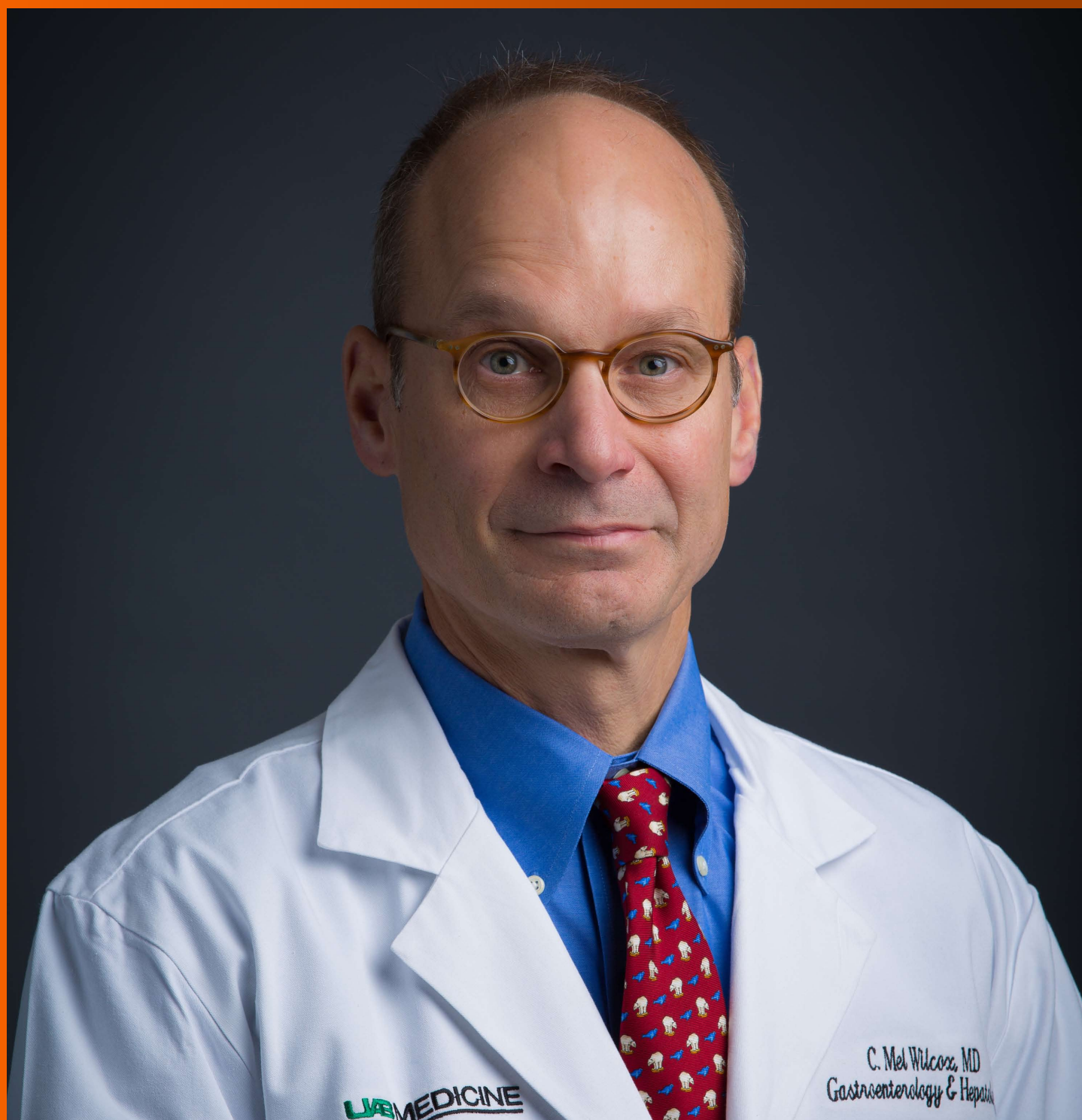


# World Journal of *Gastroenterology*

*World J Gastroenterol* 2018 July 21; 24(27): 2921-3054



**EDITORIAL**

- 2921 Indocyanine green-based fluorescence imaging in visceral and hepatobiliary and pancreatic surgery: State of the art and future directions  
*Baiocchi GL, Diana M, Boni L*

**REVIEW**

- 2931 Perioperative thromboprophylaxis in liver transplant patients  
*De Pietri L, Montalti R, Nicolini D, Troisi RI, Moccheggiani F, Vivarelli M*
- 2949 MicroRNAs in the prognosis and therapy of colorectal cancer: From bench to bedside  
*To KK, Tong CW, Wu M, Cho WC*
- 2974 Pathogenesis of non-alcoholic fatty liver disease in children and adolescence: From "two hit theory" to "multiple hit model"  
*Fang YL, Chen H, Wang CL, Liang L*

**MINIREVIEWS**

- 2984 Role of aldehyde dehydrogenase 2 in ischemia reperfusion injury: An update  
*Panisello-Roselló A, Lopez A, Folch-Puy E, Carbonell T, Rolo A, Palmeira C, Adam R, Net M, Roselló-Catafau J*
- 2995 Multiparametric analysis of colorectal cancer immune responses  
*Leman JK, Sandford SK, Rhodes JL, Kemp RA*

**ORIGINAL ARTICLE****Retrospective Study**

- 3006 Push vs pull method for endoscopic ultrasound-guided fine needle aspiration of pancreatic head lesions: Propensity score matching analysis  
*Sugimoto M, Takagi T, Suzuki R, Konno N, Asama H, Sato Y, Irie H, Watanabe K, Nakamura J, Kikuchi H, Waragai Y, Takasumi M, Hashimoto M, Hashimoto Y, Hikichi T, Ohira H*
- 3013 Liver intravoxel incoherent motion diffusion-weighted imaging for the assessment of hepatic steatosis and fibrosis in children  
*Shin HJ, Yoon H, Kim MJ, Han SJ, Koh H, Kim S, Lee MJ*

**Clinical Trials Study**

- 3021 New fecal test for non-invasive *Helicobacter pylori* detection: A diagnostic accuracy study  
*Iannone A, Giorgio F, Russo F, Riezzo G, Girardi B, Pricci M, Palmer SC, Barone M, Principi M, Strippoli GF, Di Leo A, Ierardi E*

**Observational Study**

- 3030 Long-term outcomes of endoscopic resection for small ( $\leq 4.0$  cm) gastric gastrointestinal stromal tumors originating from the muscularis propria layer  
*Zhang Y, Mao XL, Zhou XB, Yang H, Zhu LH, Chen G, Ye LP*

**SYSTEMATIC REVIEWS**

- 3038 Systematic overview of hepatitis C infection in the Middle East and North Africa  
*Chaabna K, Cheema S, Abraham A, Alrouh H, Lowenfels AB, Maisonneuve P, Mamtani R*

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## Systematic overview of hepatitis C infection in the Middle East and North Africa

Karima Chaabna, Sohaila Cheema, Amit Abraham, Hekmat Alrouh, Albert B Lowenfels, Patrick Maisonneuve, Ravinder Mamtani

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### Abstract

#### AIM

To assess the quality of and to critically synthesize the available data on hepatitis C infections in the Middle East and North Africa (MENA) region to map evidence gaps.

#### METHODS

We conducted an overview of systematic reviews (SRs) following an a priori developed protocol (CRD42017076736). Our overview followed the preferred reporting items for systematic reviews and meta-analyses guidelines for reporting SRs and abstracts and did not receive any funding. Two independent reviewers systematically searched MEDLINE and conducted a multistage screening of the identified articles. Out of 5758 identified articles, 37 SRs of hepatitis C virus (HCV) infection in populations living in 20 countries in the MENA region published between 2008 and 2016 were included in our overview. The nine primary outcomes of interest were HCV antibody (anti-) prevalences and incidences in different at-risk populations; the HCV viremic (RNA positive) rate in HCV-positive individuals; HCV viremic prevalence in the general population (GP); the prevalence of HCV co-infection with the hepatitis B virus, human



immunodeficiency virus, or schistosomiasis; the HCV genotype/subtype distribution; and the risk factors for HCV transmission. The conflicts of interest declared by the authors of the SRs were also extracted. Good quality outcomes reported by the SRs were defined as having the population, outcome, study time and setting defined as recommended by the PICOTS framework and a sample size > 100.

## RESULTS

We included SRs reporting HCV outcomes with different levels of quality and precision. A substantial proportion of them synthesized data from mixed populations at differing levels of risk for acquiring HCV or at different HCV infection stages (recent and prior HCV transmissions). They also synthesized the data over long periods of time (*e.g.*, two decades). Anti-HCV prevalence in the GP varied widely in the MENA region from 0.1% (study dates not reported) in the United Arab Emirates to 2.1%-13.5% (2003-2006) in Pakistan and 14.7% (2008) in Egypt. Data were not identified for Bahrain, Jordan, or Palestine. Good quality estimates of anti-HCV prevalence in the GP were reported for Algeria, Djibouti, Egypt, Iraq, Morocco, Pakistan, Syria, Sudan, Tunisia, and Yemen. Anti-HCV incidence estimates in the GP were reported only for Egypt (0.8-6.8 per 1000 person-year, 1997-2003). In Egypt, Morocco, and the United Arab Emirates, viremic rates in anti-HCV-positive individuals from the GP were approximately 70%. In the GP, the viremic prevalence varied from 0.7% (2011) in Saudi Arabia to 5.8% (2007-2008) in Pakistan and 10.0% (2008) in Egypt. Anti-HCV prevalence was lower in blood donors than in the GP, ranging from 0.2% (1992-1993) in Algeria to 1.7% (2005) in Yemen. The reporting quality of the outcomes in blood donors was good in the MENA countries, except in Qatar where no time framework was reported for the outcome. Some countries had anti-HCV prevalence estimates for children, transfused patients, contacts of HCV-infected patients, prisoners, sex workers, and men who have sex with men.

## CONCLUSION

A substantial proportion of the reported outcomes may not help policymakers to develop micro-elimination strategies with precise HCV infection prevention and treatment programs in the region, as nowcasting HCV epidemiology using these data is potentially difficult. In addition to providing accurate information on HCV epidemiology, outcomes should also demonstrate practical and clinical significance and relevance. Based on the available data, most countries in the region have low to moderate anti-HCV prevalence. To achieve HCV elimination by 2030, up-to-date, good quality data on HCV epidemiology are required for the GP and key populations such as people who inject drugs and men who have sex with men.

**Key words:** Hepatitis C; Meta-research; Risk factors; Incidence; Genotype; Middle East and North Africa; Systematic review; Micro-elimination; Pakistan; Gulf Cooperation Council

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**Core tip:** To achieve hepatitis C virus (HCV) infection elimination goals by 2030, precise prevention strategies targeting specific populations at higher risk of acquiring HCV infection and treatment programs require the development of evidence-based health policies. HCV infection epidemiology in the countries of the Middle East and North Africa was characterized in 37 systematic reviews (SR) during the last decade. Our systematic overview critically analyzes and synthesizes the findings of these SRs to map the evidence gaps in the region. Additionally, we assessed the quality of the reported outcomes and documented conflicts of interest of the SR authors who disclosed financial relationships with pharmaceuticals.

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## INTRODUCTION

In 2017, the World Health Organization estimated that 71 million people suffer from chronic hepatitis C virus (HCV) infection worldwide<sup>[1]</sup>. In 2015, HCV infection resulted in 399000 deaths<sup>[1]</sup>, predominantly from complications such as liver cirrhosis and hepatocellular carcinoma (HCC)<sup>[1,2]</sup>. Egypt had the largest iatrogenic transmission of blood-borne pathogens in the general population (GP) worldwide<sup>[3]</sup>. The use of parenteral anti-schistosomiasis therapy in Egypt, extensively practiced with poor sterile techniques since the 1920s, is considered to be the leading cause of the dramatic increase in the human HCV reservoir in the GP<sup>[3]</sup>. In Egypt, HCV antibody (anti-) prevalence was estimated to be 15% in 2008<sup>[4]</sup> and 6% in 2014<sup>[5]</sup>. Globally, Pakistan has the second largest number of people with viremic HCV infection, after China<sup>[6]</sup>. Due to the high burden of HCV infection in Egypt and Pakistan, the MENA region has been identified as the region most affected region by HCV worldwide.

Our primary objective was to assess the quality of the data reported by the published systematic reviews (SRs) of HCV epidemiology in MENA countries taking into account conflict of interest disclosed by the authors of these SRs. Secondly, we aimed to critically analyze all data reported by the SRs to map evidence gaps and to report a comprehensive synthesis.

## MATERIALS AND METHODS

We conducted an overview of SRs based on the Cochrane

Handbook for Systematic Reviews of Interventions<sup>[7]</sup>. This overview is part of the Population Health Publications Assessment Project that aims to assess the methodological quality of published SRs on population health issues in the MENA region. The ultimate goal of this meta-research (*i.e.*, research on research<sup>[8]</sup>) is to evaluate and contribute to the improvement of population health research practices in the MENA region<sup>[9]</sup>.

An *a priori* protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO registration number CRD42017076736)<sup>[10]</sup>. We report this overview according to the standards set out in the preferred reporting items for systematic reviews and meta-analyses (PRISMA) 2009 guidelines<sup>[11-13]</sup>. PRISMA checklists for SRs<sup>[11,12]</sup> and abstracts<sup>[13]</sup> are reported as Supplementary Materials 1 and 2, respectively. We also assessed the methodological quality of our overview using the Assessment of Multiple Systematic Reviews (AMSTAR) tool<sup>[14]</sup>. The AMSTAR checklist is provided as Supplementary Material 3.

### Inclusion and exclusion criteria

We included all SRs (publication date: January 2008 to December 2016) of HCV infection related to the countries in the MENA region published in peer-reviewed journals since 2008, the publication year of the first version of the Cochrane Handbook for Systematic Reviews of Interventions<sup>[7]</sup>. We included MENA countries where Arabic, English, French, and/or Urdu are the primary official languages and/or the medium of instruction in the colleges/universities. These languages are those spoken by the authors of this overview.

### Population of interest

Our population of interest was the population living in the following 20 countries: Algeria, Bahrain, Djibouti, Egypt, Iraq, Jordan, Kuwait, Lebanon, Libya, Morocco, Oman, Pakistan, Palestine, Qatar, Saudi Arabia, Sudan, Syria, Tunisia, the United Arab Emirates (UAE), and Yemen. These selected MENA countries have a combined population of over 560 million people, accounting for approximately 8% of the world's population<sup>[15]</sup>. We excluded SRs of HCV infection in populations from countries outside the MENA region and SRs with military personnel who were based in the MENA region but not from the region.

### Primary outcomes

We extracted the following variables: Anti-HCV prevalence and incidence in different at-risk populations, HCV viremic rates in HCV positive individuals, and HCV viremic prevalence in the GP. Viremic infection represents the presence of HCV in the bloodstream detected with polymerase chain reaction (HCV RNA-positive). We also extracted the prevalence of co-infection with HBV (hepatitis B surface antigen, HBsAg), human immunodeficiency virus (HIV), or schistosomiasis; HCV genotype/subtype distributions; and risk factors for

HCV transmission. Additionally, we extracted conflicts of interest reported by the SR authors.

### Literature search and data management

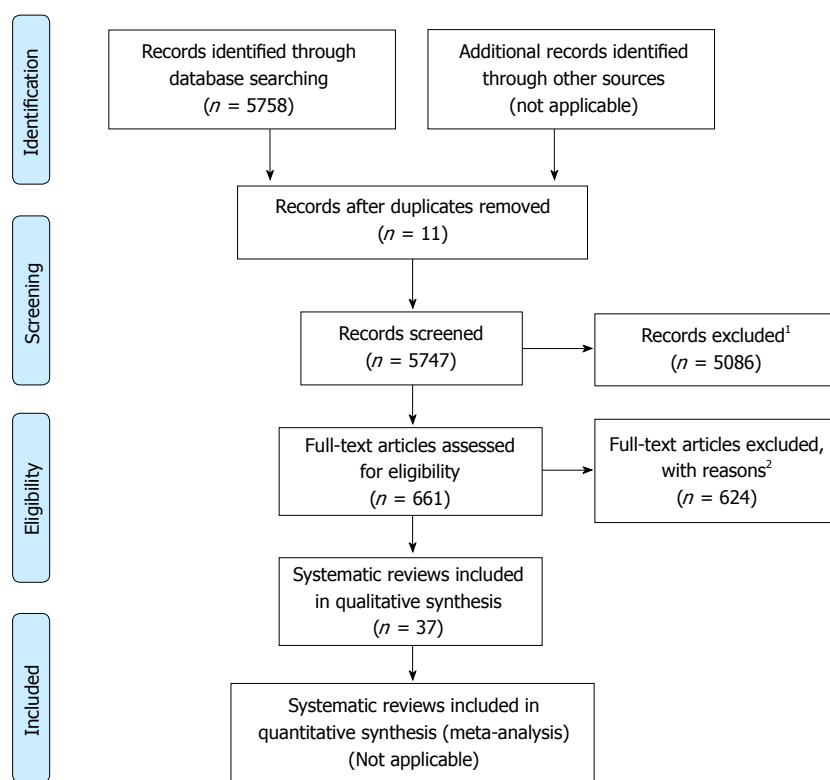
Two reviewers (AA and HA) independently and systematically searched the Medical Literature Analysis and Retrieval System Online (MEDLINE) through the search engine PubMed<sup>[16]</sup> using broad search criteria (Supplementary Material 4). The search criteria, limited to reviews, systematic reviews, and meta-analysis, identified 5758 reviews (Figure 1). After removing duplicate publications of the same reviews with Endnote<sup>[17]</sup>, title/abstract screening and then full-text screening were conducted by AA and HA with Rayyan software<sup>[18,19]</sup>. Discrepant inclusions of SRs were discussed by AA, HA, and KC under the supervision of the senior authors. We eventually included 37 SRs of HCV infection in MENA countries (Figure 1). The characteristics of these included SRs are described in Supplementary Material 5. Data extraction was conducted by AA and KC and crosschecked for accuracy.

### Conflicts of interest

We recorded the conflicts of interest reported by the SR authors who disclosed financial relationships. An asterisk (\*) was inserted next to the outcomes reported by SRs with at least one author who disclosed direct or indirect financial relationships with Gilead Science, AbbVie, Merck, Bristol-Myers Squibb, or Janssen Therapeutics. In 2013, Gilead Science launched sofosbuvir-based regimens to cure chronic infections with HCV genotypes 1, 2, 3, and 4<sup>[20]</sup> (viremic cases) that made elimination of HCV infection achievable for the first time. A large proportion of patients (> 90%) treated with sofosbuvir associated with another direct-acting antiviral drug (DAA) demonstrated a sustained virological response<sup>[21]</sup>. The recommended regimens and treatment durations differ according to the HCV genotype infection. Additionally, sofosbuvir-based regimens appear to be relatively safe<sup>[21]</sup>. However, cases of cardiac events have been reported when sofosbuvir-based treatments were administered in combination with amiodarone and/or propranolol<sup>[22,23]</sup>. Since then, new DAAs have been developed by other pharmaceuticals (AbbVie, Merck, Bristol-Myers Squibb, and Janssen Therapeutics)<sup>[24]</sup>.

### Quality assessment and conflict of interest

Good quality outcomes reported by the SRs were defined as having the population, outcome, timing, and setting defined as recommended by the PICOTS framework<sup>[25,26]</sup> (intervention and comparator being irrelevant in our overview) and a sample size > 100<sup>[27]</sup>. A maximum score of six was given to the outcome if the following measures were included: (1) Population profile, such as pregnant women and patients under hemodialysis; (2) the method used for the outcome estimation, such as meta-analysis or weighted average; (3) the data collection period; (4) the study geographic location; (5) the number of studies;



**Figure 1** PRISMA 2009 Flow diagram describing the selection of the systematic reviews reporting hepatitis C outcomes in our systematic overview. Reasons of exclusion: <sup>1</sup>Systematic reviews were excluded from the overview because they did not meet our inclusion criteria; <sup>2</sup>Not a systematic review ( $n = 116$ ), no hepatitis C outcomes ( $n = 472$ ), not a population from MENA ( $n = 34$ ), duplicate ( $n = 1$ ), and publication in Portuguese ( $n = 1$ ).

and (6) a total sample size  $> 100$ .

## Synthesis

We narratively synthesized the data on HCV infection in each of the 20 MENA countries in at-risk populations. We defined the GP as individuals from the community who are not in any specific population category such as blood donors or outpatients. More specifically, we reported HCV epidemiology in the GP separately from that in blood donors. Blood donors are selected healthy populations that may not be representative of the GP<sup>[28,29]</sup>. Therefore, if a SR reported an outcome for the GP including specific population categories, we reported this GP specifying all the included population categories.

Extracted data from the included SRs were compiled into evidence tables. We reported anti-HCV prevalence in at-risk populations from the SRs and the quality assessment of the reported prevalence (Supplementary Materials 6 and 7). Country-level anti-HCV prevalence was classified into low ( $< 1.5\%$ ), moderate ( $1.5\%–3.5\%$ ), and high ( $> 3.5\%$ ) levels<sup>[30]</sup>. If available, we also reported the viremic rate in anti-HCV positive individuals and the viremic prevalence in the GP.

For each country, we mapped evidence gaps with the most up-to-date anti-HCV prevalence with the best quality assessment (highest quality assessment score) in the GP; blood donors; pregnant women; children; patients on dialysis; hemophiliac, thalassemic, and transfused patients; patients with HCC, acute liver disease, chronic liver disease (CLD), HIV and/or other

sexually transmitted infections; healthcare workers; barbers; contacts of HCV-infected patients; people who inject drugs (PWID); prisoners; sex workers; and men who have sex with men (MSM) (Tables 1–3). We took financial disclosures into account when assessing and reporting these outcomes<sup>[31]</sup>. Whenever two outcomes describing the same population in the same country had the same quality score, we reported the outcome extracted from the SR the authors of which disclosed no financial relationship with HCV DAA pharmaceutical companies.

## RESULTS

### Quality assessment - PICOTS framework

Only six out of 37 SRs of HCV epidemiology in the MENA region published after 2008 conducted a quality assessment of the studies included<sup>[6,27,32–35]</sup>. HCV prevalence or incidence is meaningful only when the population, the outcome, the study setting, and the study period are stated (PICOTS framework)<sup>[25]</sup>. Additionally, for SRs, reporting the quantitative synthesis method used and the number of studies included in the synthesis as recommended by PRISMA guidelines<sup>[11–13]</sup> is critical to enable the assessment of the quality of the outcome (Tables 1–3). Some SRs failed to precisely report the methodology they used for their quantitative synthesis<sup>[36–38]</sup>.

In addition to providing a time framework for morbidity measurements, reporting the collection period for HCV prevalence is essential because changes in

**Table 1** Hepatitis C antibody prevalence evidence gap mapping with quality assessment, North Africa and Pakistan

	Algeria	Djibouti	Egypt	Libya	Morocco	Sudan	Tunisia	Pakistan
Blood donors	0.2% (1992-1993) <sup>1</sup>	0.3% (1998-2000) <sup>1</sup>	1.7%-16.8% (2006-2009) <sup>1</sup>	0.9%-6.6% (1992-2001) <sup>1</sup>	0.2%-0.8% (2005-2011) <sup>1</sup>	0.0%-1.3% (2005-2007) <sup>1</sup>	0.1%-0.9% (2000-2010) <sup>1</sup>	0.2%-8.6% (2000-2006) <sup>1</sup>
Pregnant women	0.6% (2008) <sup>1</sup>	No data	8.6%-12.7% (-) <sup>3</sup>	0.4%-2.3% (-) <sup>3</sup>	1.0% (-) <sup>2</sup>	0.6% (2006) <sup>1</sup>	0.2% (2006) <sup>1</sup>	5.3% (2001-2006) <sup>1</sup>
Children	No data	No data	2.1%-5.8% (2002-2005) <sup>1</sup>	No data	No data	No data	No data	1.7% (-) <sup>2</sup>
Hemodialysis, renal dialysis, and/or dialysis patients	39.0% (-) <sup>3</sup>	No data	46.1%-100% (2002-2009) <sup>1</sup>	32.3% (2009-2010) <sup>1</sup>	54.1%-68.3% (2003-2004) <sup>1</sup>	8.5%-23.7% (2005-2010) <sup>1</sup>	14.6%-32.6% (2000-2002) <sup>1</sup>	38.8% (2003-2005) <sup>1</sup>
Hemophilic or other bleeding disorder patients	30.0% (2010-2011) <sup>2</sup>	No data	No data	No data	2.3%-42.4% (1981-2006) <sup>1</sup>	13.0% (2008) <sup>2</sup>	55.7% (-) <sup>2</sup>	25.0%-56.0% (2000-2002) <sup>1</sup>
Transfused patients	No data	No data	11.1%-81.6% (2000-2008) <sup>1</sup>	10.8% (1999-2001) <sup>1</sup>	No data	No data	4.7% (2008-2009) <sup>1</sup>	13.2%-15.4% (2002) <sup>1</sup>
Thalassemic patients	No data	No data	19.5%-69.6% (2000-2010) <sup>1</sup>	No data	68.3%-76.0% (-) <sup>3</sup>	No data	6.1% (-) <sup>2</sup>	36.2%-56.8% (1999-2003) <sup>1</sup>
Patients with hepatocellular carcinoma	No data	No data	85.9% (1997-2004) <sup>1</sup>	No data	57.3% (2003-2006) <sup>2</sup>	11.0% (1996-1998) <sup>1</sup>	19.0%-63.5% (1982-< 1995) <sup>2</sup>	53.7% (-) <sup>2</sup>
Patients with acute liver disease	No data	No data	No data	No data	0.0% (1999) <sup>1</sup>	6.3% (2007) <sup>2</sup>	8.0%-48.0% (< 1995) <sup>3</sup>	No data
Patients with chronic liver disease	No data	No data	No data	No data	73.7% (1983-1986) <sup>2</sup>	No data	80.5% (2005-2008) <sup>2</sup>	0.0%-86.6% (2000-2005) <sup>1</sup>
Healthcare workers	No data	No data	No data	2.0%-6.8% (1992-2001) <sup>1</sup>	No data	0.0% (2005-2007) <sup>1</sup>	1.0% (2005) <sup>1</sup>	5.6%-6.0% (2001-2002) <sup>1</sup>
Barbers	No data	No data	12.3% (-) <sup>3</sup>	No data	1.1%-5.0% (2001-2007) <sup>1</sup>	No data	No data	No data
Contact of patients with hepatitis C	No data	No data	No data	No data	No data	No data	No data	4.3%-38.0% (2000-2004) <sup>1</sup>
People who inject drugs	No data	No data	63.0% (-) <sup>2</sup>	94.2% (2010) <sup>1</sup>	22.9%-79.2% (2010-2012) <sup>1</sup>	No data	21.7%-29.1% (2009-2012) <sup>1</sup>	57.0% (-) <sup>2</sup>
Prisoners	No data	No data	No data	23.7% (2006) <sup>1</sup>	No data	No data	No data	No data
Patients with HIV and/or other sexually transmitted infection	No data	No data	No data	44.9%-54.1% (2003) <sup>1</sup>	5.4% (2006-2010) <sup>1</sup>	1.7% (2010-2012) <sup>1</sup>	35.5% (1997-2006) <sup>1</sup>	No data
Sex workers	No data	No data	No data	5.2%-7.3% (2010-2011) <sup>1</sup>	No data	0.0%-5.1% (2011-2012) <sup>1</sup>	1.1% (2007) <sup>1</sup>	No data
Men who have sex with men	No data	No data	No data	No data	No data	0.0%-5.9% (2011-2012) <sup>1</sup>	No data	No data

Prevalence, year of data collection. <sup>1</sup>Good quality; <sup>2</sup>Average quality; <sup>3</sup>Poor quality.

risk factors for HCV were demonstrated over time in Egypt and other countries<sup>[39]</sup>. Out of the 29 SRs reporting the anti-HCV prevalence, 16 (55%) failed to accurately report the years during which data collection occurred<sup>[32,34,36-38,40-50]</sup>. Thirteen SRs did not report the data collection years at all<sup>[34,36-38,40-48]</sup>, two reported the publication year as or instead of the data collection period of the study<sup>[32,49]</sup>, and one SR published in 2011 stated "unless indicated the estimates were for 2004 because of lack of more recent data"<sup>[50]</sup>. The choice of this year, *i.e.*, 2004, was not justified and appears arbitrary. For instance, the authors reported an anti-HCV prevalence in individuals with sexually transmitted diseases (STD) in Saudi Arabia of 15.9%\* in 2004, as no year was indicated<sup>[50]</sup>. Remarkably, the actual study that estimated the prevalence in individuals with STDs in Saudi Arabia reported 1990 as the year of data collection<sup>[51]</sup>. Additionally, we identified SRs pooling the prevalence measured over a long time period such as a pooled estimate for 1982-2010 in Tunisia<sup>[52]</sup> or for 1989-2012 in Sudan<sup>[27]</sup>. These estimates that encompass long time periods do not reflect changes in prevalence over time and do not accurately describe the past and current HCV

epidemiology in a population.

Similarly, for genotype distribution, only two<sup>[50,53]</sup> of the 18 SRs<sup>[6,27,33,37,38,40,43-45,48-50,53-58]</sup> reported HCV genotype/subtype distributions, and one<sup>[50]</sup> of the 12 SRs<sup>[27,39,40,44,45,50,52,53,57,59-61]</sup> reported risk factors with the data collection year provided, which would be an indicator if changes in genotype/subtype geographical distributions or in risk factors occurred over time. However, regarding incidence, six SRs<sup>[33,48,50,52,59,61]</sup> identified data points, and all of them reported the data collection years as those provided by the included studies.

Regarding the definitions of populations, we identified SRs pooling anti-HCV prevalences from populations at differing risk levels for acquiring HCV infections<sup>[27,33,37,41,52,59,62,63]</sup>. We question the meaningfulness of these estimated outcomes for mixed populations. How would clinicians and policymakers interpret and use an estimated anti-HCV prevalence for a mixed population including, for instance, patients with lymphoproliferative disorders, prisoners, patients with depression, mothers, and sex workers<sup>[41]</sup>? Regarding the GP, we identified SRs that combined blood donors with the GP<sup>[27,33,52,59,62]</sup>. Healthy blood donors (voluntary and non-remunerated)



**Table 2** Hepatitis C antibody prevalence evidence gap mapping with quality assessment, Arab Peninsula

	Bahrain	Kuwait	Oman	Qatar	Saudi Arabia	United Arab Emirates	Yemen
Blood donors	No data	0.8%-1.2% (nationals) (2002) 5.4%-13.5% (migrants) (2002) <sup>1</sup>	0.4%-0.7% (2006-2011) <sup>1</sup>	1.1% (nationals and migrants) 0.5% (nationals) (-) <sup>2</sup>	0.0%-5.6% (nationals and migrants, 1988-2009) 0.4%-4.2% (nationals, 1990-2009) 0.0%-34.0% (migrant, 1990-2002) <sup>1</sup>	0.5%-1.1% (2004-2009) <sup>1</sup>	1.7% (2005) <sup>1</sup>
Pregnant women	No data	No data	No data	No data	0.1%-4.6% (1989-2002) <sup>1</sup>	13.0%-13.4% (migrants) (1994-1996) <sup>1</sup>	3.3%-8.5% (2011) <sup>1</sup>
Children	No data	No data	No data	No data	0.7%-1.8% (1989-2002) <sup>1</sup>	No data	2.1% (2007-2009) <sup>1</sup>
Hemodialysis, renal dialysis, and/or dialysis patients	9.2% (-) <sup>3</sup>	27.0%-71.0% (1992-1995) <sup>1</sup>	26.5% (1991) <sup>1</sup>	44.6% (-) <sup>2</sup>	14.7%-78.2% (1995-2008) <sup>1</sup>	24.4% (1991-1993) <sup>1</sup>	40.0%-62.7% (1997-2013) <sup>1</sup>
Hemophiliac or other bleeding disorder patients	60.0% (1992) <sup>2</sup>	No data	No data	No data	78.6% (-) <sup>3</sup>	No data	No data
Transfused patients	No data	No data	No data	No data	4.6%-78.6% (1990-2011) <sup>1</sup>	No data	No data
Thalassemic patients	No data	33.0% (1965-1995) <sup>1</sup>	No data	No data	12.7%-70.0% (1990-2000) <sup>1</sup>	18.8% (1990-2001) <sup>2</sup>	No data
Patients with hepatocellular carcinoma	No data	No data	No data	No data	48.5% (2006-2008) <sup>1</sup>	No data	28.4%-38.2% (2001-2010) <sup>1</sup>
Patients with acute liver disease	No data	No data	No data	No data	3.4%-40.7% (2000-2005) <sup>1</sup>	1.2% (2006-2007) <sup>1</sup>	6.4%-8.8% (1997-1999) <sup>1</sup>
Patients with chronic liver disease	No data	37.8% (-) <sup>2</sup>	No data	29.4 (2000-2005) <sup>1</sup>	11.9%-65.0% (1989-2004) <sup>1</sup>	43.7% (-) <sup>2</sup>	33.8% (-) <sup>3</sup>
Healthcare workers	No data	0.9% (-) <sup>2</sup>	0.0% (-) <sup>2</sup>	No data	0.0%-0.3% (2001-2005) <sup>1</sup>	No data	1.1%-3.5% (-) <sup>3</sup>
Barbers	No data	No data	No data	No data	No data	No data	No data
Contact of patients with hepatitis C	No data	No data	No data	No data	0.0%-1.6% (-) <sup>2</sup>	27.0% (1994-1996) <sup>1</sup>	No data
People who inject drugs	No data	No data	48.1% (2011) <sup>1</sup>	No data	14.4%-54.7% (1995-2004) <sup>1</sup>	No data	No data
Prisoners	No data	No data	No data	No data	No data	No data	No data
Patients with HIV and/or other sexually transmitted infection	No data	0.9% (2012) <sup>1</sup>	No data	No data	12.0%-15.9% (1985-2010) <sup>1</sup>	No data	No data
Sex workers	No data	No data	No data	No data	No data	No data	No data
Men who have sex with men	No data	No data	No data	No data	No data	No data	No data

Prevalence, year of data collection. <sup>1</sup>Good quality; <sup>2</sup>Average quality; <sup>3</sup>Poor quality.

recruited with selection programs likely have lower anti-HCV prevalence than the GP<sup>[64]</sup>. Hence, in SRs pooling blood donor estimates with the GP estimates, the pooled estimates likely underestimate the actual anti-HCV prevalence in the GP. Furthermore, as meta-analyses give greater weight to studies with higher sample sizes and the sample sizes of studies describing anti-HCV prevalence in blood donors are often large, these pooled anti-HCV prevalences are more likely to be underestimated. In a country such as Djibouti where there were no identified studies reporting in the GP and only one identified study reporting on blood donors, reporting the estimate in blood donors as the lower limit of possible anti-HCV prevalence in the GP<sup>[6]</sup> might be relevant because of the scarcity of data. Riou *et al.*<sup>[35]</sup> used that estimate to provide an adjusted estimate for the GP. We believe that in countries where data points among the GP are available, blood donors should be

excluded.

Similarly, for reported genotype/subtype distributions and risk factors, mixing populations limited the ability to analyze that data in-depth.

### Conflict of interest

Out of the 37 SRs included in our overview, 32 SRs had authors who disclosed no conflict of interest. In one SR<sup>[65]</sup>, authors disclosed financial support from a US National Science Foundation Graduate Research Fellowship, a Sigma Xi Grant-in-Aid of Research, and the Global Health Program at the University of Michigan School of Public Health. Four SRs<sup>[6,34,50,56]</sup> reported at least one author who disclosed a direct or indirect financial relationship with pharmaceutical companies; among these SRs, three reported financial support from HCV DAA pharmaceutical companies<sup>[6,50,56]</sup>. Gower *et al.*<sup>[6]</sup> reported indirect financial support from Gilead Science,

**Table 3** Hepatitis C antibody prevalence evidence gap mapping with quality assessment, Fertile Crescent region

	Iraq	Jordan	Lebanon	Palestine	Syria
General population	0.0%-4.0 % (2004-2012) <sup>1</sup>	No data	0.6%-2.9% (-) <sup>2</sup>	No data	2.8% (2004) <sup>1</sup>
Blood donors	0.2%-2.8% (2003-2013) <sup>1</sup>	0.1%-0.9% (2003-2011) <sup>1</sup>	0.0%-3.4% (< 2003) <sup>1</sup>	0.2%-0.3% (2003-2013) <sup>1</sup>	0.4% (2000-2011) <sup>1</sup>
Pregnant women	0.0%-5.1% (2004-2010) <sup>1</sup>	No data	No data	No data	No data
Children	0.0% (2007-2009) <sup>1</sup>	No data	No data	No data	No data
Hemodialysis, renal dialysis, and/or dialysis patients	4.9%-42.6% (2002-2011) <sup>1</sup>	21.0%-49.8% (2003-2008) <sup>1</sup>	16.0%-27.0% (-) <sup>2</sup>	17.9%-27.4% (2007-2013) <sup>1</sup>	21.0% (2006) <sup>1</sup>
Hemophiliac or other bleeding disorder patients	6.7%-40.3% (2006-2012) <sup>1</sup>	No data	10.0% (-) <sup>3</sup>	No data	20.5% (2007-2011) <sup>1</sup>
Transfused patients	3.4%-4.5% (2004-2008) <sup>1</sup>	No data	No data	No data	13.3% (2000) <sup>2</sup>
Thalassemic patients	4.0%-46.0% (2003-2012) <sup>1</sup>	32.8% (2008) <sup>1</sup>	0.0%-14.0% (> 1999) <sup>1</sup>	No data	No data
Patients with hepatocellular carcinoma	26.1% (2000-2003) <sup>2</sup>	No data	19.6% (1998-2003) <sup>2</sup>	No data	No data
Patients with acute liver disease	0.0%-71.9% (2007-2011) <sup>1</sup>	No data	No data	No data	1.0%(1995-1998) <sup>1</sup>
Patients with chronic liver disease	3.8%-62.0% (2005-2009) <sup>1</sup>	No data	No data	No data	No data
Healthcare workers	0.0%-9.1% (2002-2010) <sup>1</sup>	0.7% (1999) <sup>1</sup>	0.4% (1999) <sup>1</sup>	No data	3.0%-3.8% (-) <sup>2</sup>
Barbers	0.3% (1999-2001) <sup>1</sup>	No data	No data	No data	No data
Contact of patients with hepatitis C	1.2%-1.4% (1996-2001) <sup>1</sup>	No data	No data	No data	No data
People who inject drugs	No data	No data	52.8% (2007-2008) <sup>1</sup>	45.2% (2010) <sup>1</sup>	60.5% (-) <sup>3</sup>
Prisoners	0.6% (1996-2001) <sup>1</sup>	No data	3.4% (-) <sup>3</sup>	No data	No data
Patients with HIV and/or other sexually transmitted infection	1.2% (-) <sup>2</sup>	No data	7.7% (-) <sup>3</sup>	No data	No data
Sex workers	No data	No data	0.0% (2007-2008) <sup>1</sup>	No data	2.0% (-) <sup>2</sup>
Men who have sex with men	No data	No data	0.0% (2007-2008) <sup>1</sup>	No data	No data

Prevalence, year of data collection. <sup>1</sup>Good quality; <sup>2</sup>Average quality; <sup>3</sup>Poor quality.

AbbVie, and Bristol-Myers Squibb. Bruggmann *et al*<sup>[56]</sup> and Sievert *et al*<sup>[50]</sup> reported financial support from Gilead Science, AbbVie, Merck, Bristol-Myers Squibb, and Janssen Therapeutics. Bruggmann *et al*<sup>[56]</sup> had 34 authors who disclosed direct or indirect financial relationships with at least one of the HCV DAA pharmaceutical companies (37% of the total number of authors). Furthermore, six authors did not disclose their conflict of interest. In Sievert *et al*<sup>[50]</sup>, out of the 29 authors, 13 (45% of the total number of authors) disclosed direct or indirect financial relationships with at least one of the HCV DAA pharmaceuticals.

Interestingly, two<sup>[6,56]</sup> of the three SRs that reported financial support from HCV DAA pharmaceutical companies were published in 2014 and were the only ones that estimated the total number of viremic cases in the GP. They were also the only SRs that estimated the genotype/subtype distributions in the GP of the MENA region, except for Morocco<sup>[43]</sup>, Pakistan<sup>[50,55]</sup>, and Tunisia<sup>[43]</sup> where the distributions were also computed by a couple of additional SRs. In Saudi Arabia, the third SR estimating genotype/subtype distributions also had authors who disclosed financial relationships with HCV DAA pharmaceutical companies<sup>[50]</sup>. Remarkably, in both SRs<sup>[6,56]</sup>, the authors did not follow the PRISMA guidelines (2009)<sup>[11]</sup> for reporting their reviews in detail; thus, we question the replicability of the reviews. Flow diagrams depicting the numbers of records identified,

included, excluded, and, most importantly, the reasons for the exclusions were not presented in those SRs<sup>[6,56]</sup>. Bruggmann *et al*<sup>[56]</sup> did not report the search criteria, eligibility criteria, or the risk of bias assessment of the included studies. Additionally, Bruggmann *et al*<sup>[56]</sup> reported that an expert panel reviewed the findings and analysis, and Gower *et al*<sup>[6]</sup> reported including "personal communication with experts within countries". However, the authors did not report how they defined "expert" or any conflicts of interest of these experts<sup>[6,56]</sup>. These reviews<sup>[6,56]</sup> had been cited 185<sup>[56]</sup> and 890<sup>[6]</sup> times, respectively, by February 12, 2018 (Google Scholar citations) and published in journals with impact factors of 3.9 and 11.3 (in 2014), respectively.

### HCV prevalence

In the GP, the estimations of the most up-to-date anti-HCV prevalence with the best quality ranged widely across MENA countries (Figure 2 and Tables 1-3). We identified low prevalence (< 1.5%) in Djibouti, Kuwait, Oman, Qatar, and UAE; moderate prevalence (1.5%-3.5%) in Algeria, Iraq, Lebanon, Libya, Morocco, Saudi Arabia, Sudan, Syria, and Tunisia; and high prevalence (> 3.5%) in Egypt, Pakistan, and Yemen. In Pakistan, anti-HCV prevalence may have increased from 5.4% in 1996-2007<sup>[62]</sup> to 6.7%\* in 2007-2008<sup>[6]</sup>. No reported data in the GP was identified for Bahrain, Jordan, or Palestine.

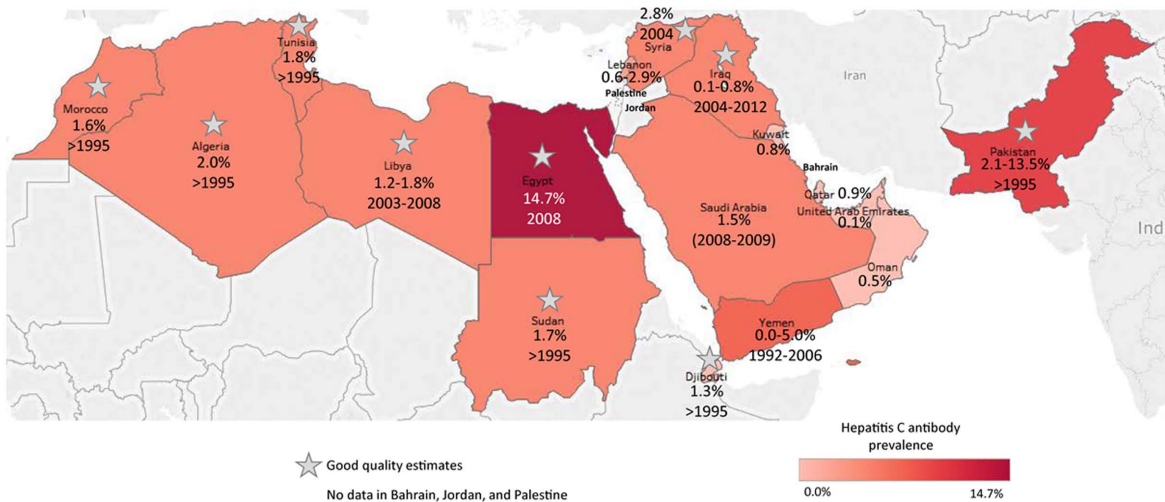


Figure 2 Hepatitis C antibody prevalence evidence gap mapping with quality assessment, general population, MENA. MENA: Middle East and North Africa.

Summary points pertaining to the estimated anti-HCV prevalences in blood donors, pregnant women, children, and patients with acute liver disease or CLD and HCC are highlighted in Supplementary Materials 8.

We identified that HCV transmission most likely occurs in healthcare settings. In all 20 MENA countries, patients with blood disorders such as hemophilia and thalassemia, patients undergoing hemodialysis, and patients who received transfusions had higher prevalences of anti-HCV than the prevalence in the GP. This suggests that transfusion-associated HCV infection may have occurred in these patients (Supplementary Material 8). Additionally, anti-HCV prevalences in healthcare workers in Iraq, Libya, and Syria suggest that in these countries, HCV transmission may also be due to occupational exposure (Supplementary Material 8). Community-acquired HCV infection may also occur in the MENA countries; however, we identified evidence gaps in the region (Supplementary Material 8).

Anti-HCV prevalence measures were not often identified for key populations such as PWID, prisoners, and MSM. Anti-HCV prevalence data were predominantly missing for the countries of the Arab Peninsula. No reported data were identified for MSM, prisoners, or sex workers in Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, the UAE, or Yemen. For PWID, anti-HCV prevalence data were identified in Egypt, Lebanon, Libya, Morocco, Oman, Pakistan, Palestine, Saudi Arabia, Syria, and Tunisia. For prisoners, reported anti-HCV prevalence data were identified in Iraq, Lebanon, and Libya.

Sexual transmission may also be a cause of HCV infection in some MENA countries. Anti-HCV prevalence data in patients with HIV or other STDs were missing for Algeria, Bahrain, Djibouti, Egypt, Jordan, Oman, Pakistan, Palestine, Qatar, Syria, the UAE, and Yemen. Anti-HCV prevalences in sex workers were reported for a few countries.

### HCV incidence

The incidence rate reflects the status of HCV transmission

in a population. Nevertheless, up-to-date incidence data in MENA countries were lacking (Tables 4 and 5). In the GP, the anti-HCV incidence rate was reported only in Egypt, at 0.8-6.8 per 1000 person-year in 1997-2003. The incidence rate was the highest in patients undergoing hemodialysis in the UAE, at 108 per 1000 person-year in 2003-2004. The incidence rates in patients undergoing hemodialysis were reported for Iraq, Jordan, Morocco, Tunisia, and the UAE. These findings suggest ongoing HCV transmission within healthcare settings in these countries.

### Viremic rate

In the GP, the HCV viremic rate among anti-HCV positive individuals was 51.6%\* (2011) in Saudi Arabia<sup>[6]</sup>; approximately 70%\* in Egypt (2008)<sup>[6]</sup>, Morocco (2005-2011)<sup>[6]</sup>, and the UAE (study dates not reported)<sup>[6]</sup>; 80.0%\* (2012) in Tunisia<sup>[6]</sup>; and 87.4%\* (2007-2008) in Pakistan<sup>[6]</sup>. Country-level HCV viremic prevalences ranged between 0.7%\* [95% confidence interval (CI): 0.3%-3.8%, 2011]<sup>[6]</sup> in Saudi Arabia and 10.0%\* (CI: 7.0%-12.2%, 2008)<sup>[6]</sup> in Egypt. The viremic prevalence was 1.1%\* (0.4%-1.4%, 2005-2011)<sup>[6]</sup> in Morocco, 1.0%\* (0.2%-2.0%, 2012)<sup>[52]</sup> in Tunisia, and 5.8%\* (1.4%-8.7%, 2007-2008)<sup>[6]</sup> in Pakistan. In anti-HCV positive blood donors, the viremic rate was 60.0% in Libya (1992-2001)<sup>[52]</sup> and 20.0% in Saudi Arabia (1988-2009)<sup>[59]</sup>. In healthcare workers, the viremic rate was reported in Libya as 69.2% (1992-2004)<sup>[52]</sup>. In dialysis patients, the HCV viremic rate was 51.0% in Tunisia before 2000<sup>[52]</sup> and 60.5%-93.3% in 2000-2003<sup>[52]</sup>; in Libya, it was 72.0% (before 2001)<sup>[52]</sup>. In HIV-infected patients in Morocco, the viremic rate was reported as 70.4% (study dates not reported)<sup>[49]</sup>.

### Co-infection with hepatitis B virus, HIV, or schistosomiasis

We identified two SRs<sup>[36,47]</sup> that reported HBV (HBsAg) and anti-HCV co-infection prevalence estimates; these estimates were only in HCC patients, and neither of

**Table 4** Hepatitis C antibody incidence and/or seroconversion risk rate relative to the total sample size, and evidence gap mapping, Middle East and North Africa

Country	Systematic review	Literature search period	Number of studies identified	Number of subjects	Population type	Estimation time period	HCV incidence rate (per 1000 person-year)	Loss of follow-up	HCV sero-conversion risk (%)	Duration of follow-up
Algeria	Fadlalla, 2015 <sup>[52]</sup>	1980-Unknown	0	0						
Libya	Fadlalla, 2015 <sup>[52]</sup>	1980-Unknown	0	0						
Morocco	Fadlalla, 2015 <sup>[52]</sup>	1980-Unknown	1	303	Hemodialysis patients	2003-2004	97	-	-	-
Tunisia	Fadlalla, 2015 <sup>[52]</sup>	1980-Unknown	1	276	Hemodialysis patients	2000-2002	28	-	-	-
Djibouti	Chaabna, 2016 <sup>[27]</sup>	Inception-2015	0	0						
Sudan	Chaabna, 2016 <sup>[27]</sup>	Inception-2015	0	0						
Egypt	Hussein, 2016 <sup>[48]</sup>	Inception-Unknown	-	-	-	-	6.9	-	-	-
	Mohamoud, 2013 <sup>[61]</sup>	Inception-Unknown	2	2852	Children of villages with high HCV prevalence	2000-2006	2.7	-	-	-
	Mohamoud, 2013 <sup>[61]</sup>	Inception-Unknown	3	10318	General population	1997-2003	0.8-6.8	-	-	-
	Mohamoud, 2013 <sup>[61]</sup>	Inception-Unknown	1	2177	Pregnant women	1997-2006	5.2	-	-	-
	Sievert, 2011 <sup>[50]</sup>	Unknown	-	-	Pregnant women	-	5.2	-	-	-
Pakistan	Sievert, 2011 <sup>[50]</sup>	Unknown	0	0						

these SRs<sup>[36,47]</sup> reported study dates/years. In Egypt, Pakistan, Saudi Arabia, and Tunisia, the anti-HCV prevalence was higher than the HBsAg prevalence, while the opposite finding was observed in Lebanon, Sudan, and Yemen (Supplementary Materials 9).

In Libya, 90.1% (CI: 78.2%-100%) of HIV-infected prisoners had an HCV co-infection (study dates not reported)<sup>[49]</sup>. In HIV-infected children, the prevalence of HCV co-infection was 43.0%-46.0% (1998-1999)<sup>[52]</sup>. The most up-to-date estimates of HCV co-infection in HIV-infected patients were 5.4% (2006-2010) in Morocco<sup>[52]</sup>, 1.7% (CI: 0.2%-2.3%, study date not reported) in Sudan<sup>[27]</sup>, 33.5% (CI: 20.4%-46.6%, 1997-2005) in Tunisia<sup>[49,52]</sup>, and 7.7% (study dates not reported) in Lebanon<sup>[33]</sup>.

Studies on schistosomiasis and HCV co-infection were reported for Egypt<sup>[45,61]</sup>, Sudan<sup>[27,45,46]</sup>, and Saudi Arabia<sup>[59]</sup>. In Egypt, 7.7%-84.0% (2002-2011) of the schistosomiasis patients were also infected by HCV<sup>[61]</sup>. Prior to 2000, HCV prevalence in schistosomiasis patients was 16.3%-42.5%<sup>[61]</sup>. In Sudan, the prevalence of schistosomiasis and HCV co-infection ranged from 4.5%<sup>[27]</sup> to 31.0% in 2001<sup>[27]</sup>. In Saudi Arabia, 17.9% of schistosomiasis patients were also infected with HCV<sup>[59]</sup>.

### HCV genotype and subtype

In the GP, genotype 1 was the most common genotype in Algeria (69.2%\*)<sup>[6]</sup>, Morocco (75.9%\*)<sup>[6,43]</sup>, Tunisia (84.0%\*)<sup>[6,43]</sup>, and Jordan (73.3%\*)<sup>[6]</sup>, while in Pakistan the most common genotype was genotype 3 (67.5%-86.7%\*)<sup>[40]</sup>.

No data in the GP was reported for Bahrain, Djibouti, Oman, Qatar, or Yemen. In the other MENA countries it was genotype 4 (45.2%-93.1%\*)<sup>[6,43,50,54,56]</sup> (Supplementary Materials 10 and 11). Interestingly, in Jordan, systematic reviews reporting genotype 4 as the most common genotype in the country had pooled estimates from the GP and other at-risk populations. In Morocco and Tunisia, subtype 1b was the most common genotype in the GP<sup>[43]</sup>, while in Pakistan<sup>[50,55]</sup> and Saudi Arabia<sup>[50]</sup>, it was 3a. In pregnant women, genotype 4 was reported as the most common genotype in Algeria, Egypt, Iraq, Libya, Saudi Arabia, Sudan, Tunisia, and Yemen<sup>[44]</sup>, whereas genotype 1 was the most common genotype in Morocco<sup>[44]</sup>. Genotype distributions in blood donors<sup>[38]</sup> and in clinical populations, such as patients with CLD, non-Hodgkin lymphoma, thalassemia, or hemophilia, were similar to the distributions identified in the general population<sup>[38,57]</sup>. However, in PWID in Saudi Arabia, genotype 1 was reported as the most common genotype (48%), followed by genotype 3 (36.0%\*)<sup>[50]</sup>, whereas in Lebanon, genotype 3 was the most common genotype (26.3%-57.0%), followed by genotype 1 (21.0%-42.1%) and genotype 4 (18.0-34.6%\*)<sup>[38]</sup>.

### Risk factors associated with HCV infection

The risk factors for acquiring an HCV infection reported for MENA countries were factors associated with medical practices (blood transfusion, catheter use, hemodialysis, nosocomial exposure, and invasive procedures, among others)<sup>[27,39,40,44,45,50,52,53,57,59-61]</sup> (Supplementary Material 12).



**Table 5** Hepatitis C antibody incidence and/or sero-conversion risk rate relative to the total sample size, and evidence gap mapping, Middle East and North Africa

Country	Systematic review	Literature search period	Number of studies identified	Number of subjects	Population type	Estimation time period	HCV incidence rate (per 1000 person-year)	Loss of follow-up	HCV sero-conversion risk (%)	Duration of follow-up
Iraq	Chemaitelly, 2015 <sup>[33]</sup>	1985-2015	1	57	Hemodialysis patients	2009	-	0	40.3	12 mo
	Chemaitelly, 2015 <sup>[33]</sup>	1985-2015	1	123	Pediatric patients with acute lymphoblastic leukemia	2007	-	0	3.2	30 mo (median)
	Chemaitelly, 2015 <sup>[33]</sup>	1985-2015	1	26	Newborn to HCV infected women	-	-	0	0	6 mo
	Chemaitelly, 2015 <sup>[33]</sup>	1985-2015	1	85	Pediatric cancer patients on chemotherapy	2006-2007	-	22	3.2	12 mo
	Chemaitelly, 2015 <sup>[33]</sup>	1985-2015	1	60	Healthy children	2007-2009	-	0	0	6 mo
	Chemaitelly, 2015 <sup>[33]</sup>	1985-2015	1	29	Pediatric patients with leukemia on chemotherapy	2007-2009	-	0	3.5	6 mo
	Chemaitelly, 2015 <sup>[33]</sup>	1985-2015	1	27	Pediatric patients with leukemia who have had their baseline screening prior to chemotherapy	2007-2009	-	0	0	6 mo
Lebanon	Chemaitelly, 2015 <sup>[33]</sup>	1985-2015	0	0						
Palestine	Chemaitelly, 2015 <sup>[33]</sup>	1985-2015	0	0						
Jordan	Chemaitelly, 2015 <sup>[33]</sup>	1985-2015	1	1300	Hemodialysis patients	2003	-	-	9.2	12 mo
Syria	Bashour, 2016 <sup>[39]</sup>	Unknown	0	0						
	Sievert, 2011 <sup>[50]</sup>	Unknown	0	0						
United Arab Emirates	Mohamoud, 2016 <sup>[59]</sup>	Unknown	1	-	Hemodialysis patients	1995	108	-	-	-
Yemen	Chaabna, 2016 <sup>[27]</sup>	Inception-2015	0	0						

These risk factors suggest that iatrogenic transmission is specifically found in Egypt<sup>[39,44,45,50,60,61]</sup>, Iraq<sup>[44]</sup>, Pakistan<sup>[40,50,53,57]</sup>, Saudi Arabia<sup>[50]</sup>, Sudan<sup>[44,45]</sup>, Syria<sup>[50]</sup>, and Yemen<sup>[44]</sup>. In Egypt, Pakistan, Saudi Arabia, Sudan, and Syria, factors associated with the community were also reported (contacts of HCV-infected patients, sharing razors, circumcision, injection from informal health provider, and tattooing, among others)<sup>[39,40,44,45,50,53,57,60,61]</sup>. Age<sup>[45,59,61]</sup>, level of education in Yemen<sup>[44]</sup>, intravenous drug use in Pakistan<sup>[57]</sup> and Syria<sup>[50]</sup>, and homosexuality in Pakistan<sup>[57]</sup> were also associated with HCV infection.

## DISCUSSION

Stretching from North Africa through the Middle East and into central Asia, the MENA region demonstrates a wide range of anti-HCV and viremic prevalences and diversity in HCV genotype distributions. For each country, our mapping of evidence gaps and quality assessment of outcomes reported on the available HCV morbidity measurements, their quality, and how well the SRs

reported them and emphasized the opportunities for further population health research to better characterize HCV epidemiology in the region.

### Quality assessment

Our overview of SRs identified that a substantial proportion of SRs on HCV epidemiology in MENA failed to report their outcomes following the PICOTS framework<sup>[25,26]</sup>. This can potentially lead to imprecise reported information that can, in turn, mislead data interpretation<sup>[26]</sup>. In addition to providing accurate information on HCV epidemiology, outcomes should also demonstrate practical and clinical significance and relevance. While most SRs of clinical research were determined to not be useful because their conclusions were false or exaggerated<sup>[66]</sup>, it appears that we should also question the usefulness of SRs of population health research on HCV epidemiology in the MENA region. The SRs of HCV epidemiology in the MENA region stated that their aim was to provide a clear picture of the situation in the region. However, a substantial proportion of the

SRs in our overview lacked the key identified features of transparency ("are methods, data, and analyses verifiable and unbiased?"<sup>[66]</sup>) and pragmatism ("inferences should be applicable to real-life circumstances"<sup>[66]</sup>), which also are lacking in clinical research<sup>[66]</sup>.

To reach the Global Health Sector Strategy on Viral Hepatitis (GHSS-VH) 2030 elimination goal<sup>[67]</sup>, SRs of HCV epidemiology should assist policymakers in developing treatment programs and effective, precise prevention strategies for micro-elimination targeting specific populations at higher risk of acquiring HCV infections. Additionally, SRs of HCV epidemiology should guide changes to make clinical practices safer. Hence, an accurate picture is not obtainable by pooling population estimates of groups at different risk of acquiring HCV infections, such as patients undergoing hemodialysis combined with PWID, MSM combined with healthcare workers, or the GP combined with blood donors. Furthermore, estimated HCV outcomes should be as up-to-date as is reasonably possible, encompassing a narrow interval of time to attempt to depict the current situation in the region. The outcomes can be pooled by period, so potential changes in the epidemiological profile can be demonstrated. As such, dissemination of pooled estimates that combine data from many studies, some conducted two decades ago, in order to increase the statistical power does not appear to be useful in nowcasting the epidemiology of HCV in the region and is not helpful in developing effective preventive and treatment programs essential to attaining the 2030 HCV infection elimination goal.

### Conflict of interest

The evaluation of SRs should not be limited to the assessment of the reported methods, assumptions, data, and results<sup>[31]</sup>. Our overview emphasizes the significance of considering the disclosure of financial relationships while assessing research<sup>[31]</sup>. Researchers can be influenced by financial relationships while making judgments and decisions at a subconscious level such that they are not aware of the influence<sup>[31]</sup>. In the era of DAA treatment, the only published SRs providing the number of chronically HCV-infected individuals in the MENA region have substantial proportions of their authors who disclosed financial relationships with HCV DAA pharmaceutical companies. Our overview identifies a need in the MENA region for estimates of the number of chronically HCV-infected individuals who are candidates for DAA treatment by researchers who have not received financial assistance from Gilead Science.

### Status of HCV epidemiology in the MENA region:

#### Incidence

HCV infection is usually a slow progressive disease, which can lead to liver cirrhosis a couple of decades post-HCV infection<sup>[68]</sup>. Patients with liver cirrhosis are at 1%-5% annual risk of HCC and a 3%-6% annual risk of hepatic decompensation<sup>[68]</sup>. As such, a long period with non-specific symptoms passes before

manifestations of HCV-related hepatic and extra-hepatic dysfunctions occur<sup>[69]</sup>, which may then lead to the diagnosis of HCV infection. The distributions of these dysfunctions and diseases reflect past HCV infection transmission<sup>[69,70]</sup>. Hence, the prevalence of anti-HCV provides a retrospective snapshot of HCV transmission in a population, while the incidence describes the current HCV status in that population. Our overview also identifies research evidence gaps pertaining to up-to-date anti-HCV incidence data in all MENA countries. Therefore, we recommend that additional research be conducted to measure the HCV incidence to assess current HCV transmission trends. Incidence studies in the GP and populations at differing levels of risk for acquiring HCV will allow real-time measurement of HCV transmission. Nowcasting will help policymakers to develop and implement efficient prevention strategies alongside treatment programs.

### Status of HCV epidemiology in the MENA region:

#### Prevalence in the general population

Among the 20 MENA countries, anti-HCV prevalence in the GP varied widely. Egypt, Pakistan, and Yemen were classified as having high prevalences of anti-HCV. In the six Gulf Nations, namely, Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, and the UAE, the reporting quality of the anti-HCV prevalence data was poor (no data for Bahrain). Nevertheless, the available data in the GP demonstrate low-to-moderate prevalences of anti-HCV in these countries. Remarkably, in these countries, the data from blood donors were of better reporting quality. Among blood donors, the anti-HCV prevalence was lower in nationals than in migrants, suggesting that the demographic characteristics of these Gulf Nations (nationals vs migrants) should be considered when describing the HCV epidemiology<sup>[71]</sup>. In these countries, population size increased rapidly in the last two decades due to the immigration of temporary workers<sup>[72]</sup>. More than 30% of the populations of the Gulf Nations are migrants; in Qatar and the UAE in 2014, this figure was over 80%<sup>[73,74]</sup>. In Qatar, Egyptian and Pakistani migrants accounted for 9% and 5% of the population, respectively, while Qatari nationals accounted for 12% (2016)<sup>[75]</sup>. HCV prevalence in a GP including both nationals and migrants in a country such as Qatar will be influenced by the HCV epidemiology profiles of the migrants' countries of origin. Of note, migrants have to be negative for HIV, HBV, and HCV upon arrival in the Gulf Nations; however, screening is not mandatory thereafter, except for some professions such as those in the healthcare sector<sup>[76-81]</sup>. Thus, HCV-infected migrants in these countries would most likely have been infected while visiting their countries of origin.

#### Status of HCV epidemiology in MENA: Prevalence in blood donors

In countries that (1) prohibit persons at higher risk of acquiring blood-borne infection from donating blood and (2) systematically implement pre-transfusion screening

of blood donation for these infections, the prevalence of blood-borne infections in blood donors should be lower than that in the GP<sup>[28,29]</sup>. In some MENA countries, the anti-HCV prevalence was higher in blood donors than in the GP. Furthermore, in MENA countries, prevalence and incidence measurements in transfused patients and in patients with blood disorders suggest that HCV transmission in healthcare settings is prevalent and is likely to be ongoing. There is a need to ensure that patients receive the safest possible blood products. The management of all blood units and their components should guarantee that only those with negative HCV screening assays are sent to the hospitals to be used in transfusions. Strong regulatory policies for all blood banks must be implemented and enforced to achieve this.

### **Status of HCV epidemiology in the MENA region: Prevalence in healthcare settings**

In Pakistan, HCV transmission due to unsafe injections (*i.e.*, using contaminated needles and syringes) was identified in 2000<sup>[82]</sup>, and in 2006, the proportion of people sharing injection equipment during their last injection was between 8.5% and 33.6%<sup>[83]</sup>, suggesting that HCV transmission in healthcare settings was still ongoing. Additionally, we report that the prevalence of anti-HCV is higher in healthcare workers than in the GP in Iraq (2002-2010), Libya (1992-2004), Syria, and Yemen (study dates not reported). In 1999, HCV transmission in healthcare workers due to needle injuries from HCV-positive patients was reported in Pakistan<sup>[84]</sup>. The identified evidence suggests that occupational exposure to HCV occurs in healthcare settings in some MENA countries. In 2000, in order to prevent the transmission of HCV and other blood-borne infections in healthcare settings, the World Health Organization recommended the implementation of strategies targeting healthcare workers and patients, focusing on achieving behavioral changes to reduce re-use and over-use of injections, increase the exclusive use of sterile syringes and needles, and increase the proper disposal of sharp waste after use<sup>[85]</sup>.

### **Status of HCV epidemiology in the MENA region: Key populations**

Intravenous drug use appears to drive HCV infection in half the MENA countries, namely, Egypt, Lebanon, Libya, Morocco, Oman, Pakistan, Palestine, Saudi Arabia, Syria, and Tunisia. Relatively up-to-date data with good reporting quality were identified for these countries. However, missing data for the other MENA countries impact the evaluation of role of intravenous drug use in HCV transmission in a substantial part of the region. Prisoners are a key population rarely studied in MENA countries. We identified HCV outcomes in prisoners in only three countries (Libya, Iraq, and Lebanon). It appears that incarcerated individuals are at higher risk of acquiring HCV infections, especially

HIV positive prisoners. Similarly, HCV epidemiology in MSM was described only in Sudan and Lebanon, and no data from HIV-infected MSM were identified. Lebanon, Libya, Sudan, Syria, and Tunisia reported higher anti-HCV prevalences in female sex workers than in the GP, demonstrating that this population may be at higher risk of acquiring HCV infections. Consequently, population health research studies are needed in these key populations to comprehensively characterize HCV epidemiology in the MENA countries, which will facilitate better planning, development, and implementation of precise preventive strategies and treatment programs.

### **Status of HCV epidemiology in the MENA region: HBV and HIV co-infection, vertical transmission, and community**

Co-infections with HCV and HBV or HIV, which share common modes of transmission, namely, through exposure to infected blood and sexual transmission<sup>[86]</sup>, reminds us of the need for a holistic approach to tackle the population health issue of blood-borne infections. Additionally, the identified evidence regarding HCV morbidity (incidence and prevalence) in pregnant women and in children in Egypt, Pakistan, Saudi Arabia, and Yemen suggested that vertical HCV transmission may also occur. As for vertical transmission, little evidence was identified regarding community-acquired HCV infections. Additional research studies are needed to explore these transmission modes.

### **Status of HCV epidemiology in the MENA region: Genotype geographical pattern**

Genotype/subtype 1b is omnipresent across the region. Genotype 4 appears to be the most common in Egypt. In the Gulf Nations, the dominance of genotype 4 might be explained by the high proportion of migrants from Egypt. Genotype 3 is the most common in Pakistan, suggesting that intravenous drug use is likely the driver of HCV transmission in this country<sup>[87,88]</sup>. Genotype 3a in Pakistan appears to have emerged around the 1920s<sup>[88]</sup>.

Many SRs reported HCV genotype/subtype distributions and pooled frequencies without specifying the temporality of their identified geographical pattern. HCV genotypes differ according to the mode of transmission. For instance, while HCV-1b is the most prevalent HCV genotype/subtype globally<sup>[6]</sup>, HCV-3 and 1a are linked to PWID, and in Asia, HCV-1a is also linked to PWID<sup>[87]</sup>. A birth cohort analysis demonstrated that the distribution of HCV genotypes is changing in Japan and appears to be associated with the establishment of the prevention of HCV transmission through blood transfusions or nosocomial infections in 1990<sup>[89]</sup>. In Japan, genotype 1b is associated with the former mode of transmission, while genotypes 2a and 2b are associated with the latter mode of transmission<sup>[89]</sup>. Unfortunately, because of how genotype/subtype data are pooled and reported for the MENA region, we were not able to identify differences in time trends and geographic patterns.

### Quality assessment, strengths and limitations of our overview

We followed PRISMA guidelines<sup>[11-13]</sup> in reporting our work. All PRISMA required items regarding the abstract and the different sections of the main text were reported. Furthermore, we assessed our methodology using the AMSTAR tool<sup>[14]</sup>. We answered eight of the 11 questions of this tool in the affirmative and reported the pages where the information can be found. The three remaining questions were not applicable to our work (e.g., "Were the methods used to combine the findings of studies appropriate<sup>[14]</sup>? Was not applicable because we did not conduct a meta-analysis).

The quality assessment of SRs we conducted was limited to all SRs of HCV epidemiology in the MENA region that were published in peer-reviewed journals indexed on Medline as identified through PubMed, which may not be representative of SRs of HCV epidemiology in the MENA region in general. However, PubMed has been recognized as the first public digital archive; as such, we can assume that we have assessed the quality of the majority of SRs of HCV epidemiology published in peer-reviewed journals<sup>[90]</sup>. Additionally, we critically synthesized all available data on HCV morbidity and risk factors reported by those SRs. Knowing that most of the 37 SRs included in our overviews conducted a multi-source literature search including, in some SRs, a search for gray literature, we assumed that our synthesis in this overview is comprehensive. However, we might have missed some studies published recently that were not included in the SRs included in our overview. For instance, in Egypt, anti-HCV prevalence was estimated to be 6% in 2014<sup>[5]</sup>, yet none of the SRs we included reported that estimate.

## CONCLUSION

To reach the 2030 HCV infection elimination goal set by the GHSS-VH<sup>[67]</sup>, evidence-based health policies need to be developed and implemented to optimize the allocation of financial resources and to alleviate the burden of disease due to HCV infection. Correct measures of anti-HCV prevalence, viremia, and genotype distribution are essential for developing strategies to manage and eliminate HCV infection. Evidence gap mapping and quality assessment, along with reviewing reported conflicts of interest, revealed countries and specific populations where data are scarce and/or lacking in quality. We identified areas of opportunity to further develop population health research to comprehensively characterize HCV infection in the MENA region. Currently, the available estimates of the numbers of chronically HCV-infected patients who are candidates for the new DAA regimens are computed by researchers, a substantial proportion of whom have indirect or direct financial relationships with HCV DAA pharmaceutical companies. Additionally, a substantial proportion of the included SRs did not report precise outcomes, which can lead to misinterpretation of the data. Evidence-

based policies should be established from up-to-date information generated from rigorously designed studies and reported outcomes.

Our synthesis of the published SRs of HCV epidemiology in the MENA region demonstrates that despite the region being recognized as having the greatest HCV burden, a majority of the 20 countries have low to moderate anti-HCV prevalence. Only Egypt, Pakistan, and Yemen demonstrated a high anti-HCV prevalence. Iatrogenic transmission of HCV in patients and occupational exposure in healthcare workers are likely to be ongoing in the MENA countries. There is an urgent need for safer blood products and the implementation of safe medical practice guidelines. Intravenous drug use appears to be another common mode of HCV transmission in half the MENA countries. Research studies are needed to characterize the status of HCV epidemiology in PWID in countries where data are lacking. To develop effective prevention strategies and treatment programs to achieve HCV elimination, characterizing HCV epidemiology in key populations such as MSM and sex workers is essential and cannot be overlooked.

## ARTICLE HIGHLIGHTS

### Research background

The Middle East and North Africa (MENA) has been identified as the region most affected by hepatitis C virus (HCV) infection worldwide predominantly due to the high HCV infection burden in Egypt and Pakistan. Since 2013, chronic infections with HCV genotypes 1, 2, 3, and 4 are curable, making elimination of HCV infection achievable for the first time. However, access and availability of the new direct-acting antiviral drug (DAA) regimens remains a challenge owing to country-level economic matters.

### Research motivation

Developing and prioritizing evidence-based strategies for prevention programs and treatment scale-up require up-to-date information generated from rigorously designed studies and reported outcomes. A substantial number of systematic reviews of HCV infection in the MENA region have been published. What is the quality of these systematic reviews and what is the quality of the studies included in these systematic reviews? Researchers can be influenced by financial relationships while making judgments and decisions at a subconscious level such that they are not aware of the influence. The use and interpretation of the outcomes in the systematic reviews need to be viewed keeping in mind the reported conflict of interests by the authors of the systematic reviews. Our overview was also motivated because of the following questions: what do we know about hepatitis C epidemiology in the MENA region? High country-level anti-HCV prevalence has been identified in Egypt and Pakistan. What is the status of the other 18 MENA countries? What are the identified potential modes of transmission and populations at higher risk of acquiring hepatitis C infection?

### Research objectives

The primary objective of our overview is to assess the quality of the data reported by the published systematic reviews of HCV epidemiology in the MENA countries taking into account conflict of interest disclosed by the authors of these systematic reviews. Our secondary objective is to produce a comprehensive picture of HCV infection epidemiology in the 20 countries of the MENA region.

### Research methods

An *a priori* protocol of our overview is registered with the International Prospective Register of Systematic Reviews (PROSPERO registration number CRD42017076736). We conducted an overview of systematic reviews based



on the Cochrane Handbook for Systematic Reviews of Interventions. We used broad search criteria to include all systematic reviews on HCV infection in the MENA region published after 2008 - the publication year of the first version of the Cochrane Handbook for Systematic Reviews of Interventions. We extracted all relevant outcomes related to HCV infection epidemiology. The nine primary outcomes of interest were HCV antibody (anti-) prevalences and incidences in different at-risk populations; the HCV viremic (RNA positive) rate in HCV-positive individuals; HCV viremic prevalence in the general population; the prevalence of HCV co-infection with the hepatitis B virus, human immunodeficiency virus, or schistosomiasis; the HCV genotype/subtype distribution; and the risk factors for HCV transmission. Thereafter, we critically analyzed and synthesized the extracted data by assessing their quality - using PICOTS framework, by evaluating conflict of interests disclosed by the authors of the systematic reviews, and by mapping the evidence and the gaps. Our overview is reported following PRISMA guidelines and assessed using AMSTAR tool.

## Research results

Data reporting in a substantial proportion of systematic reviews on HCV infection in MENA may mislead the interpretation of these data. Our overview identified that a substantial proportion of the systematic reviews failed to report their outcomes following the PICOTS framework. Additionally, a substantial proportion of the systematic reviews lacked the key identified features of transparency and pragmatism. Our overview emphasizes the significance of considering the disclosure of financial relationships while assessing research and its reported outcomes. In the era of DAA treatment, the only published systematic reviews providing the number of chronically HCV-infected individuals in the MENA region - number of candidates for DAA treatment, have a large number of authors who disclosed financial relationships with HCV DAA pharmaceutical companies. We identified low prevalence of anti-HCV (< 1.5%) in Djibouti, Kuwait, Oman, Qatar, and UAE; moderate prevalence (1.5%-3.5%) in Algeria, Iraq, Lebanon, Libya, Morocco, Saudi Arabia, Sudan, Syria, and Tunisia; and high prevalence (> 3.5%) in Egypt, Pakistan, and Yemen. In Pakistan, anti-HCV prevalence may have increased from 5.4% in 1996-2007 to 6.7% in 2007-2008. No reported data in the general population was identified for Bahrain, Jordan, or Palestine. Intravenous drug use appears to drive HCV infection in Egypt, Lebanon, Libya, Morocco, Oman, Pakistan, Palestine, Saudi Arabia, Syria, and Tunisia. Relatively up-to-date data with good reporting quality were identified for these countries. However, missing data for the other ten MENA countries affect the evaluation of role of intravenous drug use in HCV transmission in a substantial part of the region. Furthermore, we identified that HCV transmission most likely occurs in healthcare settings due to iatrogenic and/or occupational exposures. Community-acquired HCV infection may also occur in the MENA countries; however, we identified evidence gaps in the region. Often, anti-HCV prevalence measures were not identified for key populations such as prisoners, men who have sex with men, and sex workers. Anti-HCV prevalence data were predominantly missing for the countries of the Gulf Cooperation Council and Yemen.

## Research conclusions

Correct measures of anti-HCV prevalence, viremia, and genotype distribution are essential for developing strategies to manage and eliminate HCV infection. Evidence gap mapping and quality assessment, along with reviewing reported authors conflict of interest, revealed MENA countries and specific populations where data are scarce and/or lacking in quality. Our overview comprehensively characterizes hepatitis C epidemiology in the 20 countries of the MENA region and emphasizes their needs in terms of treatment and prevention. This will help policy makers of these countries to develop and prioritize evidence-based strategies for prevention programs and treatment scale-up in the region. This overview will contribute to the improvement of population health research practices in order to build research capacity in the MENA region

## Research perspectives

Future systematic reviews on HCV epidemiology in the MENA region should strive to provide accurate information on HCV epidemiology demonstrating practical and clinical significance and relevance. To facilitate the development of precise prevention strategies and treatment programs, we recommend when estimating and reporting HCV prevalence and incidence, to avoid mixing populations at differing risk of acquiring HCV. Furthermore, up-to-date and good

quality data are required in order to nowcast HCV epidemiology in the region. When data is available for long time periods, reporting should reflect changes in prevalence or incidence over time, which will allow to accurately describe the past and current HCV epidemiology in a population.

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