Research Article

Estimating Seroprevalence of Herpes Simplex Virus Type 1 among Different Middle East and North African Male Populations Residing in Qatar[†]

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ABSTRACT

Background: HSV-1 epidemiology in the Middle East and North Africa (MENA) remains poorly understood. Our study aimed to measure HSV-1 antibody prevalence (seroprevalence) and its age-distribution among select MENA populations residing in Qatar.

Methods: Sera were collected from male blood donors attending Hamad Medical Corporation 2013-2015. A total of 2,077 sera were tested for anti-HSV-1 antibodies using HerpeSelect® 1 ELISA IgG kits (Focus Diagnostics, USA). Robust Poisson regression was conducted to estimate adjusted infection prevalence ratios.

Results: Country-specific HSV-1 seroprevalence was estimated for 10 national populations: 97.5% among Egyptians, 92.6% among Yemenis, 90.7% among Sudanese, 88.5% among Syrians, 86.5% among Jordanians, 82.3% among Qataris, 81.4% among Iranians, 81.4% among Lebanese, 80.5% among Palestinians, and 77.0% among Pakistanis. Age-specific HSV-1 seroprevalence was estimated for Egypt, the Fertile Crescent (Iraq, Jordan, Lebanon, Palestine, and Syria), and Qatar. Seroprevalence increased with age among Fertile Crescent and Qatari nationals. Seroprevalence increased from 70.0% among those aged ≤24 years up to 98.0% among those aged ≥55 years among Fertile Crescent nationals. Seroprevalence was consistently above 90% for all ages among Egyptians.

Conclusions: HSV-1 seroprevalence is high in MENA, though with some variation across countries. The seroprevalence appears to have declined among current young age cohorts compared to its levels a few decades ago.

KEYWORDS

Herpes Simplex Virus Type 1, Prevalence, Middle East and North Africa, Sexually Transmitted Infection, Herpes.

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INTRODUCTION

Herpes simplex virus type 1 (HSV-1) infection is endemic globally and is the primary cause of orolabial herpes.[1-4] HSV-1 is highly infectious, with most infections occurring during childhood.[1,5] Following initial acquisition, the virus introduces latency in nerve cell clusters causing an infection that persists for life.[3,6] HSV-1 is commonly transmitted by non-sexual contact (primarily through oral secretions), with most infections showing no apparent symptoms.[3,7,8] When symptomatic, infection is often characterized by oral or facial lesions, that is at the initial portal of entry.[6,7] HSV-1 infection is associated with oral, cutaneous, ocular, and central nervous system manifestations, and thus infection can lead to mild to serious or severe morbidity, such as gingivostomatitis, herpes labialis, herpetic whitlow, neonatal herpes, corneal blindness, meningitis, and encephalitis.[6,9]

HSV-1 can also be transmitted to susceptible persons through oral sex or sexual intercourse resulting in genital herpes, given the genital portal of initial entry.[3,7,10] Recent evidence from Western countries indicates a growing role for HSV-1 as a sexually transmitted infection (STI) and a leading, if not the leading, cause of genital herpes.[7,11-15]

With continued improvement in hygiene and living conditions, HSV-1 antibody prevalence (seroprevalence) appears to be declining at least in Western countries.[1,5,16-22] HSV-1 seroprevalence has declined by about 30% over the last three decades among adolescents 14-19 years of age in the United States.[8] Evidence suggests that a striking transition in HSV-1 epidemiology, from an oral to increasingly genital infection, is already taking place in Western countries,[7,8,23] and is resulting in significant clinical and psychosocial morbidity.[4,7,23-25]

In context of limited data on HSV-1 seroprevalence in MENA,[1] the aim of our study was to assess HSV-1 seroprevalence among select MENA national populations and to characterize the infection's age-distribution. Specifically, we assessed HSV-1 seroprevalence among male blood donors, from 11 MENA nationalities, who are currently residing in Qatar. Qatar is a MENA country situated in the Arabian Peninsula with a population of 2.2 million in 2014.[26] Qataris constitute only 12% of the total population, with the vast majority of the population being recent short-term expatriate residents coming for contractual employment for specific number of years.[26]

With a large fraction of these expatriates coming from other MENA countries, Qatar provided an opportune setting for a comparative study of HSV-1 seroprevalence among different MENA populations. HSV-1 seroprevalence among these expatriates should be comparable to HSV-1 seroprevalence in their home countries. These expatriates are predominantly recent short-term residents in Qatar and spent most of their lifetime in their home countries—their seroprevalence should be more representative of the exposure risk in their home countries, rather than in Qatar. HSV-1 seroprevalence among men should also be representative of that among women, as existing global evidence suggests no major sex-specific differences.[1,2] Since HSV-1 is mainly transmitted orally with a general-population epidemiology, we would further expect that the seroprevalence among blood donors should be comparable to that in the wider population, as supported also by existing evidence.[1]

MATERIALS AND METHODS

Study design and participants

This was an opportunistic cross-sectional study on volunteer blood donors from different MENA nationalities attending Hamad Medical Corporation, the main healthcare provider in Qatar, between June 2013 and June 2016. Blood donation in Qatar is a common practice, and individuals from diverse socioeconomic strata participate in blood donation campaigns. A total of 5,973 blood donors consented to provide blood specimens and basic demographic information including nationality, age, and sex. No identifiable information was collected. The blood specimens were collected for other studies,[27-30] but remaining specimens were used for this study. The research work was approved by the ethics boards and research committees at Qatar University, Hamad Medical Corporation, and Weill Cornell Medicine-Qatar.

The sample comprised Qataris and expatriates (MENA and non-MENA nationals) residing in Qatar, men and women, and adults ≥18 years of age. The sample included 5,799 men and 152 women, with gender missing for 22 subjects. The number of female participants was small and consequently women were excluded. All specimens from non-MENA male nationals (n = 1,295) were also excluded. An additional MENA specimen (n = 1) was omitted due to missing gender information. The remaining 4,525 MENA specimens served as the original sampling cohort for selection of the final sample.

Final sample sizes were calculated for a significance level of $\alpha = 0.05$. Sample size of 50 was estimated for each five-year age group in each country to assess an age-specific HSV-1 seroprevalence of 88% with a 10% precision level. Sample size of 200 was estimated for each country to assess the country's overall HSV-1 seroprevalence of 88% with a 5% precision level.

The 88% seroprevalence was based on observed HSV-1 seroprevalence in a study from Saudi Arabia,[31] also a MENA country.

For estimating HSV-1 age-specific seroprevalence, a random sample of 50 subjects per age group was selected for each of Egypt, the Fertile Crescent (Iraq, Jordan, Lebanon, Palestine, and Syria), and Qatar (Table I). If serum was not sufficient for a subject, a replacement subject was randomly chosen with the same nationality and age group. There were not always sufficient subjects or serum to conduct the serology to reach the 50 target sample size per age category. Due to insufficient sample size in each country individually, the neighboring countries of Iraq, Jordan, Lebanon, Palestine, and Syria were merged together as one national unit, the Fertile Crescent, as they share similar socio-economic and socio-cultural attributes. No sufficient sample size was available to assess the age-specific seroprevalence in other countries.

For estimating country-specific HSV-1 seroprevalence in countries where we did not have sufficient sample size to estimate the age-specific seroprevalence, a random sample of 200 subjects was selected for each of Jordan, Pakistan, Palestine, and Syria. For Iran, Lebanon, Sudan, and Yemen, all available specimens were included in the study sample, as <200 were available for each of these countries (Table I). For countries with <100 subjects, no country-specific estimate was conducted (Algeria, Iraq, Morocco, Oman, and Tunisia).

Biological sample collection and laboratory analysis

A portion of sera (50 µL) was aliquoted from existing sera samples that were stored at -80°C until used for serology testing. Sera were tested for the presence of anti-HSV-1 IgG using HerpeSelect® 1 enzyme linked immunosorbent assay (ELISA) kits (Cat. No. EL0910G-5, Focus Diagnostics, USA). This kit was designed for qualitative detection of type-specific IgG

antibodies to HSV-1 in human serum using a 96-microwell polystyrene plate coated with a purified recombinant HSV-1 glycoprotein-G antigen (gG1). The kit was approved for laboratory diagnosis of anti-HSV-1 IgG by the United States Food and Drug Administration.[32]

Analysis and results were interpreted according to the manufacturer's instructions: sera with optical density index values (cut-off) <0.90 were considered negative, values >1.10 were considered positive, and values ranging between 0.90 and 1.10 were considered equivocal.[32] All equivocal specimens were retested. Those that remained equivocal were reported as equivocal.

Data analysis

Data was analyzed using the Statistical Package for the Social Sciences (SPSS) version 24. Age was categorized into eight five-year bands: ≤24, 25-29, 30-34, 35-39, 40-44, 45-49, 50-54, and ≥55. Cross-tabulation between age and HSV-1 serostatus was performed for Egypt, the Fertile Crescent, and Qatar to describe the age-specific HSV-1 seroprevalence of the study population. Trends were assessed using the Cochran–Armitage test for trend. Robust Poisson regression [33] was conducted to estimate the crude and adjusted effects of age and nationality on HSV-1 seroprevalence. Significance level was defined at $\alpha = 0.05$.

RESULTS

In total, 2,077 serum specimens from subjects from 11 MENA countries were tested for HSV-1 antibodies (Table I). The median age among those tested was 37 years. Serological testing identified 1,796 sera as positive, 280 as negative, and one as equivocal.

The country-specific overall HSV-1 seroprevalence among men was estimated for 10 MENA national populations. The highest seroprevalence was among Egyptians at 97.5% (95% CI 95.3-98.7%), and the lowest among Pakistanis at 77.0% (95% CI 70.7-82.3%). Seroprevalence for all national populations is presented in Table II.

The age-specific HSV-1 seroprevalence was estimated for Egyptians, nationals of the Fertile Crescent (Iraq, Jordan, Lebanon, Palestine and Syria), and Qataris (Table III). Among Egyptians, HSV-1 seroprevalence was >90% in all age groups, with no evidence for growing or declining trend with age (p-value for trend = 0.259). Among Fertile Crescent nationals, HSV-1 seroprevalence increased steadily with age starting from 70.0% (95% CI 56.3-80.9%) among those aged ≤24 years up to 98.0% (95% CI 89.5-99.7%) among those aged ≥55 years (p-value < 0.001). Among Qataris, HSV-1 seroprevalence also increased with age (p-value < 0.001), and was lowest at 62.0% (95% CI 48.2-74.1%) among those aged 25-29 years.

Both age and nationality were found to be associated factors with HSV-1 infection in both univariable and multivariable analyses (Table IV). There was a significant positive association between seroprevalence and age in the univariable analysis. Compared to those aged ≤24 years, all older age groups had higher seroprevalence. The crude prevalence ratios (PRs) increased from 1.11 (95% CI 1.00-1.22) for those aged 25-29 years to 1.32 (95% CI 1.21-1.44) for those aged ≥55 years.

There were also significant differences in seroprevalence with nationality in the univariable analysis. The crude prevalence ratios were significantly higher among Jordanians (PR = 1.12; 95% CI 1.02-1.23), Syrians (PR = 1.15, 95% CI 1.05-1.26), Sudanese (PR = 1.18, 95% CI 1.07-1.29), Yemenis (PR = 1.20, 95% CI 1.10-1.31), and Egyptians (PR = 1.27, 95% CI 1.17-1.37), compared to Pakistanis.

Age and nationality remained significantly associated with seroprevalence in the multivariable analysis (Table IV). However, the prevalence ratio for Jordanians (PR = 1.08, 95% CI 0.98-1.15) was no longer significantly different compared to Pakistanis after age adjustment.

DISCUSSION

This is to our knowledge the most comprehensive HSV-1 seroprevalence study of different MENA populations and different age groups. We found that overall seroprevalence remains high, but for most nationalities, at lower levels than expected, based on earlier evidence and historical pattern.[1,17,34-40] The seroprevalence decline appears to reflect lower seroprevalence among the younger age cohorts in recent time; as much as 30% of those <30 years of age have not been exposed to HSV-1. The high overall HSV-1 seroprevalence in MENA suggests that there may be significant HSV-1-related morbidity in the population at large that needs to be quantified and addressed including diseases such as gingivostomatitis, herpetic whitlow, corneal blindness, and encephalitis among others.[6,9]

Our results indicated variation in HSV-1 seroprevalence across countries, and observed rates are consistent with the global evidence suggesting an association between HSV-1 infection and

socio-economic status.[1,8] Seroprevalence was higher in the lower-income countries of Egypt, Sudan, and Yemen, than in the relatively higher-income countries of Iran, Jordan, Lebanon, Palestine, Qatar, and Syria. A recent study from Saudi Arabia, a higher-income country, found also a seroprevalence similar to our results for the higher-income countries.[31]

Pakistan though was a notable exception by being a lower seroprevalence (77%) and also a lower-income country. This finding remains to be confirmed and explained, but we are not aware of other comparable HSV-1 studies from Pakistan. Of note, however, HSV-1 seroprevalence in India, a neighboring country of Pakistan with similar socio-economic level, was reported to be at only 60%.[2] These results may hint that the association between HSV-1 infection and socio-economic status is more nuanced than previously thought.

Our study has limitations. The specimens were only from male blood donors with no population- and probability-based sampling, exposing the study to potential selection bias. Specimens were collected from individuals of different nationalities, but all individuals were residing in Qatar at that time. HSV-1 seroprevalence among these expatriates may not necessarily reflect the seroprevalence in their home countries. Very basic socio-demographic variables were collected, limiting our ability to assess relevant individual-level associations such as education, socio-economic status, or specific socio-cultural practices. Two different methods were used to select the testing samples depending on primary purpose, overall versus age-specific seroprevalence. For the overall seroprevalence, we chose the specimens randomly among all specimens for that nationality. Meanwhile, for the age-specific seroprevalence, we chose a fixed number of specimens (also randomly) for each age group, and then determined the overall seroprevalence in this sample based on the number of positives in all age groups. There is evidence for variation in

the sensitivity and specificity of HSV-1 assays by population,[32,41,42] thereby potentially also affecting the estimated seroprevalence levels.

Despite these limitations, selection bias may be less of an issue for HSV-1, as it is predominantly transmitted orally with a general-population epidemiology. In these blood-donor samples, the bias will probably be towards older populations, given that the median age in MENA countries is most often <25 years of age.[43] Our estimated seroprevalence could be higher than actual seroprevalence, and our findings are possibly conservative about the extent of seroprevalence decline among youth in recent time. Though all tested individuals were Qatar residents, expatriates are not permanent migrants in Qatar, typically stay for only few years, and the vast majority have moved to Qatar recently thanks to economic expansion over the last decade. The assay used in this study (Focus HerpeSelect®) is highly regarded, approved by the United States Food and Drug Administration, and is among the most commonly used herpes assays in the literature.[32] Lastly, these limitations should be considered in light of the logistical challenges and prohibitive costs to conduct HSV-1 nationally-representative studies on probability-based samples, limitations in availability of HSV-1 epidemiologic data globally,[8] and the present opportunity to conduct this large-scale study by country and age group on existing samples. This is the first time HSV-1 seroprevalence data will appear in the literature for several of the included countries.

In conclusion, HSV-1 seroprevalence is high in MENA though with some variation across countries. The seroprevalence appears also to have declined in recent decades, possibly reflecting reduced exposure during childhood. These findings highlight the need for monitoring of trends in HSV-1 seroprevalence, and etiological surveillance of diagnosed genital herpes and HSV-1

related morbidities. These findings argue also for rapid development of prevention interventions to control HSV-1 infection transmission and to prevent the associated clinical disease burden.

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Contributors

LJA, GKN, and SRD designed the study and developed the research methodology. GKN provided the specimens and led the laboratory component of this study including testing of all specimens. LIM conducted laboratory work on the specimens and contributed to data management. SRD conducted the data analysis, interpretation of the results, and wrote the initial draft of the article. LJA conceived the study and led the data analysis, interpretation of the results, and drafting of the article. All authors contributed to the interpretation of the results and drafting and revision of the article.

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TABLES

Table I Stratification of samples by nationality

	Original sample size N=4,525	Studied sample size N=2,077
Male populations with sample size ≥200*		
Egypt	1001	358#
Jordan	367	200
Pakistan	231	200
Palestine	309	200
Qatar	1130	400
Syria	776	200
Male populations with 100 ≤ sample size ≤ 200		
Iran	115	113$
Lebanon	118	118
Sudan	132	129&
Yemen	152	148&
Other populations with sample size <100		
Iraq	43	11
Other	151	0

* Sample was randomly selected

Only 39 and 19 sera were available for age groups 50-54 and ≥ 55, respectively

& Not enough serum for serology testing

Table II Estimates of HSV-1 country-specific seroprevalence among male blood donors currently residing in Qatar but from different Middle East and North African countries

Country	Sample size	Seroprevalence N+, (%)	Seroprevalence 95% CI
Egypt	358	349 (97.5)	95.3-98.7
Iran	113*	92 (81.4)	73.3-87.5
Jordan	200	173 (86.5)	81.0-90.5
Lebanon	118	96 (81.4)	73.4-87.4
Pakistan	200	154 (77.0)	70.7-82.3
Palestine	200	161 (80.5)	74.2-85.2
Qatar	400	329 (82.3)	78.2-85.7
Sudan	129	117 (90.7)	84.5-94.6
Syria	200	177 (88.5)	83.9-92.6
Yemen	148	137 (92.6)	87.2-95.8

* One final equivocal HSV-1 result

Table III Estimates of HSV-1 age-specific seroprevalence among male blood donors currently residing in Qatar but from Egypt, the Fertile Crescent (including Iraq, Jordan, Lebanon, Palestine, and Syria), and Qatar

	Egypt			Fertile Crescent			Qatar		
Age group	Sample size	Seroprevalence N+, (%)	Seroprevalence 95% CI	Sample size	Seroprevalence N+, (%)	Seroprevalence 95% CI	Sample size	Seroprevalence N+, (%)	Seroprevalence 95% CI
≤24 years	50	46 (92.0)	81.2-96.9	50	35 (70.0)	56.3-80.9	50	35 (70.0)	56.3-80.9
25-29 years	50	50 (100.0)	92.9-100.0	50	36 (72.0)	58.3-82.5	50	31 (62.0)	48.2-74.1
30-34 years	50	49 (98.0)	89.5-99.7	50	41 (82.0)	69.2-90.2	50	40 (80.0)	67.0-88.8
35-39 years	50	49 (98.0)	89.5-99.7	50	42 (84.0)	71.5-91.7	50	41 (82.0)	69.2-90.2
40-44 years	50	49 (98.0)	89.5-99.7	50	42 (84.0)	71.5-91.7	50	42 (84.0)	71.5-91.7
45-49 years	50	50 (100.0)	92.9-100.0	50	47 (94.0)	83.8-97.9	50	48 (96.0)	86.5-98.9
50-54 years	39	37 (94.9)	83.1-98.6	50	49 (98.0)	89.5-99.7	50	46 (92.0)	81.2-96.9
≥55 years	19	19 (100.0)	83.2-100.0	50	49 (98.0)	89.5-99.7	50	46 (92.0)	81.2-96.9

Table IV Crude and adjusted prevalence ratios (95% confidence intervals) for HSV-1 seroprevalence among 2,077 male blood donors currently residing in Qatar but from different Middle East and North African countries

	Crude prevalence ratio (95% CI)	Adjusted prevalence ratio* (95% CI)
Age		
≤24 years	Ref	Ref
25-29 years	1.11 (1.00-1.22)	1.10 (1.00-1.21)
30-34 years	1.14 (1.04-1.25)	1.15 (1.05-1.26)
35-39 years	1.22 (1.12-1.34)	1.24 (1.13-1.35)
40-44 years	1.24 (1.13-1.35)	1.25 (1.14-1.36)
45-49 years	1.29 (1.18-1.41)	1.30 (1.19-1.42)
50-54 years	1.32 (1.22-1.44)	1.32 (1.22-1.44)
≥55 years	1.32 (1.21-1.44)	1.35 (1.24-1.47)
Nationality		
Pakistan	Ref	Ref
Qatar	1.07 (0.98-1.17)	1.04 (0.95-1.15)
Egypt	1.27 (1.17-1.37)	1.25 (1.16-1.35)
Iran	1.08 (0.96-1.21)	1.06 (0.95-1.19)
Jordan	1.12 (1.02-1.23)	1.08 (0.98-1.18)
Lebanon	1.06 (0.94-1.19)	1.03 (0.92-1.15)
Palestine	1.05 (0.94-1.16)	1.03 (0.93-1.13)
Sudan	1.18 (1.07-1.29)	1.17 (1.07-1.28)
Syria	1.15 (1.05-1.26)	1.15 (1.05-1.26)
Yemen	1.20 (1.10-1.31)	1.21 (1.11-1.31)

* Adjusted for nationality and age