


Hepatitis C virus genotypes in the Middle East and North Africa: Distribution, diversity, and patterns

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Our objective was to characterize the distribution, diversity and patterns of hepatitis C virus (HCV) genotypes in the Middle East and North Africa (MENA). Source of data was a database of HCV genotype studies in MENA populated using a series of systematic literature searches. Pooled mean proportions were estimated for each genotype and by country using DerSimonian-Laird random-effects meta-analyses. Genotype diversity within countries was assessed using Shannon Diversity Index. Number of chronic infections by genotype and country was calculated using the pooled proportions and country-specific numbers of chronic infection. Analyses were conducted on 338 genotype studies including 82 257 genotyped individuals. Genotype 1 was dominant ($\geq 50\%$) in Algeria, Iran, Morocco, Oman, Tunisia, and UAE, and was overall ubiquitous across the region. Genotype 2 was common (10-50%) in Algeria, Bahrain, Libya, and Morocco. Genotype 3 was dominant in Afghanistan and Pakistan. Genotype 4 was dominant in Egypt, Iraq, Jordan, Palestine, Qatar, Saudi Arabia, and Syria. Genotypes 5, 6, and 7 had limited or no presence across countries. Genotype diversity varied immensely throughout MENA. Weighted by population size, MENA's chronic infections were highest among genotype 3, followed by genotype 4, genotype 1, genotype 2, genotype 5, and genotype 6. Despite ubiquitous presence of genotype 1, the vast majority of chronic infections were of genotypes 3 or 4, because of the sizable epidemics in Pakistan and Egypt. Three sub-regional patterns were identified: genotype 3 pattern centered in Pakistan, genotype 4 pattern centered in Egypt, and genotype 1 pattern ubiquitous in most MENA countries.

KEYWORDS

epidemiology, genotype, Hepatitis C virus, meta-analysis, Middle East and North Africa, transmission

1 | INTRODUCTION

Hepatitis C virus (HCV) is a blood-borne pathogen, with the majority of chronically infected individuals showing clinical manifestations 20-30

years after the onset of infection.¹ Chronic HCV infection causes several morbidities, such as liver cirrhosis and liver cancer, and is a main indication for liver transplantation.²⁻⁴ HCV related morbidity and mortality place a burden on healthcare systems worldwide, as an

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estimated 62–79 million people are chronically infected, globally.⁵ The Middle East and North Africa (MENA) region is the most affected by HCV infection, with over 15 million chronically infected individuals.^{5,6}

HCV demonstrates substantial genetic diversity and can be classified into seven main genotypes, numbered from one to seven, and 67 subtypes.⁷ HCV genotype distribution varies across the globe.^{7,8} Genotypes 1 and three are prevalent genotypes worldwide, while genotype two is common in West Africa and South America, and genotypes 4 and 6 are common in Central/North Africa and East/Southern Asia, respectively.^{7,8}

Knowledge of HCV genotype distribution, diversity, and patterns contribute to effective control of HCV infection.⁹ Genotype distribution can reveal inferences about the modes of transmission and sources of infection.^{7,10} Importantly, HCV genotype is a predictor of response to direct-acting antiviral (DAA) treatment, and is therefore integral in selection and duration of interferon-free DAA regimens.¹¹ As such, this study aims to characterize the distribution, diversity, and patterns of HCV genotypes in MENA by (1) estimating the country-specific pooled mean proportions of HCV genotypes; (2) assessing the country-specific genotype diversity; and (3) estimating the country-specific number of chronically infected individuals by genotype. This study was conducted under the umbrella of the MENA HCV Epidemiology Synthesis Project, an on-going effort to characterize HCV epidemiology and inform key public health research, policy and programming priorities in MENA.^{12–20}

2 | MATERIALS AND METHODS

2.1 | Data sources

The source of data for our study was the MENA HCV Epidemiology Synthesis Project database, a comprehensive database of HCV epidemiological measures.^{12–20} The database consists of several sub-databases such as an HCV genotype frequency sub-database comprised of 338 HCV genotype studies among 82 257 participants, an HCV antibody prevalence sub-database comprised of 2543 antibody prevalence studies among 51 598 736 participants, and an HCV RNA prevalence (among antibody positive persons) database comprised of 178 RNA prevalence studies among 19 593 HCV antibody positive participants. The MENA HCV Epidemiology Synthesis Project database was populated through a series of systematic reviews for HCV infection across MENA.^{12–20} The reviews were informed by Cochrane Collaboration handbook²¹ and reported their findings using the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) guidelines.²²

Data sources for these reviews included peer-reviewed publications identified through international scientific databases (PubMed and Embase), regional and country-level scientific databases (World Health Organization [WHO] Index Medicus for the Eastern Mediterranean Region, the Iraqi Academic Scientific Journals' database, Iran's Scientific Information Database, among others), MENA HIV/AIDS Epidemiology Synthesis Project database,^{23,24} abstract archives of non-indexed international conferences, and gray literature comprised of public health reports and routine data reporting. Broad search criteria were used combining medical index terms exploded to cover all subheadings and free

text terms for HCV and country names, to ensure inclusiveness. No language restrictions were used as non-English articles were extracted by native speakers. Screening of articles was restricted to those published after 1989, the year in which HCV was first identified.^{25,26}

Our definition of MENA included 24 countries: Afghanistan, Algeria, Bahrain, Djibouti, Egypt, Iran, Iraq, Jordan, Kuwait, Lebanon, Libya, Mauritania, Morocco, Oman, Pakistan, Palestine, Qatar, Saudi Arabia, Somalia, Sudan, Syria, Tunisia, the United Arab Emirates (UAE), and Yemen. Genotype information for all articles retrieved during these systematic literatures searches were extracted and subsequently used to populate the HCV genotype sub-database. Individuals with untypeable HCV genotypes were removed from the overall sample size in each study. Individuals with mixed HCV genotypes and subtype contributed separately to the quantification of each genotype and subtype.

2.2 | Meta-analyses of genotype proportions

DerSimonian-Laird random-effects meta-analyses with inverse variance weighting²⁷ were performed to estimate the country-specific pooled mean proportion for each HCV genotype and the corresponding 95% confidence interval (CI). The variance was stabilized using the Freeman-Tukey type arcsine square-root transformation.²⁸ Cochran's Q test was conducted to assess heterogeneity in effect size; a *P*-value <0.1 was considered significant.^{27,29} The I^2 was calculated to assess the proportion of between-study variation in effect size that is due to true differences between studies rather than chance.²⁷ The meta-analyses were performed when at least three measures were available for each pooled category. The mean of reported proportions was calculated whenever only two measures were available. A genotype was considered dominant if the mean proportion was $\geq 50\%$, common if the mean proportion was between 10% and 50%, and limited if the mean proportion was <10%. Statistical analyses were performed on R version 3.1.2,³⁰ and geographical mapping was conducted on Tableau 10.1.³¹

2.3 | Analyses of genotype diversity

The diversity of HCV genotypes was assessed by calculating the Shannon Diversity Index, with higher scores indicating more diversity.³² Assuming equal distribution of the seven HCV genotypes (that is highest diversity possible),⁷ the highest Shannon Diversity Index score attainable is 1.95.³²

2.4 | Estimation of number of HCV chronically infected individuals with each genotype

The country-specific number of chronically infected individuals with each genotype was calculated by multiplying the country-specific pooled mean proportion for each genotype by the number of individuals with chronic HCV infection in each country as estimated by Chemaitelly et al³³ The latter was calculated based on mathematical modeling and meta-analyses using the HCV antibody prevalence and HCV RNA prevalence sub-databases of the MENA HCV Epidemiology Synthesis Project database.^{12–20} The country-specific pooled mean proportion for each genotype was adjusted so that the sum of all

genotype proportions totaled 100%. Demographics for each country was obtained from the United Nations 2015 World Population Prospects database.³⁴

3 | RESULTS

3.1 | Scope of the evidence

Supplementary Table S1 lists the details of the 338 identified HCV genotype studies in MENA including 82 257 genotyped individuals. Genotype information was available for 20 of the 24 included countries, 15 of which had sufficient number of studies to conduct meta-analyses (Table 1). There were too few studies from Bahrain, Kuwait, Oman, Qatar, and Sudan to perform meta-analyses. Additionally, the study from Sudan had an insignificant sample size ($n = 4$; all of which were genotype 4), and therefore was excluded from further analyses. No studies were identified from Djibouti, Mauritania, Somalia, and Yemen; these countries were also excluded from further analysis. Pakistan had the largest number of studies ($n = 92$) and the largest sample size of genotyped individuals ($N = 36\,111$). Iran was second with 66 studies including 23 134 genotyped individuals. Each of the remaining countries had less than 10 000 genotyped individuals (Table 1).

The genotyped populations varied across these studies but often included clinical populations at high-risk of exposure to HCV such as thalassemia, hemophilia, and hemodialysis patients (Supplementary Table S1). Other genotyped populations included chronic liver disease patients, people who inject drugs (PWID), blood donors, pregnant women, and healthcare workers, among others.

3.2 | Meta-analyses of the distribution of HCV genotypes

Table 1 lists the estimated pooled mean proportion for each HCV genotype by country. Figure 1 displays the distribution of genotypes by country. Figure 2 maps the dominant genotype by country.

3.2.1 | Genotype 1

Genotype 1 was dominant ($\geq 50\%$) in Algeria, Iran, Lebanon, Morocco, Oman, Tunisia, and UAE, with the highest level observed in Tunisia at 85.9% (95%CI: 78.0-92.5). Genotype 1 was common (10-50%) in Afghanistan, Bahrain, Iraq, Jordan, Kuwait, Lebanon, Libya, Palestine, Qatar, Saudi Arabia, and Syria. Genotype 1 was limited ($\leq 10\%$) in Pakistan and Egypt. For the whole MENA sample, the pooled mean proportion for genotype 1 was 30.2% (95%CI: 26.7-33.7).

3.2.2 | Genotype 2

Genotype 2 was not dominant in any MENA country, but was common in Algeria, Bahrain, Morocco, and Libya, with the highest level observed in Libya at 17.7% (95%CI: 15.3-20.0). Genotype 2 was limited in remaining countries, with little to no cases observed in each of Afghanistan, Iraq, Jordan, Kuwait, Palestine, and Syria. For the whole

MENA sample, the pooled mean proportion for Genotype 2 was 2.5% (95%CI: 1.6-3.4).

3.2.3 | Genotype 3

Genotype 3 was dominant in Afghanistan and Pakistan, with the highest level observed in Pakistan at 81.4% (95%CI: 77.9-84.8). Genotype 3 was common in Bahrain, Iran, Kuwait, Libya, Qatar, and UAE. Genotype 3 was limited in Algeria, Iraq, Lebanon, Morocco, Oman, Saudi Arabia, Syria, and Tunisia. Little to no cases were observed in each of Egypt, Jordan, and Palestine. For the whole MENA sample, the pooled mean proportion for Genotype 3 was 26.7% (95% CI: 22.3-31.4).

3.2.4 | Genotype 4

Genotype 4 was dominant in Egypt, Iraq, Jordan, Kuwait, Libya, Qatar, Saudi Arabia, and Syria, with the highest level observed in Egypt at 93.1% (95%CI: 89.8-95.9). Genotype 4 was common in Bahrain, Kuwait, Lebanon, Libya, Oman, and UAE. Genotype 4 was limited in Algeria, Iran, Morocco, Pakistan, and Tunisia. No cases were observed in Afghanistan. For the whole MENA sample, the pooled mean proportion for Genotype 4 was 17.5% (95%CI: 14.2-21.0).

3.2.5 | Genotypes 5, 6, and 7

Genotype 5 was neither dominant nor common in any MENA country. It was limited in Syria at 7.6% (95%CI: 0.0-23.0), but otherwise was not observed, or was observed at extremely low levels, in the remaining MENA countries. For the whole MENA sample, the pooled mean proportion for Genotype 5 was 0.0% (95%CI: 0.0-0.0).

Genotype 6 was not observed or was observed at extremely low levels in all countries, leading to a pooled mean proportion of 0.0% (95%CI: 0.0-0.0) for the whole MENA sample. Genotype 7 was not observed in any country.

3.3 | Genotype diversity

Supplementary Table S2 lists the estimated genotype diversity by country as assessed using Shannon Diversity Index (H). Figure 3 maps genotype diversity across MENA. Lebanon had the highest genotype diversity ($H = 1.27$ out of 1.95; 68.2%), followed by Bahrain ($H = 1.24$ out of 1.95; 63.7%) and UAE ($H = 1.14$ out of 1.95; 58.8%). Egypt had the lowest diversity ($H = 0.27$ out of 1.95; 14.4%), right behind Pakistan (0.61 out of 1.95; 33.1%) and Afghanistan (0.66 out of 1.95; 34.1%).

3.4 | Number of HCV chronically infected individuals by genotype

Table 2 lists the estimated number of HCV chronically infected individuals by genotype across MENA countries. Overall for the region, the largest number of chronically infected individuals was that for genotype 3 at 6.0 million, followed by genotype 4 at 5.9 million,

TABLE 1 Country-specific pooled mean proportion for each hepatitis C virus (HCV) genotype across the Middle East and North Africa (MENA)

Country	Studies Total N	Samples Total n	Proportion (actual studies) Range (%)	Proportion (meta-analysis)		Heterogeneity measures	
				Mean (%)	95%CI ^a	Q (P-value) ^b	I ² (confidence limits) ^c
Genotype 1							
Afghanistan	3	71	0.0-47.8	34.6	20.8-49.5	1.7 (P = 0.440)	
Algeria	7	3806	55.6-88.8	78.0	70.2-85.0	110.7 (P < 0.001)	
Bahrain	2	107	47.9-55.6	48.6	39.3-58.0		
Egypt	47	5031	0.0-25.0	2.5	1.3-4.1	177.6 (P < 0.001)	
Iran	66	23 134	13.5-100	56.3	52.9-59.6	1022.4 (P < 0.001)	
Iraq	19	681	0.0-71.4	34.7	22.6-47.7	143.1 (P < 0.001)	
Jordan	4	71	0.0-73.3	22.8	0.0-66.8	31.8 (P < 0.001)	
Kuwait	1	108		27.8	20.2-36.9		
Lebanon	20	543	0.0-100	38.9	30.4-47.7	51.7 (P < 0.001)	
Libya	6	4236	28.6-35.8	32.8	31.0-34.7	8.5 (P = 0.132)	
Morocco	13	2636	35.6-100	69.4	53.7-83.2	386.4 (p < 0.001)	
Oman	1	33		54.5	38.0-70.2		
Pakistan	92	36 111	0.0-64.1	9.1	7.4-11.0	1962.9 (P < 0.001)	
Palestine	4	152	8.7-50.0	19.9	7.4-35.6	5.7 (P = 0.129)	
Qatar	1	400		19.8	16.1-23.9		
Saudi Arabia	23	2652	0.0-75.0	34.4	27.5-41.6	213.2 (P < 0.001)	
Syria	3	674	10.0-60.7	33.5	12.1-58.9	13.4 (P < 0.001)	
Tunisia	22	1578	50.0-100	85.9	78.0-92.5	196.2 (P < 0.001)	
UAE	4	233	26.9-75.0	52.4	30.8-73.7	23.5 (P < 0.001)	
MENA	338	82 257	0.0-100	30.2	26.8-33.8	31841 (P < 0.001)	
Genotype 2							
Afghanistan	3	71	0.0-0.0	0.0		0.6 (P = 0.732)	
Algeria	7	3806	8.6-37.0	15.3	9.6-22.0	98.8 (P < 0.001)	
Bahrain	2	107	9.2-33.3	11.2	6.5-18.6		
Egypt	47	5031	0.0-55.6	0.2	0.0-1.1	230.2 (P < 0.001)	
Iran	66	23 134	0.0-38.0	0.4	0.0-1.0	575.1 (P < 0.001)	
Iraq	19	681	0.0-6.0	0.0	0.0-0.0	12.2 (P = 0.838)	
Jordan	4	71	0.0-0.0	0.0	0.0-1.1	0.4 (P = 0.933)	
Kuwait	1	108		0.0	0.0-3.4		
Lebanon	20	543	0.0-80.0	7.4	1.1-16.8	127.6 (P < 0.001)	
Libya	6	4236	13.9-21.2	17.7	15.3-20.0	21.7 (P < 0.001)	
Morocco	13	2636	0.0-63.2	16.7	4.3-34.4	614.8 (P < 0.001)	
Oman	1	33		9.1	3.1-23.6		
Pakistan	92	36 111	0.0-50.8	4.1	2.6-5.8	3041.6 (P < 0.001)	
Palestine	4	152	0.0-4.4	0.0	0.0-1.8	3.9 (P = 0.271)	
Qatar	1	400		0.5	0.1-1.8		
Saudi Arabia	23	2652	0.0-7.4	1.4	0.4-2.8	49.3 (P < 0.001)	
Syria	3	674	0.0-0.8	0.0	0.0-0.2	0.1 (P = 0.928)	
Tunisia	22	1578	0.0-37.5	5.1	1.5-9.9	128.7 (P < 0.001)	
UAE	4	233	0.0-33.3	1.2	0.0-6.5	7.1 (P = 0.067)	
MENA	338	82 257	0.0-63.2	2.5	1.6-3.5	11940.7 (P < 0.001)	
Genotype 3							
Afghanistan	3	71	52.2-100	65.4	50.5-79.2	1.7 (P = 0.437)	
Algeria	7	3806	0.0-10.4	3.0	1.6-4.9	25 (P < 0.001)	

(Continues)

TABLE 1 (Continued)

Country	Studies Total N	Samples Total n	Proportion (actual studies) Range (%)	Proportion (meta-analysis)		Heterogeneity measures	
				Mean (%)	95%CI ^a	Q (P-value) ^b	I ² (confidence limits) ^c
Bahrain	2	107	0.0-20.4	18.7	12.4-27.1		
Egypt	47	5031	0.0-33.3	0.0	0.0-0.5	164.4 (P < 0.001)	72.0 (62.6-79.1)
Iran	66	23 134	0.0-65.7	38.8	35.7-41.9	878.9 (P < 0.001)	92.6 (91.3-93.7)
Iraq	19	681	0.0-21.7	0.2	0.0-3.3	68.8 (P < 0.001)	73.8 (58.9-83.3)
Jordan	4	71	0.0-0.0	0.0	0.0-1.1	0.4 (P = 0.933)	0.0 (0.0-0.0)
Kuwait	1	108		25.0	17.8-33.9		
Lebanon	20	543	0.0-58.6	7.8	2.3-15.3	78.6 (P < 0.001)	75.8 (62.8-84.3)
Libya	6	4236	6.0-21.0	13.7	9.1-19.1	112.7 (P < 0.001)	95.6 (92.6-97.3)
Morocco	13	2636	0.0-50.0	3.2	0.4-7.9	124.6 (P < 0.001)	90.4 (85.4-93.7)
Oman	1	33		9.1	3.1-23.6		
Pakistan	92	36 111	0.0-100	81.4	77.9-84.8	4410.5 (P < 0.001)	97.9 (97.7-98.1)
Palestine	4	152	0.0-8.7	0.0	0.0-7.7	6.7 (P = 0.081)	55.5 (0.0-85.3)
Qatar	1	400		15.8	12.5-19.6		
Saudi Arabia	23	2652	0.0-33.3	0.8	0.0-2.3	75.2 (P < 0.001)	70.7 (55.4-80.8)
Syria	3	674	0.0-1.7	0.3	0.0-1.2	0.2 (P = 0.903)	0.0 (0.0-0.0)
Tunisia	22	1578	0.0-25.0	0.7	0.0-3.4	100.3 (P < 0.001)	79.1 (68.9-85.9)
UAE	4	233	0.0-33.6	11.8	0.1-33.1	32 (P < 0.001)	90.6 (79.0-95.8)
MENA	338	82 257	0.0-100	26.8	22.4-31.5	60629.7 (P < 0.001)	99.4 (99.4-99.5)
Genotype 4							
Afghanistan	3	71	0.0-0.0	0.0	0.0-0.0	0.6 (P = 0.732)	0.0 (0.0-66.6)
Algeria	7	3806	0.0-7.4	1.4	0.6-2.4	14.1 (P = 0.028)	57.5 (1.5-81.6)
Bahrain	2	107	11.1-22.4	21.5	14.8-30.2		
Egypt	47	5031	22.2-100	93.1	89.8-95.9	432.6 (P < 0.001)	89.4 (86.7-91.5)
Iran	66	23 134	0.0-25.0	0.0	0.0-0.1	238.1 (P < 0.001)	72.7 (65.2-78.6)
Iraq	19	681	21.4-100	60.0	46.3-73.1	157.9 (P < 0.001)	88.6 (83.7-92.0)
Jordan	4	71	26.7-100	77.2	33.2-100	31.8 (P < 0.001)	90.6 (78.9-95.8)
Kuwait	1	108		47.2	38.1-56.6		
Lebanon	20	543	0.0-100	31.5	20.6-43.4	102.6 (P > 0.001)	81.5 (72.4-87.6)
Libya	6	4236	27.6-45.3	35.3	30.2-40.6	63.96 (P < 0.001)	92.2 (85.7-95.7)
Morocco	13	2636	0.0-18.8	0.9	0.0-2.8	44.4 (P < 0.001)	72.9 (52.9-84.5)
Oman	1	33		27.3	15.1-44.2		
Pakistan	92	36 111	0.0-17.1	0.1	0.0-0.6	1188.6 (P < 0.001)	92.3 (91.2-93.4)
Palestine	4	152	50.0-85.7	75.0	66.9-82.3	1.6 (P = 0.652)	0.0 (0.0-71.8)
Qatar	1	400		64.0	59.2-68.6		
Saudi Arabia	23	2653	9.4-90.9	56.6	49.0-64.0	225.9 (P < 0.001)	90.3 (86.7-92.9)
Syria	3	674	39.3-60.0	53.8	40.3-67.1	4.1 (P = 0.127)	51.5 (0.0-86.0)
Tunisia	22	1578	0.0-19.4	1.7	0.0-5.3	128 (P < 0.001)	83.6 (76.3-88.7)
UAE	4	233	0.0-46.3	21.3	5.4-42.8	25.6 (P < 0.001)	88.3 (72.5-95.0)
MENA	338	82 257	0.0-100	17.3	14.1-20.6	43318.8 (P < 0.001)	99.2 (99.2-99.3)
Genotype 5							
Afghanistan	3	71	0.0-0.0	0.0	0.0-0.0	0.6 (P = 0.732)	0.0(0.0-66.6)
Algeria	7	3806	0.0-0.9	0.0	0.0-0.0	6.3 (P = 0.389)	5.0 (0.0-72.3)
Bahrain	2	107	0.0-0.0	0.0	0.0-3.5		
Egypt	47	5031	0.0-31.6	0.0	0.0-0.0	45.2 (P = 0.507)	0.0 (0.0-32.6)
Iran	66	23 134	0.0-3.5	0.0	0.0-0.0	89.7 (P = 0.023)	27.5 (1.2-46.8)

(Continues)

TABLE 1 (Continued)

Country	Studies Total N	Samples Total n	Proportion (actual studies) Range (%)	Proportion (meta-analysis)		Heterogeneity measures	
				Mean (%)	95%CI ^a	Q (P-value) ^b	I ² (confidence limits) ^c
Iraq	19	681	0.0-0.0	0.0	0.0-0.0	3.9 (P = 0.100)	0.0 (0.0-0.0)
Jordan	4	71	0.0-0.0	0.0	0.0-1.1	0.4 (P = 0.933)	0.0 (0.0-0.0)
Kuwait	1	108		0.0	0.0-3.4		
Lebanon	20	543	0.0-3.0	0.0	0.0-0.3	4.8 (P = 0.100)	0.0 (0.0-0.0)
Libya	6	4236	0.0-0.1	0.0	0.0-0.1	1.0 (P = 0.959)	0.0 (0.0-0.0)
Morocco	13	2636	0.0-0.1	0.0	0.0-0.0	3.7 (P = 0.988)	0.0 (0.0-0.0)
Oman	1	33		0.0	0.0-10.4		
Pakistan	92	36 111	0.0-4.1	0.0	0.0-0.0	192.6 (P < 0.001)	52.7 (40.0-62.8)
Palestine	4	152	0.0-0.0	0.0	0.0-0.0	1.2 (P < 0.751)	0.0 (0.0-62)
Qatar	1	400		0.0	0.0-1.0		
Saudi Arabia	23	2652	0.0-5.1	0.0	0.0-0.0	31.1 (P < 0.094)	29.3 (0.0-57.6)
Syria	3	674	0.0-30.0	7.6	0.0-23.0	9.1 (P < 0.010)	78.1 (29.4-93.2)
Tunisia	22	1578	0.0-0.0	0.0	0.0-0.0	7.9 (P < 0.996)	0.0 (0.0-0.0)
UAE	4	233	0.0-0.0	0.0	0.0-0.0	0.7 (P < 0.875)	0.0 (0.0-33.7)
MENA	338	82 257	0.0-31.6	0.0	0.0-0.0	706.8 (P < 0.001)	52.3 (45.9-57.8)
Genotype 6							
Afghanistan	3	71	0.0-0.0	0.0	0.0-0.0	0.6 (P = 0.732)	0.0 (0.0-66.6)
Algeria	7	3806	0.0-0.0	0.0	0.0-0.0	2.4 (P = 0.882)	0.0 (0.0-26.2)
Bahrain	2	107	0.0-0.0	0.0	0.0-3.5		
Egypt	47	5031	0.0-0.0	0.0	0.0-0.0	20.3 (P = 0.100)	0.0 (0.0-0.0)
Iran	66	23 134	0.0-0.7	0.0	0.0-0.0	38.8 (P = 0.100)	0.0 (0.0-0.0)
Iraq	19	681	0.0-0.0	0.0	0.0-0.0	3.9 (P = 0.100)	0.0 (0.0-0.0)
Jordan	4	71	0.0-0.0	0.0	0.0-1.1	0.4 (P = 0.933)	0.0 (0.0-0.0)
Kuwait	1	108		0.0	0.0-3.4		
Lebanon	20	543	0.0-0.0	0.0	0.0-0.0	5.0 (P = 0.999)	0.0 (0.0-0.0)
Libya	6	4236	0.0-0.1	0.0	0.0-0.1	0.3 (P = 0.100)	0.0 (0.0-0.0)
Morocco	13	2636	0.0-0.0	0.0	0.0-0.0	6.5 (P = 0.888)	0.0 (0.0-20.1)
Oman	1	33		0.0	0.0-10.4		
Pakistan	92	36 111	0.0-3.4	0.0	0.0-0.0	161 (P < 0.001)	43.5 (27.5-55.9)
Palestine	4	152	0.0-0.0	0.0	0.0-0.0	1.2 (P < 0.751)	0.0 (0.0-62.0)
Qatar	1	400		0.0	0.0-1.0		
Saudi Arabia	23	2652	0.0-0.9	0.0	0.0-0.0	8.2 (P < 0.997)	0.0 (0.0-0.0)
Syria	3	674	0.0-0.0	0.0	0.0-0.0	1.3 (P < 0.524)	0.0 (0.0-83.9)
Tunisia	22	1578	0.0-0.0	0.0	0.0-0.0	7.9 (P < 0.996)	0.0 (0.0-0.0)
UAE	4	233	0.0-0.0	0.0	0.0-0.0	0.7 (P < 0.875)	0.0 (0.0-33.7)
MENA	338	82 257	0.0-3.4	0.0	0.0-0.0	317.3 (P < 0.001)	0.0 (0.0-7.4)

Djibouti, Mauritania, Somalia, Sudan, and Yemen excluded due to either no studies available or small sample size.

^aCI: Confidence interval.

^bQ: The Cochran Q statistic is a measure assessing the existence of heterogeneity in effect size (proportion of each genotype).

^cI²: A measure assessing the magnitude of between-study variation that is due to differences in effect size (proportion of each genotype) across studies rather than chance.

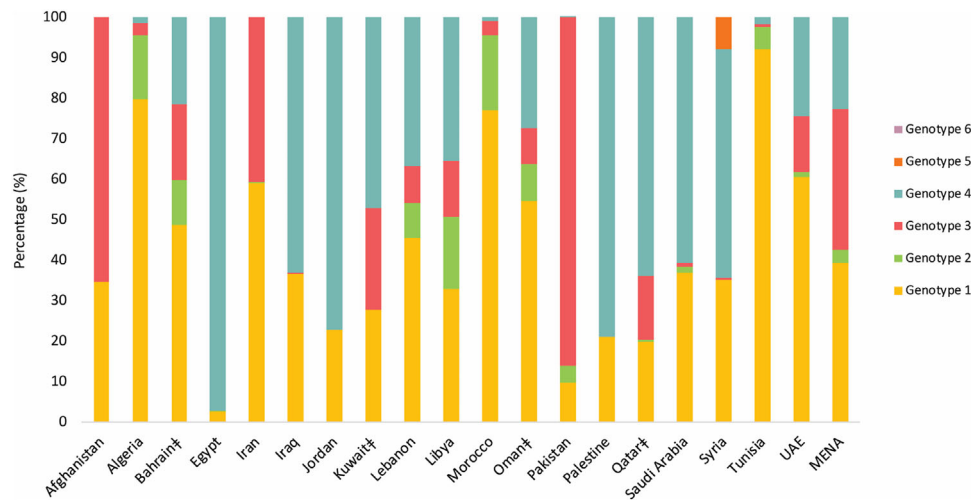


FIGURE 1 The country-specific distribution of hepatitis C virus (HCV) genotypes across the Middle East and North Africa (MENA) region. Legend: ‡ Countries in which less than three studies were available. Djibouti, Mauritania, Somalia, Sudan, and Yemen were excluded either due to no studies available or small sample size

genotype 1 at 2.0 million, and genotype 2 at 0.4 million. Genotype 5 contributed a mere 10 500 infections with virtually no contribution for genotype 6. The vast majority of genotype 3 chronically infected individuals were in Pakistan (5.7 out of 6.0 million), and the vast majority of genotype 4 infected individuals were in Egypt (5.0 out of 5.9 million).

Weighted by population size in each country, the highest proportion of chronically infected individuals was that of genotype 3 (41.9%), followed by genotype 4 (41.0%), genotype 1 (14.2%), genotype 2 (2.9%), genotype 5 (0.1%), and genotype 6 (0.0%).

4 | DISCUSSION

We presented a comprehensive characterization of HCV genotype distribution, diversity, and patterns in MENA. We found that the

distribution varied from one country to another, with evidence for sub-regionalization patterns for specific genotypes. Most chronically infected individuals were infected with genotypes 3 or 4, with nearly equal contributions for each at just over 40%. However, these large contributions merely reflected the dominance of these genotypes in Pakistan (genotype 3) and Egypt (genotype 4), by far the largest two HCV epidemics in MENA. Over 75% of MENA's chronically infected individuals are found in these two countries.³³

While genotype 1 was present throughout the region, and was dominant or common in most countries, it had limited presence in both Egypt and Pakistan, and hence its contribution did not exceed 15%. Genotypes 2, 5, 6, and 7 did not have significant presence in MENA. While there was considerable genotype diversity in most countries, there was limited diversity in both Egypt and Pakistan. These findings inform the current expansion of DAA treatment programs in MENA, and provide insights about the transmission pathways of this infection.

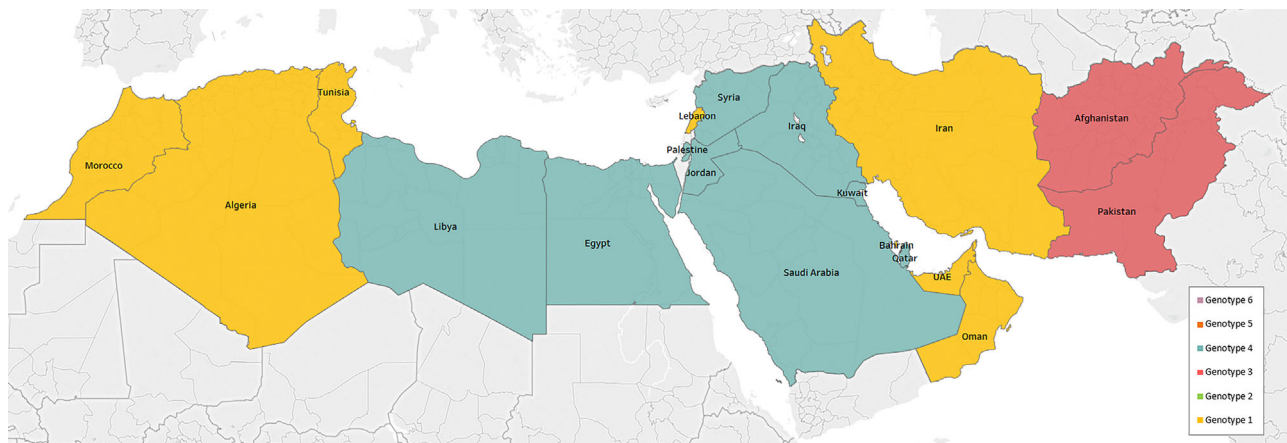


FIGURE 2 Map of the dominant hepatitis C virus (HCV) genotype across countries of the Middle East and North Africa (MENA) region. Legend: Djibouti, Mauritania, Somalia, Sudan, and Yemen were excluded either due to no studies available or small sample size



FIGURE 3 Map showing the genotype diversity across countries of the Middle East and North Africa (MENA) region, quantified by Shannon Diversity Index. Legend: Djibouti, Mauritania, Somalia, Sudan, and Yemen were excluded either due to no studies available or small sample size

The distribution of HCV genotypes in MENA appears to reflect three sub-regional patterns (Figure 2). The first is that of dominance of genotype 3, a pattern found in Pakistan and Afghanistan, and to some extent in Iran (Figures 1 and 2). This pattern is possibly explained by the fact that these are neighboring countries with mass cross-border population movements and porous borders.^{35,36}

The second pattern is that of dominance, or large presence, of genotype 4 which is found in Egypt, its neighboring countries, and/or in countries that host or have hosted large migrant labor populations from Egypt^{15,18,37} (Figures 1 and 2). This pattern is possibly explained by the unique nature of the Egyptian epidemic,^{12,38} which has led to circulation of genotype 4 through population movement to countries with strong links to Egypt. Countries that have imported large Egyptian labor populations included Iraq, Jordan, Kuwait, Libya, Oman, Qatar, Saudi Arabia, and UAE.³⁹ It bears notice, nonetheless, that the circulation of this genotype out of Egypt does not seem to have impacted significantly HCV prevalence in these countries. HCV prevalence in these countries is much lower than that in Egypt.^{12,13,15,18,38}

The third pattern is that of dominance, or large presence, of genotype 1 which is found in the Maghreb sub-region of MENA (Algeria, Morocco, Tunisia, and to some extent Libya), part of the Arabian Gulf sub-region (Oman and UAE), Iran, and to some extent Lebanon (Figure 2). This pattern is similar to the most common global pattern,^{7,9} and may reflect population movement links with countries outside MENA, such as the Maghreb sub-region migration links with Western and Southern Europe.^{40,41} There are also large and diverse expatriate populations in the Arabian Gulf sub-region, and this may have contributed to this pattern.¹⁸

While these three patterns are largely distinct, some overlap is seen such as for countries that border different patterns—Iran and Libya provide two examples (Figures 1 and 2). The Arabian Gulf sub-region also exhibits such overlap with its diverse migrant-population composition—as reflected in the high genotype diversity for the majority of Arabian Gulf countries (Figure 3, Supplementary Table S2). Lastly, genotype 2 was mainly present in the Maghreb sub-region,

possibly because of geographic proximity and population links with West Africa where this genotype is most frequent.^{7,42,43}

Genotype diversity varied across the region. The variability in genotype diversity is probably attributable to factors including, among others, specific historical events, such as the case for Egypt,^{12,38,44} how HCV was introduced to each country, such as through migrant population movements,^{40,41} and importation of blood products (mostly from Western countries) before the onset of HCV blood screening,^{24,45} Genotype diversity appears also to be influenced by the type of drivers of HCV transmission in each country, such as the role of PWID and association with genotype 3.^{46,47}

PWID may play a larger relative role in HCV transmission in the future, as exposures in the wider population are further controlled. Injecting drug use is a major challenge in MENA,^{48,49} but we found a small number of genotype studies among PWID. Available data suggests that the genotypes circulating among PWID in a given country, tend to be similar to those circulating in the wider population in this country (Supplementary Table S1). We are thus unable to see whether there are associations between specific genotypes and injecting drug use, such as the genotype 3 link seen in the global literature.^{7,50,51} As suggested by recent studies, however, there seems to be a shift toward genotype 3 in Iran.^{46,47} This is particularly among young patients, and is apparently linked to injecting drug use increasingly becoming the main route of HCV transmission.^{46,47}

Our study has several limitations. We did not find HCV genotype studies for four MENA countries, and there were too few studies to conduct meta-analyses for another five countries. The number of studies also varied by country, and sample size of genotyped individuals was small for a number of studies. Studies may have also sampled populations from specific geographic areas within a given country, or select sub-populations. We did not assess secular trends in genotype distribution, such as using meta-regressions, as such analyses are challenged by the heterogeneity in available data and by the fact that genotype diversity is very low in the two countries that contribute most chronic infections in this region (namely, Egypt and Pakistan; Table 2). Accordingly, available genotype data may not have

TABLE 2 Number of hepatitis C virus (HCV) chronically infected individuals by genotype across countries of the Middle East and North Africa (MENA)

Country	Total population ³⁵	Number of HCV chronically infected individuals by genotype (95% confidence interval)						
		Genotype 1	Genotype 2	Genotype 3	Genotype 4	Genotype 5	Genotype 6	
Afghanistan	32 527 000	178 875	61 891 (37 206-88 543)	0 (0-0)	116 984 (90 332-141 669)	0 (0-0)	0 (0-0)	0 (0-0)
Algeria	39 667 000	191 828	153 148 (137 833-166 892)	30 041 (18 849-43 196)	5890 (3 142-9 621)	2749 (1178-4712)	0 (0-0)	0 (0-0)
Bahrain	1 377 000	5033	2446 (1 980-2 917)	564 (329-935)	941 (626-1364)	1082 (744-1520)	0 (0-175)	0 (0-175)
Egypt	91 508 000	5 127 729	133 813 (69 583-219 454)	10 705 (0-58 878)	0 (0-26 763)	4 983 210 (4 806 577-5 133 081)	0 (0-0)	0 (0-0)
Iran	79 109 000	504 631	297 495 (279 529-314 932)	2114 (0-5 284)	205 023 (188 642-221 404)	0 (0-528)	0 (0-0)	0 (0-0)
Iraq	36 423 000	123 046	44 992 (29 303-61 847)	0 (0-0)	259 (0-4279)	77 795 (60 032-94 780)	0 (0-1426)	0 (0-0)
Jordan	7 595 000	38 264	8724 (0-25 560)	0 (0-421)	0 (0-421)	29 539 (12 703-38 264)	0 (0-0)	0 (0-421)
Kuwait	3 892 000	56 207	15 626 (11 359-20 729)	0 (0-1928)	14 052 (9 999-19 071)	26 530 (21 392-31 796)	0 (0-1928)	0 (0-1928)
Lebanon	5 851 000	15 405	6993 (7590-11 910)	1334 (275-4195)	1406 (574-3820)	5672 (5143-10 836)	0 (0-75)	0 (0-0)
Libya	6 278 000	52 916	17 444 (16 486-18 454)	9413 (8137-10 636)	7286 (4840-10 158)	18 773 (16 061-21 592)	0 (0-53)	0 (0-53)
Morocco	34 378 000	344 116	264 763 (204 867-317 410)	63 711 (16 405-131 237)	12 208 (1526-30 139)	3434 (0-10 682)	0 (0-0)	0 (0-0)
Oman	4 491 000	22 481	12 252 (8541-15 773)	2046 (706-5299)	2046 (706-5299)	6137 (3388-9939)	0 (0-2345)	0 (0-2345)
Pakistan	188 925 000	6 575 046	631 815 (513 784-763 733)	284 664 (180 519-402 696)	5 651 623 (5 408 618-5 887 686)	6943 (0-41 658)	0 (0-0)	0 (0-0)
Palestine	4 668 000	25 057	5254 (1954-9336)	0 (0-475)	0 (0-2033)	19 803 (17 664-21 730)	0 (0-0)	0 (0-0)
Qatar	2 235 000	24 775	4901 (3995-5923)	124 (35-446)	3911 (3096-4861)	15 840 (14 647-16 966)	0 (0-235)	0 (0-235)
Saudi Arabia	31 540 000	496 894	183 403 (146 616-221 790)	7464 (2133-14 928)	4265 (0-12 262)	301 762 (261 242-341 215)	0 (0-0)	0 (0-0)
Syria	18 502 000	131 860	46 400 (16 760-81 582)	0 (0-277)	416 (0-1662)	74 518 (55 819-92 939)	10 527 (0-31 857)	0 (0-0)
Tunisia	11 254 000	93 360	85 863 (77 966-92 460)	5098 (1499-9896)	700 (0-3399)	1699 (0-5298)	0 (0-0)	0 (0-0)
UAE	9 157 000	119 817	72 415 (42 565-101 851)	1658 (0-8983)	16 307 (138-45 743)	29 436 (29 436-59 148)	0 (0-0)	0 (0-0)
MENA	609 377 000	14 127 340	2 049 638 (1 607 916-2 541 096)	418 935 (228 885-699 708)	6 043 317 (5 712 239-6 431 653)	5 604 923 (5 306 028-5 936 686)	10 527 (0-38 094)	0 (0-5157)
Genotype distribution in MENA weighted by population size (%)			14.5 (11.4-18.0)	3.0 (1.6-5.0)	42.8 (40.4-45.5)	39.7 (37.6-42.0)	0.1 (0.0-0.3)	0.0 (0.0-0.0)

Djibouti, Mauritania, Somalia, Sudan, and Yemen were excluded either due to no studies available or small sample size.

captured the diversity and true distribution of genotypes in the wider population of each country.

Key strengths of our study are the systematic and comprehensive searches that yielded our input data, and the fact that we synthesized and analyzed these data using state of the art quantitative methods. In addition to international databases, we identified a volume of data through regional and national databases, and included non-English articles, public health reports, and routine data reporting. We have therefore identified much more data than is present in existing global or regional studies of HCV genotypes,^{7,9,52} and presented a detailed picture of HCV genotypes and their patterns and diversity in MENA.

In conclusion, genotypes 3 and 4 are the most common genotypes in MENA, with equal contributions, in large part because of the sizable HCV epidemics in Pakistan and Egypt. While genotype 1 was ubiquitous, and was dominant or common in most countries, its overall contribution was still small compared to those of genotypes 3 and 4. Three sub-regional genotype patterns were identified, and these appeared to reflect cross-border population movements and geographic proximity. Two patterns were centered in each of Pakistan (genotype 3 pattern) and Egypt (genotype 4 pattern), while the third (genotype 1 pattern) was similar with the most common global pattern. While genotype diversity was limited in Egypt and Pakistan, it was considerable in the other countries. Genotypes 2, 5, 6, and 7 did not have significant presence. These findings inform the DAA treatment programs that are being expanded in MENA, and provide insights into HCV transmission pathways.

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AUTHORS' CONTRIBUTIONS

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

CONFLICTS OF INTEREST

The authors have no conflicts of interest to disclose.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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