systematic review

Prevailing genotypes of hepatitis C virus in Saudi Arabia: a systematic analysis of evidence

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BACKGROUND AND OBJECTIVES: Although hepatitis C virus (HCV) genotype 4 has been reported to be prevalent in some countries of the Middle East, the genotype distribution in some geographical areas is not conclusive. We aimed to perform a meta-analysis on available literature on this issue in an attempt to identify or confirm the prevailing HCV genotypes in Saudi Arabia.

METHODS: We searched for reports describing genotypes in Saudi Arabia. A meta-analysis was performed on the samples in 18 studies, published between 1995 and 2011, in which HCV genotypes were identified.

RESULTS: A total of 2277 specimens from 18 studies showed that 617, 82, 119 and 1198 subjects were HCV-positive for genotypes 1, 2, 3 and 4, respectively. The meta-analyses showed that there is a great deal of heterogeneity in estimated prevalence among the studies. The highest prevalence was found in genotype HCV-4, followed by HCV-1, HCV-3, and HCV-2.

CONCLUSION: Our meta-analysei emphasizes that HCV genotype 4 is the most prevalent, followed by genotype 1. Further studies on genotype determination and subtype distribution are warranted.

Hepatitis C virus (HCV) infection is a global disease, with 2% to 3% infected people worldwide.[1] It can progress to a chronic and persistent infection, possibly leading to liver cirrhosis and hepatocellular carcinoma.[2,3] HCV belongs to the genus *Hepacivirus* from the Flaviviridae family. It is a small, enveloped virus, with about a 10-kb single-stranded RNA molecule as its genome.[4] The virus mutates frequently leading to changes in the envelope proteins which may help the virus to evade the immune system. Significant genomic variations have been reported, with six major genotypes and more than fifteen subtypes.[5] The six major genotypes may differ from one another in relation to response to treatment, rate of mutation, and seriousness of liver injury.[6,7] The widely-known combination therapy of pegylated interferon-alpha (2a or 2b) and ribavirin was beneficial in reducing the morbidity of the virus infection, albeit with limited success and high costs.[8] Predictors of sustained virologic response (virus eradication) with this therapy are many, including virus genotypes and quasispecies, with plenty of amino acid sequence variations.[9-11] Therefore, the determination of HCV genotypes is beneficial not only for predicting the response to treatment (type, duration, and dose) and for vaccine investigation, but for epidemiological purposes as well.

Although the data are limited, information has been published in relation to the HCV genotypes described in Saudi Arabia. Most reports showed that HCV genotype 4 is the most prevalent, while others contest this conclusion.[12-29] In this paper, we aimed to apply a meta-analysis on the current information, regardless of the purpose of the study, to pinpoint the most prevalent HCV genotypes in this part of the world. The lack of sufficient information on HCV genotypes in Saudi Arabia may reduce the effectiveness of this study. However, such an analysis is timely and needed for the community.

METHODS

MEDLINE, PubMed, and the Cochrane Clinical Trials were searched by two investigators (SMA and MNA) independently. English language restriction was applied. All reports of clinical trials that identified HCV

genotypes have been searched. The Medical Subject Heading (MesH) terms used in the MEDLINE search were hepatitis C virus, hepatitis C virus genotypes distribution, hepatitis C virus genotype prevalence, hepatitis C virus genotypes and treatment with pegylated interferon alpha (2a or 2b) and ribavirin, and hepatitis C virus genotypes in Saudi Arabia. Searching the Cochrane databases of randomized, controlled trials was used to complete the MEDLINE exploration. Two investigators reviewed the abstracts and the articles (MMS, and AAA) independently.

Prior to commencing this study, the inclusion criteria decided upon were to involve studies written only in English, on males or females, of a sample number containing 20 subjects or more, with any method of HCV genotyping, and at different risks of different chronic diseases of patients. Eighteen articles were found to meet these criteria, and were published between 1995 and 2011. Previous to 1995, no information on HCV genotypes in Saudi Arabia was found.

We assessed the heterogeneity among the studies, separately, for each genotype with the chi-square test (with a *P* value <.05 indicating the presence of significant heterogeneity). The presence of significant heterogeneity was the reason for using the random effects model to construct an overall estimate of prevalence and confidence intervals for each HCV genotype. The methodological approach described in Sidek and Jankman[30] for testing heterogeneity, constructing weighted averages for the overall prevalence, taking into account the effect of heterogeneity, and constructing confidence intervals was used.

RESULTS

The outcome measures for each study included in the meta-analysis were the point estimates of prevalence together with their estimated standard errors. After an extensive search for HCV genotypes in Saudi Arabia, only 18 citations comprising 2277 specimens were found to include HCV genotyping, although the purpose of each study may be different. Our search did not reveal any study before 1995. **Table 1** is a summary of these studies, most of them from the two major cities (Riyadh and Jeddah) in Saudi Arabia. HCV genotypes 5 and 6 were not analyzed since their prevalence is negligible (11 and 0, respectively, out of a total of 2277 samples from those studies) compared to the other four genotypes. The prevalence of the other, more common, four genotypes was analyzed for each genotype using information in each study and in all studies. The upper and lower limits of the 95% confidence intervals on the population prevalence are shown on each study and to the far right for all studies showing HCV-1, HCV-2, HCV-3, and HCV-4 in **Figure 1, Figure 2, Figure 3,** and **Figure 4**, respectively. In **Table 2**, the *P* values indicate that the hypothesis of homogeneity among the studies is not supported by the data for all genotypes. The *P* value for testing heterogeneity was less than .0001. Therefore, the constructed confidence interval on the common prevalence is based on the random effects model which assumes non-zero variations among the studies. The random effect model based on 95% confidence intervals is shown in **Table 2**.

DISCUSSION

The major aim of our review was to establish baseline information about the most prevalent HCV genotypes in Saudi Arabia. Since the estimates varied from one study to another, we used meta-analysis—an approach that combines information from a variety of studies. Such baseline information is essential prior to planning any intervention strategy. None of the studies referenced here reported information on age, gender, ethnicity, or other co-morbidities. A meta-regression test would have been performed if the information were available from all the studies used in this report.

HCV infection is a worldwide problem, with a prevalence of 0.9% in the general population of Saudi Arabia.[31] Genotypes of HCV result from the mutation of the virus during replication and there are six major genotypes, 1-6. Determination of the genotype of HCV in a given patient is important, since it can affect the success of the treatment and the length of time the medication will need to be taken.[32] Moreover, the identification of HCV genotypes in different geographical areas of the world and knowing the prevailing genotype will assist scholars in their quest for better diagnosis and for obtaining an effective, universal vaccine.[33] HCV-1 is the most common around the world, and prevails in the Americas, Europe and Japan.[33] In Saudi Arabia, the generally accepted conclusion is that HCV-4 is the main genotype.[31] However, with advanced technologies, such as HCV gene sequencing, more genotypes became evident.[16]

Our electronic search revealed that the number of published studies and the amount of data are not sufficient to allow solid conclusions. The strength of data used in our study may not be concrete, although a random effects model for meta-analysis was assumed to account for the heterogeneity among the studies. We believe, however, that pooling the available data for

Table 1. Summary of the studies included in the meta-analysis of HCV genotypes in Saudi Arabia.

Study no.	City	HCV patients	Sample no.	HCV -1	HCV-2	HCV-3	HCV-4	HCV-5	HCV-6	Reference no.
1	Riyadh	CH, HD	60	25	2	-	33	-	-	12
2	Riyadh	CH	119	32	3	2	57	-	-	13
3	Jeddah	Various	61	21	1	0	39	0	0	14
4	Jeddah	CH, HD, DU	154	44	-	-	92	-	-	15
5	All	Unknown	80	6	-	44	30	-	-	16
6	Riyadh	CH	76	17	3	2	42	-	-	17
7	Jeddah	CH, Cirrhosis	140	34	2	0	97	2	0	18
8	Jeddah	CH	107	32	5	6	59	-	-	19
9	South	CH	22	11	-	-	11	-	-	20
10	All	CH	492	119	36	29	305	2	-	21
11	Riyadh	CH	62	19	-	-	40	-	-	22
12	Riyadh	CH	48	10	2		28	-	-	23
13	Riyadh	CH	272	60	30		148	-	-	24
14	Jeddah	CH	240	46	9	15	82	1	-	25
15	Dammam	IVDU	131	97	1	15	13	5	0	26
16	Riyadh	OLT	46	-	-	-	29	-	-	27
17	Qatif	SCA	51	13	20	6	8	1	NT	28
18	Riyadh	CH	116	31	-	-	85	-	-	29
Total			**2277**	**617**	**82**	**119**	**1198**	**11**	**-**	

CH: chronic hepatitis, HD: hemodialysis, DU: drug users, OLT: orthotopic liver transplantation, SCA: sickle cell anemia, NT: not tested

meta-analysis would release important information despite the heterogeneity of the cited studies. A few deficiencies exist in this study; some are inherent with the method of meta-analysis. First, the size of many individual studies may not be sufficient to produce a reliable estimate. Second, the strong heterogeneity among the studies can be another limitation. The presence of unobserved sources of heterogeneity (such as many migrant workers living in Saudi Arabia, particularly from Asia and North Africa) may interfere with the validity of this work. Third, it is possible that the popular conclusion of HCV-4 being the major HCV genotype in Saudi Arabia may change if there were studies that involve specimens representing the true population of Saudi Arabia and taken from every part of this vast country.

Basing our analysis on 4-nomial joint distributions would produce the same results. The multinomial distribution can be utilized only if we were interested in comparing the prevalence of genotypes (eg, testing the hypothesis that genotype 1 is less prevalent than genotype 4), and that would be the only advantage of it. In this case one needs to use the covariance between the estimated prevalence, which is obtained from the 4-nomial distribution. Such a comparison is trivial and is not of any particular interest.

Table 2. Confidence limits (95%) on combined estimates of prevalence based on the random effects model.

Limits	HCV-1	HCV-2	HCV-3	HCV-4
Lower	0.22	0.01	0.02	0.43
Upper	0.36	0.11	0.20	0.59

$P<.0001$ for each genotype.

In conclusion, the meta-analysis we performed shows that HCV genotype 4 is the most prevalent, followed by genotype 1. Further studies on genotype determination and, more importantly, on subtype distribution are merited. The overall estimated preva-

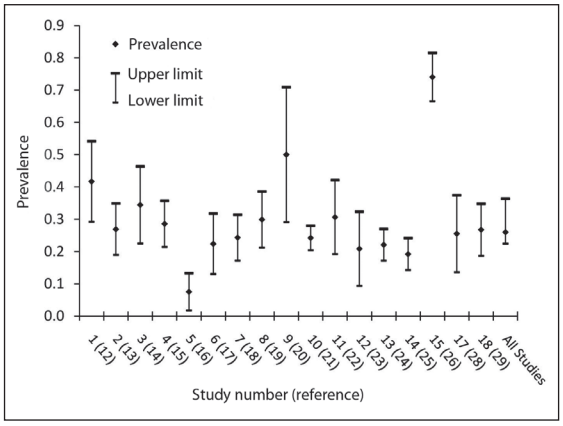

Figure 1. Prevalence of HCV-1 by study reference (17 studies). Upper limits and the lower limits of the 95% confidence intervals on the population prevalence are shown. The last line (far right, all studies) shows the confidence limits of the combined estimated prevalence.

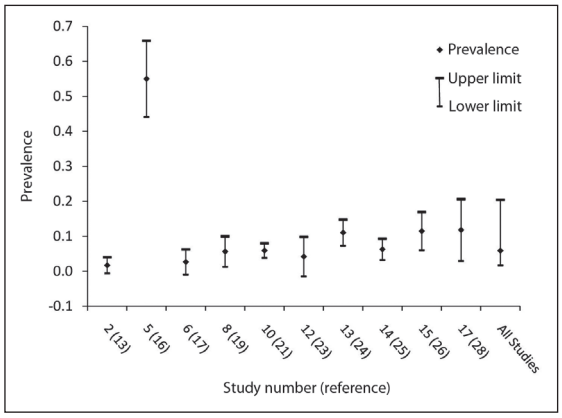

Figure 3. Prevalence of HCV-3 by study reference (10 studies). Upper limits and the lower limits of the 95% confidence intervals on the population prevalence are shown. The last line (far right, all studies) shows the confidence limits of the combined estimated prevalence.

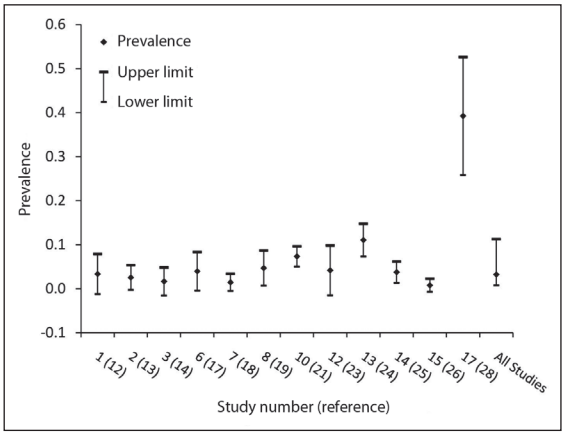

Figure 2. Prevalence of HCV-2 by study reference (12 studies). Upper limits and the lower limits of the 95% confidence intervals on the population prevalence are shown. The last line (far right, all studies) shows the confidence limits of the combined estimated prevalence.

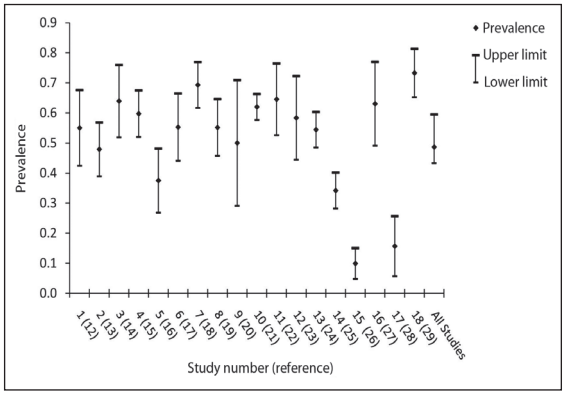

Figure 4. Prevalence of HCV-4 by study reference (18 studies). Upper limits and the lower limits of the 95% confidence intervals on the population prevalence are shown. The last line (far right, all studies) shows the confidence limits of the combined estimated prevalence.

lence of HCV genotypes may be used as a benchmark to evaluate the likely size of the problem and deciding on the course of intervention. Our study will provide a baseline for further investigations that may involve larger specimen numbers, better diagnostic techniques, and involvement of HCV subtype identification.

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