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Original article

Individual-level key associations and modes of exposure for hepatitis C virus infection in the Middle East and North Africa: a systematic synthesis

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ABSTRACT

Purpose: To identify, map, and synthesize the individual-level key associations and modes of exposure for hepatitis C virus (HCV) infection in the Middle East and North Africa (MENA), the most affected region by HCV.

Methods: Source of data was the MENA HCV Epidemiology Synthesis Project database, populated through systematic literature searches. Risk factors determined to be statistically significant after adjustment for confounders were extracted and categorized into key associations or modes of exposure.

Results: In total, 329 risk factors were identified from 109 articles in 14 of 24 MENA countries. Among key associations, age was most frequently reported (n = 39; 34.2%), followed by other infections/diseases (n = 20; 17.5%), and incarceration (n = 17; 14.9%). Among modes of exposure, health care–related exposures were most frequently reported (n = 127; 59.5%), followed by injecting drug use exposures (n = 45; 20.9%), community-related exposures (n = 34; 15.8%), and sexual-related exposures (n = 8; 3.7%). Blood transfusion, hemodialysis, surgical and other medical procedures, dental work, and medical injections were identified as key health care–related exposures.

Conclusions: Health care appears to be the primary driver of prevalent (and possibly incident) infections in MENA, followed by injecting drug use. HCV screening should target the identified modes of exposure. Commitment to prevention should be an integral component of HCV response to achieve HCV elimination by 2030, with focus on strengthening infection control in health care facilities, improving injection safety and blood screening, and expanding harm reduction services for people who inject drugs.

Introduction

Hepatitis C virus (HCV) is a blood-borne pathogen and a cause of several morbidities, such as liver fibrosis, cirrhosis, and cancer [1]. With a global estimate of 62–79 million people being chronically infected [2], HCV-related morbidity and mortality place a burden on health care systems worldwide [3]. The Middle East and North Africa (MENA) region is the most affected by HCV, with over 15 million chronically infected individuals [2,4].

A series of systematic reviews and meta-analyses were conducted recently to characterize HCV epidemiology in MENA [5–14]. Varying HCV prevalence in the general population was observed across MENA countries. Countries with the highest HCV prevalence were Egypt at 11.9% [6] and Pakistan at 6.2% [14]. For the remaining countries, HCV prevalence was comparable to global levels, ranging from 0.2% in Iraq, Lebanon, and Palestine [9], to 1.9% in Yemen [10]. HCV genotype distribution and its regional trends were also delineated [15,16]. HCV viremic rate, that is, the proportion of HCV chronically infected individuals of all ever-infected individuals, was also recently assessed [17]. Two-thirds of HCV antibody-positive individuals in MENA were found chronically infected and in need of treatment [17]. The systematic reviews conducted quality assessments of included HCV studies, and existing evidence was found to be of reasonable quality [5–14]. The diagnostic tests used

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were also overall of quality, with most studies using the more sensitive and specific third- or fourth-generation assays for HCV antibody detection, with many studies using confirmatory tests also [5–14].

The recent development of the highly efficacious direct-acting antivirals provides avenues for achieving major reductions in HCV infection and disease burden [18,19]. As such, a global target has been set to eliminate HCV as a public health concern by 2030 [20,21]. However, screening those chronically infected and ensuring access to treatment remain major challenges across MENA [22,23]. Prevention of new HCV infections is also integral to achieving elimination by 2030 [21].

The key associations and modes of exposures for HCV infection vary across regions and countries [24–26]. For example, health care–related exposures appears to be an important mode of exposure in low- and middle-income countries; however, it is no longer a major mode of exposure in many developed countries [24–26]—such as the United States where most exposures appear to be related to injecting drug use [26,27]. This highlights the need to identify, for each region or country, the specific modes of exposures for HCV infection to inform HCV response and progress toward HCV elimination by 2030.

Against this background, the specific aim of our study is to delineate and map, through comprehensive systematic searches of HCV literature in MENA, the individual-level key associations and modes of exposure for HCV infection. The overarching goals of our study are to inform HCV prevention by identifying the modes of exposures and settings of vulnerability for this infection and to inform the development of cost-effective screening strategies that can identify infected individuals with a high yield. To our knowledge, this is the first systematic synthesis for any world region of HCV key associations and modes of exposure.

This work was conducted as part of the MENA HCV Epidemiology Synthesis Project—an ongoing effort to describe and understand HCV epidemiology and to inform key public health research, resource allocation, policy, and programming priorities in the region [5–15,17,28–31].

Methods

Data sources

The source of data for our study was the MENA HCV Epidemiology Synthesis Project database, a comprehensive database of HCV epidemiological measures in MENA [5–14]. The database consists of several subdatabases of studies for different outcomes, such as HCV antibody prevalence subdatabase comprised of 2543 antibody prevalence studies among 51,598,736 participants, ribonucleic acid prevalence (among antibody-positive persons) subdatabase comprised of 178 ribonucleic acid prevalence studies among 19,593 HCV antibody-positive participants, and genotype frequency subdatabase comprised of 338 HCV genotype studies among 82,257 participants. The database also includes a subdatabase of individual-level HCV risk factors including 329 risk factors identified from 109 studies. The latter subdatabase is the focus of our analyses in the present article. The MENA HCV Epidemiology Synthesis Project database was constructed through a series of systematic reviews for HCV infection across MENA [5–14].

Systematic reviews: overview

The systematic reviews were informed by the Cochrane Collaboration Handbook [32] and reported their findings using the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines [33]. The Preferred Reporting Items for Systematic Reviews and Meta-analyses flow diagrams describing the selection process by which studies were included can be found in the respective systematic reviews [5–14]. Reviewed evidence included peer-reviewed publications identified through international scientific databases (PubMed and Embase), regional-and country-level scientific databases, MENA HIV/AIDS Epidemiology Synthesis Project database [34,35], abstract archives of nonindexed international conferences, and gray literature comprised of public health reports and routine data reporting.

Broad search criteria were used in these reviews 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 identified as a virus for the first time [36,37].

Inclusion and exclusion criteria

The systematic reviews used the same inclusion and exclusion criteria adapted for the subregion or country of interest [5–14]. The specific inclusion and exclusion criteria can be found in detail in the respective systematic reviews [5–14]. Briefly, all studies included in the reviews qualified for inclusion if they reported HCV antibody incidence and/or antibody prevalence based on biological assays and on primary data, in any population, in 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, or Yemen. Studies had to have a minimum sample size of 25. The exclusion criteria encompassed case reports, case series, editorials, letters to editors, commentaries, literature reviews, and studies reporting HCV prevalence based on self-reporting. Studies referring to HCV as non-A non-B hepatitis, or were performed before 1989, were also excluded.

Extraction of risk factors and conceptual mapping

These systematic searches identified studies that assessed individual-level risk factors for incident HCV infection (in prospective or retrospective incidence studies) or individual-level factors associated with being infected with HCV infection (in cross-sectional studies of prevalent HCV infections). While these two types of factors are technically different and have been derived using different epidemiologic study designs, our focus in the present study is to identify factors that are predictive of HCV infection, whether they are potentially causal factors (such as injecting drug use or blood transfusion) or just reflect associations with HCV infection (such as age or socioeconomic status).

We extracted from the retrieved articles of the systematic searches only risk factors determined to be statistically significant through multivariable regression analyses—that is, after controlling for potential confounding factors. These risk factors were subsequently used to populate the HCV risk factors subdatabase indicated previously.

The extracted risk factors were classified into two categories: key associations and modes of exposure. A key association was defined as a characteristic associated with being infected with HCV (such as age or socioeconomic status), but is not a mode of exposure (or transmission). A mode of exposure was defined as an exposure factor that was potentially responsible for acquiring HCV infection (such as injecting drug use or blood transfusion). Conceptual maps by type of risk factors were developed based on the identified risk factors in the systematic searches.

Table 1
Number of articles reporting individual-level risk factors for incident HCV infection (in prospective or retrospective incidence studies) or individual-level factors associated with being infected with HCV infection (in cross-sectional studies of prevalent HCV infections) in the Middle East and North Africa (MENA)

Country	Number of articles reporting risk factors
Egypt	53
Iran	26
Pakistan	11
Iraq	3
Libya	3
Morocco	2
Saudi Arabia	2
Tunisia	2
Yemen	2
Afghanistan	1
Kuwait	1
Qatar	1
Sudan	1
Syria	1
Middle East and North Africa	109

All reported risk factors that met the definition of a key association were included in the conceptual map for the key associations. Similarly, all reported risk factors that met the definition of a mode of exposure were included in the conceptual map for the modes of exposure, and were further categorized into health care–related exposures, injecting drug use–related exposures, community-related exposures, and sexual-related exposures, based on the type of risk factor.

Results

Scope of evidence

Table 1 lists (by country) the number of articles reporting statistically significant risk factors after adjustment for confounders. Risk factor data were available for 14 of the 24 MENA countries, 11 of which had less than five articles reporting risk factor information. Egypt had the largest number of articles ($n = 53$), followed by Iran ($n = 26$) and Pakistan ($n = 11$). In the 109 articles reporting risk factors, a total of 329 risk factors were identified.

Conceptual mapping of risk factors

Figure 1 provides a conceptual mapping of the key associations with HCV infection as discerned from the extracted risk factors. Diverse associations have been identified that range from basic sociodemographic attributes, to occupational or incarceration contexts, to other infection or disease status conditions.

Figure 2 provides a conceptual mapping of HCV modes of exposure as discerned from the extracted risk factors. Three main settings of exposure have been identified for HCV infection in MENA: health care–related exposures, exposures related to injecting drug use, and community-related exposures. A fourth setting, although limited in extent, was also identified: sexual exposures. Within each of these settings, different specific modes of exposure to HCV infection or associated factors were identified.

Key associations

Table 2 reports the frequency of reported key associations in MENA. A total of 114 key associations were reported, that is, 34.7% of all occasions in which a risk factor was reported.

Age was by far the most reported key association—it was reported in 39 studies, comprising 34.2% of all occasions in which a key association was reported. Following age was the category of other infections or diseases—it was reported in 20 studies, comprising 17.5% of occasions. This category included conditions such as diabetes, malaria, jaundice, and HIV, among others. Next was the category of an incarceration context—it was reported in 17 studies, comprising 14.9% of occasions. Other notable reported key associations included: sex, education, marital status, socioeconomic status, rural versus urban location, and specific geographical regions.

Modes of exposure

Table 3 reports the frequency of reported modes of exposure in MENA, comprising 65.3% of all reported risk factors.

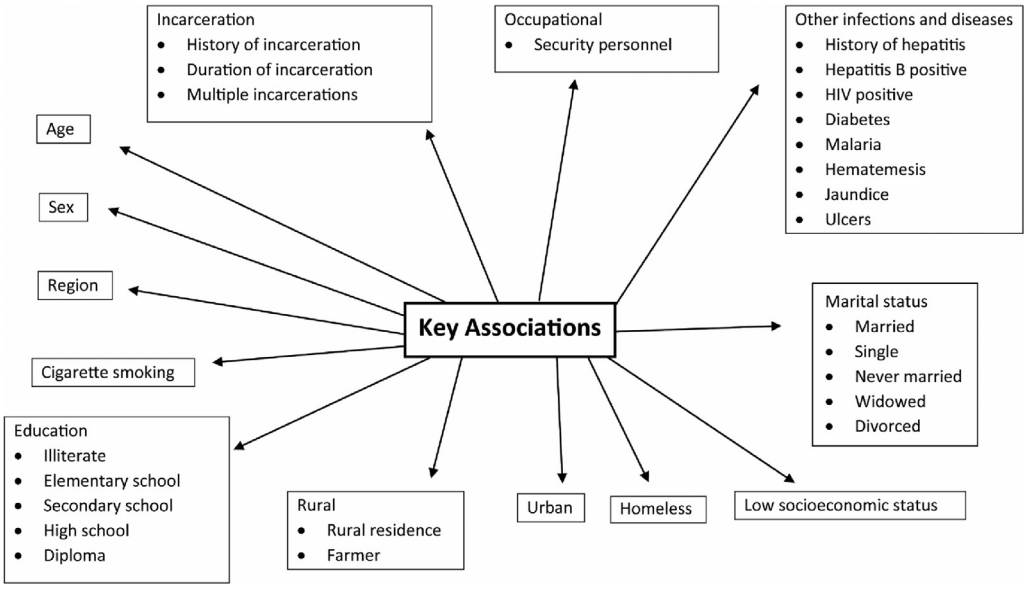

Fig. 1. Conceptual mapping of the key associations with HCV infection as discerned from the extracted risk factors. A key association is defined as a characteristic associated with being infected with HCV, but is not a mode of exposure (or transmission).

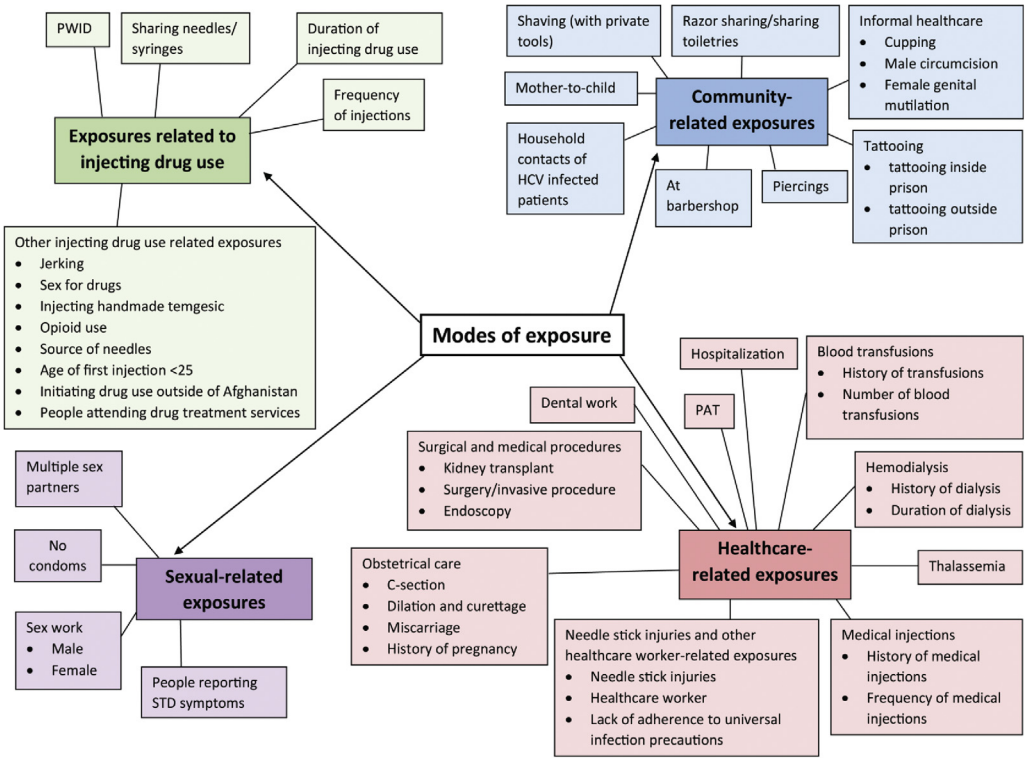

Fig. 2. Conceptual mapping of HCV modes of exposure as discerned from the extracted risk factors. A mode of exposure is defined as an exposure factor that was potentially responsible for acquiring HCV infection. PWID, people who inject drugs; STD, sexually transmitted disease.

Health care–related exposures

HCV infection was often associated with health care–related exposures, comprising over half of the reported modes of exposure (59.5%). Blood transfusion was the most commonly reported mode of exposure—it was reported in 32 studies comprising 14.9% of occasions in which a mode of exposure was reported. Parenteral antischistosomal therapy (PAT) was second (24 studies; 11.2% of occasions) and all of these studies were strictly from Egypt. Hemodialysis was next, where it was reported in 21 studies, comprising 9.8% of occasions. This was followed by surgical and other medical procedures (16 studies; 7.4% of occasions), dental work (10 studies; 4.7% of occasions), and medical injections (9 studies; 4.2% of occasions). Other notable health care–related exposures included: health care worker–related exposures, hospitalization, and obstetrical care.

Exposures related to injecting drug use

Exposures (and associated factors) related to injecting drug use comprised 20.9% of all reported modes of exposure. History of injecting drug use was the most commonly reported factor (17 studies; 7.9% of occasions), followed by sharing of needles or syringes (11 studies; 5.1% of occasions), and duration of injecting drug use (6 studies; 2.8% of occasions).

Community-related exposures

Community-related exposures comprised 15.8% of all reported modes of exposure. Tattooing was the most commonly reported risk factor (10 studies; 4.7% of occasions), followed by household contacts of HCV-infected patients (7 studies; 3.3% of occasions), and informal health care practices, including cupping, male circumcision, and female genital mutilation (5 studies; 2.3% of occasions). Other notable community-related exposures included: mother-to-child transmission (4 studies; 1.9% of occasions), and exposures at barbershops (4 studies; 1.9% of occasions).

Sexual exposures

Sexual exposures were the least frequently reported modes of exposure (3.7%), among which, multiple sex partners (3 studies; 1.4% of occasions) was the most commonly reported risk factor.

Discussion

We presented a comprehensive mapping of HCV key associations and modes of exposure in MENA, to our knowledge the first such comprehensive and systematic analysis of the key associations and modes of exposure for any world region. Our results demonstrate that there are three key “collective clusters” of HCV exposures in MENA. The first relates to health care, which given the aforementioned results, appears to be the primary driver of prevalent (and possibly incident) infections. The second cluster relates to injecting drug use, whereas the third relates to community-related exposures. Despite some suggestive evidence for sexual-related exposures, these appear to play a minimal role. All identified modes of exposure confirm our overall understanding of HCV epidemiology—no unusual modes of exposure were identified in our study.

These results highlight the role that health care has played in the HCV epidemic in MENA, leading to this region being the most affected by HCV infection worldwide [2]. They also confirm our understanding of HCV epidemiology in this region, as delineated recently through a series of systematic reviews of HCV antibody prevalence [5–14]. Indeed, the pattern of HCV antibody prevalence in these studies mirrored closely that of the pattern of HCV risk factors, as analyzed in the present study. These findings testify to the need for expansion of HCV prevention in MENA through proper

Table 2
Frequency of reported statistically significant key associations with hepatitis C virus (HCV) infection

Key associations	Reported effect nature and direction	Frequency	Proportion of occasions in which this key association was reported	References
Age	Increased age associated with higher OR	39	34.2%	[38–74]
Other infections and diseases	Other infections and diseases associated with higher OR	20	17.5%	[44,51,56,61,63,70,73,75–79]
Incarceration	Incarceration and risk factors associated with incarceration associated with higher OR	17	14.9%	[40,47,54,78,80–91]
Sex	Male ($n = 6$), female ($n = 2$), and unspecified sex ($n = 2$), associated with higher OR	10	8.8%	[45,59,61,74,75,82,84,87,92,93]
Education	Less education associated with higher OR	6	5.3%	
Marital status	Single, divorced, and widowed associated with higher OR	6	5.3%	[56,59,73,74,82,85]
Rural location	Rural residence associated with higher OR	5	4.4%	[45,56,59,94,95]
Region	Specific regions associated with higher OR	4	3.5%	[87,95,96]
Occupation	Specific occupations associated with higher OR	1	0.9%	[47,53]
Urban location	Urban residence associated with higher OR	2	1.8%	
Socioeconomic status	Lower socioeconomic status associated with higher OR	2	1.8%	
Homeless	Being homeless associated with higher OR	1	0.9%	
Cigarette smoking	Cigarette smoking associated with higher OR	1	0.9%	[86]
Total		114	100%	

OR, odds ratio.
A key association is defined as a characteristic associated with being infected with HCV, but is not a mode of exposure (or transmission).

Table 3
Frequency of reported statistically significant modes of exposure for hepatitis C virus (HCV) infection

Modes of exposure broad category	Modes of exposure specific category	Number of studies reporting the mode of exposure	Proportion of occasions in which this mode of exposure was reported	Proportion of occasions in which this mode of exposure was reported within its broad category	References
Health care–related exposures					
	Blood transfusions	32	14.9%	25.0%	[41,45,46,50–53,55,56,58,64,66,67,69,73,79,86,93,94,97–107]
	Parenteral antischistosomal therapy (PAT)	24	11.2%	18.8%	[43,53,55,56,59–64,67,68,70,101,102,105,108–113]
	Hemodialysis	21	9.8%	16.4%	[41,52,77,92,100,106,107,114–125]
	Surgical and other medical procedures	16	7.4%	12.5%	[45,46,56–58,64,69,71,77,92,93,101,103,112,126,127]
	Dental work	10	4.7%	7.8%	[44,54,56,58,63,79,98,101,127,128]
	Medical injections	9	4.2%	7.0%	[44,69,95,101,103,128,129]
	Health care worker–related exposures	6	2.8%	4.7%	[41,49,56,69,130]
	Hospitalization	4	1.9%	3.1%	[56,73,103,117]
	Obstetrical care	4	1.9%	3.1%	[98,101,130,131]
	Having thalassemia	2	0.9%	1.6%	[83]
	Total within category	128	59.5%	100%	
Injecting drug use exposures					
	History of injecting drug use	17	7.9%	37.8%	[40,45–49,54,56,69,73,75,76,86,87,90,132]
	Sharing needles or syringes	11	5.1%	24.4%	[38,45,56,64,81,82,84,88,91,133,134]
	Duration of drug use	6	2.8%	13.3%	[38,78,82,84,91,135]
	Frequency of injections	3	1.4%	6.7%	[38,82,91]
	Other injecting drug use related exposures	8	3.7%	17.8%	[38,39,46,80,89,96,135]
	Total within category	45	20.9%	100%	
Community-related exposures					
	Tattooing	10	4.7%	29.4%	[40,54,56,78,80,88,90,97,126]
	Household contacts of HCV infected patients	7	3.3%	20.6%	[55,66,86,111,118,127,136]
	Informal health care	5	2.3%	14.7%	[56,65,79,97,111]
	At barbershop	4	1.9%	11.8%	[57,61,64,135]
	Mother-to-child	4	1.9%	11.8%	[137–140]
	Other community exposures	4	1.9%	11.8%	[56,75,78]
	Total within category	34	15.8%	100.0	
Sexual-related exposures					
	Multiple sex partners	3	1.4%	37.5%	[55,126,141]
	Other sexual exposures	5	2.3%	62.5%	[46,75,96,134]
	Total within category	8	3.7%	100%	
Total		215	100.0%	100%	

A mode of exposure is defined as an exposure factor that was potentially responsible for acquiring HCV infection.

and universal implementation of blood safety, injection safety, and infection control programs. They also inform the expansion of HCV screening and direct-acting antivirals treatment programs, by targeting the individual-level key associations and modes of exposure as delineated in the present study.

A main highlight of our study is that very specific health care exposures were repeatedly identified as risk factors, namely blood transfusion and hemodialysis. This may suggest that these exposures contribute more than previously thought to HCV incidence in the population, and therefore, even limited rollout of interventions focused on such specific exposures may result in substantial decline in HCV incidence. This seems to be supported by the large decline in HCV incidence observed in the United States immediately after the introduction of blood screening and other basic measures after identification of the virus [142]. National governments of resource-limited countries could focus initially on HCV prevention through blood safety and proper infection control in hemodialysis as a first step to advance the broader agenda of HCV prevention. Ultimately, although, with the evidence for a broad range of health care exposures contributing to HCV infection transmission, such as medical injections and dental work (Table 3), all different health care–related modes of exposure need be addressed.

The role that blood transfusion plays in HCV exposures should not be surprising in context of continued concerns about blood safety in MENA [143]. Fragmented blood transfusion services, inappropriate clinical use of blood and blood products, and use of low-cost low-sensitivity screening kits have been observed in several MENA countries [143], such as in Pakistan, which has one of the largest HCV epidemics worldwide [30]. Establishing a centralized blood transfusion service, such as in Iran, may markedly improve accessibility to safe blood and blood products [143].

Similarly, the role of medical injections in HCV exposures should not be surprising given that this region has the highest rate of medical injections of all regions, at 4.3 per person per year [144,145]. A large proportion of these medical injections are administered unnecessarily, based on patients' perception that injectable medications are more effective than other types of equally effective therapies [146,147]. It is critical for MENA countries to ensure safe injection practices and to adopt the new World Health Organization guidelines for the use of safety-engineered syringes [148–150].

Our results highlight that exposures related to injecting drug use are a main driver of HCV infection in MENA, similar to that observed globally [151]. However, unlike many developed countries such as the United States where injecting drug use is the main driver of HCV incidence [27,152], the role of this cluster of exposures appears second to that of health care in MENA. This should not distract from the fact that injecting drug use is a major source of exposures that needs to be addressed urgently with harm reduction services, given the scale of this practice in this region [153]. Although seven MENA countries have implemented needle/syringe exchange programs, their coverage remains limited, apart from Iran, where successful needle and syringe programs have been operational for over a decade [151,154].

Although less frequently, HCV transmission has been linked to unsafe practices in the community, particularly those including the use/reuse of unsterile needles/syringes and contaminated sharp objects (Table 3). Among the frequently reported community-related exposures are tattooing, engagement in informal health care practices (such as cupping, male circumcision, and female genital mutilation), and using services at a barbershop. Opportunities for reducing these exposures, or reducing the risk of exposure through them, should be explored.

Among the key associations identified in this study, age was most commonly reported. This affirms the strong association between age and HCV infection, reflecting age as a proxy for the cumulative risk of exposure, and possibly suggesting that the likelihood of exposure could be age dependent—say more encounters with health care with older age. Another key association was incarceration. Incarcerated populations may engage in various high risk behaviors (before or during incarceration), such as injecting drug use, tattooing, and unprotected anal sex [155].

Although age and incarceration were common key associations across the region, other identified key associations appear to be location-dependent reflecting the nature of the HCV epidemics in individual countries, or in subnational units of these countries. Rural residence, for example, is a risk factor for HCV infection in Egypt [5,156], but may not be so in other countries. The sex effect (male vs. female) may vary also in nature and strength across the region. This is demonstrated in Table 1 where although most studies reported an association between male sex and HCV infection, several other studies reported that but for female sex. These variations across the region extend also to some of the modes of exposure. PAT, in particular, appears to be a mode of exposure but only in Egypt, confirming the link between mass PAT campaigns and the HCV epidemic in Egypt [157,158].

This study has limitations. Although we aimed to provide a regional picture of HCV key associations and modes of exposure, there is large heterogeneity in availability of evidence. Few countries, such as Egypt and Iran, contributed multiple studies, whereas no studies were available for 10 MENA countries. This may limit the generalizability of the identified key associations and modes of exposures to countries with limited data. Relatively small number of studies were identified from Pakistan (only 11), although Pakistan is enduring a large epidemic with an HCV antibody prevalence of about 5% and over six million chronically infected individuals [14,30]. Unlike Egypt whose epidemic, drivers, and modes of exposure are relatively well understood [5,6,29,159,160], the nature of HCV transmission in this country remains poorly understood—this highlights the need for analytical epidemiologic studies in Pakistan to assess the specific modes of exposure and their relative role.

Another limitation of our study is that we used citation frequency to indicate the significance of the key associations and modes of exposures in the population, but citation frequency may not necessarily reflect the actual distribution of key associations and modes of exposures in the wider infected population—beyond the studied populations included in the present analysis. Furthermore, this delineation of key associations and modes of exposure may relate more to prevalence, rather than current incidence of infection. For example, blood safety and infection control appear to have improved markedly in recent years in multiple MENA countries [28,143,161]. Prevalent infections may therefore reflect decade's old HCV exposures not representative of current exposures—the relative role of health care may have decreased but the role of injecting drug use may have increased. Further analytical epidemiologic studies, as well as viral hepatitis surveillance [162], are needed to determine current trends, particularly with a focus on incident infections.

About 400,000 new HCV infections are occurring in MENA every year [2], stressing the need to implement effective preventative strategies targeting the main clusters of exposure. Health care and injecting drug use appear to be the main drivers of the HCV epidemic in MENA, along with a smaller contribution from community-related exposures. Commitment to HCV prevention should be an integral component of HCV response to achieve HCV elimination by 2030. This commitment should entail expansion and quality assurance of blood and injection safety and infection control

programs, as well as harm reduction for people who inject drugs and in prisons.

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