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MAJOR ARTICLE

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

Lara Khadr,[1,2,a] Manale Harfouche,[1,a] Ryosuke Omori,[3] Guido Schwarzer,[4] Hiam Chemaitelly,[1] and Laith J. Abu-Raddad[1,5,6]

[1]Infectious Disease Epidemiology Group, Weill Cornell Medicine–Qatar, Cornell University, Qatar Foundation–Education City, Doha; [2]Department of Epidemiology, University of Michigan School of Public Health, Ann Arbor; [3]Division of Bioinformatics, Research Center for Zoonosis Control, Hokkaido University, Sapporo, Japan; [4]Institute of Medical Biometry and Statistics, Faculty of Medicine and Medical Center, University of Freiburg, Germany; [5]Department of Healthcare Policy and Research, Weill Cornell Medicine, Cornell University, New York, New York; and [6]College of Health and Life Sciences, Hamad bin Khalifa University, Doha, Qatar

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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[a]L. K. and M. H. contributed equally to this work.

Correspondence: L. J. Abu-Raddad, Infectious Disease Epidemiology Group, Weill Cornell Medicine–Qatar, Qatar Foundation–Education City, PO Box 24144, Doha, Qatar (lja2002@qatar-med.cornell.edu).

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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,

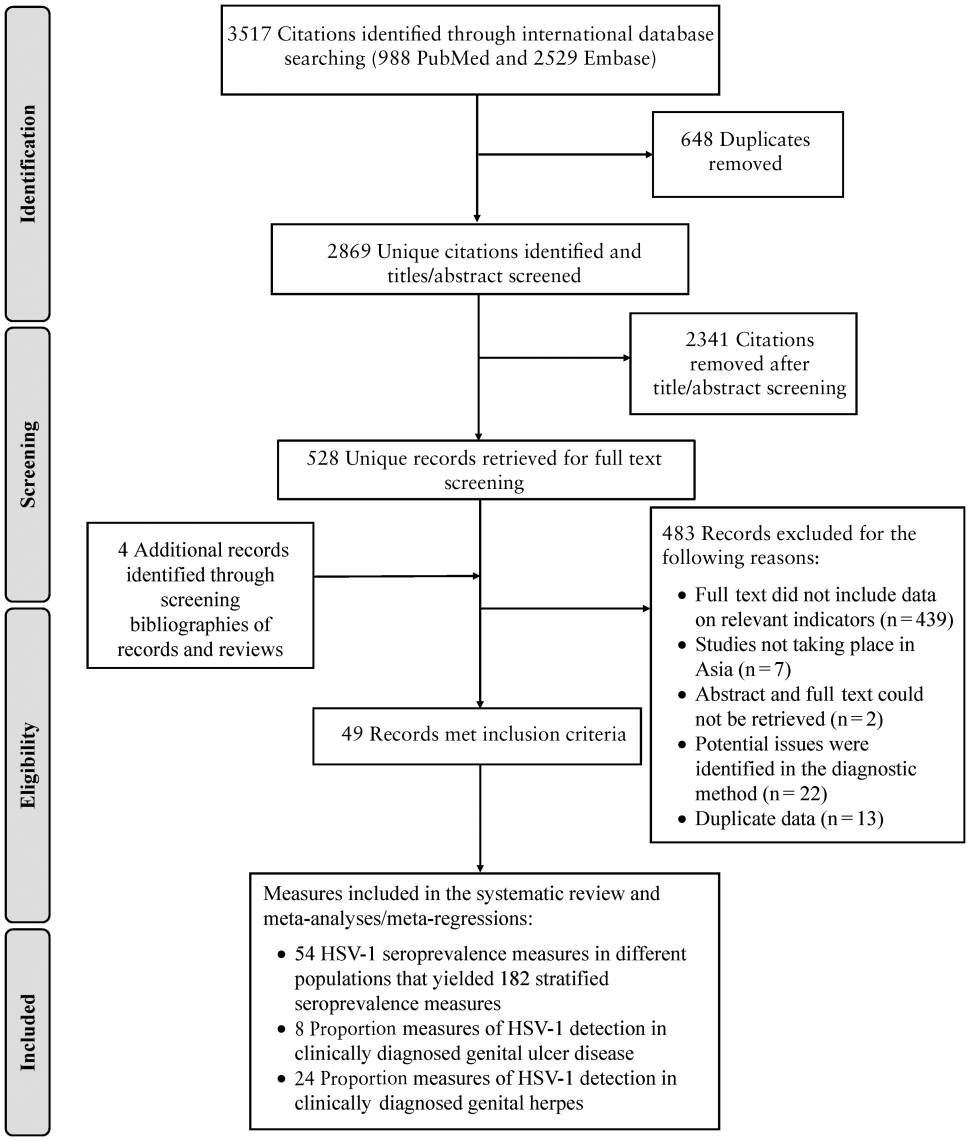

Figure 1. Flow chart of article selection for the systematic review of herpes simplex virus type 1 (HSV-1) in Asia, as adapted from the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) 2009 guidelines [32].

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 immunoassay	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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Disclaimer. The findings reported herein are solely the responsibility of the authors.

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