mean (95% CI) | Heterogeneity Measures[a] | | |
|---|---|---|---|---|---|---|---|---|
| | | | Range | Median | | Q (*P* Value) | $I^2$ (95% CI), % | Prediction Interval, % |
| Healthy general populations | | | | | | | | |
| Children | 19 | 1131 | 11.1–78.3 | 46.8 | 48.5 (37.8–59.3) | 228.6 (<.001) | 92.1 (89.1–94.3) | 7.1–91.2 |
| Adults | 103 | 9514 | 14.1–100 | 78.5 | 77.4 (73.4–81.1) | 1841.6 (<.001) | 94.5 (93.7–95.1) | 34.9–100 |
| Mixed ages | 4 | 1441 | 52.0–94.1 | 74.8 | 68.9 (56.3–80.3) | 36.5 (<.001) | 91.8 (82.2–96.2) | 16.6–100 |
| All healthy general populations | 126 | 12 086 | 11.1–100 | 73.4 | 73.1 (68.9–77.1) | 2955.4 (<.001) | 95.8 (95.3–96.2) | 25.3–100 |
| Clinical populations | | | | | | | | |
| Children | 7 | 720 | 16.7–75.9 | 53.1 | 54.2 (40.5–67.6) | 78.4 (<.001) | 92.3 (86.8–95.6) | 11.0–93.9 |
| Adults | 23 | 2601 | 32.1–95.8 | 67.5 | 67.1 (56.7–76.8) | 456.4 (<.001) | 95.2 (93.8–96.3) | 17.3–100 |
| Mixed ages | 1[b] | 2317 | - | - | 73.8 (71.9–75.6) | -[b] | -[b] | -[b] |
| All clinical populations | 31 | 5638 | 16.7–95.8 | 67.5 | 64.3 (56.3–71.9) | 809.2 (<.001) | 96.3 (95.5–97.0) | 21.1–97.0 |
| Other populations | | | | | | | | |
| HIV-infected patients | 8 | 1476 | 53.0–94.3 | 87.6 | 83.3 (74.0–91.0) | 119.4 (<.001) | 94.1 (90.6–96.3) | 45.7–100 |
| MSM | 3 | 1774 | 53.3–97.4 | 56.5 | 69.7 (42.9–91.7) | 15.5 (<.001) | 87.1 (63.2–95.5) | 0.0–100 |
| Sex workers | 8 | 1606 | 67.9–92.7 | 84.9 | 84.1 (77.6–89.7) | 63.2 (<.001) | 88.9 (80.5–93.7) | 59.3–98.6 |
| Healthy/ clinical adult populations | 6 | 3732 | 74.3–82.0 | 75.9 | 77.0 (74.4–79.5) | 18.0 (.003) | 72.3 (36.0–88.0) | 68.1–84.8 |
| Age groups | | | | | | | | |
| <20 y | 37 | 3101 | 11.1–94.1 | 51.6 | 55.5 (47.5–63.4) | 654.8 (<.001) | 94.5 (93.3–95.5) | 11.7–94.6 |
| 20–39 y | 48 | 5601 | 14.1–96.7 | 67.7 | 67.9 (62.4–73.3) | 784.3 (<.001) | 94.0 (92.8–95.0) | 23.0–96.0 |
| ≥40 y | 44 | 4966 | 48.0–100 | 89.3 | 87.5 (83.4–91.1) | 633.6 (<.001) | 93.2 (91.7–94.4) | 55.2–100 |
| All children | 26 | 1851 | 11.1–78.3 | 47.6 | 50.0 (41.3–58.7) | 343.6 (<.001) | 92.7 (90.5–94.4) | 10.2–89.8 |
| All adults | 151 | 20 705 | 14.1–100 | 77.8 | 76.5 (73.3–79.6) | 3951.1 (<.001) | 96.2 (95.8–96.5) | 34.2–100 |
| All mixed-age groups | 5 | 3758 | 52.0–94.1 | 73.8 | 70.6 (59.4–80.8) | 112.8 (<.001) | 96.5 (94.0–97.9) | 29.6–98.3 |
| **All studies/ strata** | **182** | **26 314** | **11.1–100** | **74.1** | **72.9 (69.8–75.9)** | **5038.0 (.001)** | **96.4 (96.1–96.7)** | **30.3–99.4** |

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; HSV-1, herpes simplex virus type 1; MSM, men who have sex with men.

[a]The Cochran *Q* statistic is a measure assessing the existence of heterogeneity in effect size; $I^2$, a measure that assesses the magnitude of between-study variation due to actual differences in effect size across studies rather than chance; and prediction interval, a measure that estimates the distribution (95% interval) of true effect sizes around the estimated mean.

[b]No meta-analysis was done owing to the small number of studies (n < 3).

**Table 3. Univariable and Multivariable Meta-regression Analyses of Herpes Simplex Virus Type 1 Seroprevalence Among Different Populations in Asia**

| Variable | Outcome Measures, Total No. | Samples, Total No. | Univariable Analysis | | | Multivariable Analysis | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Model 1[a] | | Model 2[b] | |
| | | | RR (95% CI) | *P* Value | Variance Explained, Adjusted $R^2$, % | ARR (95%CI) | *P* Value | ARR (95% CI) | *P* Value |
| Age bracket | | | | | | | | | |
| Children | 26 | 1851 | 1.0 | … | | 1.0 | … | … | … |
| Adults | 151 | 20705 | 1.5 (1.3–1.7) | <.001 | | 1.5 (1.3–1.7) | <.001 | … | … |
| Mixed ages | 5 | 3758 | 1.4 (1.1–1.9) | .01 | 18.6 | 1.5 (1.1–2.0) | .006 | … | … |
| Age group | | | | | | | | | |
| <20 y | 37 | 3101 | 1.0 | … | | … | … | 1.0 | … |
| 20–39 y | 48 | 5601 | 1.2 (1.0–1.4) | .008 | | … | … | 1.3 (1.0–1.5) | <.001 |
| ≥40 y | 44 | 4966 | 1.5 (1.3–1.8) | <.001 | | … | … | 1.6 (1.4–1.9) | <.001 |
| Mixed | 53 | 12646 | 1.3 (1.1–1.5) | <.001 | 21.1 | … | … | 1.3 (1.1–1.5) | <.001 |
| Assay type | | | | | | | | | |
| Western blot | 9 | 2859 | 1.0 | … | | 1.0 | … | 1.0 | … |
| ELISA | 137 | 20032 | 0.8 (.6–1.0) | .09 | | 0.9 (.8–1.1) | .63 | 0.9 (.7–1.0) | .28 |
| Others | 36 | 3423 | 0.8 (.6–1.0) | .13 | 0.5 | 1.0 (.8–1.2) | .98 | 1.0 (.8–1.2) | .72 |
| Country's income | | | | | | | | | |
| LMIC | 58 | 8047 | 1.0 | … | | 1.0 | … | 1.0 | … |
| UMIC | 55 | 10084 | 1.2 (1.0–1.3) | .02 | | 1.1 (1.0–1.3) | .01 | 1.1 (1.0–1.3) | .03 |
| HIC | 69 | 8183 | 0.9 (.8–1.1) | .39 | 7.1 | 0.9 (.8–1.2) | .13 | 0.9 (.8–.9) | .01 |
| Population type | | | | | | | | | |
| Healthy general populations | 126 | 12086 | 1.0 | … | | 1.0 | … | 1.0 | … |
| Clinical populations | 31 | 5638 | 0.9 (.8–1.0) | .17 | | 1.0 (.8–1.1) | .74 | 1.0 (.9–1.1) | .87 |
| Other populations | 25 | 8590 | 1.1 (1.0–1.3) | .07 | 0.2 | 1.1 (.9–1.2) | .53 | 1.0 (.9–1.2) | .52 |
| Sample size[c] | | | | | | | | | |
| <100 | 22 | 905 | 1.0 | … | | … | … | … | … |
| ≥100 | 160 | 25409 | 0.9 (.8–1.1) | .65 | 0.0 | … | … | … | … |
| Sampling method | | | | | | | | | |
| Probability based | 33 | 7104 | 1.0 | … | | 1.0 | … | 1.0 | … |
| Non–probability based | 149 | 19210 | 0.9 (.8–1.0) | .04 | 1.4 | 1.0 (.9–1.2) | .67 | 1.0 (.8–1.1) | .93 |
| Sex | | | | | | | | | |
| Female | 56 | 5665 | 1.0 | … | | … | … | … | … |
| Male | 55 | 6422 | 0.9 (.8–1.1) | .29 | | … | … | … | … |
| Mixed | 71 | 14227 | 0.9 (.8–1.1) | .46 | 1.4 | … | … | … | … |
| Year of data collection | 182 | 26314 | 1.0 (1.0–1.0) | .84 | 0.0 | … | … | … | … |
| Year of publication | 182 | 26314 | 1.0 (1.0–1.0) | .58 | 0.0 | … | … | … | … |

Abbreviations: ARR, adjusted risk ratio; CI, confidence interval; ELISA, enzyme-linked immunosorbent assay; HIC, high-income country; LMIC, lower-middle-income country; RR, risk ratio; UMIC, upper-middle-income country.

[a]The variance explained by the final multivariable model 1 (adjusted $R^2$) was 26.0%

[b]The variance explained by the final multivariable model 2 (adjusted $R^2$) was 33.9%

[c]Sample size denotes the sample size for each study population found in the original publication.

Two final multivariable analyses were conducted, instead of one, because of collinearity between age bracket and age group. The model including age bracket, assay type, country's income, population type, and sampling method explained 26.0% of seroprevalence variation. Seroprevalence in adults was 1.5-fold (95% CI, 1.3–1.7-fold) higher than in children. Seroprevalence in upper-middle-income countries was 1.1-fold (95% CI, 1.0–1.3-fold) higher than in lower-middle-income countries. No association with assay type, population type, and sampling method was found.

The model including age group instead of age bracket explained 33.9% of seroprevalence variation and yielded similar results. Seroprevalence in individuals aged 20–39 years was 1.3-fold (95% CI, 1.0–1.5-fold) higher than in individuals <20, and for those aged ≥40 years, it was 1.6-fold (1.4–1.9-fold) higher.

### HSV-1 Detection in GUD and Genital Herpes

Table 4 summarizes the studies reporting proportion of HSV-1 detection in GUD (n = 8) and genital herpes (n = 24). Table 5 shows the results of meta-analyses, with strong evidence for heterogeneity. Forest plots are shown in Supplementary Figure 2.

The proportion of HSV-1 detection in GUD ranged between 0.0% and 28.4%, with a median of 2.5%. The pooled mean proportion was 5.6% (n = 8; 95% CI, 0.8%–13.6%). The proportion of HSV-1 detection in genital herpes ranged between 0.0% and 62.0%, with a median of 16.3%. The pooled mean proportion was 18.8% (n = 24; 95% CI, 12.0%–26.7%). HSV-1 was more frequently detected in first-episode genital herpes than in recurrent genital herpes (Table 4).

### Quality Assessment

Outcomes of the quality assessment are shown in Supplementary Table 2. Overall, seroprevalence studies were of reasonable quality. Of all studies, 70.4% were of high precision, 7.4% had low ROB in the sampling method domain, and 38.9% had low ROB in the response rate domain. Only 7.4% of studies had high ROB in both quality domains.

## DISCUSSION

We presented a comprehensive systematic review and synthesis of HSV-1 epidemiology in Asia. Fifty percent of children and 75% of adults were infected. Seroprevalence increased with age, with most infections acquired in childhood. No evidence was found for a temporal trend; seroprevalence appeared stable for 3 decades. Nonetheless, seroprevalence was 60% higher in those aged ≥40 than in those aged <20 years, possibly reflecting a higher exposure risk in earlier times, and an earlier transition toward lower seroprevalence.

**Table 4. Studies From Asia Reporting Proportion of Herpes Simplex Virus Type 1 (HSV-1) Viral Detection in Clinically Diagnosed Genital Ulcer Disease, or Proportion of HSV-1 Viral Detection in Clinically Diagnosed Genital Herpes**

| Authors (Year) | Year(s) of Data Collection | Country | Study Site | Study Design | Sampling Method | HSV-1 Biological Assay | Population | Sample Size, No. | Proportion of HSV-1 Detection, % |
|---|---|---|---|---|---|---|---|---|---|
| **HSV-1 Detection in Clinically Diagnosed GUD (n = 8)** | | | | | | | | | |
| Chu et al (2006) [73] | NA | Thailand | Hospital | CS | Conv | PCR | Patients with genital ulcers | 26 | 0.0 |
| Chua and Cheong (1995) [80] | 1993 | Singapore | Outpatient clinic | CS | Conv | CF | Male patients with primary genital ulcers | 121 | 8.3 |
| Chua and Cheong (1995) [80] | 1993 | Singapore | Outpatient clinic | CS | Conv | CF | Female patients with primary genital ulcers | 54 | 27.8 |
| Chua and Cheong (1995) [80] | 1993 | Singapore | Outpatient clinic | CS | Conv | CF | Male patients with recurrent genital ulcer | 181 | 1.6 |
| Chua and Cheong (1995) [80] | 1993 | Singapore | Outpatient clinic | CS | Conv | CF | Female patients with recurrent genital ulcers | 24 | 0.0 |
| Hooi et al (2002) [81] | 1990–1999 | Malaysia | Hospital | CS | Conv | IF | Patients attending a university hospital | 102 | 28.4 |
| Hooi et al (2002) [81] | 1990–1999 | Malaysia | Outpatient clinic | CS | Conv | IF | Patients attending an STD clinic | 204 | 3.4 |
| Thirumoorthy et al (1986) [82] | 1984 | Singapore | Outpatient clinic | CS | Conv | IF | Male patients with penile ulcers | 80 | 0.0 |
| **HSV-1 Detection in Clinically Diagnosed Genital Herpes (n = 24)** | | | | | | | | | |
| Cheong et al (1990) [83] | 1986–1987 | Singapore | Hospital | CS | Conv | IF | First genital herpes episode | 62 | 33.9 |
| Chiam et al (2010) [84] | 1982–2008 | Malaysia | Hospital | CS | Conv | DFA | Malaysian patients | 49 | 61.2 |
| Chiam et al (2010) [84] | 1982–2008 | Malaysia | Hospital | CS | Conv | DFA | Indian patients | 36 | 50.0 |
| Chiam et al (2010) [84] | 1982–2008 | Malaysia | Hospital | CS | Conv | DFA | Chinese patients | 30 | 6.7 |
| Chio et al (2015) [46] | 2014 | Singapore | Outpatient clinic | CS | Conv | PCR | Patients with genital herpes | 193 | 13.9 |
| Chua and Cheong (1995) [80] | 1993 | Singapore | Outpatient clinic | CS | Conv | CF | Male patients with primary genital herpes | 98 | 10.2 |

**Table 4. Continued**

| Authors (Year) | Year(s) of Data Collection | Country | Study Site | Study Design | Sampling Method | HSV-1 Biological Assay | Population | Sample Size, No. | Proportion of HSV-1 Detection, % |
|---|---|---|---|---|---|---|---|---|---|
| Chua and Cheong (1995) [80] | 1993 | Singapore | Outpatient clinic | CS | Conv | CF | Female patients with primary genital herpes | 52 | 28.9 |
| Chua and Cheong (1995) [80] | 1993 | Singapore | Outpatient clinic | CS | Conv | CF | Male patients with recurrent genital herpes | 116 | 2.5 |
| Chua and Cheong (1995) [80] | 1993 | Singapore | Outpatient clinic | CS | Conv | CF | Female patients with recurrent genital herpes | 19 | 0.0 |
| Doraisingham et al (1987) [85] | 1984–1986 | Singapore | Hospital | CS | Conv | IF | Genital lesions positive for HSV | 215 | 21.4 |
| Doraisingham et al (1987) [85] | 1984–1986 | Singapore | Hospital | CS | Conv | IF | Genital HSV isolates | 49 | 32.7 |
| Hooi et al (2002) [81] | 1990–1999 | Malaysia | Hospital | CS | Conv | IF | Patients attending a university hospital | 55 | 52.7 |
| Hooi et al (2002) [81] | 1990–1999 | Malaysia | Outpatient clinic | CS | Conv | IF | Patients attending an STD clinic | 165 | 4.2 |
| Ishiguro et al (1982) [86] | 1975–1978 | Japan | Outpatient clinic | CS | Conv | Nab | Patients with genital herpes | 13 | 53.8 |
| Jacob et al (1989) [87] | 1983–1986 | India | Outpatient clinic | CS | Conv | IF | Patient with primary genital herpes | 10 | 10.0 |
| Jacob et al (1989) [87] | 1983–1986 | India | Outpatient clinic | CS | Conv | IF | Patient with recurrent genital herpes | 42 | 0.0 |
| Kao et al (1991) [88] | 1981–1990 | Taiwan | Hospital | CS | Conv | IF | Genital HSV isolates in men | 53 | 0.0 |
| Kao et al (1991) [88] | 1981–1990 | Taiwan | Hospital | CS | Conv | IF | Genital HSV isolates in women | 96[a] | 9.4 |
| Kawana et al (1982) [47] | NA | Japan | Outpatient clinic | CS | Conv | Nab | Patients with primary genital herpes | 50 | 62.0 |
| Kawana et al (1982) [47] | NA | Japan | Outpatient clinic | CS | Conv | Nab | Patients with recurrent genital herpes | 49 | 10.2 |
| Puthavathana et al (1998) [89] | 1994–1996 | Thailand | Hospital | CS | Conv | IF | Women with genital herpes | 75 | 18.7 |
| Sen et al (2008) [90] | 1996–2006 | Singapore | Outpatient clinic | CS | Conv | PCR | Patients with genital herpes | 13 | 53.8 |
| Theng and Chan (2004) [91] | 2001 | Singapore | Outpatient clinic | CS | Conv | IF | First genital herpes episode | 114 | 19.3 |
| Theng and Chan (2004) [91] | 2001 | Singapore | Outpatient clinic | CS | Conv | IF | Recurrent genital herpes episode | 127 | 4.7 |

Abbreviations: CF, complement fixation; Conv, convenience; CS, cross-sectional; DFA, direct fluorescent assay; GUD, genital ulcer disease; HSV-1, herpes simplex virus type 1; IF, immunofluorescence; NA, not available; Nab, neutralization antibody test; PCR, polymerase chain reaction; STD, sexually transmitted disease.

[a]This population included a mix of patients with clinically diagnosed genital herpes and patients suspected of a viral infection from whom cervical swab samples were collected (n = 47).

As many as 50% of youth reach sexual debut with no protective antibodies against HSV-1, and thus potentially at risk of sexual acquisition. Remarkably, based on virological diagnosis studies, there was a substantial role for HSV-1 in genital herpes and GUD: 19% of genital herpes cases were due to HSV-1 (as opposed to HSV-2), and 6% of GUD cases. These findings suggest an apparently ongoing HSV-1 epidemiological transition, as in Western countries [5, 7, 26], possibly mediated by Asia's rapid socioeconomic modernization.

The seroprevalence of HSV-1 varied somewhat by country income but was highest in upper-middle-income countries (including China). The weaker socioeconomic association may relate to recent modernization, say for China, and to unexplained low seroprevalence in populations on the Indian

**Table 5. Pooled Proportions in Asia of Herpes Simplex Virus Type 1 Viral Detection in Clinically Diagnosed Genital Ulcer Disease or Genital Herpes**

| Population Type | Measures, Total No. | Samples, Total No. | Proportion of HSV-1 Detection, % | | Pooled Proportion of HSV-1 Detection Mean (95% CI), % | Heterogeneity Measure[a] | | |
|---|---|---|---|---|---|---|---|---|
| | | | Range | Median | | Q (*P* Value) | $I^2$ (95% CI), % | Prediction Interval, % |
| Patients with clinically diagnosed GUD | 8 | 792 | 0.0–28.4 | 2.5 | 5.6 (.8–13.6) | 91.1 (<.001) | 92.3 (87.2–95.4) | 0.0–43.7 |
| Patients with clinically diagnosed genital herpes | 24 | 1781 | 0.0–62.0 | 16.3 | 18.8 (12.0–26.7) | 330.4 (<.001) | 93.0 (90.8–94.7) | 0.0–62.9 |

Abbreviations: CI, confidence interval; GUD, genital ulcer disease; HSV-1, herpes simplex virus type 1.

[a]The Cochran *Q* statistic is a measure assessing the existence of heterogeneity in effect size; $I^2$, a measure that assesses the magnitude of between-study variation due to actual differences in effect size across studies rather than chance; and prediction interval, a measure that estimates the distribution (95% interval) of true effect sizes around the estimated mean.

subcontinent [92]; seroprevalence in adults was 93% in China but only 67% in India.

Strikingly, there were no differences in seroprevalence by sex, population type, assay type, sampling method, or sample size. Age was the only major predictor of seroprevalence. This speaks for how HSV-1 is a general-population infection that permeates all strata of society. This also demonstrates the ease of sampling a representative sample to measure seroprevalence, provided that the sample age distribution is representative of the underlying population age distribution.

Although seroprevalence was much higher in older than in younger cohorts, there was no evidence for a recent temporal decline in seroprevalence. This finding may be explained by an earlier transition toward lower seroprevalence, or (speculatively) by a demographic effect. HSV-1 seroincidence could be declining, but with rapidly declining fertility and increasing life expectancy rates, the overall seroprevalence could remain stable, masking the decline in seroincidence. Findings from community-based Japanese study (performed over 2 decades) seem to support such a conjecture; seroprevalence in persons aged 20–49 years declined by nearly 10% every decade [59].

Our study has limitations. Data availability varied by country and no data were identified for 13 mostly lower-income countries and territories (Bhutan, Brunei, Cambodia, Hong Kong, Laos, Macau, Mongolia, Myanmar, Nepal, Papua New Guinea, North Korea, Tibet, and Timor-Leste). Seroprevalence showed high heterogeneity, but examined predictors explained only 34% of the variation. Different diagnostic assays were used across studies, but assays may vary by sensitivity and specificity (eg, ELISA vs Western blot) [43, 44], as well as in the differential effect of HSV-2 antibodies—particularly for the classic "relative reactivity" methods [93–95]. However, no evidence was found for differences in seroprevalence by assay type (Table 3).

Similarly, various diagnostic assays were used for viral detection (immunofluorescence, direct fluorescent assay, neutralization antibody test, and nucleic acid amplification test), but these may differ in HSV-1 detection [96]. HSV-1 detection in GUD and genital herpes varied across studies, possibly reflecting variation in the underlying epidemiology. For example, a Malaysian study found >50% HSV-1 detection rates in genital herpes in a university hospital, but <5% in a sexually transmitted disease clinic [81], probably reflecting differences in the populations attending these facilities (general vs sexual high-risk population).

In conclusion, HSV-1 seroprevalence remains high in Asia, with 50% of children and 75% of adults testing seropositive. However, there seems to be an epidemiological transition, with lower seroprevalence in younger cohorts. Close to 50% of youth reach sexual debut uninfected and potentially at risk of sexual acquisition. HSV-1 is possibly playing an influential role as an STI, explaining a fraction of GUD and genital herpes diagnoses. These findings demonstrate the importance of seroprevalence monitoring and GUD/genital herpes etiological surveillance, as well as expansion of HSV-1 epidemiology research in different age groups and countries; for half of countries, no data were available. These findings also highlight the need to accelerate HSV-1 vaccine development to control transmission and prevent associated clinical and psychosocial disease burden.

## Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

## Notes

***Author contributions.*** L. K. and M. H. conducted the systematic search, screening, data extraction, and data analysis. R. O. contributed to data extraction. G. S. contributed to the statistical analysis. H. C. provided support in study design and data extraction. L. J. A.-R. conceived the study and supervised study conduct and analyses. L. K., M. H., and L.

J. A.-R. wrote the first draft of the manuscript. All authors have read and approved the final manuscript.

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