Received: 8 August 2019 | Accepted: 22 October 2019

DOI: 10.1002/jmv.25614

SHORT COMMUNICATION

JOURNAL OF MEDICAL VIROLOGY WILEY

Key associations for hepatitis C virus genotypes in the Middle East and North Africa

Sarwat Mahmud[1] | Hiam S. Chemaitelly[1] | Silva P. Kouyoumjian[1] | Zaina Al Kanaani[1] | Laith J. Abu-Raddad[1,2,3]

[1]Infectious Disease Epidemiology Group, Weill Cornell Medicine-Qatar, Cornell University, Qatar Foundation-Education City, Doha, Qatar

[2]Department of Healthcare Policy & Research, Weill Cornell Medicine, Cornell University, New York, New York

[3]College of Health and Life Sciences, Hamad Bin Khalifa University, Doha, Qatar

Correspondence
Sarwat Mahmud and Professor Laith J. Abu-Raddad, PhD, Infectious Disease Epidemiology Group, Weill Cornell Medicine-Qatar, Qatar Foundation-Education City, P.O. Box 24144, Doha, Qatar.
Email: sam2072@qatar-med.cornell.edu (SM) and lja2002@qatar-med.cornell.edu (LJA)

Funding information
Qatar National Research Fund, Grant/Award Numbers: 12S-0216-190094, 9-040-3-008

Abstract

This study aimed to investigate the epidemiology of hepatitis C virus (HCV) genotypes in the Middle East and North Africa (MENA) through an analytical and quantitative meta-regression methodology. For the most common genotypes 1, 3, and 4, country/subregion explained more than 77% of the variation in the distribution of each genotype. Genotype 1 was common across MENA, and was more present in high-risk clinical populations than in the general population. Genotype 3 was much more present in Afghanistan, Iran, and Pakistan than the rest of countries, and was associated with transmission through injecting drug use. Genotype 4 was broadly disseminated in Egypt in all populations, with overall limited presence elsewhere. While genotype 2 was more present in high-risk clinical populations and people who inject drugs, most of the variation in its distribution remained unexplained. Genotypes 5, 6, and 7 had low or no presence in MENA, limiting the epidemiological inferences that could be drawn. To sum up, geography is the principal determinant of HCV genotype distribution. Genotype 1 is associated with transmission through high-risk clinical procedures, while genotype 3 is associated with injecting drug use. These findings demonstrate the power of such analytical approach, which if extended to other regions and globally, can yield relevant epidemiological inferences.

KEYWORDS
genotype, HCV, meta-regression, Middle East and North Africa, transmission

1 | INTRODUCTION

The hepatitis C virus (HCV) is a major global health challenge.[1] An estimated 20% of all individuals chronically infected with HCV are residing in the Middle East and North Africa (MENA).[2,3] Chronic HCV infection leads to various morbidities, such as liver fibrosis, cirrhosis, and cancer,[4] all of which strains healthcare systems.[5]

HCV displays extensive genetic diversity and is categorized into seven genotypes (numbered from 1 to 7).[6] Although genotypes 1 and 3 are common worldwide,[6] genotype distribution can vary from one geographical area to another.[6,7] Specific HCV genotypes have been hypothesized to be associated with specific modes of acquisition, or with specific populations.[6-8] However, any specific genotype circulating within a specific population tends also to be reflective of the circulating genotypes in the wider population of that country.[7]

Delineating the epidemiology of HCV genotypes is critical as it can convey inferences about the modes of transmission and their dynamics in a given population.[6,9] Despite this, existing studies tend to be descriptive and qualitative in nature.[6-8] Against this background, we aimed to demonstrate, to our knowledge for the first

time, an analytical and quantitative approach to investigate the epidemiology of HCV genotypes, through meta-regressions, as applied to HCV genotype distribution in MENA. This study is part of the MENA HCV Epidemiology Synthesis Project, an ongoing endeavor to delineate HCV epidemiology and inform key public health research, policy, and programming priorities in MENA.[7,10-26]

2 | METHODS

Studies reporting HCV genotype data were retrieved from the MENA HCV Epidemiology Synthesis Project database,[2] originally for an earlier study of HCV genotypes in MENA.[7] This comprehensive database consists of several subdatabases on different HCV epidemiological measures, and was populated through a series of systematic reviews for HCV infection across MENA.[10-17,26] The reviews followed the same methodology, informed by the Cochrane Collaboration handbook,[27] and used the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) guidelines[28] to report their findings.

In these reviews, genotype information were extracted from individual studies to populate the HCV genotype subdatabase. Participants with untypeable genotype were removed from the sample size of the study. Participants with mixed genotypes contributed separately to the quantification of each genotype. The population of each study was classified into six risk categories based on the exposure risk to HCV infection, as presented in Figure 1 and as informed by existing literature[29-31] and our earlier studies.[10-17,26] A total of 175 genotype studies on 15 960 participants were included.

Univariable and multivariable random effects meta-regressions were conducted for the proportion of each HCV genotype, based on established statistical methodology,[27] to assess the association between genotype and each of country/subregion and population classification. Variables with a likelihood ratio test $P < .2$ in the univariable analysis qualified for inclusion in the multivariable analysis. Relative risks and adjusted relative risks (ARRs) with a P value between .05 and .10 in the multivariable model, for any association between genotype and a given factor, indicated *good evidence* for the association. $P \leq .05$ indicated *strong evidence* for the association.

General population (populations at low risk)
These included populations at low risk of exposure to HCV infection, such as blood donors, children, pregnant women, among others.

High-risk clinical populations
These included populations at high risk of exposure to HCV infection due to frequent exposure to blood transfusions and/or medical injections, such as thalassemia, hemophilia, and hemodialysis patients, among others.

Populations at intermediate risk
These included populations with a lower risk of exposure to HCV infection than that of populations at high risk, but higher than the general population, such as healthcare workers, patients with diabetes, among others.

Special clinical populations
These included clinical populations in whom the risk of exposure to HCV infection is difficult to determine such as patients with dermatological manifestations, and renal disorders, among others.

Populations with liver conditions
These included patients with various liver-related conditions of particular epidemiological significance to HCV infection, such as patients with liver cirrhosis, hepatocellular carcinoma, and chronic liver disease, among others.

People who inject drugs
These included populations at high risk of exposure to HCV infection due to injecting drug use.

FIGURE 1 Population classification into categories by risk of exposures to hepatitis C virus (HCV) infection

3 | RESULTS

The results of the meta-regressions are shown in Table 1 with key results described in the following subsections.

3.1 | Genotype 1

There was strong evidence for variation in genotype 1 distribution by country/subregion, and good evidence for variation by population. Relative to Egypt, all countries/subregions had much higher presence of genotype 1, apart from Pakistan. Genotype 1 was also more present in high-risk clinical populations (ARR of 1.2 [95% confidence interval [CI]:1.0-1.5]) than in the general population. Country/subregion and population explained the vast majority of the variation in genotype 1 distribution (84.4%), mostly through the country/subregion variable.

3.2 | Genotype 2

There was strong evidence for variation in genotype 2 distribution by country/subregion and by population. Relative to Egypt, the Gulf, Fertile Crescent, Maghreb, and Pakistan had higher presence of genotype 2. Genotype 2 was also more present in high-risk clinical populations, populations at intermediate risk, and people who inject drugs (PWID), relative to the general population. Country/subregion and population explained only 28.8% of the variation in genotype 2 distribution, mostly through the country/subregion variable, with most variation remaining unexplained.

3.3 | Genotype 3

There was strong evidence for variation in genotype 3 distribution by country/subregion, and good evidence for variation by population. Relative to Egypt, all countries/subregions had substantially higher presence of genotype 3. This was particularly so for Afghanistan, Iran, and Pakistan, that had much higher presence of this genotype. Genotype 3 was also more present in PWID (ARR of 1.7 [95% CI: 1.0-3.0]) than in the general population. Country/subregion and population explained the vast majority of the variation in genotype 3 distribution (77.9%), mostly through the country/subregion variable.

A sensitivity analysis (Table S1) was performed in which the meta-regressions were performed excluding countries in which genotype 3 was the most dominant genotype (Afghanistan and Pakistan but not Iran[7]). The analysis was conducted to assess the purported global association between this genotype and PWID.[6] It

TABLE 1 Univariable and multivariable meta-regression models for hepatitis C virus (HCV) genotypes in the Middle East and North Africa (MENA)

			Univariable analysis				Multivariable analysis		
		Number of studies	RR (95% CI)	*P* value	LR test *P* value	Variance explained (adjusted R^2 (%))	ARR (95% CI)	*P* value	Variance explained (adjusted R^2 (%))
Genotype 1									
Population classification	General population	32	1	…			1	…	
	High-risk clinical populations	63	2.0 (1.4-3.0)	<.001			1.2 (1.0-1.5)	.098	
	Populations at intermediate risk	16	0.8 (0.4-1.6)	.605			1.0 (0.7-1.4)	.927	
	Populations with liver-related conditions	28	0.6 (0.3-0.9)	.018			1.1 (0.8-1.4)	.619	
	PWID	13	1.2 (0.7-2.1)	.569			0.9 (0.6-1.2)	.378	
	Special clinical populations	13	1.5 (0.8-3.1)	.210			1.3 (0.9-1.9)	.229	
	Mixed populations	10	1.1 (0.6-2.1)	.784	<.001	22.0	0.9 (0.6-1.2)	.367	
Country/subregion	Egypt	38	1	…			1	…	
	Afghanistan	3	5.5 (3.0-10.3)	<.001			6.5 (3.3-12.8)	<.001	
	Gulf[a]	11	6.8 (4.7-9.8)	<.001			6.1 (4.1-9.0)	<.001	
	Iran	33	7.7 (5.9-10.2)	<.001			7.2 (5.4-9.6)	<.001	
	Fertile Crescent[b]	45	5.7 (4.3-7.5)	<.001			5.3 (4.0-7.1)	<.001	
	Maghreb[c]	29	10.8 (8.3-14.2)	<.001			10.2 (7.7-13.5)	<.001	
	Pakistan	16	1.4 (1.0-2.0)	.075	<.001	83.1	1.3 (0.9-1.9)	.111	84.4[d]
Genotype 2									
Population classification	General population	32	1	…			1	…	
	High-risk clinical populations	63	2.9 (1.2-7.0)	.020			2.3 (1.0-5.5)	.056	
	Populations at intermediate risk	16	3.9 (1.2-12.6)	.025			5.1 (1.7-15.7)	.005	
	Populations with liver-related conditions	28	1.6 (0.6-4.5)	.364			1.4 (0.5-3.8)	.465	
	PWID	13	2.9 (0.8-10.5)	.110			2.9 (0.9-10.0)	.086	
	Special clinical populations	13	1.3 (0.3-7.0)	.720			1.0 (0.2-5.3)	.961	
	Mixed populations	10	3.1 (0.9-11.0)	.075	.176	3.0	3.0 (0.9-9.6)	.069	
Country/subregion	Egypt	38	1	…			1	…	
	Afghanistan	3	0.6 (0.0-25.4)	.774			0.4 (0.0-21.6)	.668	
	Gulf[a]	11	3.8 (1.2-11.9)	.021			5.0 (1.4-17.3)	.012	
	Iran	33	1.4 (0.5-3.5)	.512			1.4 (0.5-4.0)	.576	
	Fertile Crescent[b]	45	3.4 (1.3-8.9)	.011			3.4 (1.3-9.2)	.017	
	Maghreb[c]	29	7.4 (3.0-18.0)	<.001			7.1 (2.6-19.2)	<.001	
	Pakistan	16	3.6 (1.4-9.5)	.009	<.001	23.2	4.8 (1.7-13.6)	.003	28.8[d]

(Continues)

TABLE 1 (Continued)

			Univariable analysis				Multivariable analysis		
		Number of studies	RR (95% CI)	*P* value	LR test *P* value	Variance explained (adjusted R^2 (%))	ARR (95% CI)	*P* value	Variance explained (adjusted R^2 (%))
Genotype 3									
Population classification	General population	32	1	…			1	…	
	High-risk clinical populations	63	1.0 (0.5-2.2)	.983			0.9 (0.6-1.4)	.646	
	Populations at intermediate risk	16	0.6 (0.2-2.2)	.430			1.9 (0.8-4.2)	.124	
	Populations with liver-related conditions	28	1.4 (0.5-3.7)	.486			1.3 (0.7-2.4)	.330	
	PWID	13	3.1 (1.1-8.5)	.029			1.7 (1.0-3.0)	.074	
	Special clinical populations	13	0.8 (0.2-3.4)	.745			1.4 (0.5-3.7)	.518	
	Mixed populations	10	0.5 (0.1-1.6)	.228	.055	13.2	0.8 (0.4-1.6)	.525	
Country/subregion	Egypt	38	1	…			1	…	
	Afghanistan	3	60.9 (21.5-172.3)	<.001			45.4 (14.3-143.8)	<.001	
	Gulf[a]	11	7.5 (2.5-22.9)	<.001			7.5 (2.3-24.6)	<.001	
	Iran	33	33.8 (15.6-73.0)	<.001			43.9 (18.9-101.8)	<.001	
	Fertile Crescent[b]	45	9.2 (4.0-21.2)	<.001			11.2 (4.6-27.0)	<.001	
	Maghreb[c]	29	4.4 (1.9-10.3)	<.001			5.4 (2.2-13.1)	<.001	
	Pakistan	16	71.7 (32.4-158.9)	<.001	<.001	77.0	69.6 (31.2-155.5)	<.001	77.9[d]
Genotype 4									
Population classification	General population	32	1	…			1	…	
	High-risk clinical populations	63	0.3 (0.2-0.7)	.004			0.8 (0.6-1.1)	.250	
	Populations at intermediate risk	16	1.3 (0.5-3.5)	.580			1.0 (0.7-1.5)	.915	
	Populations with liver-related conditions	28	0.8 (0.4-1.9)	.654			1.0 (0.7-1.3)	.957	
	PWID	13	0.4 (0.1-1.2)	.104			1.0 (0.6-1.7)	.851	
	Special clinical populations	13	1.3 (0.5-3.9)	.583			1.0 (0.7-1.5)	.985	
	Mixed populations	10	0.6 (0.2-1.8)	.341	.007	9.9	0.8 (0.5-1.3)	.348	
Country/subregion	Egypt	38	1	…			1	…	
	Afghanistan	3	0.0 (0.0-0.5)	.023			0.0 (0.0-0.5)	.021	
	Gulf[a]	11	0.5 (0.4-0.7)	<.001			0.5 (0.3-0.8)	.002	
	Iran	33	0.0 (0.0-0.0)	<.001			0.0 (0.0-0.1)	<.001	
	Fertile Crescent[b]	45	0.6 (0.5-0.8)	<.001			0.6 (0.5-0.8)	<.001	
	Maghreb[c]	29	0.1 (0.1-0.1)	<.001			0.1 (0.1-0.1)	<.001	
	Pakistan	16	0.0 (0.0-0.1)	<.001	<.001	91.1	0.0 (0.0-0.1)	<.001	90.3[d]

(Continues)

TABLE 1 (Continued)

			Univariable analysis				Multivariable analysis		
		Number of studies	RR (95% CI)	*P* value	LR test *P* value	Variance explained (adjusted R^2 (%))	ARR (95% CI)	*P* value	Variance explained (adjusted R^2 (%))
Genotype 5									
Population classification	General population	32	1	…			1	…	
	High-risk clinical populations	63	0.3 (0.1-1.0)	.055			0.3 (0.1-1.2)	.087	
	Populations at intermediate risk	16	0.6 (0.1-3.7)	.540			0.7 (0.1-4.6)	.694	
	Populations with liver-related conditions	28	0.7 (0.2-2.7)	.594			1.0 (0.2-4.2)	.956	
	PWID	13	1.1 (0.2-5.7)	.875			1.9 (0.3-10.9)	.478	
	Special clinical populations	13	6.6 (1.4-30.2)	.015			12.2 (2.4-62.7)	.003	
	Mixed populations	10	0.1 (0.0-0.8)	.031	<.001	45.9	0.2 (0.0-1.2)	.080	
Country/subregion	Egypt	38	1	…			1	…	
	Afghanistan	3	1.7 (0.0-86.2)	.778			1.0 (0.0-59.0)	.995	
	Gulf[a]	11	3.3 (0.6-18.9)	.187			1.1 (0.2-5.7)	.945	
	Iran	33	0.5 (0.1-2.1)	.323			0.9 (0.2-4.5)	.929	
	Fertile Crescent[b]	45	2.3 (0.6-8.5)	.227			4.7 (1.2-17.6)	.024	
	Maghreb[c]	29	0.5 (0.1-2.1)	.313			1.1 (0.2-5.5)	.881	
	Pakistan	16	0.9 (0.2-4.5)	.940	.157	11.5	1.2 (0.3-5.8)	.789	57.3[d]

Abbreviations: ARR, adjusted relative risk; CI, confidence interval; LR, likelihood ratio; PWID, people who inject drugs; RR, relative risk.

[a]Countries include Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, and United Arab Emirates.

[b]Countries include Iraq, Jordan, Lebanon, Palestine, and Syria.

[c]Countries include Algeria, Libya, Mauritania, Morocco, and Tunisia.

[d]The adjusted R-squared for the full model.

was found that there is indeed strong evidence for an association between this genotype and PWID (ARR of 2.7 [95% CI: 1.2-5.8]). The sensitivity analysis also confirmed the strong evidence for variation by country/subregion—country/subregion and population explained the majority of the variation (66.4%), mostly through the country/subregion variable.

3.4 | Genotype 4

There was strong evidence for variation in genotype 4 distribution by country/subregion, with most countries having substantially lower (Gulf and Fertile Crescent), or much lower (Afghanistan, Iran, Maghreb, and Pakistan) presence of this genotype compared with Egypt. No significant evidence was found for variation in genotype 4 distribution by population, probably reflecting the broadly disseminated nature of the genotype 4 epidemic in Egypt.[7,10] Country/subregion and population explained the vast majority of the variation in genotype 4 distribution (90.3%), nearly all of which through the country/subregion variable.

3.5 | Genotype 5

Unlike the other genotypes, most of the variation in the distribution of genotype 5 was explained by the population variable, rather than the country/subregion variable. Paradoxically also, compared with the general population, there was strong evidence for *higher* presence of this genotype in special clinical populations, but *lower* presence in high-risk clinical populations. Moreover, of all countries/subregions, only the Fertile Crescent had higher presence of genotype 5 relative to Egypt. Population and country/subregion explained 57.3% of the variation in genotype 5 distribution. These results, which are epidemiologically not easy to interpret, could be an artifact of the very low presence of this genotype in the MENA region.[7] Genotype 5 was identified in only 3.9% of all genotype studies, with only 0.1% of infections being with this genotype.

3.6 | Genotype 6 and genotype 7

There were too few studies in which genotype 6 was identified (1.7%), resulting in very broad confidence intervals of limited implications, thus no analyses are reported for this genotype. No study identified the presence of genotype 7 in MENA.

4 | DISCUSSION

We used a quantitative analytical approach to investigate epidemiological associations for HCV genotypes, with application to the MENA region. The utility of this approach was demonstrated—the study yielded estimates for the differences in genotype distributions by country/subregion and by population type. Overall, country/subregion explained most of the variation, highlighting geography as the *principal* determinant of genotype distribution. Interestingly, we found evidence for an association between genotype 1 and high-risk clinical populations, possibly explaining, with the global presence of these populations, the common presence of this genotype across countries.[6] This finding also supports existing literature suggesting such an association.[6] We further found an association between genotype 3 and PWID, thereby supporting an apparently global role for this genotype in HCV transmission through injecting drug use.[6] While these findings were generated for MENA, they may reflect generic results of global relevance.

Genotype epidemiology in the region may have been influenced by several factors. The importation of contaminated blood products, before the onset of blood screening, primarily from Western countries, has been linked to a fraction of reported HIV cases,[32,33] and presumably helped disseminate HCV genotype 1 across the region.[6] Genotype 1 was ubiquitous across most countries and subregions of MENA, which may also be attributed to population movement links to countries outside of MENA, as genotype 1 is the most common genotype globally.[6,30] For example, the presence of genotype 1 was highest in the Maghreb subregion, almost 11-fold higher than in Egypt, a subregion which has strong migration links with western and southern Europe.[34,35]

The emerging HIV epidemics among PWID in MENA, and specifically in Afghanistan, Iran, and Pakistan, have been linked to overlapping injecting networks across these countries.[36-38] This may have (partially) contributed to the relatively larger presence of genotype 3 among PWID in these countries. A strong presence of genotype 4 was found in Egypt. Phylogenetic evidence has shown that genotype 4 in this country originated from central Africa,[39] and circulated endemically until the mass expansion of the HCV epidemic through the parenteral antischistosomal therapy (PAT) campaigns and other healthcare practices.[10,11,39-43] Genotype 4 was also found to be present in countries that host large migrant labor populations from Egypt,[44] such as in countries of the Fertile Crescent[13] and Gulf[26] subregions of MENA.[7,18]

This study had limitations. HCV genotype data were not available for several countries. The number of studies also varied by population type and country/subregion, and the sample size of genotyped individuals was small for a number of studies—we may not have had sufficient statistical power to discern specific associations. This may explain the lack of a clear interpretation/identification of epidemiological associations for genotype 5. We assessed associations for specific key factors that were available in extracted data, but we were unable to assess the role of a broader set of factors. This may clarify why most variation in genotype 2 distribution remained unexplained. Despite these limitations, we were able to utilize a breadth of genotype data that was systematically gathered and that allowed us to conduct such analysis, yielding relevant inferences about genotype distribution and HCV transmission dynamics.

In conclusion, geography appears to be the principal determinant of HCV genotype distribution. Genotype 1 is associated with transmission through high-risk clinical procedures, such as blood transfusions, hemodialysis, and medical injections; while genotype 3 is associated with transmission through injecting drug use. These findings

demonstrate the power of such an analytical approach, which if extended to other regions and globally, may yield relevant epidemiological inferences that can inform control and treatment programs.

ACKNOWLEDGMENTS

This publication was made possible by NPRP grant number 12S-0216-190094 and NPRP grant number 9-040-3-008, 12S-0216-190094 from the Qatar National Research Fund (a member of Qatar Foundation). The statements made herein are solely the responsibility of the authors. The authors are also grateful for support provided by the Biostatistics, Epidemiology, and Biomathematics Research Core at Weill Cornell Medicine-Qatar. The open-access publication of this article was funded by the Qatar National Library.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

SM conducted data extraction and analyses and wrote the first draft of the paper. LJA conceived and led the design of the study, analyses, and drafting of the article. All authors contributed to the extraction of data and writing of the manuscript.

ORCID

Laith J. Abu-Raddad http://orcid.org/0000-0003-0790-0506

REFERENCES

1. Stanaway JD, Flaxman AD, Naghavi M, et al. The global burden of viral hepatitis from 1990 to 2013: findings from the Global Burden of Disease Study 2013. *Lancet*. 2016;388(10049):1081-1088.
2. Chemaitelly H, Mahmud S, Chaabna K, Kouyoumjian SP, Mumtaz GR, Abu-Raddad LJ. *The Epidemiology of Hepatitis C Virus in the World Health Organization Eastern Mediterranean Region: Implications for Strategic Action*. Geneva, Switzerland: World Health Organization; 2019.
3. WHO. Global Hepatitis Report, 2017; 2017. http://www.who.int/hepatitis/publications/global-hepatitis-report2017/en/
4. Lauer GM, Walker BD. Hepatitis C virus infection. *N Engl J Med*. 2001;345(1):41-52.
5. Adler M, Goubau P, Nevens F, Van Vlierberghe H. Hepatitis C virus: the burden of the disease. *Acta Gastroenterol Belg*. 2002;65(2):83-86.
6. Messina JP, Humphreys I, Flaxman A, et al. Global distribution and prevalence of hepatitis C virus genotypes. *Hepatology*. 2015;61(1):77-87.
7. Mahmud S, Al-Kanaani Z, Chemaitelly H, Chaabna K, Kouyoumjian SP, Abu-Raddad LJ. Hepatitis C virus genotypes in the Middle East and North Africa: distribution, diversity, and patterns. *J Med Virol*. 2018;90(1):131-141.
8. Robaeys G, Bielen R, Azar DG, Razavi H, Nevens F. Global genotype distribution of hepatitis C viral infection among people who inject drugs. *J Hepatol*. 2016;65(1):1094-1103.
9. Zein NN. Clinical significance of hepatitis C virus genotypes. *Clin Microbiol Rev*. 2000;13(2):223-235.
10. Kouyoumjian S, Chemaitelly H, Abu-Raddad LJ. Characterizing hepatitis C virus epidemiology in Egypt: systematic reviews, meta-analyses, and meta-regressions. *Sci Rep*. 2018;8(1):1661.
11. Mohamoud YA, Mumtaz GR, Riome S, Miller D, Abu-Raddad LJ. The epidemiology of hepatitis C virus in Egypt: a systematic review and data synthesis. *BMC Infect Dis*. 2013;13(1):288.
12. Mahmud S, Akbarzadeh V, Abu-Raddad LJ. The epidemiology of hepatitis C virus in Iran: systematic review and meta-analyses. *Sci Rep*. 2018;8(1):150.
13. Chemaitelly H, Chaabna K, Abu-Raddad LJ. The epidemiology of hepatitis C virus in the fertile crescent: systematic review and meta-analysis. *PLOS One*. 2015;10(8):e0135281.
14. Fadlalla FA, Mohamoud YA, Mumtaz GR, Abu-Raddad LJ. The epidemiology of hepatitis C virus in the Maghreb region: systematic review and meta-analyses. *PLOS One*. 2015;10(3):e0121873.
15. Chaabna K, Kouyoumjian SP, Abu-Raddad LJ. Hepatitis C virus epidemiology in Djibouti, Somalia, Sudan, and Yemen: systematic review and meta-analysis. *PLOS One*. 2016;11(2):e0149966.
16. Chemaitelly H, Mahmud S, Rahmani AM, Abu-Raddad LJ. The epidemiology of hepatitis C virus in Afghanistan: systematic review and meta-analysis. *Int J Infect Dis*. 2015;40:54-63.
17. Al Kanaani Z, Mahmud S, Kouyoumjian SP, Abu-Raddad LJ. The epidemiology of hepatitis C virus in Pakistan: systematic review and meta-analyses. *R Soc Open Science*. 2018;5(4):180257.
18. Mahmud S, Kouyoumjian SP, Al Kanaani Z, Chemaitelly H, Abu-Raddad LJ. Individual-level key associations and modes of exposure for hepatitis C virus infection in the Middle East and North Africa: a systematic synthesis. *Ann Epidemiol*. 2018;28:452-461.
19. Harfouche M, Chemaitelly H, Kouyoumjian SP, et al. Hepatitis C virus viremic rate in the Middle East and North Africa: Systematic synthesis, meta-analyses, and meta-regressions. *PLOS One*. 2017;12(10):e0187177.
20. Harfouche M, Chemaitelly H, Mahmud S, et al. Epidemiology of hepatitis C virus among hemodialysis patients in the Middle East and North Africa: systematic syntheses, meta-analyses, and meta-regressions. *Epidemiol Infect*. 2017;145:3243-3263.
21. Ayoub H, Abu-Raddad LJ. Impact of treatment on hepatitis C virus transmission and incidence in Egypt: A case for treatment as prevention. *J Viral Hepatitis*. 2017;24(6):486-495.
22. Ayoub HH, Al Kanaani Z, Abu-Raddad LJ. Characterizing the temporal evolution of the hepatitis C virus epidemic in Pakistan. *J Viral Hepatitis*. 2018;25:670-679.
23. Chemaitelly H, Mahmud S, Kouyoumjian SP, Al-Kanaani Z, Hermez JG, Abu-Raddad LJ. Who to test for hepatitis C virus in the Middle East and North Africa?: Pooled analyses of 2,500 prevalence measures including 49 million tests. *Hepatol Commun*. 2019;3:325-339.
24. Ayoub HH, Chemaitelly H, Omori R, Abu-Raddad LJ. Hepatitis C virus infection spontaneous clearance: has it been underestimated? *Int J Infect Dis*. 2018;75:60-66.
25. Ayoub HH, Abu-Raddad LJ. Treatment as prevention for hepatitis C virus in Pakistan: mathematical modelling projections. *BMJ Open*. 2019;9(5):e026600.
26. Mohamoud YA, Riome S, Abu-Raddad LJ. Epidemiology of hepatitis C virus in the Arabian Gulf countries: systematic review and meta-analysis of prevalence. *Int J Infect Dis*. 2016;46:116-125.
27. Higgins JP, Green S. Cochrane handbook for systematic reviews of interventions. Vol 4. Hoboken, New Jersey: John Wiley & Sons; 2011.
28. Moher D, Liberati A, Tetzlaff J, Altman DG PRISMA group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLOS Med*. 2009;6:e1000097.
29. Lavanchy D. Evolving epidemiology of hepatitis C virus. *Clin Microbiol Infect*. 2011;17(2):107-115.

30. Gower E, Estes C, Blach S, Razavi-Shearer K, Razavi H. Global epidemiology and genotype distribution of the hepatitis C virus infection. *J Hepatol*. 2014;61(1 suppl):S45-S57.
31. Nelson PK, Mathers BM, Cowie B, et al. Global epidemiology of hepatitis B and hepatitis C in people who inject drugs: results of systematic reviews. *Lancet*. 2011;378(9791):571-583.
32. Abu-Raddad LJ, Akala FA, Semini I, Riedner G, Wilson D, Tawil O. *Characterizing the HIV/AIDS Epidemic in the Middle East and North Africa: Time for Strategic Action*. Washington, DC: World Bank; 2010.
33. Mohamoud YA, Miller FD, Abu-Raddad LJ. Potential for human immunodeficiency virus parenteral transmission in the Middle East and North Africa: an analysis using hepatitis C virus as a proxy biomarker. *World J Gastroenterol*. 2014;20(36):12734-12752.
34. Sievers W, Fassman H, Bommes M. *Migration from the Middle East and North Africa to Europe: Past Developments, Current Status and Future Potentials*. Amsterdam: Amsterdam University Press; 2014.
35. International Organization for Migration. Global migration flows, 2015. https://www.iom.int/world-migration. Accessed May, 2017.
36. Mumtaz GR, Weiss HA, Abu-Raddad LJ. Hepatitis C virus and HIV infections among people who inject drugs in the Middle East and North Africa: a neglected public health burden? *J Int AIDS Soc*. 2015;18(1):20582.
37. Mahmud S, Mumtaz GR, Chemaitelly H, et al. The status of hepatitis C virus infection among people who inject drugs in the Middle East and North Africa. (under review).
38. Mumtaz GR, Weiss HA, Thomas SL, et al. HIV among people who inject drugs in the Middle East and North Africa: systematic review and data synthesis. *PLOS Med*. 2014;11(6):e1001663.
39. Iles JC, Raghwani J, Harrison GLA, et al. Phylogeography and epidemic history of hepatitis C virus genotype 4 in Africa. *Virology*. 2014;464-465(100):233-243.
40. Ayoub H, Chemaitelly H, Kouyoumjian SP, Abu-Raddad LJ Characterizing the historical role of parenteral antischistosomal therapy in hepatitis C virus transmission in Egypt. (under review).
41. Frank C, Mohamed MK, Strickland GT, et al. The role of parenteral antischistosomal therapy in the spread of hepatitis C virus in Egypt. *Lancet*. 2000;355(9207):887-891.
42. Miller FD, Abu-Raddad LJ. Evidence of intense ongoing endemic transmission of hepatitis C virus in Egypt. *Proc Natl Acad Sci U S A*. 2010;107(33):14757-14762.
43. Cuadros DF, Branscum AJ, Miller FD, Abu-Raddad LJ. Spatial epidemiology of hepatitis C virus infection in Egypt: analyses and implications. *Hepatology*. 2014;60(4):1150-1159.
44. Feiler G. Migration and recession: Arab labor mobility in the Middle East, 1982-89. *Popul Dev Rev*. 1991;17:134-155.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Mahmud S, Chemaitelly HS, Kouyoumjian SP, Al Kanaani Z, Abu-Raddad LJ. Key associations for hepatitis C virus genotypes in the Middle East and North Africa. *J Med Virol*. 2019;1–8. https://doi.org/10.1002/jmv.25614