Received: 30 November 2022 | Accepted: 20 February 2023

DOI: 10.1002/jmv.28603

RESEARCH ARTICLE

JOURNAL OF MEDICAL VIROLOGY WILEY

Epidemiology of herpes simplex virus type 2 in the Middle East and North Africa: Systematic review, meta-analyses, and meta-regressions

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Funding information
Qatar National Research Fund; Biomedical Research Program at Weill Cornell Medicine in Qatar

Abstract

Herpes simplex virus type 2 (HSV-2) infection is a prevalent, sexually transmitted infection with poorly characterized prevalence in the Middle East and North Africa (MENA) region. This study characterized HSV-2 epidemiology in MENA. HSV-2 reports were systematically reviewed as guided by the Cochrane Collaboration Handbook and findings were reported following PRISMA guidelines. Random-effects meta-analyses and meta-regressions were performed to estimate pooled mean outcome measures and to assess predictors of HSV-2 antibody prevalence (seroprevalence), trends in seroprevalence, and between-study heterogeneity. In total, sixty-one overall (133 stratified) HSV-2 seroprevalence measures and two overall (four stratified) proportion measures of HSV-2 detection in laboratory-confirmed genital herpes were extracted from 37 relevant publications. Pooled mean seroprevalence was 5.1% (95% confidence interval [CI]: 3.6%–6.8%) among general populations, 13.3% (95% CI: 8.6%–18.7%) among intermediate-risk populations, 20.6% (95% CI: 5.3%–42.3%) among female sex workers, and 18.3% (95% CI: 3.9%–39.4%) among male sex workers. Compared to Fertile Crescent countries, seroprevalence was 3.39-fold (95% CI: 1.86–6.20) and 3.90-fold (95% CI: 1.78–8.57) higher in Maghreb and Horn of Africa countries, respectively. Compared to studies published before 2010, seroprevalence was 1.73-fold (95% CI: 1.00–2.99) higher in studies published after 2015. Pooled mean proportion of HSV-2 detection in genital herpes was 73.8% (95% CI: 42.2%–95.9%). In conclusion, MENA has a lower HSV-2 seroprevalence than other world regions. Yet, 1 in 20 adults is chronically infected, despite conservative prevailing sexual norms. Seroprevalence may also be increasing, unlike other world regions. Findings support the need for expansion of surveillance and monitoring of HSV-2 infection in MENA.

KEYWORDS
genital, genital herpes, genital ulcer disease, Herpes, HSV-2, MENA, prevalence, seroprevalence, sexually transmitted infection

Asalah Alareeki and Aisha M. M. Osman contributed equally to this study.

1 | INTRODUCTION

Herpes simplex virus type 2 (HSV-2) infection is a chronic, incurable, and globally prevalent sexually transmitted infection (STI),[1–3] known for persistent reactivation and frequent shedding.[4,5] When individuals are symptomatic, HSV-2 infection presents in the form of recurrent painful genital lesions that are associated with sexual and psychological comorbidities.[1,6–8] HSV-2 can also be passed vertically from mother to child, leading to neonatal herpes, a serious condition for neonates that causes high morbidity and mortality.[9] HSV-2 infection has overlapping epidemiology with HIV infection,[10] with evidence suggesting an epidemiologic synergy between these two infections.[11–13] HSV-2 infection is associated with increased HIV acquisition and transmission, and people living with HIV may suffer from increased severity of HSV-2 infection.[13–15]

Despite burdensome sequelae, inadequate understanding of the epidemiology of STIs in the global context and their impact on sexual, reproductive, and psychosocial health lowered their priority on health policy agendas.[16–18] To address this concern, the World Health Organization (WHO) and global partners are leading efforts to control or eliminate STIs as a public health concern by 2030 by integrating preventive, therapeutic, and control frameworks,[16,17] one of which is developing an HSV-2 vaccine, a long overdue public health priority.[19,20]

To inform these efforts, and as part of a global project to understand the epidemiology of HSV-1 and HSV-2 infections,[21–30] a systematic review was conducted to characterize HSV-2 epidemiology in the Middle East and North Africa (MENA) region. HSV-2 antibody prevalence (seroprevalence) and proportions of HSV-2 detection in clinically diagnosed genital ulcer disease (GUD) and in laboratory-confirmed genital herpes were identified and synthesized, pooled means were estimated, and predictors of high seroprevalence and temporal trends were investigated.

2 | METHODS

Methods used in this study are described in Box 1 and briefly below. The methods for investigating epidemiology of HSV-2 infection were adapted based on a series of published systematic reviews and meta-analytics assessing HSV-2 epidemiology in other WHO regions.[26–30]

BOX 1. Description of the methodology for this study

Methodology	Detailed description
Data sources and search strategy	- Search conducted up to March 30, 2022 in international and regional databases (PubMed, Embase, Index Medicus of Eastern Mediterranean Region, Iraq Academic Scientific Journals, Scientific Information Database of Iran, and PakMediNet of Pakistan). - Search strategies included exploded MeSH/Emtree terms and broad terms with no language or time restrictions. - The definition of MENA included 23 countries classified into four subregions: o Fertile Crescent: Egypt, Iraq, Jordan, Lebanon, Palestine, Syria. o Gulf: Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, United Arab Emirates (UAE). o Horn of Africa: Djibouti, Somalia, Sudan, Yemen. o Maghreb: Algeria, Libya, Morocco, Tunisia. o Afghanistan. o Iran. o Pakistan.
Study selection and inclusion and exclusion criteria	- Search results were imported into the reference manager Endnote (Thomson Reuters, USA). - Screening was performed in four stages: 1. Duplicate publications were identified and excluded. 2. Titles and abstracts were screened for relevant and potentially relevant publications. 3. Full texts of relevant and potentially relevant publications were retrieved and screened for relevance. 4. Bibliographies of relevant publications and reviews were checked for additional potentially relevant publications. - Inclusion criteria were any publication, including a study with a minimum sample size of 10, reporting primary data on any of the following outcome measures: 1. HSV-2 antibody incidence as detected by a type-specific diagnostic assay. 2. HSV-2 antibody prevalence (seroprevalence) as detected by a type-specific diagnostic assay. 3. Proportion of HSV-2 in GUD as detected by standard viral detection and subtyping methods. 4. Proportion of HSV-2 in laboratory-confirmed genital herpes (as opposed to HSV-1), as detected by standard viral detection and subtyping methods. - Exclusion criteria were: o Case reports, case series, reviews, editorials, commentaries, and qualitative studies. o Measures reporting seroprevalence in infants <6 months-old as their antibodies can be maternal in origin. - In this study, the term "publication" refers to a document reporting one or several outcome measures. "Study" or "measure" refers to a specific outcome measure and its details.

Methodology	Detailed description
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 (e.g., sex and age), sample size, HSV-2 outcome measures, and diagnostic assay. - Overall outcome measures and their stratified measures were extracted, provided the sample size in each stratum is ≥10. - For studies including overall sample size, but no individual strata sample sizes, the sample size of each stratum was assumed equal to overall sample size divided by the number of strata in the study. - Stratification hierarchy for incidence and seroprevalence in descending order of preference were: 1. Population type as defined in Supporting Information: Box S1. 2. Sex. 3. Age group classified as (groups optimized to best fit reported data): o <25 years old. o 25–35 years old. o >35 years old. - Stratification hierarchy for GUD and genital herpes included genital herpes episode status and study site: 1. Genital herpes episode status classified as: o First episode genital herpes. o Recurrent genital herpes. 2. Study site stratification classified as: o Hospital. o Sexually transmitted disease clinic. - Measures reporting any HSV-2 outcome among children <15 years old were only reported but not included in the analyses.
Quality assessments	The Cochrane's approach for risk of bias assessment included: - Study's precision classification into low versus high based on the sample size (<200 vs. ≥ 200). - Study's appraisal into low versus high risk of bias was determined using two quality domains: o Sampling method: Probability-based *versus* non-probability-based. o Response rate: ≥80% vs. <80% or unclear.
Meta-analyses	- Meta-analyses were conducted using DerSimonian-Laird random-effects models with inverse variance weighting. The variance of each outcome measure was stabilized using the Freeman-Tukey arcsine square-root transformation. - Pooled mean HSV-2 seroprevalence was estimated for each population type by sex, and for general populations by subregion, age group, year of data collection category, and year of publication category. - Pooled proportions of HSV-2 detection in GUD and in genital herpes cases were estimated. - Heterogeneity assessment was based on three complementary metrics: o Cochran's Q statistic to assess existence of heterogeneity in effect size (p-value < 0.1 indicated heterogeneity). o I^2 heterogeneity measure to assess the percentage of between-study variation in effect size that is due to actual differences in effect size rather than chance. o Prediction interval to describe the distribution of true outcome measures around the pooled mean.
Meta-regressions	- Univariable and multivariable random-effects meta-regression analyses using log-transformed proportions were carried out to identify predictors of HSV-2 seroprevalence. - Factors in the univariable model with a p-value < 0.1 were included in the multivariable analyses. - Factors in the multivariable model with a p-value ≤ 0.05 were deemed to be significant predictors. - Variables included in the univariable meta-regression model for HSV-2 seroprevalence were: o Population type. o Age group. o Sex. o Subregion. o National income: LIC, LMIC, UMIC, and HIC according to the World Bank classification. o Assay type (western blot, ELISA, and rapid test). o Sample size. o Sampling method. o Response rate. o Year of data collection. o Year of publication. o Year of data collection category (<2005, 2005–2010, >2010). o Year of publication category (<2010, 2010–2015, >2015). - The year of data collection had a few missing variables that were imputed by adjusting the year of publication using the median difference with the year of data collection.

Abbreviations: ELISA, Enzyme-linked immunosorbent type-specific assay; GUD, Genital ulcer disease; HIC, High-income country; HSV-2, Herpes simplex virus type 2; LIC, Low-income country; LMIC, Lower-middle-income country; UMIC, Upper-middle-income country.

The methods for searching specifically data in the MENA region, including search criteria and databases, were adapted from a published systematic review assessing HSV-1 epidemiology in MENA.[21]

2.1 | Data sources and search strategy

Data sources of this study are listed in Box 1 and the search strategy is detailed in Supporting Information: Table S1. The search was conducted in international, national, and regional databases up to March 30, 2022, with no language or time restrictions. The definition for the MENA region included 23 countries and was informed by the WHO's definition for this region.[31] The Cochrane Collaboration Handbook[32] guided this systematic review and findings were reported following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.[33,34] The PRISMA checklist is found in Supporting Information: Table S2.

2.2 | Study selection, eligibility criteria, data extraction, and data synthesis

Screening of retrieved citations and articles was implemented in four stages by MH. Screening stages and study inclusion and exclusion criteria are described in Box 1. Measures reporting seroprevalence in infants <6 months-old were excluded, as their antibodies can be maternal in origin. Measures reporting any HSV-2 outcome among children <15 years old were only reported but not included in the analyses. Measures reporting an HSV-2 outcome among individuals ≥15 years old were reported and included in the analyses.

Data extraction was performed by MH. Double extraction was performed by AMO. Discrepancies were discussed in consultation with LJA to reach consensus. Extracted variables are indicated in Box 1 and listed in Supporting Information: Box S2.

To attain a comprehensive understanding of the epidemiology as much as possible, both antibody incidence (seroincidence) and seroprevalence measures were investigated. Overall seroprevalence measures and their stratified measures were extracted provided the sample size in each stratum is ≥10. Since the focus in this study is on generating pooled mean estimates of HSV-2 seroprevalence, as opposed to a single study estimate, there was more leeway in relaxing the minimum sample size, as the statistical precision comes from pooling all available studies even if the statistical precision of one specific study is low.

2.3 | Quality assessments

Due to known limitations in diagnostic performance of HSV-2 serological assays,[35–37] validity and reliability of each assay in each study was assessed by Professor Rhoda Ashley-Morrow—a leading expert in HSV-2 serological assays who has investigated and evaluated different HSV assays for three decades. Details of each assay used in each study were shared with Professor Ashley-Morrow, who then used her expert judgment to identify whether each assay was valid and reliable to be included. Only assays deemed as valid and reliable were included. Precision and risk of bias (ROB) assessments, as informed by the Cochrane approach[38] and described in Box 1, were then conducted on each included study.

2.4 | Meta-analyses

Extracted measures were described using summary statistics, including medians, ranges, and pooled mean estimates and their 95% confidence intervals (CI). The DerSimonian-Laird random-effects model[39] was used to conduct meta-analyses accounting for both sampling variation and heterogeneity in effect size between studies (Box 1).[39,40] The variance of each outcome measure was stabilized using the Freeman-Tukey arcsine square-root transformation,[41] after ensuring its applicability.[42] Heterogeneity was assessed based on Cochran's Q statistic, I^2 heterogeneity measure, and prediction interval. All meta-analyses were conducted with R version 4.41.3[43] using the "meta" package,[44] by adapting existing codes to conduct these analyses.

2.5 | Meta-regressions

Univariable and multivariable meta-regressions of log-transformed seroprevalence measures were conducted in Stata/SE version 16[45] using the "metareg" package,[46] as described in Box 1, by adapting existing codes to conduct these analyses. All stratified seroprevalence measures in all population types, as defined in Supporting Information: Box S1, were utilized in these meta-regressions. Variables in the univariable analyses with a p-value < 0.1 were included in the multivariable meta-regression models.

3 | RESULTS

3.1 | Search results and scope of evidence

The study selection process followed PRISMA guidelines (Figure 1).[33,34] Overall, 3519 citations were identified; 2421 citations through international databases (PubMed = 633 and Embase = 1788) and 1098 citations through national and regional databases (Index Medicus for Eastern Mediterranean Region = 601, Iraqi Academic Scientific Journals Database = 123, Scientific Information Database of Iran = 262, and PakMediNet of Pakistan = 112). Following deduplication and title and abstract screening, 385 unique citations were identified as relevant or potentially relevant. Full-text screening of these publications identified 37 publications that met the inclusion criteria. Bibliography screening of relevant articles yielded no additional publications.

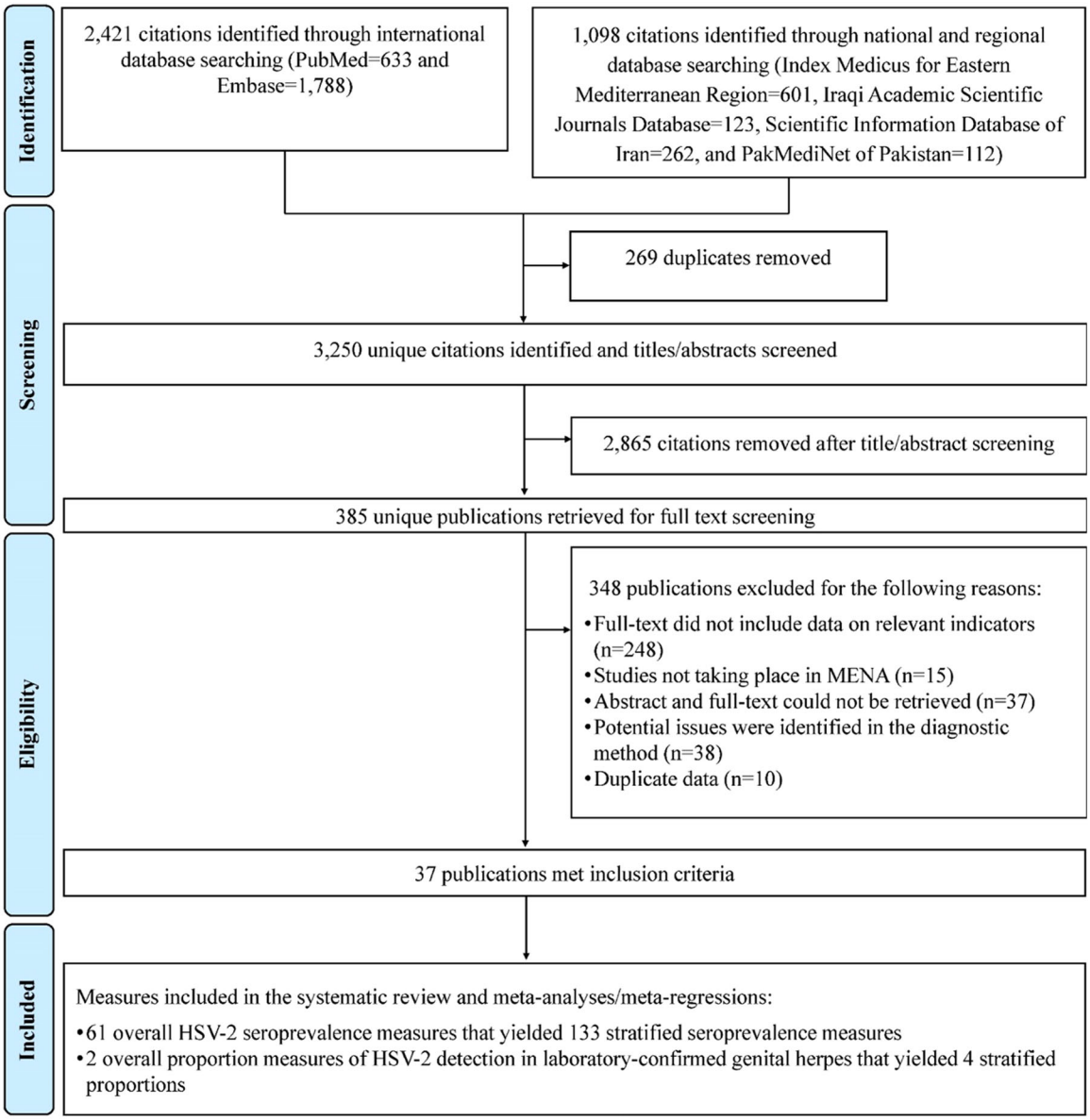

FIGURE 1 Flow chart of article selection for this systematic review of herpes simplex virus type 2 (HSV-2) epidemiology in the Middle East and North Africa, per PRISMA guidelines.[33,34] MENA, Middle East and North Africa; PRISMA, preferred reporting items for systematic reviews and meta-analyses.

Outcome measures extracted from the 37 relevant publications included: 61 overall and 133 stratified HSV-2 seroprevalence measures, and two overall and four stratified proportion measures of HSV-2 detection in laboratory-confirmed genital herpes. No data were identified for HSV-2 seroincidence or for the proportion of HSV-2 detection in clinically diagnosed GUD.

3.2 | HSV-2 seroprevalence overview

Overall extracted HSV-2 seroprevalence measures ($n = 61$) are listed in Supporting Information: Table S3. Although the earliest study was published in 2000, most studies ($n = 35$, 57.4%) were published after 2010. Most studies ($n = 46$, 75.4%) used convenience sampling methods.

Stratified HSV-2 seroprevalence measures are described in Table 1. General populations had the most extracted stratified seroprevalence measures ($n = 90$). Seroprevalence varied across populations and had a median of 4.1% among general populations ($n = 90$), 15.6% among intermediate-risk populations (including prisoners, military personnel, people who inject drugs, and people who work in bars, among others as listed in Supporting Information: Table S3; $n = 13$), 13.0% among female sex workers (FSWs; $n = 5$), 14.0% among male sex workers (MSWs; $n = 5$), and 11.4% among people living with HIV and people in HIV-discordant couples ($n = 4$). Definitions of these populations can be found in Box S1.

TABLE 1 Pooled mean estimates of HSV-2 seroprevalence by population type and sex in the Middle East and North Africa.

Population type	Outcome measures	Sample size	HSV-2 seroprevalence (%)		Pooled mean HSV-2 seroprevalence	Heterogeneity measures		
	Total *n*	Total *N*	Range	Median	Mean (%) (95% CI)	Q[a] (*p*-value)	I^2[b] (%) (95% CI)	Prediction interval[c] (%)
General populations	90	15 310	0.0–57.8	4.1	5.1 (3.4–6.8)	1,041.5 ($p < 0.001$)	91.5 (90.1–92.6)	0.0–25.6
Women	30	6655	0.0–57.8	4.9	7.2 (3.7–11.6)	725.0 ($p < 0.001$)	96.0 (95.1–96.7)	0.0–41.1
Men	53	7330	0.0–20.0	3.2	4.1 (2.7–5.7)	240.1 ($p < 0.001$)	78.3 (72.1–83.3)	0.0–14.8
Women and men	7	1325	0.0–9.0	1.9	2.8 (0.9–5.5)	27.3 ($p < 0.001$)	78.1 (54.5–89.4)	0.0–14.6
Intermediate-risk populations[d]	13	7416	3.0–27.0	15.6	13.3 (8.6–18.7)	363.0 ($p < 0.001$)	96.7 (95.5–97.6)	0.4–38.7
Women	4	749	15.6–26.3	20.3	20.6 (14.6–27.2)	11.6 ($p = 0.009$)	74.2 (28.0–90.8)	1.9–51.1
Men	9	6667	3.0–27.0	8.4	10.5 (5.7–16.6)	207.0 ($p < 0.001$)	96.1 (94.3–97.4)	0.0–37.3
Higher-risk populations	10	1732	2.5–55.5	13.5	19.4 (8.5–33.3)	397.0 ($p < 0.001$)	97.7 (96.9–98.3)	0.0–76.1
FSWs	5	817	4.7–55.5	13.0	20.6 (5.3–42.3)	194.9 ($p < 0.001$)	97.9 (96.8–98.7)	0.0–97.2
MSWs	5	915	2.5–54.0	14.0	18.3 (3.9–39.4)	199.9 ($p < 0.001$)	98.0 (96.9–98.7)	0.0–96.1
STI clinic attendees and symptomatic populations	1[e]	21	-	-	9.5 (0.2–26.6)	-	-	-
Women and men	1[e]	21	-	-	9.5 (0.2–26.6)	-	-	-
People living with HIV and people in HIV-discordant couples	4	311	4.0–18.1	11.4	9.9 (3.3–19.0)	13.2 ($p = 0.004$)	77.2 (38.1–91.6)	0.0–57.4
Women	1[e]	17	-	-	17.6 (2.6–40.0)	-	-	-
Men	1[e]	153	-	-	5.2 (2.2–9.4)	-	-	-
Women and men	2[e]	141	4.0–18.1	11.0	11.5 (1.6–27.3)	-	-	-
Other populations[f]	15	723	0.0–87.8	5.3	7.1 (0.9–17.2)	329.7 ($p < 0.001$)	95.8 (94.3–96.9)	0.0–63.5
Women	5	287	1.6–87.8	8.0	19.2 (0.1–55.2)	226.7 ($p < 0.001$)	98.2 (97.3–98.8)	0.0–100
Men	4	223	0.0–13.6	4.7	8.2 (3.7–13.8)	4.7 ($p = 0.195$)	36.3 (0.0–77.9)	0.0–31.1
Women and men	6	213	0.0–16.0	0.0	1.0 (0.0–6.0)	17.8 ($p = 0.003$)	71.8 (34.8–87.8)	0.0–25.8

Abbreviations: CI, confidence interval; FSWs, female sex workers; HIV, human immunodeficiency virus; HSV-2, Herpes simplex virus type 2; MSWs, male sex workers; STI, sexually transmitted infection.

[a]Q: Cochran's Q statistic assesses the existence of heterogeneity in seroprevalence.

[b]I^2: A measure that assesses the magnitude of between-study variation that is due to actual differences in seroprevalence across studies, rather than sampling variation.

[c]Prediction interval: A measure that estimates the distribution (95% interval) of true seroprevalence around the estimated mean.

[d]Intermediate-risk populations include people who presumably have frequent sexual contacts with populations engaging in high sexual risk behavior and have therefore a higher risk of exposure to HSV-2 than the general population such as prisoners, military personnel, people who inject drugs, and people who work in bars, among others.

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

[f]Other populations include populations with an undetermined risk of acquiring HSV-2 infection, such as patients with cervical cancer and infertility clinic attendees.

3.3 | Pooled mean estimates for HSV-2 seroprevalence

Pooled mean HSV-2 seroprevalence stratified by sex among the different populations is provided in Table 1. Pooled mean seroprevalence was lowest among general populations (5.1%; 95% CI: 3.4%–6.8%) and was highest among higher-risk populations (19.4%; 95% CI: 8.5%–33.3%), including FSWs (20.6%; 95% CI: 5.3%–42.3%) and MSWs (18.3%; 95% CI: 3.9%–39.4%). Pooled mean was 9.9% (95% CI: 3.3%–19.0%) among people living with HIV and people in HIV-discordant couples, and 13.3% (95% CI: 8.6%–18.7%) among intermediate-risk populations. Compared to men, women had higher

pooled mean across all populations. Forest plots of these meta-analyses confirmed substantial heterogeneity in seroprevalence measures (Supporting Information: Figure S1).

Pooled mean HSV-2 seroprevalence among subgroups of the general populations is provided in Table 2. By subregion, the pooled mean was lowest in the Fertile Crescent subregion at 2.2% (95% CI: 1.1%–3.6%), and highest in the Maghreb and Horn of Africa subregions at 15.8% (95% CI: 11.3%–20.8%) and 16.7% (95% CI: 13.3%–20.6%), respectively. Across age groups, the pooled mean increased from 3.7% (95% CI: 0.7%–28.2%) among individuals <25-years old, to 7.2% (95% CI: 3.9%–11.2%) among individuals 25–35-years old, and 9.0% (95% CI: 5.9%–12.4%) among individuals >35-years old.

Virtually all meta-analyses showed evidence of heterogeneity (p-value < 0.01), as confirmed by wide prediction intervals (Tables 1 and 2). Heterogeneity was due to true differences in seroprevalence across studies rather than sampling variation (I^2 > 50%).

3.4 | Predictors of HSV-2 seroprevalence and between-study heterogeneity

Results of univariable and multivariable meta-regression analyses for HSV-2 seroprevalence are described in Table 3. The first multivariable regression model, including year of publication as a categorical variable, explained 44.9% of the variation in seroprevalence. The second model, including year of data collection as a continuous linear variable, explained 40.5% of the variation in seroprevalence.

In the first model, compared to general populations, HSV-2 seroprevalence was 2.18-fold (95% CI: 1.22–3.92) higher among intermediate-risk populations and 3.29-fold (95% CI: 1.64–6.62) higher among higher-risk populations (FSWs and MSWs). Compared to the Fertile Crescent subregion, seroprevalence was 3.39-fold (95% CI: 1.86–6.20) higher in the Maghreb and 3.90-fold (95% CI: 1.78–8.57) higher in the Horn of Africa subregions. Seroprevalence decreased with higher national income (Table 3).

Compared to studies with a sample size <200, seroprevalence was 0.58-fold (95% CI: 0.36–0.94) lower in studies with sample sizes ≥200. Compared to studies published before 2010, seroprevalence was 1.73-fold (95% CI: 1.00–2.99) higher in studies published after 2015.

There was no evidence for a statistically significant association between seroprevalence and age, sex, assay type, sampling method, or response rate. The second model yielded overall similar results, but there was no evidence for an overall increasing or decreasing trend in seroprevalence.

3.5 | HSV-2 detection in genital herpes

Overall extracted proportion measures of HSV-2 detection in laboratory-confirmed genital herpes (n = 2) are listed in Supporting Information: Table S4. The proportion of HSV-2 detection in genital herpes among the four stratified measures had a median of 75.1% and a pooled mean of 73.8% (95% CI: 42.2%–95.9%; Table 4).

The meta-analysis showed evidence of high heterogeneity (p-value < 0.01, I^2 > 50%, and wide prediction interval). A forest plot of this meta-analysis confirmed substantial heterogeneity (Supporting Information: Figure S2).

3.6 | Quality assessments

Quality assessments of diagnostic assays used excluded 38 publications due to potential validity and/or reliability issues with the employed diagnostic method in relation to sensitivity, specificity, and importantly, potential cross-reactivity with HSV-1 antibodies[35,37,47–49] (Figure 1). For validity, it is essential for any assay to be able to detect antibodies to the type-2 specific glycoprotein, G-2 (gG-2).[50,51] The issue of cross reactivity with HSV-1 antibodies is of substantial consequence in a region that has high seroprevalence of HSV-1 infection but low seroprevalence of HSV-2 infection, such as the MENA region.[21,52–54] Measured seroprevalence can also be affected by the choice of ELISA optical density cutoff for positivity.[37,52,55] Studies were excluded if the assay was not type specific or if clearly an inappropriate cutoff was used.

Results of the quality assessment conducted on 61 overall seroprevalence measures are summarized in Supporting Information: Table S5. Briefly, 25 (41.0%) studies had high precision, 15 (24.6%) had low ROB in the sampling method domain, and 1 (1.6%) had low ROB in the response rate domain. Meanwhile, 36 (59.0%) studies had low precision, 46 (75.4%) had high ROB in the sampling method domain, and 2 (3.3%) had high ROB in the response rate domain. Fifty-eight (95.1%) studies had an unclear ROB for the response rate domain.

4 | DISCUSSION

HSV-2 seroprevalence in the adult general population of MENA averaged 5% over the last two decades, with lower seroprevalence than Africa at 37%,[27] Asia at 12%,[26] Europe at 12%,[30] Latin America and the Caribbean at 21%,[28] and the United States of America at about 15%.[56–59] However, there was no evidence for declines in seroprevalence in recent times, unlike other world regions where seroprevalence has been declining at a rate of 1%–2% per year over the last three decades.[26–28,30,56–59] To the contrary, results suggested that seroprevalence may have increased in recent years.

The results indicated substantial variability in seroprevalence across MENA. Subregion alone explained >15% of the variation in seroprevalence. Seroprevalence was low at 2% in the Fertile Crescent countries, but was several folds higher in the Maghreb and Horn of Africa countries. Seroprevalence was also lower in higher income countries compared to lower income countries. This subregional variability is higher than that observed in other world regions,[26–30]

TABLE 2 Pooled mean estimates of HSV-2 seroprevalence among general populations in the Middle East and North Africa.

Population classification	Outcome measures Total *n*	Sample size Total *N*	HSV-2 seroprevalence (%) Range	Median	Pooled mean HSV-2 seroprevalence Mean (%) (95% CI)	Heterogeneity measures Q[a] (*p*-value)	I^2[b] (%) (95% CI)	Prediction interval[c] (%)
Subregions								
Fertile Crescent[d]	48	2350	0.0–20.0	1.9	2.2 (1.1–3.6)	90.9 ($p < 0.001$)	48.3 (27.6–63.1)	0.0–10.3
Gulf[e]	12	6034	0.0–10.0	6.0	6.4 (2.9–11.1)	131.4 ($p < 0.001$)	91.6 (87.3–94.5)	0.0–28.7
Maghreb[f]	10	2450	7.5–34.5	17.3	15.8 (11.3–20.8)	79.5 ($p < 0.001$)	88.7 (81.3–93.2)	2.7–36.5
Horn of Africa[g]	2[h]	419	5.5–57.8	31.6	16.7 (13.3–20.6)	–	–	–
Iran	10	1437	0.0–42.9	3.0	4.7 (0.5–11.2)	140.0 ($p < 0.001$)	94.3 (91.2–96.3)	0.0–42.4
Pakistan	8	2620	1.7–6.0	3.2	3.2 (2.2–4.4)	13.4 ($p = 0.022$)	57.3 (6.2–80.5)	0.7–7.1
Age group								
<25 years	9	935	0.0–16.7	2.7	3.7 (0.7–28.2)	50.9 ($p < 0.001$)	84.3 (71.8–91.2)	0.0–23.5
25–35 years	11	882	0.0–18.5	3.3	7.2 (3.9–11.2)	34.0 ($p < 0.001$)	70.6 (45.4–84.1)	0.0–21.6
>35 years	31	2035	0.0–34.5	6.7	9.0 (5.9–12.4)	107.1 ($p < 0.001$)	73.9 (62.4–81.8)	0.0–29.3
Mixed age groups	39	11 458	0.0–57.8	2.0	3.2 (1.4–5.5)	499.5 ($p < 0.001$)	92.4 (90.5–93.9)	0.0–24.0
Year of data collection category								
<2005	20	3923	0.0–34.5	7.9	7.9 (4.4–12.1)	223.2 ($p < 0.001$)	91.5 (88.3–93.8)	0.0–33.5
2005–2010	11	3243	1.2–42.9	2.5	4.7 (1.4–9.5)	125.3 ($p < 0.001$)	92.0 (87.7–94.8)	0.0–30.8
>2010	59	8144	0.0–57.8	2.0	4.3 (2.5–6.4)	418.4 ($p < 0.001$)	86.1 (82.9–88.8)	0.0–23.5
Year of publication category								
<2010	20	3923	0.0–34.5	7.9	7.9 (8.6–10.4)	223.2 ($p < 0.001$)	91.5 (88.3–93.8)	0.0–33.5
2010–2015	18	8574	0.0–42.9	2.2	3.3 (1.2–6.1)	188.1 ($p < 0.001$)	91.0 (87.2–93.6)	0.0–20.6
>2015	52	2813	0.0–57.8	4.3	4.9 (2.8–7.4)	305.7 ($p < 0.001$)	83.3 (78.8–86.9)	0.0–25.7
All studies	90	15 310	0.0–57.8	4.1	5.1 (3.4–6.8)	1041.5 ($p < 0.001$)	91.5 (90.1–92.6)	0.0–25.6

Abbreviations: CI, confidence interval; HSV-2, Herpes simplex virus type 2.

[a]Q: Cochran's Q statistic assesses the existence of heterogeneity in seroprevalence.

[b]I^2: A measure that assesses the magnitude of between-study variation that is due to actual differences in seroprevalence across studies, rather than sampling variation.

[c]Prediction interval: A measure that estimates the distribution (95% interval) of true seroprevalence around the estimated mean.

[d]Countries included Egypt, Iraq, Jordan, Lebanon, Palestine, Syria.

[e]Countries included Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, United Arab Emirates.

[f]Countries included Algeria, Libya, Morocco, Tunisia.

[g]Countries included Djibouti, Somalia, Sudan, Yemen.

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

TABLE 3 Univariable and multivariable meta-regression analyses of HSV-2 seroprevalence in the Middle East and North Africa.

			Outcome measures	Sample size	Univariable analysis				Multivariable analysis[a]			
									Model 1[b]		Model 2[c]	
			Total *n*	Total *N*	*RR* (95%CI)	*p*-value	LR test *p*-value	Adjusted R^2 (%)	*ARR* (95% CI)	*p*-value	*ARR* (95% CI)	*p*-value
Population characteristics	Population type	General populations	90	15310	1.00	–	0.027	7.60	1.00	–	1.00	–
		Intermediate-risk populations[d]	13	7416	1.78 (1.04–3.04)	0.037			2.18 (1.22–3.92)	0.009	2.19 (1.19–4.04)	0.012
		Higher-risk populations	10	1732	2.34 (1.28–4.33)	0.007			3.29 (1.64–6.62)	0.001	3.02 (1.50–6.10)	0.002
		People living with HIV and people in HIV-discordant couples	4	311	1.49 (0.54–4.09)	0.435			1.28 (0.49–3.33)	0.610	1.32 (0.49–3.53)	0.577
		Other populations[e]	15	723	1.69 (0.88–3.26)	0.117			1.32 (0.67–2.62)	0.418	1.26 (0.62–2.54)	0.513
	Age group	<25 years	9	935	1.00	–	0.416	0.00	–	–	–	–
		25–35 years	11	882	1.09 (0.38–3.13)	0.871			–	–	–	–
		>35 years	32	2138	1.56 (0.63–3.86)	0.334			–	–	–	–
		Mixed age groups	81	21 558	1.05 (0.45–2.46)	0.901			–	–	–	–
	Sex	Women	45	8525	1.00	–	0.117	4.15	–	–	–	–
		Men	72	15 288	0.70 (0.47–1.05)	0.084			–	–	–	–
		Women and men	16	1700	0.55 (0.27–1.13)	0.103			–	–	–	–
	Subregions	Fertile Crescent	65	3061	1.00	–	0.003	15.27	1.00	–	1.00	–
		Gulf	12	6034	0.74 (0.40–1.37)	0.335			0.96 (0.55–1.67)	0.879	0.91 (0.51–1.60)	0.737
		Maghreb	12	3312	2.03 (1.14–3.62)	0.016			3.39 (1.86–6.20)	0.000	3.01 (1.59–5.68)	0.001
		Horn of Africa	4	720	3.89 (1.61–9.41)	0.003			3.90 (1.78–8.57)	0.001	4.34 (1.97–9.54)	0.000
		Afghanistan	4	5298	0.87 (0.35–2.14)	0.753			0.95 (0.28–3.21)	0.933	0.57 (0.19–1.69)	0.310
		Iran	19	2619	1.15 (0.67–1.98)	0.607			1.16 (0.69–1.95)	0.562	1.15 (0.68–1.96)	0.602
		Pakistan	17	4469	0.79 (0.46–1.34)	0.373			0.84 (0.39–1.81)	0.646	0.57 (0.28–1.17)	0.123
	National income[f]	LIC	34	7177	1.00	–	0.016	7.54	–	–	–	–
		LMIC	64	10 905	0.76 (0.48–1.21)	0.244			–	–	–	–
		UMIC	23	1397	0.33 (0.16–0.71)	0.005			–	–	–	–
		HIC	12	6034	0.48 (0.24–0.94)	0.032			–	–	–	–

(Continues)

TABLE 3 (Continued)

			Outcome measures	Sample size	Univariable analysis				Multivariable analysis[a]			
									Model 1[b]		Model 2[c]	
			Total *n*	Total *N*	*RR* (95%CI)	*p*-value	LR test *p*-value	Adjusted R^2 (%)	*ARR* (95% CI)	*p*-value	*ARR* (95% CI)	*p*-value
Study methodology characteristics	Assay type	Western Blot	46	2041	1.00	–	0.554	0.00	–	–	–	–
		ELISA	81	22 826	0.80 (0.52–1.24)	0.319			–	–	–	–
		Rapid test	6	646	0.68 (0.24–1.97)	0.477			–	–	–	–
	Sample size[g]	<200	43	3070	1.00	–	0.004	11.8	1.00	–	1.00	–
		≥200	90	22 443	0.55 (0.37–0.82)	0.004			0.58 (0.36–0.94)	0.029	0.61 (0.38–0.99)	0.048
	Sampling method	Probability based	68	11 832	1.00	–	0.067	4.15	1.00	–	1.00	–
		Non-probability-based	65	13 681	1.42 (0.97–2.07)	0.067			0.77 (0.45–1.32)	0.339	0.58 (0.35–0.96)	0.033
	Response rate	<80%	7	2725	1.00	–	0.009	10.50	1.00	–	1.00	–
		≥80%	1	4750	0.87 (0.14–5.28)	0.882			0.44 (0.08–2.57)	0.358	0.52 (0.08–3.20)	0.477
		Unclear	125	18 038	2.71 (1.36–5.41)	0.005			1.34 (0.58–3.10)	0.497	1.59 (0.69–3.65)	0.275
Temporal variables	Year of data collection category	<2005	34	5299	1.00	–	0.272	0.74	–	–	–	–
		2005–2010	32	6390	0.72 (0.43–1.18)	0.191			–	–	–	–
		>2010	67	13 824	0.69 (0.43–1.11)	0.126			–	–	–	–
	Year of publication category	<2010	43	7148	1.00	–	0.014	8.76	1.00	–	–	–
		2010–2015	31	14 622	0.51 (0.32–0.81)	0.005			0.99 (0.58–1.66)	0.955	–	–
		>2015	59	3743	0.84 (0.54–1.31)	0.444			1.73 (1.00–2.99)	0.050	–	–
	Year of data collection		131	25 329	0.97 (0.94–1.00)	0.036	0.036	3.59	–	–	1.01 (0.97–1.04)	0.711
	Year of publication		131	25 329	0.98 (0.95–1.01)	0.163	0.163	1.04	–	–	–	–

Abbreviations: ARR; adjusted risk ratio; CI, confidence interval; ELISA, Enzyme-linked immunosorbent type-specific assay; HIC, high-income countries; HIV, human immunodeficiency virus; HSV-2, herpes simplex virus type 2; LIC, low-income countries; LMIC, lower-middle-income countries; LR, Likelihood ratio; RR, risk ratio; STI, sexually transmitted infection; UMIC, upper-middle-income countries.

[a]Two models were conducted due to collinearity between year of publication category (Model 1) and year of data collection (Model 2).

[b]Variance explained by multivariable model 1 (adjusted R^2) = 44.88%.

[c]Variance explained by multivariable model 2 (adjusted R^2) = 40.54%.

[d]Intermediate-risk populations include people who presumably have frequent sexual contacts with populations engaging in high sexual risk behavior and have therefore a higher risk of exposure to HSV-2 than the general population such as prisoners, military personnel, people who inject drugs, and people who work in bars, among others.

[e]Other populations include populations with an undetermined risk of acquiring HSV-2 infection, such as patients with cervical cancer and infertility clinic attendees. This category also includes one measure for STI clinic attendees.

[f]National income was not included in the multivariable model due to collinearity with subregion.

[g]Sample size denotes the sample size of each study population found in the original publication.

TABLE 4 Pooled mean proportion of HSV-2 detection in laboratory-confirmed genital herpes cases in the Middle East and North Africa.

	Outcome measures	Sample size	Proportion of HSV-2 detection (%)			Pooled mean proportion of HSV-2 detection	Heterogeneity measures		
Population type	Total *n*	Total *N*	Range	Median	Mean (%) (95% CI)	Q^a (*p*-value)	I^{2b} (%) (95% CI)	Prediction interval[c] (%)
Patients with genital herpes	4	228	35.5–95.3	75.1	73.8 (42.2–95.9)	77.5 ($p < 0.001$)	96.1 (92.8–97.9)	0.0–100
Women	2[d]	134	35.5–90.3	62.9	65.7 (11.3–100)	-	-	-
Men	2[d]	79	60.0–95.3	77.7	81.3 (38.2–100)	-	-	-

Abbreviations: CI, confidence interval; HSV-2, Herpes simplex virus type 2; MSWs, male sex workers; STI, sexually transmitted infection.

[a]Q: Cochran's Q statistic assesses the existence of heterogeneity in pooled outcome measures, here proportion of HSV-2 virus detection in laboratory-confirmed genital herpes.

[b]I^2: A measure that assesses the magnitude of between-study variation that is due to actual differences in proportion of HSV-2 virus detection across studies, rather than sampling variation.

[c]Prediction interval: A measure that estimates the distribution (95% interval) of true proportion of HSV-2 virus detection around the estimated mean.

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

and may reflect differences in sexual networking across the region.[10,60–62]

This study demonstrated classic attributes in HSV-2 epidemiology that are also observed in other world regions.[26–28,30,56–59] These include strong hierarchy in seroprevalence by level of sexual risk behavior (Tables 1 and 3), increasing seroprevalence with age, reflecting cumulative exposure to the infection (Table 2), and larger seroprevalence among women than men (Table 1).[26–28,30,56–59] The latter supports a higher bio-anatomical susceptibility to HSV-2 acquisition among women.[63,64]

Though this study clarified aspects of HSV-2 epidemiology in MENA, it also identified major gaps in evidence. Seroprevalence among FSWs and MSWs was surprisingly low, being only 20%, lower than in other world regions.[26–30] However, the lower seroprevalence may reflect inadequate representativeness of actual seroprevalence among these populations in MENA. Only 10 studies were identified for these populations in this region. Seroprevalence was also low among people living with HIV, but this may reflect not only the small number of studies, but also that HIV is mainly transmitted through injecting drug use in countries in which these studies were conducted.[65–67] The proportion of HSV-2 detection in laboratory-confirmed genital herpes was estimated at 74%, within the range observed in other world regions,[26–30] but this estimate may not be representative, as only two outdated studies conducted three decades ago were identified, and both came from only one country, Iraq. No data were available for the proportion of HSV-2 detection in clinically diagnosed GUD. Despite these gaps in evidence, the number of studies in MENA has increased in recent years, unlike other world regions in which the number of studies has been decreasing.[26–28,30]

This study has limitations. Data availability varied by country and no data were available for 9 of 23 MENA countries. Most seroprevalence measures were in general populations, with insufficient sampling of measures in key populations, such as FSWs and men who have sex with men. There was evidence of a small-study effect,[18] as observed in other world regions,[26,28] with larger studies reporting lower seroprevalence. Studies differed by assay type, sampling method, and response rate, yet these factors did not appear to affect observed seroprevalence in the meta-regression analyses. Unexpectedly, there was no evidence for a statistically significant association between seroprevalence and age, sex, and sampling method, but this finding likely reflected the insufficient number of seroprevalence measures to precisely quantify these associations. Included studies exhibited heterogeneity, but nearly half of this heterogeneity was subsequently explained through the meta-regression analyses in terms of effects of subregion and population type on seroprevalence.

5 | CONCLUSIONS

MENA has a lower HSV-2 seroprevalence than other world regions. Yet, about one in twenty adults is chronically infected with HSV-2 despite conservative prevailing sexual norms. Seroprevalence may also be

increasing, unlike other world regions, where it is decreasing. HSV-2 infection appears to be the cause of most genital herpes cases in this region. Despite progress in understanding the epidemiology of this infection, major gaps in evidence persist in relation to seroprevalence in key populations and contributions of HSV-2 infection to GUD and genital herpes. These findings demonstrate the need to expand HSV-2 research and surveillance by conducting integrated bio-behavioral surveillance surveys in key populations and national population-based seroprevalence surveys, as well as by monitoring etiology of GUD and genital herpes cases. These findings also advocate for increased momentum and funding for slowly progressing efforts of therapeutic and prophylactic HSV-2 vaccine development.

AUTHOR CONTRIBUTIONS

Manale Harfouche conducted the systematic search, data extraction, and data analyses. Aisha M. M. Osman double extracted the data. Asalah Alareeki and Manale Harfouche wrote the first draft of the paper. Laith J. Abu-Raddad conceived the study and led the data extraction, analyses, and interpretation of the results. All authors contributed to drafting and revising the manuscript.

ACKNOWLEDGMENTS

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

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data set supporting the conclusions of this article is included within the article (and its additional files).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Harfouche M, Alareeki A, Osman AMM, Alaama AS, Hermez JG, Abu-Raddad LJ. Epidemiology of herpes simplex virus type 2 in the Middle East and North Africa: systematic review, meta-analyses, and meta-regressions. *J Med Virol*. 2023;95:e28603. doi:10.1002/jmv.28603