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Herpes simplex virus type 1 epidemiology in Africa: Systematic review, meta-analyses, and meta-regressions

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SUMMARY

Objective: To assess herpes simplex virus type 1 (HSV-1) epidemiology in Africa.
Methods: This systematic review was conducted per the Cochrane Collaboration guidelines. Findings were reported following the PRISMA guidelines. Research questions were addressed using random-effects meta-analyses and meta-regressions.
Results: Forty-three overall (and 69 stratified) HSV-1 seroprevalence measures, and 18 and eight proportions of HSV-1 viral detection in genital ulcer disease (GUD) and in genital herpes, respectively, were extracted from 37 reports. Pooled mean seroprevalence was 67.1% (95% confidence interval (CI): 54.7–78.5%) in children, and 96.2% (95% CI: 95.0–97.3%) in adults. Across age groups, pooled mean was 44.4% (95% CI: 29.9–59.3%) in ≤5 years-old, 85.6% (95% CI: 81.0–89.6%) in 6–15 years-old, 93.3% (95% CI: 89.2–96.6%) in 16–25 years-old, and 93.8% (95% CI: 84.6–99.4%) in >25 years-old. Age explained 78.8% of seroprevalence variation. Pooled mean proportion of HSV-1 detection was 0.4% (95% CI: 0.0–1.5%) in GUD, and 1.2% (95% CI: 0.0–4.0%) in genital herpes.
Conclusions: HSV-1 is universally prevalent in Africa, at higher levels than other regions, with no evidence for declines in seroprevalence in recent decades. Nearly every person acquires the infection in childhood through oral-to-oral transmission, before sexual debut. Sexual oral-to-genital and genital-to-genital transmission appear very limited.

Introduction

Herpes simplex virus type 1 (HSV-1) is endemic worldwide.[1] The virus is predominantly acquired and transmitted orally leading to a lifelong infection.[2,3] Infection with HSV-1 is the underlying cause of multiple diseases, though the most common clinical manifestation is that of oral herpes.[2–4] HSV-1 acquisition usually occurs in childhood, well before sexual debut, where proximity to parents and other family members, as well as to peers, increases the likelihood of exposure and transmission.[2,4] Development of an HSV-1 vaccine is a focus of ongoing international multi-sectorial effort, led in part by the World Health Organization (WHO).[5,6]

Mounting evidence from Western countries,[2,7–14] Asia,[15] and Latin America and the Caribbean[16] suggests that HSV-1 is increasingly acquired genitally, and less so orally. Indeed, in several countries, HSV-1 is already the primary cause of genital herpes.[2,17–21] This remarkable epidemiological transition appears to be driven by a progressively decreasing exposure in childhood—a large fraction of youth are first exposed to the virus genitally through oral sex.[2,14,21] The extent to which this transition is occurring globally, beyond Western, Asian, and Latin American and Caribbean countries, remains unknown.

This study aimed to provide a comprehensive understanding of HSV-1 epidemiology in Africa by systematically reviewing and synthesizing available epidemiological data on HSV-1 infection, estimating HSV-1 antibody prevalence (seroprevalence) levels in different population strata, assessing associations with seroprevalence, and estimating the role of HSV-1 in the etiology of clinically-diagnosed genital ulcer disease (GUD) and clinically-diagnosed genital herpes.

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Materials and methods

The methodology for this study follows and adapts that developed recently to investigate HSV-1 epidemiology in Asia.[15]

Data sources and search strategy

The systematic review was conducted with guidance of the Cochrane Collaboration Handbook.[22] The findings were reported following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (checklist in Supplementary Table 1).[23]

The systematic literature search was performed up to July 30, 2018, in PubMed, Embase, and African Index Medicus databases. The search strategies included exploded MeSH/Emtree terms as well as broad keywords and were not restricted by language or year (Supplementary Box 1). The definition for the African region included 45 countries, and was based on the WHO definition for this region.[24] Included countries are found in Supplementary Box 2.

Study selection and eligibility criteria

Study selection was conducted in Endnote, a reference manager. Screening of studies was performed in four stages: duplicate reports identification and removal; title and abstract screening for relevant and potentially relevant reports; full-text screening for relevant and potentially relevant reports; and screening of bibliographies of relevant reports and reviews for any additional relevant publications.

Inclusion criteria encompassed any report documenting primary data on any of the following HSV-1 epidemiological outcome measures: (1) HSV-1 seroprevalence, (2) proportion of HSV-1 detection in GUD, or (3) proportion of HSV-1 detection in genital herpes. Only HSV-1 seroprevalence measures based on quality type-specific (glycoprotein G-based) assays were included. Measures of HSV-1 detection in GUD or genital herpes were based on detecting, isolating, and typing of the virus using genital ulcer swabs collected from clinically-diagnosed patients with GUD and/or genital herpes. Only measures including at least 10 participants were considered.

The following types of records were excluded: case reports, case series, reviews, editorials, letters-to-editors, commentaries, qualitative studies, and animal studies. Studies reporting HSV-1 seroprevalence in infants (<3 months of age) were also excluded because of maternal antibodies.

In this article, a "report" is a publication comprising a relevant HSV-1 outcome measure. A "study" refers to all details of one specific outcome measure. One report may include several studies. Multiple reports of the same dataset were identified as duplicates and deemed as one study.

Data extraction and synthesis

Data from relevant reports were double extracted by MH and HC. Among the extracted variables are publication details, study design and sampling methodology, study population characteristics, and HSV-1 epidemiological outcome measures. A detailed list of extracted variables is in Supplementary Box 3.

Extracted HSV-1 outcome measures were replaced by their strata, whenever the stratum subsample size was ≥10. The stratification hierarchy for HSV-1 seroprevalence was population type, age bracket (≤15 years of age (children) versus >15 years of age (adults)), and age group (≤5, 6–15, 16–25, and >25 years of age). These age stratifications were informed by epidemiological relevance and actual available extracted data.

The population-type stratification was based on the following criteria: (1) healthy general populations including populations with no or minor disease conditions; (2) clinical populations including populations with serious disease conditions or morbidities; and (3) other populations including mixed-health status populations and populations with potentially different (or unknown) exposure level to HSV-1 infection than the other two categories (HIV patients and female sex workers, among others).

The stratification hierarchy for the proportions of HSV-1 detection in GUD and in genital herpes included only primary versus recurrent episode and study site (sexually transmitted infection (STI) clinic versus hospital).

Meta-analyses

The pooled mean HSV-1 seroprevalence was estimated, for each population type, age bracket, and age group, using DerSimonian-Laird random-effects models with inverse variance weighting,[25] provided ≥3 outcome measures for each stratum were available. This meta-analysis methodology takes into account sampling variation and heterogeneity in effect sizes (here HSV-1 seroprevalence). The variance of each seroprevalence measure was stabilized using the Freeman-Tukey arcsine square-root transformation.[26] The same statistical method was applied to estimate the pooled mean proportions of HSV-1 detection in GUD and in genital herpes.

Existence of heterogeneity was assessed using the Cochran's Q statistic (p-value <0.1 indicated strong evidence for heterogeneity).[25,27] Extent of between-study variation, due to true difference in prevalence across studies and not chance, was calculated using the I^2 measure.[25] Distribution of true prevalence measures around the pooled mean was estimated using prediction intervals.[25,28]

Meta-analyses were conducted in R version 3.4.1[29] using the meta package.[30]

Meta-regressions

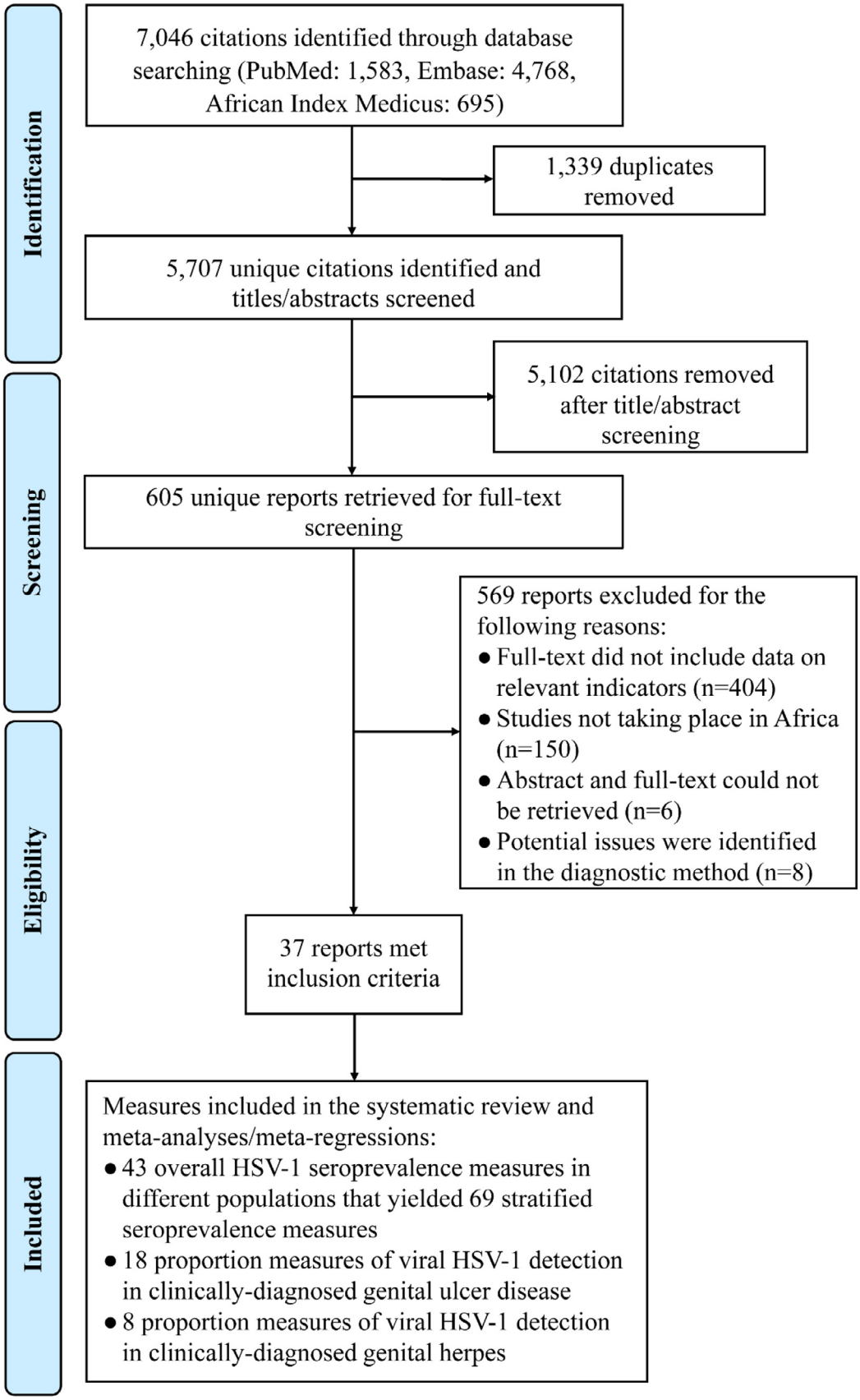
Factors associated with higher HSV-1 seroprevalence and sources of between-study heterogeneity were investigated using random-effects meta-regression analyses (by regressing the log-transformed seroprevalence proportions). In the univariable analyses, variables with a p-value ≤0.1 qualified for inclusion in the multivariable analyses. In the multivariable analyses, a p-value ≤0.05 constituted strong evidence for an association.

The investigated factors were set *a priori* and included: age bracket, age group, assay type (Western blot, enzyme-linked immunosorbent assay (ELISA), and neutralizing antibodies assay (NAb)), country's income, population type, response rate (≥80% versus otherwise), sample size (<100 versus ≥100), sampling methodology (probability-based sampling versus non-probability sampling), sex, year of data collection, and year of publication.

The country's income variable followed the World Bank classification.[31] Accordingly, countries with available HSV-1 data were classified as: low-income countries (Central African Republic, Eritrea, Ethiopia, Mali, Uganda, United Republic of Tanzania, and Zimbabwe), lower-middle-income countries (Kenya, Lesotho, and Nigeria), upper-middle-income countries (South Africa), and mixed for studies including samples from different countries.

For the year of data collection, missing values were imputed using the year of publication adjusted for the median difference with the year of data collection, for studies with available data.

Meta-regressions were conducted in Stata/SE version 13[32] using the metareg package.[33]



Abbreviations: HSV-1 = Herpes simplex virus type 1.

Fig. 1. Flow chart of article selection for the systematic review of HSV-1 infection in Africa, per the PRISMA guidelines.[23]

Table 1
Studies reporting HSV-1 seroprevalence in Africa.

Author, year	Year(s) of data collection	Country	Study site	Study design	Sampling methodology	Population	HSV-1 serological assay	Sample size	HSV-1 seroprevalence (%)
Healthy children populations (*n* = 16)									
Ghebrekian, 1999[45]	1995–95	Eritrea	Outpatient clinic	CS	Conv	5–12 years old children	ELISA	84	97.0
Ghebrekian, 1999[45]	1995–95	Eritrea	Outpatient clinic	CS	Conv	1–5 years old children	ELISA	54	59.0
Johnson, 1981[46]	–	Nigeria	Hospital	CC[a]	Conv	1–4 years old children	NAb	64	26.0
Kasubi, 2006[47]	–	Tanzania	Outpatient clinic	CS	Conv	1–4 years old children	ELISA	101	73.0
Kasubi, 2006[47]	–	Tanzania	Outpatient clinic	CS	Conv	5–8 years old children	ELISA	111	83.8
Kasubi, 2006[47]	–	Tanzania	Outpatient clinic	CS	Conv	9–12 years old children	ELISA	123	85.4
LeGoff, 2011[48]	–	Central African Republic	Outpatient clinic	CS	Conv	<5 years old children	ELISA	73	58.9
LeGoff, 2011[48]	–	Central African Republic	Outpatient clinic	CS	Conv	6–10 years old children	ELISA	70	88.0
LeGoff, 2011[48]	–	Central African Republic	Outpatient clinic	CS	Conv	11–15 years old children	ELISA	39	90.0
Sogbetun, 1979[49]	–	Nigeria	Outpatient clinic	CS	Conv	4–11 months old babies	NAb	29	6.9
Sogbetun, 1979[49]	–	Nigeria	Community	CS	Conv	1–2 years old children	NAb	64	26.6
Sogbetun, 1979[49]	–	Nigeria	Community	CS	Conv	3–5 years old children	NAb	64	56.3
Sogbetun, 1979[49]	–	Nigeria	Community	CS	Conv	6–10 years old children	NAb	49	75.5
Sogbetun, 1979[49]	–	Nigeria	Community	CS	Conv	11–15 years old children	NAb	82	82.9
Wagner, 1994[50]	1989	Uganda	Community	CS	Conv	<9 years old children	WB	14	78.6
Wagner, 1994[50]	1989	Uganda	Community	CS	Conv	10–14 years old children	WB	31	90.3
Healthy adult populations (*n* = 28)									
Ashley-Morrow, 2004[34]	2000–01	Nigeria	Community	CS	Conv	>15 years old women	WB	100	100
Ghebrekian, 1999[45]	1995–95	Eritrea	Community	CS	Conv	Guerilla fighters	ELISA	73	88.0
Ghebrekian, 1999[45]	1995–95	Eritrea	Community	CS	RS	Truck drivers	ELISA	53	85.0
Ghebrekian, 1999[45]	1995–95	Eritrea	Community	CS	RS	Port workers	ELISA	48	92.0
Ghebrekian, 1999[45]	1995–95	Eritrea	Outpatient clinic	CS	Conv	Rashaida tribe individuals	ELISA	45	84.0
Ghebrekian, 1999[45]	1995–95	Eritrea	Outpatient clinic	CS	Conv	Pregnant women	ELISA	113	97.0
Gwanzura, 1998[51]	–	Zimbabwe	Community	CS	Conv	Male factory workers	WB	191	100
Hogrefe, 2002[52]	1989	Uganda	Community	CS	RS	Healthy women	WB	227	100
Hogrefe, 2002[52]	–	South Africa	Community	CS	RS	Healthy individuals	WB	150	89.0
Kasubi, 2006[47]	–	Tanzania	Outpatient clinic	CS	Conv	17–20 years old adults	ELISA	130	92.0
LeGoff, 2011[48]	–	Central African Republic	Outpatient clinic	CS	Conv	16–17 years old adults	ELISA	18	100
Leutscher, 2005[53]	2002	Madagascar	Community	CS	Conv	Healthy women	WB	333	95.0
Leutscher, 2005[53]	2002	Madagascar	Community	CS	Conv	Healthy men	WB	310	98.0
Marrazzo, 2013[54]	2009–11	South Africa, Uganda, Zimbabwe	Community	RCT[b]	Conv	Healthy women	ELISA	4996	95.0
Mihret, 2002[55]	1996–96	Ethiopia	Community	CS	Conv	>15 years old women	WB	243	94.7
Mihret, 2002[55]	1996–96	Ethiopia	Community	CS	Conv	>15 years old men	WB	263	92.8
Nakku-joloba, 2014[56]	2004–04	Uganda	Community	CS	MSC	15–65 years old adults	ELISA	1124	98.0
Neal, 2011[57]	–	Uganda	Community	CS	Conv	Healthy adults	WB	415	93.0
Patnaik, 2007[58]	1985–97	Mali	Community	CS	Conv	Middle-aged women	WB	90	93.3
Perti, 2014[59]	–	South Africa	Hospital	CS	Conv	Pregnant women	WB	255	99.2

(*continued on next page*)

Table 1 (*continued*)

Author, year	Year(s) of data collection	Country	Study site	Study design	Sampling methodology	Population	HSV-1 serological assay	Sample size	HSV-1 seroprevalence (%)
Sogbetun, 1979[49]	–	Nigeria	Community	CS	Conv	16–20 years old adults	NAb	82	70.7
Tedla, 2011[60]	2002	Ethiopia	Community	CC[a]	RS	15–49 years old adults	ELISA	80	100
Wagner, 1994[50]	1989	Uganda	Community	CS	Conv	15–19 years old adults	WB	39	94.9
Wagner, 1994[50]	1989	Uganda	Community	CS	Conv	20–24 years old adults	WB	31	93.5
Wagner, 1994[50]	1989	Uganda	Community	CS	Conv	25–29 years old adults	WB	29	96.6
Wagner, 1994[50]	1989	Uganda	Community	CS	Conv	30–34 years old adults	WB	17	100
Wagner, 1994[50]	1989	Uganda	Community	CS	Conv	35–39 years old adults	WB	16	93.8
Wagner, 1994[50]	1989	Uganda	Community	CS	Conv	>40 years old adults	WB	83	84.3
Healthy age-mixed populations ($n=1$)									
Kasubi, 2006[47]	–	Tanzania	Outpatient clinic	CS	Conv	13–16 years old children	ELISA	100	84.0
Clinical children populations ($n=2$)									
Johnson, 1981[46]	–	Nigeria	Hospital	CC[a]	Conv	Children with marasmus	NAb	16	44.0
Johnson, 1981[46]	–	Nigeria	Hospital	CC[a]	Conv	Children with kwashiorkor	NAb	37	51.0
Clinical adult populations ($n=12$)									
Chen, 2000[61]	1993–94	South Africa	Outpatient clinic	CS	Conv	Men with GUD	WB	558	98.2
Chen, 2000[61]	1993–94	South Africa	Outpatient clinic	CS	Conv	Men with urethritis	WB	603	98.7
Hogrefe, 2002[52]	–	Zimbabwe	Outpatient clinic	CS	RS	Women in an STD clinic	WB	174	95.0
LeGoff, 2008[62]	–	Ghana, Central African Republic	Outpatient clinic	CS	Conv	Women with GUD	ELISA	25	100
Mbopi-keou, 2000[63]	–	Central African Republic	Outpatient clinic	CS	Conv	Women in an STD clinic	ELISA	300	99.0
Morse, 1997[64]	1993–94	Lesotho	Hospital	CS	Conv	Men with GUD	WB	47	91.5
Morse, 1997[64]	1993–94	Lesotho	Hospital	CS	Conv	Women with GUD	WB	16	100
Phipps, 2016[65]	2011–12	Uganda	Hospital	CS	Conv	Men with HSV-2	WB	11	91.0
Phipps, 2016[65]	2011–12	Uganda	Hospital	CS	Conv	Women with HSV-2	WB	28	100
Suntoke, 2009[66]	2002–06	Uganda	Outpatient clinic	CS	Conv	Patients with GUD	WB	91	88.0
Tedla, 2011[60]	2002	Ethiopia	Community	CC[a]	Conv	Patients with schizophrenia	ELISA	216	98.6
Tedla, 2011[60]	2002	Ethiopia	Community	CC[a]	Conv	Patients with bipolar disorder	ELISA	199	96.0
Other populations ($n=10$)									
Ghebrekian, 1999[45]	1995–95	Eritrea	Outpatient clinic	CS	Conv	Female sex workers	ELISA	107	89.0
Gwanzura, 1998[51]	–	Zimbabwe	Community	CS	Conv	HIV positive men	WB	224	100
Hogrefe, 2002[52]	–	Kenya	Outpatient clinic	RCT[b]	RS	HIV positive and HIV negative women	WB	235	95.0
LeGoff, 2010[67]	–	Central African Republic	Outpatient clinic	CS	Conv	HIV positive patients	ELISA	51	90.2
Morse, 1997[64]	1993–94	Lesotho	Hospital	CS	Conv	HIV positive men	WB	21	100
Morse, 1997[64]	1993–94	Lesotho	Hospital	CS	Conv	HIV positive women	WB	15	93.3
Mostad, 2000[68]	1994–96	Kenya	Outpatient clinic	CS	Conv	HIV positive women	EIA	314	94.3
Perti, 2014[59]	–	South Africa	Hospital	CS	Conv	HIV positive women	WB	132	96.2
Phipps, 2016[65]	2011–12	Uganda	Hospital	CS	Conv	HIV positive men	WB	20	100
Phipps, 2016[65]	2011–12	Uganda	Hospital	CS	Conv	HIV positive women	WB	34	91.0

[a] The original study design of the study is case-control. The included seroprevalence measures are those for each of cases and controls, separately. The population type classification was assigned based on the actual population type for each of cases and controls, separately.

[b] The original study design of the study is randomized clinical trial. The included seroprevalence measures are those for the baseline measures at the onset of the trial, before start of follow-up.

Abbreviations: Conv = Convenience, CS = Cross-sectional, CC = Case-control, ELISA = Enzyme-linked immunosorbent type-specific assay, GUD = Genital ulcer disease, HIV = Human immunodeficiency virus, HSV-1 = Herpes simplex virus type 1, MSC = Multistage cluster sampling, NAb = Neutralizing antibody, RCT = Randomized-controlled trial, RS = Random sampling, STD = Sexually transmitted disease, WB = Western blot.

Table 2
Pooled mean estimates for HSV-1 seroprevalence in different populations in Africa.

Population type	Outcome measures	Samples	HSV-1 seroprevalence		Pooled mean HSV-1 seroprevalence	Heterogeneity measures		
	Total n	Total N	Range	Median	Mean (95% CI)	Q[a] (*p*-value)	I^2[b] (%) (95% CI)	Prediction[c] Interval (%)
Healthy general populations								
Children	16	1052	6.9–97.0	71.5	69.2 (56.1–81.0)	286.0 ($p<0.0001$)	94.8 (92.8–96.2)	14.2–100
Adults	28	9554	18.0–100	94.3	95.5 (93.6–97.1)	235.7 ($p<0.0001$)	88.5 (84.6–91.5)	84.2–100
Age-mixed	1[d]	100	–	–	84.0 (75.3–90.7)	–	–	–
All healthy general populations	45	10,706	6.9–100	90.3	88.1 (84.3–91.4)	995 ($p<0.0001$)	95.6 (94.7–96.3)	57.6–100
Clinical populations								
Children	2[d]	57	44.0–51.0	47.5	49.1 (35.1–63.2)	–	–	–
Adults	12	2268	88.0–100	98.4	97.8 (96.1–99.2)	36.7 ($p<0.0001$)	70.1 (45.9–83.4)	91.1–100
All clinical populations	14	2321	44.0–100	97.1	94.8 (90.8–97.9)	123.5 ($p<0.0001$)	89.5 (84.1–93.0)	74.5–100
Other populations								
HIV positive patients	8	811	90.2–100	95.3	97.1 (92.8–99.7)	34.2 ($p<0.0001$)	79.5 (60.1–89.5)	79.0–98.7
Female sex workers	1[d]	107	–	–	98.0 (81.2–94.1)	–	–	–
Mixed healthy/clinical adult populations	1[d]	235	–	–	95.0 (91.2–97.3)	–	–	–
Age group								
≤5 years	9	502	6.9–73.0	51.0	44.4 (29.9–59.3)	86.8 ($p<0.0001$)	90.8 (84.8–94.4)	2.9–91.6
5–15 years	4	279	78.6–90.3	84.6	85.6 (81.0–89.6)	1.3 ($p=0.7364$)	0.0 (0.0–63.8)	74.9–93.8
16–25 years	3	200	92.0–94.9	93.5	93.3 (89.2–96.6)	0.2 ($p=0.9259$)	0.0 (0.0–0.0)	56.0–100
>25 years	4	145	84.3–100	95.2	93.8 (84.6–99.4)	6.8 ($p=0.0780$)	56.0 (0.0–85.4)	46.3–100
Age bracket								
All children	18	1105	6.9–97.0	70.0	67.1 (54.7–78.5)	297.7 ($p<0.0001$)	94.3 (92.3–95.8)	13.6–100
All adults	50	12,975	18.0–100	95.0	96.2 (95.0–97.3)	341.2 ($p<0.0001$)	85.6 (81.9–88.6)	86.6–100
All age-mixed	1[d]	100	–	–	84.0 (75.3–90.7)	–	–	–
All studies	**69**	**14,180**	**6.9–100**	**93.0**	**90.8 (88.2–93.0)**	**1213.3 ($p<0.0001$)**	**94.4 (93.5–95.2)**	**65.6–100**

[a] Q: The Cochran's Q statistic is a measure assessing the existence of heterogeneity in pooled outcome measures, here HSV-1 seroprevalence.
[b] I^2: A measure that assesses the magnitude of between-study variation that is due to differences in seroprevalence across studies rather than chance.
[c] Prediction interval: A measure that estimates the distribution (the 95% interval) of true seroprevalence around the estimated pooled mean.
[d] No meta-analysis was done due to small number of studies ($n < 3$).
Abbreviations: CI = Confidence interval, HIV = Human immunodeficiency virus, HSV-1 = Herpes simplex virus type 1.

Quality assessment

In light of established limitations in the sensitivity and specificity of diagnostic assays in assessing HSV-1 serology,[34,35] the quality of the diagnostic method in each study was assessed in consultation with an expert advisor, Professor Rhoda Ashley-Morrow, University of Washington, Seattle.

The quality of studies was further evaluated using the Cochrane approach for the risk of bias (ROB) assessment and precision assessment, for each included seroprevalence measure.[22] *Low* versus *high* ROB was determined using two domains: sampling methodology (probability-based sampling versus non-probability sampling), and response rate (≥80% versus >80%). Studies with missing information for a specific domain were classified as having "unclear" ROB for that domain. *Low* versus *high* precision assessment was based on the number of subjects tested in each study (<100 versus ≥100).

Results

Search results and scope of evidence

Fig. 1 shows the study selection process.[23] The search identified 7046 citations: 1583 from PubMed, 4768 from Embase, and 695 from African Index Medicus. After removing duplicates and title and abstract screening, 605 reports were considered relevant or potentially relevant. Full-text screening yielded 37 reports meeting the inclusion criteria. No additional data were identified by screening the bibliographies of relevant reports and reviews.

Extracted outcome measures included: 43 overall HSV-1 seroprevalence measures including 69 stratified seroprevalence measures, 18 proportions of HSV-1 viral detection in GUD, and eight proportions of HSV-1 viral detection in genital herpes.

Seroprevalence overview

Table 1 describes the included HSV-1 stratified seroprevalence measures. Most measures were based on convenience sampling (number of studies (n) = 67; 97.1%), and were conducted prior to 2010 (n = 52; 75.4%). Across all measures (n = 69), seroprevalence ranged between 6.9% and 100% with a median of 93.0% (Table 2).

In healthy general populations, seroprevalence ranged, for children (n = 16), between 6.9% and 97.0% with a median of 71.5%, and for adults (n = 28), between 18.0% and 100% with a median of 94.3%. In clinical populations, seroprevalence ranged, for children (n = 2), between 44.0% and 51.0% with a median of 47.5%, and for adults (n = 12), between 88.0% and 100% with a median of 98.4%. Summaries for further populations (or subpopulation categories) are shown in Table 2.

Pooled mean estimates for HSV-1 seroprevalence

Table 2 shows the pooled mean estimates for HSV-1 seroprevalence overall, in different populations, and across age groups. The overall pooled mean seroprevalence (across all data points, n = 69) was 90.8% (95% confidence interval (CI): 88.2–93.0%).

In healthy general populations, the pooled mean seroprevalence was 69.2% (n = 16; 95% CI: 56.1–81.0%) in children, and 95.5% (n = 28; 95% CI: 93.6–97.1%) in adults. In clinical populations, the pooled mean seroprevalence was 49.1% (n = 2; 95% CI: 35.1–63.2%) in children, and 97.8% (n = 12; 95% CI: 96.1–99.2%) in adults.

Across age groups, the pooled mean seroprevalence was lowest at 44.4% (n = 9; 95% CI: 29.9–59.3%) in those ≤5 years old, followed by 85.6% (n = 4; 95% CI: 81.0–89.6%) in those 6–15 years old, 93.3% (n = 3; 95% CI: 89.2–96.6%) in those 16–25 years old, and 93.8% (n = 4; 95% CI: 84.6–99.4%) in those >25 years old.

Table 3
Univariable and multivariable meta-regression analyses for HSV-1 seroprevalence in Africa.

		Outcome measures	Samples	Univariable analysis			Multivariable analysis			
		Total n	Total N	*RR* (95%CI)	*p*-value	Adjusted R^2 (%)	Model 1[a]		Model 2[b]	
							ARR (95%CI)	*p*-value	*ARR* (95%CI)	*p*-value
Age bracket	Children	18	1105	1.0	–		1.0	–	–	–
	Adults	50	12,975	1.2 (1.1–1.3)	0.000		1.1 (1.0–1.2)	0.005	–	–
	Age-mixed	1	100	1.1 (0.8–1.4)	0.565	62.4	1.0 (0.8–1.2)	0.956	–	–
Age group	≤5	9	502	1.0	–		–	–	1.0	–
	6–15	4	279	1.5 (1.3–1.7)	0.000		–	–	1.4 (1.2–1.6)	0.000
	15–25	3	200	1.6 (1.4–1.9)	0.000		–	–	1.5 (1.3–1.7)	0.000
	>25	4	145	1.6 (1.4–1.9)	0.000		–	–	1.5 (1.3–1.7)	0.000
	Mixed	49	12,639	1.7 (1.5–1.9)	0.000	78.8	–	–	1.5 (1.3–1.7)	0.000
Assay type	Western blot	39	5271	1.0	–		1.0	–	1.0	–
	ELISA	21	8422	1.0 (0.9–1.0)	0.131		1.0 (0.9–1.0)	0.479	1.0 (0.9–1.0)	0.429
	NAb	9	487	0.7 (0.6–0.8)	0.000	62.7[e]	0.7 (0.6–0.9)	0.002	0.8 (0.7–0.9)	0.000
Country's income	LIC	46	6226	1.0			1.0	–	1.0	–
	LMIC	16	1235	0.9 (0.8–1.0)	0.025		1.0 (0.9–1.1)	0.753	1.0 (1.0–1.1)	0.601
	UMIC	5	1698	1.0 (0.9–1.2)	0.521		1.0 (0.9–1.1)	0.945	1.0 (1.0–1.1)	0.945
	Mixed	2	5021	1.1 (0.8–1.3)	0.600	0.0	1.0 (0.9–1.1)	0.770	1.0 (0.9–1.1)	0.715
Population type	Healthy general populations	45	10,706	1.0	–		–	–	–	–
	Clinical populations	14	2321	1.1 (1.0–1.2)	0.214		–	–	–	–
	Other populations	10	1153	1.1 (1.0–1.2)	0.211	6.0	–	–	–	–
Response rate	≥80	29	9306	1.0	–		–	–	–	–
	Otherwise[c]	40	4874	0.9 (0.9–1.0)	0.284	0.0	–	–	–	–
Sample size[d]	<100	26	1164	1.0	–		–	–	–	–
	≥100	43	13,016	1.0 (0.9–1.1)	0.637	0.0	–	–	–	–
Sampling methodology	Non-probability	63	12,190	1.0	–		–	–	–	–
	Probability-based	6	1990	1.1 (0.9–1.2)	0.320	0.0	–	–	–	–
Sex	Female	18	7510	1.0	–		1.0	–	1.0	
	Male	13	2422	1.0 (0.9–1.1)	0.904		1.0 (0.9–1.1)	0.948	1.0 (1.0–1.0)	0.755
	Mixed	38	4248	0.9 (0.8–1.0)	0.014	20.3[f]	1.0 (0.9–1.1)	0.849	1.0 (0.9–1.0)	0.744
Year of data collection		69	14,180	1.0 (1.0–1.0)	0.002	4.3	–	–	–	–
Year of publication		69	14,180	1.0 (1.0–1.0)	0.001	12.4	1.0 (1.0–1.0)	0.714	1.0 (1.0–1.0)	0.575

[a] Variance explained by the final multivariable model 1 (adjusted R^2) = 68.3%.
[b] Variance explained by the final multivariable model 2 (adjusted R^2) = 84.9%.
[c] Otherwise indicates either response rate not included in the report or response rate was <80%.
[d] Sample size denotes the sample size of each study population found in the original publication.
[e] The high adjusted R^2 was investigated and found to be due to confounding with age. Nearly all studies that used NAb were conducted among children.
[f] The high adjusted R^2 was investigated and found to be due to confounding with age. All studies among children were mixed including both females and males.
Abbreviations: *ARR* = Adjusted risk ratio, ELISA = Enzyme-linked immunosorbent type-specific assay, CI = Confidence interval, HSV-1 = Herpes simplex virus type 1, LIC = Low-income country, LMIC = Lower-middle-income country, NAb = Neutralizing antibody, *RR* = Risk ratio, UMIC = Upper-middle-income country.

Forest plots for the two key meta-analyses (all children and all adults) can be found in Supplementary Fig. 1. Most meta-analyses showed strong evidence for heterogeneity in seroprevalence ($p < 0.1$; Table 2). Heterogeneity was mainly due to true differences in seroprevalence rather than chance ($I^2 > 50\%$). The wide prediction intervals confirmed this heterogeneity. The meta-regressions below investigated the sources of this heterogeneity.

Predictors of HSV-1 seroprevalence and sources of between-study heterogeneity

Results of the univariable and multivariable meta-regressions are in Table 3. Age bracket, age group, assay type, country's income, sex, year of data collection, and year of publication qualified for inclusion in the multivariable analyses ($p < 0.1$). Population type, response rate, sample size, and sampling methodology were not associated with seroprevalence ($p > 0.1$). Age was (by far) the variable that explained most of the heterogeneity in seroprevalence—age bracket explained 62.4% of the variation, and age group explained 78.8% of the variation.

Two multivariable models were conducted to investigate *separately* the effects of age bracket versus age group, as these two age variables are not independent. Moreover, because also of lack of independence, only year of publication variable (as it has more complete data) was included in the multivariable models, instead of the year of data collection variable.

The first model, including age bracket, explained 68.3% of seroprevalence variation. Compared to children, seroprevalence was 1.1-fold (95% CI: 1.0–1.2) higher in adults. Compared to Western blot, seroprevalence was 0.7-fold (95% CI: 0.6–0.9) lower when measured using a NAb assay. No association with each of country's income, sex, and year of publication was found ($p > 0.05$).

The second model, including age group, explained 84.9% of seroprevalence variation, with comparable results to the first model. Compared to those ≤5 years of age, seroprevalence was 1.4-fold (95% CI: 1.2–1.6) higher in those 6–15 years old, and exactly (remarkably) 1.5-fold (95% CI: 1.3–1.7) higher in each of the remaining age groups.

HSV-1 viral detection in genital ulcer disease and in genital herpes

Table 4 describes the extracted measures for the proportions of HSV-1 viral detection in GUD ($n = 18$) and in genital herpes ($n = 8$). In GUD cases, the proportion ranged between 0.0% to 6.0% with a median of 0.0%, while the pooled mean proportion was 0.4% (95% CI: 0.0–1.5%; Table 5). In genital herpes cases, the proportion ranged between 0.0% and 5.0% with a median of 2.4%, while the pooled mean proportion was 1.2% (95% CI: 0.0–4.0%; Table 5). Forest plots are shown in Supplementary Fig. 2. There was strong evidence for heterogeneity, but the prediction intervals were narrow, affirming very small proportions of HSV-1 detection in both GUD and genital herpes.

Table 4
Studies from Africa reporting proportion of HSV-1 viral detection in clinically-diagnosed genital ulcer disease (GUD), or proportion of HSV-1 viral detection in clinically-diagnosed genital herpes.

Author, year	Year(s) of data collection	Country	Study site	Study design	Sampling methodology	Population	HSV-1 biological assay	Sample size	Proportion of HSV-1 detection (%)
HSV-1 detection in clinically-diagnosed GUD ($n = 18$)									
Brankin, 2009[69]	–	Uganda	Outpatient clinic	CS	Conv	HIV positive women	PCR	16	0.0
Brankin, 2009[69]	–	Uganda	Outpatient clinic	CS	Conv	HIV negative women	PCR	24	0.0
Chen, 2000[61]	–	South Africa	Outpatient clinic	CS	Conv	Men attending different STI clinics	PCR	538	0.0
Gray, 2009[70]	–	Uganda	Outpatient clinic	CS	Conv	Circumcised men	PCR	25	0.0
Gray, 2009[70]	–	Uganda	Outpatient clinic	CS	Conv	Uncircumcised Men	PCR	56	0.0
Kamya, 1995[71]	1990–91	Uganda	Outpatient clinic	CS	Conv	Patients with GUD	IFA	98	3.1
Kularatne, 2018[72]	2007–15	South Africa	Outpatient clinic	CS	Conv	Patients attending a health care center	PCR	771	0.0
Lewis, 2012[73]	2005–06	South Africa	Outpatient clinic	RCT[a]	Conv	Men with GUD	PCR	610	3.1
Makasa, 2012[74]	2010–10	Zambia	Outpatient clinic	CS	Conv	Men with GUD	PCR	100	0.0
Makasa, 2012[74]	2010–10	Zambia	Outpatient clinic	CS	Conv	Women with GUD	PCR	100	1.0
Mungati, 2018[75]	2014–15	Zimbabwe	Outpatient clinic	CS	Conv	Patients attending different STI clinics	PCR	200	0.5
Mwansasu, 2002[76]	2002	Tanzania	Outpatient clinic	CS	Conv	Men attending a STI clinic	PCR	51	0.0
Mwansasu, 2002[76]	2002	Tanzania	Outpatient clinic	CS	Conv	Women attending a STI clinic	PCR	19	0.0
Nilsen, 2007[77]	1999–01	Tanzania	Outpatient clinic	CS	Conv	Patients with GUD	PCR	301	6.0
Paz-Bailey, 2005[78]	2001–02	Bostwana	Outpatient clinic	CS	Conv	Patients with GUD	PCR	137	0.0
Suntoke, 2009[66]	2002–06	Uganda	Outpatient clinic	CS	Conv	Men with GUD	PCR	50	6.0
Suntoke, 2009[66]	2002–06	Uganda	Outpatient clinic	CS	Conv	Women with GUD	PCR	50	0.0
Vandepitte, 2011[79]	2008–09	Uganda	Outpatient clinic	CS	Conv	Female sex workers with GUD	PCR	62	0.0
HSV-1 detection in clinically-diagnosed genital herpes ($n = 8$)									
Chen, 2000[61]	–	South Africa	Outpatient clinic	CS	Conv	Men attending different STI clinics	PCR	193	0.0
Kularatne, 2018[72]	2007–15	South Africa	Outpatient clinic	CS	Conv	Patients attending a health care center	PCR	468	0.0
Lai, 2003[80]	1993–94	South Africa	Outpatient clinic	CS	Conv	Men with genital herpes	PCR	14	0.0
Lai, 2003[80]	1998	South Africa	Outpatient clinic	CS	Conv	Men with genital herpes	PCR	57	3.5
Lewis, 2012[73]	2005–06	South Africa	Outpatient clinic	RCT[a]	Conv	Men with genital herpes	PCR	448	4.2
Morse, 1997[64]	1993–94	Lesotho	Hospital	CS	Conv	Patients with genital herpes	PCR	20	5.0
Mungati, 2018[75]	2014–15	Zimbabwe	Outpatient clinic	CS	Conv	Patients attending different STI clinics	PCR	77	1.3
Suntoke, 2009[66]	2002–06	Uganda	Outpatient clinic	CS	Conv	Patients with genital herpes	PCR	65	4.6

[a] The original study design of the study is randomized clinical trial. The included proportion measures are those for the baseline measures at the onset of the trial, before start of follow up.
Abbreviations: Conv = Convenience, CS = Cross sectional, GUD = Genital ulcer disease, HIV = Human immunodeficiency virus, HSV-1 = Herpes simplex virus type 1, IFA = Immunofluorescence, PCR = Polymerase chain reaction, RCT = Randomized-controlled trial, STI = Sexually transmitted infections.

Table 5
Pooled proportions in Africa of HSV-1 viral detection in clinically-diagnosed genital ulcer disease (GUD), and in clinically-diagnosed genital herpes.

Population type	Outcome measures	Samples	Proportion of HSV-1 detection (%)		Pooled proportion of HSV-1 detection (%)	Heterogeneity measures		
	Total n	Total N	Range	Median	Mean (95% CI)	Q[a] (p-value)	I^2[b] (%) (95% CI)	Prediction Interval[c] (%)
Patients with GUD	18	3208	0.0–6.0	0.0	0.4 (0.0–1.5)	89.1 ($p < 0.0001$)	80.9 (70.8–87.6)	0.0–7.1
Patients with genital herpes	8	1342	0.0–5.0	2.4	1.2 (0.0–4.0)	44.4 ($p < 0.0001$)	84.2 (70.7–91.5)	0.0–14.5

[a] Q: The Cochran's Q statistic is a measure assessing the existence of heterogeneity in pooled outcome measures, here proportions of HSV-1 viral detection.
[b] I^2: A measure that assesses the magnitude of between-study variation that is due to differences in proportions of HSV-1 viral detection across studies rather than chance.
[c] Prediction interval: A measure used here to estimate the distribution (the 95% interval) of true proportion of HSV-1 viral detection around the estimated pooled mean.
Abbreviations: CI = Confidence interval, GUD = Genital ulcer disease, HSV-1 = Herpes simplex virus type 1.

Quality assessment

Most seroprevalence studies (51.2%) used Western blot, the gold standard for HSV-1 serology,[36] as the diagnosis method. Summary of the results of the quality assessments are in Supplementary Table 2. Most studies had high precision (58.1%), but also high ROB in the sampling methodology domain (86.1%). For the response rate domain, 41.9% of studies had low ROB while, remaining studies (58.1%) had unclear ROB. In view of the results of the meta-regressions (Table 3), with the response rate, sample size, and sampling methodology not being associated with HSV-1 seroprevalence, the overall evidence appears to be of reasonable quality.

Discussion

A detailed and systematic assessment of HSV-1 epidemiology in Africa was conducted. The results demonstrate that HSV-1 is universally prevalent, with nearly every person acquiring the infection by age 15 (Tables 2 and 3). Strikingly, exposure to the infection appears to be immensely homogenous for the entire population, regardless of sex, country's income, or health status (Table 3). Even factors such as response rate, sampling methodology, or sample size, which often introduce bias in prevalence studies for different diseases,[37,38] did not affect the observed seroprevalence (Table 3). There was also no evidence for any change in seroprevalence over the last few decades (Table 3).

Seroprevalence in Africa was found to be much higher (Table 2) than that estimated for the global population at 67%.[1] HSV-1 seroprevalence is also well documented in different Western countries, with levels of only about 50%.[7–13,39,40] Though HSV-1 seroprevalence was found to be high in Asia, the Middle East and North Africa (MENA), and Latin America and the Caribbean in three recent systematic reviews,[15,16,41] it was not as high as that in Africa, particularly among younger adults. Moreover, no variation in seroprevalence by country, or by country's income level, was found in Africa (Tables 1 and 3). This stands in contrast to observed variations in other regions,[15,41] that are consistent with an association between HSV-1 infection and lower socio-economic status.[39,42]

Though seroprevalence is declining in developed countries,[7–13,39,40] such as the U.S.A[40,43] and Japan,[15,44] with the improvements in living and hygiene conditions,[40] such trend is not seen in Africa (Table 3). Africa continues to exhibit what can be labelled as the "historical pattern" of HSV-1 infection, whereby nearly every person acquires the infection in early childhood, through oral-to-oral transmission, and where homogeneity in exposure dominates, in contrast to the increasingly heterogonous and variable exposure elsewhere.[7–13,15,16,39–41]

Only age was a strong predictor of seroprevalence in Africa (Table 3). Remarkably, it explained also nearly 80% of seroprevalence variation—hardly any other factor was needed to explain this variation. This is to be contrasted with Asia,[15] MENA,[41] and Latin America and the Caribbean[16] where age explained only 34% 48%, and 54% of seroprevalence variation, respectively. This further affirms the universality and homogeneity of the infection in Africa—it is just a question of cumulative person-time of exposure before nearly every person acquires the infection. Seroprevalence in Africa grows very rapidly following birth (Tables 2 and 3), highlighting the strong force of infection in the community. By age 15, seroprevalence plateaus at >90%, and is independent of age for all older age groups, simply because seroprevalence reached its saturation level.

A key finding of this study is the extremely low detection of HSV-1 in both GUD and genital herpes (Tables 4 and 5), in contrast to Western countries, Asia, and Latin America and the Caribbean. In multiple Western countries, HSV-1 is already the primary cause of genital herpes,[2,17–21] and in Asia and Latin america and the Caribbean, about 20% of genital herpes is attributed to HSV-1.[15,16] The low detection in Africa is probably best explained by most persons reaching sexual debut already infected, thus with protective antibodies against genital acquisition. The observed epidemiological transition towards less oral acquisition and more genital acquisition, that is seen in multiple countries,[2,14,21] appears far from being realized in Africa.

This epidemiological assessment is limited by the quantity, quality, and representativeness of included studies. Most data were from the more populous African countries, and 31 (mostly small) countries had no identifiable data. There was evidence for a lower seroprevalence whenever a NAb assay was used as the diagnostic method (Table 3)—this may have underestimated the calculated pooled mean seroprevalence. Notably, 51.2% of the studies used Western blot, the gold standard for HSV-1 serological diagnosis,[36] in contrast to other regions where seroprevalence is most often assessed using ELISA.[15,41] This is probably explained by the well-funded and high-quality international studies that were conducted in Africa to investigate HSV-1 infection, as part of the expansion of HIV research in this continent.

Conclusions

Africa continues to exhibit the "historical pattern" of HSV-1 infection, with nearly every person acquiring the infection in childhood through oral-to-oral transmission. The infection is universally prevalent, at higher levels than other regions, with no evidence for declines in seroprevalence in recent decades. Exposure to HSV-1 is homogenous in the population at large, only one factor, age, was needed to explain most of the variation in seroprevalence. Sexual oral-to-genital and genital-to-genital transmission appear to be very limited—HSV-1 viral detection was extremely low in both GUD and genital herpes. These findings suggest a significant burden of oral herpes and related disease sequelae that remains to be quantified and tackled in this region. The findings also support the need for an HSV-1 vaccine to control transmission and prevent its disease burden.

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Declaration of Competing Interest

The authors have no competing interests to declare.

CRediT authorship contribution statement

Manale Harfouche: Data curation, Formal analysis, Investigation, Methodology, Project administration, Writing - original draft, Writing - review & editing. **Hiam Chemaitelly:** Data curation, Writing - review & editing. **Laith J. Abu-Raddad:** Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Writing - review & editing.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2019.07.012.

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