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September 15th, 2021

Dr. Saurabh Chandan
Editor-in-Chief, World Journal of Meta-Analysis

Dear Dr. Chandan,

Please find enclosed our revised manuscript entitled **'Epidemiology of Hepatitis C Virus among Blood Donors and the General Population in the Middle East and North Africa: Meta-analyses and Meta-regressions'**, along with a point-by-point reply to the reviewers' and editors' comments.

We would like to thank you for your consideration of our study for publication in *World Journal of Meta-Analysis.* We would also like to thank the reviewers for their valuable feedback and suggestions, and the critical appraisal of our work. This input has enriched our article and its contribution to the literature. In this revised version of the manuscript, and in our reply to the reviewers, we have addressed each of the reviewers' comments and suggestions. We would be pleased to accommodate any other, should the editors or reviewers have any further suggestions.

We thank you for your time and consideration.

Yours sincerely,

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Epidemiology of Hepatitis C Virus among Blood Donors and the General Population in the Middle East and North Africa: Meta-analyses and Meta-regressions

REPLY TO REVIEWERS' AND EDITORS' COMMENTS

We would like to thank the editors and reviewers for assessing our work and for their valuable feedback and suggestions. Please find below a point-by-point reply addressing each of the reviewers' comments. We have also incorporated these suggestions in the revised manuscript as noted below. We would be pleased to address any further points that the editors or reviewers may find unsatisfactory.

Note: All references to the revised manuscript pertain to the marked copy of this file including changes implemented through "track changes".

1 Peer-review report

Reviewer #1

Remarks to the Author:
The authors have done fascinating work on HCV prevalence in the Middle East and North Africa population, comparing it with the European population.

Comment: We thank the reviewer for assessing our work and for the constructive feedback on our manuscript that enriched the article and improved its readability. Please find below a point-by-point reply addressing each of the reviewer's comments.

1) *The data suggest an annual reduction in the disease incidence in both regions, which are very encouraging figures. However, there are substantial differences between the prevalence of blood donors and the general population in Europe. This phenomenon is logical in a population context with numerous clinical analyses, where most HCV cases are diagnosed. In this way, the low number of HVC in European blood donors could indicate a small number of undiagnosed people since the diagnosed subjects would not go to donate blood. Therefore, the figures observed in MENA could be an alarming indicator of the percentage of the population undiagnosed. Authors should consider reevaluating these facts in their work.*

Answer: We have now revised the manuscript to include a statement emphasizing this point, as suggested by the reviewer (Discussion, Page 15, Paragraph 1).

2) *Secondly, the methodology indicates: "The database included 685 HCV Ab prevalence measures on 46,634,214 blood donors and 528 measures on 2,358,944 individuals of the general population, such as pregnant women, healthy adults, and children, among others." The sum of the data provided in material and methods shows 1,213 HCV Ab prevalence measures on 48,993,158 individuals. Why don't the numbers match the job title?*

Answer: We thank the reviewer bringing this to our attention and apologize for the confusion. The numbers indicated in the title referred to the larger MENA HCV Epidemiology Synthesis Project Database, a database consisting of several different populations from which studies including blood donors and general populations were extracted. We acknowledge that this may be confusing to the reader and have reduced the title to comply by the word count for the title, as suggested by reviewer #2 (Title, Page 1).

3) *How are the sample size and number of samples different from previous work, entitled "Who to Test for Hepatitis C Virus in the Middle East and North Africa ?: Pooled Analyzes of 2,500 Prevalence Measures, Including 49 Million Tests"?*

Answer: The MENA HCV Synthesis Project Database, which has been used in this work and the previous work mentioned by the Reviewer, was populated through a series of previously conducted systematic reviews. Since publication of the previous work mentioned, the database has been updated through additional systematic reviews, and therefore the sample size and number of samples have changed.

4) *Finally, the sample size of blood donors is much larger than that of the general population, which could be another limitation of the study. Consider including it in study limitations.*

Answer: We have now revised the limitations to include this statement (Discussion, Page 16, Paragraph 2).

Reviewer #2

Remarks to the Author:

This is an interesting study, but you should format your manuscript and references as recommended by the publisher. The title should be shortened.

Comment: We thank the reviewer for assessing our work and for the constructive feedback on our manuscript that enriched the article and improved its readability. We have now shortened the title and have revised the references as recommended by the publisher (Title, Page 1; References, Page 26).

Reviewer #3

1) *I read the manuscript following are my opinion. The PRISMA checklist suggests page 1-8 has several details of the search, eligibility criteria, etc. However, in reality, it is almost impossible that these sections span over such a vast area of the manuscript. Since a list of references is inserted at the end of this checklist, another possibility I took into consideration is that authors might have meant by '(1-8)' as the references. It's weird to present citations in this last column of the PRISMA checklist.*

Answer: We thank the reviewer for assessing our work and for the constructive feedback on our manuscript that enriched the article and improved its readability and apologize for the confusion. The reviewer is correct in their assumption that references were used in the PRISMA checklist. This study uses the MENA HCV Epidemiology Synthesis Project Database, a database that was populated through a series of systematic reviews on HCV in MENA that were previously conducted and published as part of the MENA HCV Epidemiology Synthesis Project. For this reason, specific details, such as search strategy, can be found in each of the individual published systematic reviews referenced to in the PRISMA checklist.

2) *I am not clear how the literature search was performed. Its not clear the databases searched and their search strategy. The title doesn't clearly state if this is a systematic review, meta-analysis, or both. The study lacks clear eligibility criteria. Thank you.*

Answer: We have now edited the methodology to clarify the systematic reviews were previously conducted and specific details may be found in each of these publications that have been referenced (Methods, Page 7, Paragraph 2). The study entails meta-analyses and meta-regression of an extensive database that was populated through a series of previously conducted systematic reviews. As such, the title has been reformulated to encompass the breadth of analysis that has been performed.

2 Editorial Office's comments

1) Science Editor:

The authors have made a comprehensive analysis of HCV seropositivity in blood donors. however, the methodology is unclear. The points emphasized by the reviewers are vital and should be addressed by the authors
Language Quality: Grade B (Minor language polishing)
Scientific Quality: Grade D (Fair)

2) Editorial Office Director:

I recommend the manuscript to be published in the World Journal of Meta-Analysis.

3) Company Editor-in-Chief:

I recommend the manuscript to be published in the World Journal of Meta-Analysis.

Answer: We thank the editors for assessing our work and for the constructive feedback on our manuscript that enriched the article and improved its readability. The points raised by the reviewers have been addressed in the point-by-point replies above.

Epidemiology of Hepatitis C Virus among Blood Donors and the General Population in the Middle East and North Africa: ~~Pooled Analyses of 2,600 Prevalence Measures Including 50 Million Tests~~Meta-analyses and Meta-regressions

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Word count: Abstract: ~~262~~334, Manuscript: 3,~~027~~121

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ABSTRACT

~~**Objective:** To delineate~~ **Background:** Despite the Middle East and North Africa (MENA) region reported to have the highest prevalence of hepatitis C virus (HCV) globally, HCV epidemiology infection levels in the majority of MENA countries remains inadequately characterized. Blood donor data have been previously used as a proxy to assess levels and trends of HCV in the general population, however, it is unclear how comparable these populations are in MENA and whether blood donors provide an appropriate proxy. **Aim:** To delineate HCV epidemiology among blood donors and the general population in the Middle East and North Africa ~~(~~MENA~~).~~.

Methods: The data source was the systematically gathered MENA HCV Epidemiology Synthesis Project Database. Random-effects meta-analyses and meta-regressions were conducted. For comparison, analyses were conducted for Europe, utilizing the Hepatitis C Prevalence Database of the European Centre for Disease Prevention and Control.

Results: 1,213 HCV antibody prevalence measures and 84 viremic rate measures were analyzed for MENA. 377 antibody prevalence measures were analyzed for Europe. In MENA, pooled mean prevalence was 1.58% (95% confidence interval (CI): 1.48-1.69%) among blood donors and 4.49% (95% CI: 4.10-4.90%) in the general population. In Europe, pooled prevalence was 0.11% (95% CI: 0.10-0.13%) among blood donors and 1.59% (95% CI: 1.25-1.97%) in the general population. Prevalence in the general population was 1.72-fold (95% CI: 1.50-1.97) higher than that in blood donors in MENA, but it was 15.10-fold (95% CI: 11.48-19.86) higher in Europe. Prevalence was declining at

a rate of 4% per year in both MENA and Europe (adjusted risk ratio (ARR): 0.96 (95% CI: 0.95-0.97) in MENA and 0.96 (95% CI: 0.92-0.99) in Europe). Pooled mean viremic rate in MENA was 76.29% (95% CI: 67.64-84.02%) among blood donors and 65.73% (95% CI: 61.03-70.29%) in the general population.

Conclusions: Blood donor data provides a useful proxy for HCV infection levels and trends in the wider population in MENA, but not in Europe. These data should be utilized to improve HCV burden estimations and to assess, track, and validate progress toward HCV elimination by 2030.

Keywords: HCV, viral hepatitis, blood donors, general population, Middle East and North Africa, meta-analysis, meta-regression.

Core tip: We investigated hepatitis C virus (HCV) epidemiology among blood donors and the wider general population in Middle East and North Africa (MENA). For comparison, similar analyses were performed for Europe. Our results indicated that HCV antibody prevalence in the population of MENA and Europe appears to be declining by 4% per year. Blood donor data in MENA (but not in Europe) were found to provide a useful proxy for HCV infection levels and trends in the general population; thus it can be utilized in HCV estimates and to assess, track, and validate progress towards WHO elimination goals for HCV.

INTRODUCTION

In the Middle East and North Africa (MENA) an estimated 15 million individuals are chronically-infected with hepatitis C virus (HCV), making it the global region most affected by HCV infection [1]. Left untreated, chronic HCV infection may lead to several morbidities, including liver cancer, fibrosis, and cirrhosis, among others [2]. Prompted by development of highly efficacious direct-acting antivirals (DAA), the World Health Organization (WHO) has set a global target to eliminate HCV as a public health problem by 2030 [3].

Despite disproportionally high HCV infection levels in specific MENA countries, e.g., Egypt [4-7] and Pakistan [8-11], relative to global levels [1, 12], only three countries in this region have conducted nationally representative population-based surveys [13-15]. HCV infection levels in the remaining countries remain inadequately characterized [1].

Blood donors have been used as a proxy population to provide a crude estimate of HCV infection levels in the general population [16, 17]. However, in developed countries, such as the USA [18] and countries of the European Union [16], blood donors are not considered representative of the wider general population. In these countries, strict donor selection and blood safety regulations [19] have resulted in a large disparity in HCV infection levels between blood donors and the general populations. This raises two questions: how comparable are HCV infection levels between blood donors and the general population in MENA? Are blood donor data, which are readily available,

thanks to blood screening, an appropriate proxy for the general population in this region?

In this context, objectives of this study were to delineate HCV epidemiology in blood donors and general populations in MENA, and to assess how representative blood donor data are of HCV antibody (Ab) prevalence in the general population of this region. The study was also conducted to infer programmatic implications on blood safety in the region. These objectives were accomplished through analyses of a large, systematically gathered database, including 2,622 HCV Ab prevalence measures on 49.8 million individuals by: 1) estimating the pooled mean prevalence among blood donors and in general populations (henceforth 'the general population'), and 2) identifying predictors and trends of prevalence in these populations and sources of between-study heterogeneity. We further conducted similar analyses for Europe, a region in which stringent donor selection and blood safety processes have been implemented [19], for comparison. We did so by utilizing a large systematically gathered database including 419 HCV Ab prevalence measures for 25.7 million individuals [20], to compare outcomes with results for MENA.

METHODS

Data sources

This study was conducted as part of the MENA HCV Epidemiology Synthesis Project [1], an on-going project with the aim of delineating HCV epidemiology and informing key public health research, policy, and programming priorities in MENA. The source of data was the MENA HCV Epidemiology Synthesis Project Database [1]. The database included 685 HCV Ab prevalence measures on 46,634,214 blood donors and 528 measures on 2,358,944 individuals of the general population, such as pregnant women, healthy adults, and children, among others. The database also included 8 HCV viremic rate measures on 58,986 blood donors and 76 measures on 14,936 individuals of the general population. HCV viremic rate was defined as the proportion of those who had tested antibody positive that are subsequently confirmed to be chronically infected by testing positive for HCV ribonucleic acid (RNA)—the proportion of those HCV RNA positive among HCV antibody-positive individuals [21, 22].

The database was populated through a series of systematic reviews for HCV infection across MENA that were previously conducted as part of this project [5, 6, 8, 23-28]. All reviews followed a standardized methodology, and specific details ~~of which~~such as literature search strategy, databases searched, and eligibility criteria can be found in each of these reviews [5, 6, 8, 23-28]. In brief, the methodology used for these reviews was informed by the Cochrane Collaboration Handbook [29], and all findings were reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [30]. Literature searches were conducted to identify primary data on HCV measures in international and national/regional databases, the MENA HIV/AIDS Epidemiology Synthesis Project Database [31, 32], abstract archives of international

conferences, and grey literature, including public health reports and routine data reporting. Literature searches were broad, with no language restrictions to ensure inclusiveness. All records reporting HCV measures after 1989, the year in which the virus was officially identified [33], were included in the reviews [5, 6, 8, 23-28].

Blood donors are typically a diverse group with different rates of HCV Ab prevalence depending on the rigor of the donor selection process [19]. The vast majority of HCV Ab prevalence studies in MENA did not specify the type of blood donors, and therefore the term 'blood donors' in the present analysis encompasses the different blood donor types, including regular voluntary non-remunerated donors, one-time voluntary non-remunerated donors, family replacement donors, and paid donors.

For the MENA HCV Epidemiology Synthesis Project, the MENA region was defined to include 24 countries (Figure 1). Given the distinctive nature of the HCV epidemics in Egypt [4-7] and Pakistan [8-11], relative to other MENA countries, separate analyses were performed for each of these countries.

HCV measures in blood donors and the general population were also analyzed for Europe, a region in which stringent donor selection and blood safety regulations have been implemented for decades [19], for comparison with MENA outcomes. Europe's HCV Ab prevalence measures were retrieved from the Hepatitis C Prevalence Database of the European Centre for Disease Prevention and Control [20]. The database was populated through a systematic review [16] and multiple reports [34, 35]. The database included 257 HCV Ab prevalence measures on 25,232,790 blood donors and 120

measures on 410,444 individuals of the general population, such as pregnant women and healthy adults.

Pooled mean HCV Ab prevalence and viremic rate

Meta-analyses for countries and subregions were performed to pool HCV Ab prevalence in blood donors and the general population, whenever three or more measures were available, and a minimum sample size of 25 participants was met. Random-effects meta-analyses were performed using the DerSimonian-Laird method [36], with inverse-variance weighting to pool measures [36]. Freeman-Tukey type arcsine square-root transformation was used to stabilize the variance of each measure, factoring knowledge regarding the applicability of this transformation [37, 38]. Heterogeneity was formally assessed [36]. Forest plots were generated and examined visually, and Cochran's Q-test was conducted. Statistical significance of heterogeneity was indicated whenever the P-value was <0.10 [36, 39]. The I^2 and its confidence interval (CI) were calculated to assess the percentage of variance that is explained by true differences in prevalence across studies, rather than chance [36]. Prediction intervals were also determined to describe the distribution of prevalence around the pooled mean estimate [36]. Meta-analyses were also used to estimate the pooled mean HCV viremic rate among blood donors and in the general population. Meta-analyses and forest plots were generated using R version 3.4.3.

Predictors, trends, and sources of between-study heterogeneity

Univariable and multivariable random-effects meta-regressions were conducted following established methodology [29]. *A priori* relevant independent variables in meta-regressions included subpopulation (blood donors vs the general population), country/subregion, and year of data collection. Factors associated with HCV Ab prevalence at a p-value ≤0.20 in the univariable analysis qualified for inclusion in the multivariable analysis. Here, an adjusted relative risk (ARR) p-value ≤0.05 was considered to indicate strong evidence for an association.

In studies in which the year of data collection variable was missing, the variable was imputed. This was done by first subtracting the year of data collection (when available) from the year of publication for each study, and using the median of these values in imputing the year of data collection. Sensitivity analysis was performed without the imputed observations to determine the impact of the imputation on the results, confirming the results of the original meta-regression. Meta-regressions were performed on STATA version 13 using the *metan* command.

RESULTS

HCV Ab prevalence among blood donors and the general population in MENA

Studies on HCV Ab prevalence among blood donors and the general population in MENA are listed in Table S1 and Table S2. HCV Ab prevalence data were available for 23 of the 24 MENA countries. The largest number of data points were retrieved from Egypt, followed by the Gulf and Fertile Crescent subregions.

HCV Ab prevalence in blood donors ranged from 0.0-38.20%, with a median of 0.86% (Table 1). Studies reporting the highest HCV Ab prevalence were reported from parts of Egypt in the 1990s, a period during which HCV infection was widespread following the parenteral antischistosomal therapy (PAT) campaigns that contributed in a major way to the HCV epidemic in Egypt [5-7, 40]. The pooled mean prevalence was 1.58% (95% CI: 1.48-1.69%). It was lowest in the Fertile Crescent subregion at 0.21% (95% CI: 0.18-0.25%) and highest in Egypt at 10.40% (95% CI: 9.59-11.23%), followed by Pakistan at 3.47% (95% CI: 2.96-4.02%).

HCV Ab prevalence in the general population ranged from 0.0-73.38%, with a median of 3.14%. The pooled mean prevalence was 4.49% (95% CI: 4.10-4.90%). It was lowest in Iran at 0.33% (95% CI: 0.21-0.47%) and highest in Egypt at 13.08% (95% CI: 11.51-14.73%), followed by Pakistan at 8.81% (95% CI: 7.62-10.06).

All outlier high HCV Ab prevalence measures were investigated and found to reflect blood donors or general populations in specific settings that were affected by high exposure to the virus, such as specific villages in the Nile delta in Egypt following the PAT era [5-7, 40].

There was strong evidence for heterogeneity in HCV Ab prevalence in all meta-analyses ($p<0.01$), with almost all variation being attributed to true variation in prevalence across studies rather than chance ($I^2>99.4\%$). Heterogeneity was also confirmed by the estimated prediction intervals (Table 1).

HCV Ab prevalence among blood donors and the general population in Europe

HCV Ab prevalence data were available for 30 countries in Europe. HCV Ab prevalence in blood donors ranged from 0.0-3.28%, with a median of 0.06% (Table 2). The pooled mean prevalence was 0.11% (95% CI: 0.10-0.13%). Prevalence in the general population ranged from 0.0-16.83%, with a median of 1.11%. The pooled mean prevalence was 1.59% (95% CI: 1.25-1.97%).

There was strong evidence for heterogeneity in HCV Ab prevalence ($p<0.01$), with the majority of variation being attributed to true variation in prevalence across studies rather than chance ($I^2>98.7\%$).

HCV viremic rate of blood donors and the general population

The HCV viremic rate of blood donors in different MENA countries ranged from 61.84-93.33%, with a median of 70.78% (Table S3). The pooled mean for the entire MENA region was 76.29% (95% CI: 67.64-84.02%), indicating that approximately three-quarters of antibody-positive blood donors are chronically infected. The viremic rate ranged from 22.73-100% in the general population in different MENA countries, with a median of 68.27% (Table S3). The pooled mean for the entire MENA region was 65.73% (95% CI: 61.03-70.29%).

There was strong evidence for heterogeneity in the viremic rates ($p<0.01$), with most variation being attributed to true variation in the viremic rate across studies rather than chance ($I^2>77.4\%$).

Predictors and trends of HCV Ab prevalence in MENA

The meta-regressions for MENA indicated that HCV Ab prevalence in the general population is 1.72-fold (95% CI: 1.50-1.97) higher than that in blood donors (Table 3). They also indicated substantial variation in prevalence by country and subregion with Egypt and Pakistan having much higher prevalence than the rest of MENA countries. Importantly, the analyses indicated that HCV Ab prevalence has been declining over the last three decades at an average rate of 4% per year (ARR of 0.96; 95% CI: 0.95-0.97).

Subgroup analyses were conducted on the above results. The same regressions were repeated, but for Egypt, Pakistan, and other MENA countries individually (Table 4). These analyses indicated that HCV Ab prevalence in the general population is 1.30-fold (95% CI: 1.07-1.59) higher than that among blood donors in Egypt, 2.52-fold (95% CI: 1.89-3.36) higher in Pakistan, and 1.73-fold (95% CI: 1.42-2.11) higher in rest of MENA countries. The analyses also confirmed the same rate of decline for prevalence at 4% in the rest of MENA countries. The rate of decline was slightly higher in Egypt at 6%. There was no evidence for a decline in prevalence, however, in Pakistan.

In a sensitivity analysis, the same regressions were also repeated, but excluding all blood donor data (not shown). The analyses indicated that HCV Ab prevalence in MENA is declining at a rate of 5% per year (ARR of 0.95; 95% CI: 0.93-0.97), indicating a marginally higher rate of decline in the general population.

Predictors and trends of HCV Ab prevalence in Europe

The meta-regressions for Europe indicated that HCV Ab prevalence in the general population is 15.10-fold (95% CI: 11.48-19.86) higher than that in blood donors (Table 5).

The analyses indicated further that HCV Ab prevalence has been declining over the last three decades at a similar rate to that of MENA, at 4% per year (ARR of 0.96; 95% CI: 0.92-0.99).

A sensitivity analysis was conducted on the above results. The same regressions were repeated, but excluding all blood donor data (not shown). The analyses indicated that HCV Ab prevalence in Europe is declining at a rate of 10% per year (ARR of 0.90; 95% CI: 0.85-0.96), higher than that in MENA.

DISCUSSION

Levels and trends of HCV Ab prevalence in blood donors and in the general population of MENA were assessed using a large standardized database. There was large variability in HCV Ab prevalence by country and subregion, with Egypt and Pakistan, the largest countries in MENA by population size, having several fold higher prevalence than the rest of MENA countries. HCV Ab prevalence in the remaining MENA countries was at about 1% or less, similar to that in Europe and most other countries globally [12, 41]. These results confirm our understanding of HCV epidemiology across MENA countries and subregions [4-11, 21-28, 42-49].

Strikingly, HCV Ab prevalence is declining rapidly in both MENA and Europe, and at a similar rate of about 4% per year. The exception to this downward trend was Pakistan where there was no evidence for a decline. These declines may be reflective, in part, of the declining incidence of HCV infection within these regions through improvements to

infection control following the discovery of this virus three decades ago, and scale-up of HCV treatment worldwide [3]. They also may reflect the progressive improvement in effective blood donor selection, such as by motivating and retaining voluntary non-remunerated donors to donate regularly [19].

A major finding of this study is that HCV Ab prevalence in blood donors in MENA was quite similar to HCV Ab prevalence in the general population, very unlike the situation in Europe. While HCV Ab prevalence in the general population was almost 2-fold higher than that of HCV Ab prevalence in blood donors in MENA, it was 15-fold higher in Europe (Table 3 versus Table 5). HCV Ab prevalence in blood donors in MENA appears to closely reflect the background prevalence in the wider population. Of note that HCV Ab prevalence in blood donors is a function of not only the prevalence in the general population, but also of the effectiveness of blood donation programs to collect blood from regular voluntary non-remunerated blood donors [19]. This finding suggests that risk reduction strategies through selection and retention of safer blood donors (regular voluntary non-remunerated blood donors) are not yet effectively implemented widely in MENA as in Europe [19], where the source of blood largely comes from such donors. Indeed regulatory framework (including legislation, regulation, policies, and standards) and a functioning regulatory authority to enforce the regulatory framework is largely at its infancy in MENA [19], where, as of 2016, only 55% of MENA countries had legislation covering safety and quality of blood transfusions, and only two countries had achieved 100% voluntary non-remunerated blood donations [19, 50].

Furthermore, HCV Ab prevalence in blood donors may be reflective of people in the

general population unaware of their HCV infection status, in the context of which an individual aware of their positive HCV infection status would not donate blood.

Nevertheless, contingent on the quality of blood donor management systems implemented within countries of MENA, this finding indicates that HCV Ab prevalence in blood donors in MENA (unlike in North America [18] and Europe [16]) can be used for the time being as a proxy to estimate infection levels in the general population. This outcome has important consequences. With the lack of nationally representative population-based surveys in most countries of this region, blood donor data, which are readily available, can be easily used to assess levels and trends of this infection in the wider population. They can also be used to generate other estimates, such as those related to the disease burden of HCV sequelae, and can be leveraged to assess, track, and validate progress toward the WHO elimination goals for this infection [3]. The present study also provides adjustment factors to improve use of blood donor data (Table 2), so that they better reflect HCV levels in the wider population. These adjustment factors can be used at a regional level, or can be fine-tuned so as to be specific for individual countries.

This study had several limitations. Availability of data varied across MENA, with HCV Ab prevalence data being unavailable for Bahrain. The majority of HCV viremic rate data were collected at times before the launch of DAA treatment programs (Table S3); thus, they may not represent the current viremic rate in blood donors and in the general population. Analysis for the different blood donor types was not conducted as the

specification of blood donor type was not available for the vast majority of HCV Ab prevalence measures. The sample size of blood donors was much larger than that of the general population, however, the sample size in the general population was still substantial at 2.3 million. Despite these limitations, an immense volume of data was acquired, allowing various analyses and an array of consequential inferences to be drawn. While high heterogeneity was found, most (63%) of it was subsequently explained in meta-regression analyses in terms of prevalence variation by country and subregion within MENA.

In conclusion, HCV Ab prevalence in the wider population of MENA and Europe appears to be rapidly declining by 4% per year. Blood donor data in MENA (but not in Europe) provides a useful proxy for HCV infection levels and trends in the general population, at least in countries where effective blood donor selection and blood donor management programs are not in place; thus, it can be utilized in HCV infection and disease burden estimates and to assess, track, and validate progress toward WHO elimination goals for this infection. While these findings are specific for MENA, they may also apply to resource-limited countries of other regions.

Abbreviations

MENA, Middle East and North Africa; HCV, hepatitis C virus; DAA, direct-acting antivirals; WHO, World Health Organization; Ab, antibody; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis; CI, confidence interval; ARR, adjusted relative risk, PAT, parenteral antichistosomal.

Acknowledgment

The authors thank the European Centre for Disease Prevention and Control (ECDC) for their efforts in compiling the ECDC Hepatitis C Prevalence Database and for making this database publicly available in the service of science. The authors also thank Dr Yetmgeta E. Abdella for his valuable insights and feedback on this manuscript.

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Conflict of interest

The authors have no conflicts of interest to disclose.

Authors contributions

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

Figure 1. Map of the countries and subregions included in the ~~MENA~~Middle East and North Africa region.

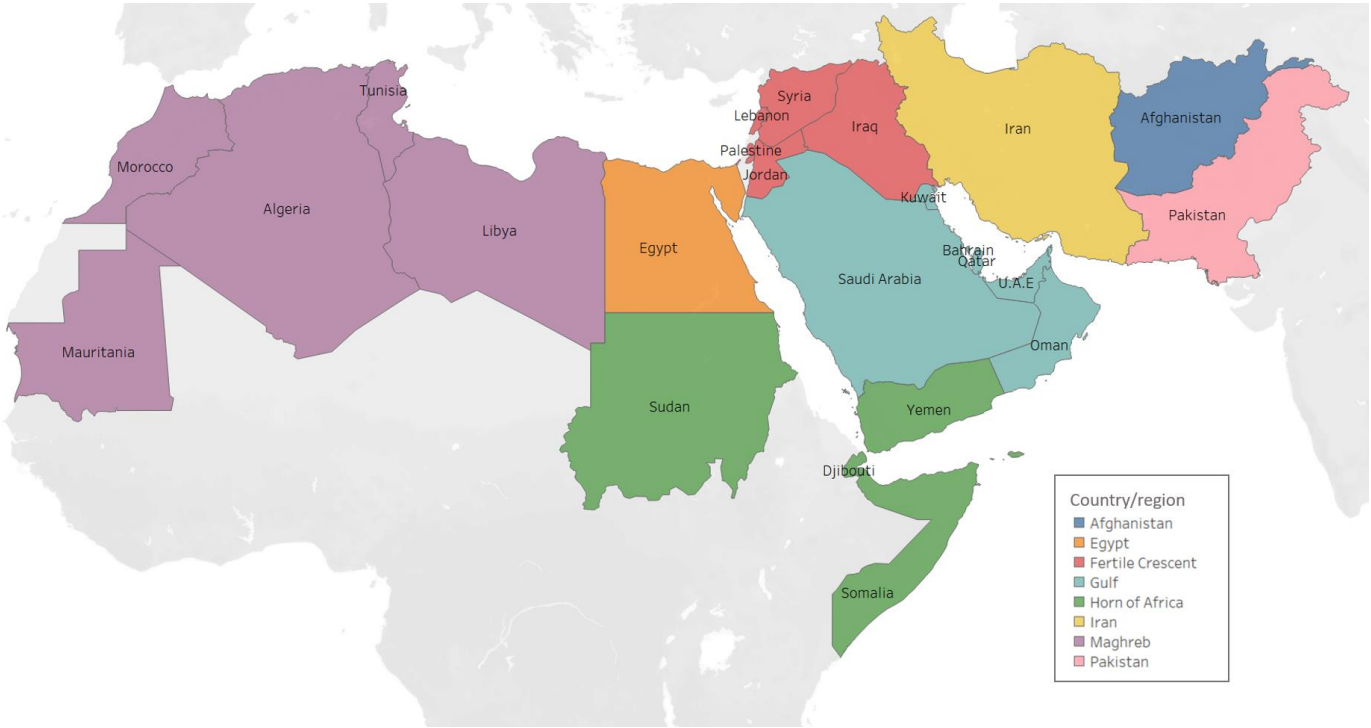

Table 1. Results of meta-analyses on studies reporting ~~HCV Ab~~hepatitis C virus antibody prevalence among blood donors and in the general population in ~~MENA~~Middle East and North Africa.

Population	Studies	Samples	HCV Ab prevalence		Pooled HCV Ab prevalence		Heterogeneity measures		
	Total N	Total n	Range (%)	Median (%)	Mean (%)	95% CI	Q (p-value)[a]	I² (confidence limits)[b]	Prediction interval (%)[c]
Blood donors									
Afghanistan	40	737,407	0.00-7.19	0.60	0.75	0.57-0.96	3046.03 (p<0.01)	98.7% (98.6-98.9%)	0.02-2.41
Egypt	116	1,566,669	0.00-38.20	10.97	10.40	9.59-11.23	24513.7 (p<0.01)	99.5% (99.5-99.6%)	3.64-19.96
Fertile Crescent[£]	157	3,488,952	0.00-3.95	0.27	0.21	0.18-0.25	3674.2 (p<0.01)	95.8% (95.4-96.1%)	0.00-0.67
Gulf[*]	156	20,891,379	0.00-27.19	0.89	0.78	0.71-0.86	29882.0 (p<0.01)	99.5% (99.5-99.5%)	0.20-1.69
Horn of Africa[∞]	22	48,076	0.00-6.03	1.00	0.97	0.57-1.45	327.8 (p<0.01)	93.6% (91.5-95.2%)	0.00-3.78
Iran	73	15,971,802	0.00-3.13	0.24	0.31	0.22-0.40	55740.9 (p<0.01)	99.9% (99.9-99.9%)	0.00-1.43
Maghreb	49	2,145,044	0.11-6.58	0.65	0.68	0.49-0.91	13475.9 (p<0.01)	99.6% (99.6-99.7%)	0.00-2.82
Pakistan	73	1,797,644	0.01-20.79	3.00	3.47	2.96-4.02	24753.7 (p<0.01)	99.7% (99.7-99.7%)	0.38-9.32
All countries/subregions	686	46,646,973	0.00-38.2	0.86	1.58	1.48-1.69	481819.0 (p<0.01)	99.9% (99.9-99.9%)	0.01-5.18
The general population									
Afghanistan	6	12,048	0.00-4.03	0.88	0.61	0.20-1.18	21.7 (p<0.01)	76.9% (48.5-89.6%)	0.00-2.68
Egypt	147	110,603	0.00-54.10	11.82	13.08	11.51-14.73	8457.0 (p<0.01)	98.3% (98.1-98.4%)	0.62-36.45
Fertile Crescent[£]	64	189,456	0.00-8.87	0.19	0.42	0.24-0.64	1117.8 (p<0.01)	94.4% (93.4-95.2%)	0.00-2.39
Gulf[*]	85	222,829	0.00-22.54	0.83	1.41	1.0-1.88	5343.3 (p<0.01)	98.4% (98.3-98.6%)	0.00-7.66
Horn of Africa[∞]	27	29,552	0.00-8.50	1.53	1.86	1.26-2.57	262.0 (p<0.01)	90.1% (86.8-92.6%)	0.00-6.13
Iran	50	101,677	0.00-2.35	0.45	0.33	0.21-0.47	206.9 (p<0.01)	76.3% (69.0-81.9%)	0.00-1.25
Maghreb	42	1,378,206	0.00-6.16	0.62	0.87	0.55-1.26	7595.3 (p<0.01)	99.5% (99.5-99.5%)	0.00-4.38
Pakistan	106	301,814	0.44-73.38	6.82	8.81	7.62-10.06	13619.0 (p<0.01)	99.2% (99.2-99.3%)	0.60-24.62
All countries/subregions	527	2,346,185	0.00-73.38	3.14	4.49	4.10-4.90	83750.3 (p<0.01)	99.4% (99.4-99.4%)	0.00-16.88

Abbreviations: Ab, antibody; CI, confidence interval; HCV, hepatitis C virus~~; MENA, Middle East and North Africa~~.

[a]Q: the Cochran's Q statistic is a measure assessing the existence of heterogeneity in effect size (here, HCV Ab prevalence) across studies.

[b]I²: a measure assessing the magnitude of between-study variation that is due to true differences in effect size (here, HCV Ab prevalence) across studies rather than chance.

[c]Prediction interval: a measure estimating the 95% interval of the distribution of true effect sizes (here, HCV Ab prevalence).

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

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

[∞]Countries include Djibouti, Somalia, Sudan, and Yemen.

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

Table 2. Results of meta-analyses on studies reporting ~~HCV Ab~~hepatitis C virus antibody prevalence among blood donors and in the general population in Europe.

Subpopulation	Studies	Samples	HCV Ab prevalence		Pooled HCV Ab prevalence		Heterogeneity measures		
	Total N	Total n	Range (%)	Median (%)	Mean (%)	95% CI	Q (p-value)[a]	I^2 (confidence limits)[b]	Prediction interval (%)[c]
Blood donors	257	25,232,790	0.0-3.28	0.06	0.11	0.10-0.13	35657.5 (P<0.01)	99.3 (99.3-99.3)	0.00-0.51
The general population	120	410,444	0.0-16.83	1.11	1.59	1.25-1.97	9176.9 (p<0.01)	98.7 (98.6-98.8)	0.0-7.57

Abbreviations: Ab, antibody; CI, confidence interval; HCV, hepatitis C virus.

[a]Q: the Cochran's Q statistic is a measure assessing the existence of heterogeneity in effect size (here, HCV Ab prevalence) across studies.

[b]I^2: a measure assessing the magnitude of between-study variation that is due to true differences in effect size (here, HCV Ab prevalence) across studies rather than chance.

[c]Prediction interval: a measure estimating the 95% interval of the distribution of true effect sizes (here, HCV Ab prevalence).

Table 3. Univariable and multivariable meta-regression models for ~~HCV Ab~~hepatitis C virus antibody prevalence among blood donors and the general population in ~~MENA~~Middle East and North Africa.

	Studies	Samples	Univariable analysis				Multivariable analysis[b]	
	Total N	Total n	*RR* (95% CI)	p-value	F p-value[a]	Variance explained R^2 (%)	*ARR* (95% CI)	p-value
Subpopulations								
Blood donors	686	46,646,973	1	-			1	-
The general population	527	2,346,185	2.92 (2.41-3.55)	<0.001	<0.001	10.73	1.72 (1.50-1.97)	<0.001
Country/subregion								
Afghanistan	46	749,455	1	-			1	-
Egypt	263	1,677,272	14.89 (10.2-21.8)	<0.001			9.48 (6.54-13.75)	<0.001
Fertile Crescent[£]	221	3,678,408	0.52 (0.35-0.77)	<0.001			0.49 (0.34-0.72)	<0.001
Gulf[*]	241	21,114,208	1.24 (0.84-1.82)	0.280			0.82 (0.56-1.19)	0.398
Horn of Africa[∞]	49	77,628	2.05 (1.25-3.37)	0.005			1.33 (0.82-2.15)	0.244
Iran	123	16,073,479	0.50 (0.33-0.77)	<0.001			0.42 (0.28-0.63)	<0.001
Maghreb[¥]	91	3,523,250	1.02 (0.66-1.56)	0.936			0.77 (0.51-1.16)	0.207
Pakistan	179	2,099,458	6.96 (4.71-10.29)	<0.001	<0.001	58.39	5.44 (3.73-7.93)	<0.001
Year of data collection	1,213	48,993,158	0.95 (0.94-0.97)	<0.001	<0.001	3.71	0.96 (0.95-0.97)	<0.001

Abbreviations: Ab, antibody; ARR, adjusted relative risk; CI, confidence interval; ~~HCV, hepatitis C virus; MENA, Middle East and North Africa;~~ RR, relative risk.

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

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

[∞]Countries include Djibouti, Somalia, Sudan, and Yemen.

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

[a]Variables with a p-value ≤ 0.2 were eligible for inclusion in the multivariable analysis.

[b]The adjusted R-squared for the full model was 62.65%.

Table 4. Subgroup analyses. Univariable and multivariable meta-regression models for ~~HCV Ab~~hepatitis C virus antibody prevalence among blood donors and the general population in Egypt, Pakistan, and rest of ~~MENA~~Middle East and North Africa countries.

	Studies	Samples	Univariable analysis				Multivariable analysis[b]	
	Total N	Total n	*RR* (95% CI)	p-value	F p-value[a]	Variance explained R^2 (%)	*ARR* (95% CI)	p-value
Egypt								
Subpopulations								
Blood donors	116	1,566,669	1	-			1	-
The general population	147	110,603	1.25 (1.00-1.57)	0.049	0.087	2.05	1.30 (1.07-1.59)	0.008
Year of data collection	263	1,677,272	0.94 (0.93-0.95)	<0.001	<0.001	24.48	0.94 (0.93-0.95)	<0.001
Pakistan								
Subpopulations								
Blood donors	73	1,797,644	1	-			-	-
The general population	106	301,814	2.52 (1.89-3.36)	<0.001	<0.001	19.03	-	-
Year of data collection	179	2,099,458	1.00 (0.98-1.03)	0.648	0.648	0.00	-	-
Rest of MENA countries								
Subpopulations								
Blood donors	497	43,282,660	1	-	-		1	-
The general population	274	1,933,768	1.80 (1.47-2.21)	<0.001	<0.001	5.44	1.73 (1.42-2.11)	<0.001
Country/subregion								
Afghanistan	46	749,455	1	-	-		1	-
Fertile Crescent[£]	221	3,678,408	0.53 (0.35-0.81)	0.003			0.50 (0.33-0.75)	0.001
Gulf[*]	241	21,114,208	1.26 (0.83-1.91)	0.273			0.86 (0.56-1.30)	0.462
Horn of Africa[∞]	49	77,628	2.08 (1.22-3.54)	0.007			1.37 (0.81-2.32)	0.247
Iran	123	16,073,479	0.51 (0.33-0.81)	0.004			0.43 (0.28-0.67)	<0.001
Maghreb[¥]	91	3,523,250	1.04 (0.65-1.64)	0.883	<0.001	11.48	0.79 (0.50-1.24)	0.298
Year of data collection	771	45,216,428	0.95 (0.94-0.96)	<0.001	<0.001	6.22	0.96 (0.95-0.98)	<0.001

Abbreviations: Ab, antibody; ARR, adjusted relative risk; CI, confidence interval; ~~HCV, hepatitis C virus;~~ RR, relative risk.

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

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

[∞]Countries include Djibouti, Somalia, Sudan, and Yemen.

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

[a]Variables with a p-value ≤ 0.2 were eligible for inclusion in the multivariable analysis. No multivariable analysis was conducted for Pakistan, as only one variable qualified for inclusion in the model.

[b]The adjusted R-squared was 27.35% for the multivariable model for Egypt and 17.92% for the multivariable model for rest of MENA countries.

Table 5. Univariable and multivariable meta-regression models for ~~HCV Ab~~hepatitis C virus antibody prevalence among blood donors and the general population in Europe.

	Studies	Samples	Univariable analysis				Multivariable analysis[b]	
	Total N	Total n	*RR* (95% CI)	p-value	F p-value[a]	Variance explained R^2 (%)	*ARR* (95% CI)	p-value
Subpopulations								
Blood donors	257	25,232,790	1	-			1	-
The general population	120	410,444	15.57 (11.83-20.49)	<0.001	<0.001	53.62	15.10 (11.48-19.86)	<0.001
Year of data collection	377	25,643,234	0.93 (0.88-0.98)	0.004	0.005	2.17	0.96 (0.92-0.99)	0.020

Abbreviations: Ab, antibody; ARR, adjusted relative risk; CI, confidence interval; ~~HCV, hepatitis C virus;~~ RR, relative risk.

[a]Variables with a p-value ≤ 0.2 were eligible for inclusion in the multivariable analysis.

[b]The adjusted R-squared for the full model was 54.27%.

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