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Low Prevalence of Anti-Hepatitis C Virus Antibodies in Mexico: A Systematic Review

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Anti-HCV antibodies in Mexico, prevalence · HCV infection, epidemiology · Hepatitis C, Mexico · Liver disease · Prevalence of anti-HCV antibodies

Abstract
Background: The prevalence of reactive tests to anti-hepatitis C virus (HCV) antibodies in Mexico is unknown, though estimated to be 1%. There is no single nation-wide study or comprehensive literature review addressing the epidemiology of HCV infection in Mexico. ***Methods:*** We did a systematic review of English- and Spanish-language literature reporting on the frequency of anti-HCV antibodies in asymptomatic persons at low risk, of studies performed in Mexico. An exhaustive search in MEDLINE, IMBIOMED, MedicLatina, ARTEMISA and MEDIGRAPHIC databases was undertaken. Weighted mean prevalence (WMP) was calculated after combining the results of each study. ***Results:*** 22 studies involving 825,377 persons at low risk, mainly blood donors, were identified. Crude seroprevalence reported in each study ranged from 0.1 to 2%, with 16 (73%) studies reporting below 1%. Overall, WMP of anti-HCV antibodies (tested by enzyme immunoassay) was 0.37% (95% CI, 0.36–0.38%), differing by country region and immunoassay generation ($p < 0.01$). The most frequent risk factor reported was blood transfusion. Confirmation of specific anti-HCV antibodies by recombinant immunoblot assay ranged from 30 to 100%, whereas confirmation of viremia by PCR ranged from 16 to 80%. In 3 studies on HCV genotype frequency, genotype 1 had crude prevalence ranging from 63 to 70%, subtype 1b being the most prevalent (21–47%). ***Conclusions:*** The prevalence of anti-HCV antibodies in Mexico might be lower than previously estimated. Transfusion of blood products is the main risk factor. HCV subtype 1b is the most prevalent among persons with confirmed viremia. Information of a nation-wide survey is mandatory.

Introduction

The prevalence and risk factors for hepatitis C virus (HCV) infection vary widely by geographic region [1]. In countries in which the abuse of illicit intravenous drugs is not frequent, the recipients of transfusion before the systematic screening for HCV in blood banks represent the larger group of persons living with HCV infection [1–4]. In Mexican blood banks, non-remunerated blood donation and screening of potential donors by using a structured questionnaire of risk factors and anti-HCV testing have been practiced by law since 1993 [5]. In this

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country the current prevalence of anti-HCV antibodies has been estimated to be about 1% [6]. However, this rough estimate on seroprevalence derives mainly from a few prior studies on blood donors. Furthermore, even when these and new reports appeared in indexed journals since 1994, they have not been included explicitly in recent international reviews regarding the epidemiology of HCV infection around the world [1, 7].

We conducted a systematic review on the prevalence of anti-HCV antibodies in Mexico and focused on studies using enzyme immunoassay tests and reporting on asymptomatic people at low risk. The present study is the first to use a systematic review and meta-analysis methodology to estimate the seroprevalence of anti-HCV antibodies in Mexico.

Methods

Operational Definitions

In the following, persons at low risk for HCV infection are considered those who lack the following antecedents: use of illicit intravenous drugs, symptoms or laboratory evidence of liver dysfunction, multiple transfusions, hemodialysis, hemophilia, imprisonment, and healthcare personnel or a remunerated blood donor [5].

Literature Search and Identification of Studies

To identify English- or Spanish-language studies published between January 1993 and October 2005 reporting on the prevalence of anti-HCV antibodies in Mexico, we first performed a computer-aided search of national and international databases. The databases searched were MEDLINE, IMBIOMED, MedicLatina, ARTEMISA and MEDIGRAPHIC. In MEDLINE, the following English text words were used as search terms: 'Hepatitis [and] Mexico', 'Hepatitis [and] Mexican population', 'HCV [and] Mexico' and 'HCV [and] Mexican population'. In the databases of Mexican and Latin-American origin, the following Spanish text words were used as search terms: 'Hepatitis', 'VHC', 'anti-VHC', 'Hepatitis C', 'Prevalencia' and 'Banco de sangre'. Also, we did a hand search of the references included in the articles retrieved by electronic search, in order to identify possible reports not initially obtained.

Eligibility Criteria

We included original contributions reporting on prevalence of anti-HCV antibodies in different Mexican groups, using the standard screening test (i.e. second- or third-generation enzyme immunoassays) [5]. Abstracts from conferences, syllabi of meetings and personal communications were not eligible for the prevalence analysis. Nevertheless, for the analysis on HCV genotypes we included a multicenter study published in an internationally-edited book and another multicenter study reported as abstract and presented on platform in the Mexican Week of Gastroenterology, November 2002. Articles from journals included or not in *Index Medicus* were considered eligible. We excluded articles not explicitly reporting the following data: country region and group of risk studied (the address of the investigators was not used as surrogate of the country region), total number of persons, number of seroreactive cases and laboratory methods used. We took measures to detect overlapping reports on the same study population or its fraction (e.g. serial cumulative reports in blood banks). These measures included analysis of the study period, sample size and centers where studies were performed.

Data Extraction

After the assessment for eligibility, the following data were extracted: year of publication, total number of persons studied, number of persons with reactivity to anti-HCV antibodies, immunoassay method, region of the country where the sampling was undertaken, population type in terms of risk for HCV infection and, when reported, independent risk factors for the infection. HCV genotype frequency was extracted from the studies reporting on >50 persons with detectable HCV RNA in serum.

Data Synthesis

Since not all studies included complete demographic data, it was not possible to obtain information regarding age, gender and economical status; therefore, these variables were not summarized. The main research objective of this systematic review was 'prevalence of anti-HCV antibodies'. From the data of primary studies we calculated the 95% confidence intervals (CI) for crude seroprevalence of each report. We did different estimates on overall seroprevalence in Mexico. The pooled prevalence (PP) was calculated as follows: $PP = \Sigma n_i/N$, where n_i = number of seroreactive cases in each study, and N = total number of persons assessed. The mean prevalence (MP) was estimated with the formula: $MP = \Sigma prev_i/S$, where $prev_i$ = prevalence in each study, and S = number of studies. We also calculated the weighted mean prevalence (WMP) in order to restrict the bias that may impose the heterogeneous nature of the reports. WMP was calculated as follows [8]: $WMP = \Sigma(\omega_i\, prev_i)/\Sigma\omega_i$, where $\omega_i = 1/[prev_i\,(1 - prev_i)/N_i]$. Here, WMP is regarded as the most accurate method to estimate prevalence of anti-HCV after considering several reports. This method has proven to be reliable when combining a number of studies with inherent heterogeneity in sample size and effects [8]. Overall seroprevalence was estimated according to generation of the immunoassay method and state of the country. All estimates on seroprevalence are expressed as proportions and the respective 95% CI. χ^2 statistics were used to test differences in prevalence estimates between studies using second- or third-generation immunoassay, and to test homogeneity among calculations for the different country states.

Results

By computer-aided and hand-search strategies we identified 37 eligible studies. Two articles were excluded because the laboratory methods were not explicitly declared. Three other studies were analyzed only for HCV genotype frequency. Of the remaining 32 studies, 22 reported on healthy people at low risk for HCV infection

Table 1. Studies reporting on the prevalence of anti-HCV antibodies in asymptomatic persons at low risk

Year of publication	City (state)	Population studied	Number	Seroprevalence % (95% CI)	Ref.
1994	Mexico City (D.F.)	Blood donors	330	1.2 (0–2.4)	9
1994	Mexico City (D.F.)	Blood donors	1,100	0.7 (0.2–1.2)	10
1994	Mexico City (D.F.)	Military blood donors	2,564	0.7 (0.4–1.0)	11
1994	Guadalajara (Jalisco)	Pregnant women	244	2 (0.3–3.7)	12
1995	Mexico City (D.F.)	Pregnant women	1,000	0.6 (0.1–1.1)	13
1996	Durango (Durango)	Blood donors	5,915	1.5 (1.2–1.8)	14
1996	Mexico City (D.F.)	Healthy children	450	0.9 (0–1.8)	15
1996	Mexico City (D.F.)	Pregnant women	1,500	0.5 (0.1–0.9)	16
1996	Monterrey (Nuevo León)	Medical students	774	1.5 (0.6–2.4)	17
1997	Monterrey (Nuevo León)	Blood donors	78,566	0.5 (0.4–0.6)	18
1997	Morelia (Michoacán)	Blood donors	7,256	0.3 (0.2–0.4)	19
1999	Lagos de Moreno (Jalisco)	Blood donors	2,439	0.1 (0–0.2)	20
1999	La Barca (Jalisco)	Blood donors	1,465	0.3 (0–0.6)	20
1999	Guadalajara (Jalisco)	Blood donors	1,224	1.7 (1–2.4)	21
1999	Mexico City (D.F.)	Blood donors	9,099	0.5 (0.4–0.6)	22
2001	León (Guanajuato)	Blood donors	44,588	0.7 (0.6–0.8)	23
2002	Mexico City (D.F.)	Blood donors	41,957	0.8 (0.7–0.9)	24
2003	Guadalajara (Jalisco)	Blood donors	57,108	0.8 (0.7–0.9)	25
2003	Irapuato (Guanajuato)	Blood donors	4,010	1.1 (0.8–1.4)	26
2004	Mexico City (D.F.)	Blood donors	3,101	0.6 (0.4–0.8)	27
2004	Mexico City (D.F.)	Blood donors	511,115	0.3 (0.28–0.32)	28
2005	León (Guanajuato)	Blood donors	49,272	0.7 (0.6–0.8)	29
2005	Mexico City (D.F.)[1]	Asymptomatic people in medical check-up	300	2 (0.4–3.6)	30

CI = Confidence interval; D.F. = Distrito Federal.

The serological method used to assess the presence of anti-HCV antibodies was a second-generation immunoassay until studies reported in 1997 (11 reports), after this year (from 1999 [18]), a third-generation assay was used (11 reports). A study in 1999 [20] reports on two separate populations from the same state.

[1] This study included 300 asymptomatic persons with two or more risk factors, however, since the most frequent risk factors identified among positive cases were manicures or pedicures, as well as more than 3 sex partners (all risk factors considered as 'minor', or with low evidence of causality), this study was included in the estimate on seroprevalence among asymptomatic people at low risk.

(mostly blood donors, age 18–65 years) and 10 on people at high risk. Of the 22 studies involving people at low risk, 11 used a second-generation immunoassay and the other 11 a third-generation method. One of the studies on people at low risk assessed blood donors attending blood banks from two different cities of the same state. Another study also reported on deferred blood donors, who were considered at high risk for the purposes of this analysis.

Prevalence of Anti-HCV Antibodies among People at Low Risk

The 22 studies on people at low risk involved 825,377 persons from six states of the country (table 1). The crude seroprevalence reported in each study ranged from 0.1 to 2%, with 16 (73%) studies reporting seroprevalence below 1%. Overall, PP was 0.46% (95% CI, 0.44–0.48%), MP was 0.87% (95% CI, 0.85–0.89%) and WMP was 0.37% (95% CI, 0.36–0.38%). However, there were differences in seroprevalence estimates when comparing studies using second- or third-generation immunoassay ($p < 0.01$ for all prevalence estimates) (table 2). There was a considerable heterogeneity among WMP estimates for each state of the country ($p = 0.006$) (table 1, fig. 1).

Risk Factors for HCV Infection

Of the 22 studies reporting on people at low risk, we identified 5 (23%) in which independent risk factors for HCV infection were described (table 3). The most fre-

Table 2. Estimates on prevalence of anti-HCV antibodies according to generation of the immunoassay method

Immunoassay	Estimates		
	pooled prevalence % (95% CI)	mean prevalence % (95% CI)	weighted mean prevalence % (95% CI)
Second generation[1]	0.54 (0.53–0.55)	0.94 (0.88–1)	0.54 (0.50–0.58)
Third generation[2]	0.45 (0.44–0.46)	0.80 (0.78–0.82)	0.36 (0.35–0.37)

CI = Confidence interval.

[1] A total of 11 reports from 1994 to 1997 using a second-generation immunoassay were included involving 99,699 persons.

[2] A total of 11 reports from 1999 to 2005 using a third-generation immunoassay were included involving 725,678 persons.

quent risk factor was blood transfusion (reported in 4 out of 5 studies). In the study in which major surgeries arose as the unique independent risk factor [9], the authors declared that blood transfusion could not be discarded with the study methodology applied.

Prevalence of Anti-HCV Antibodies among Special Groups of Persons at High Risk

We identified 10 studies reporting on special groups of persons who are at supposed high risk for HCV infection (table 4). The crude prevalence reported in each study ranged from 1 to 32%. Patients with liver cirrhosis had the highest prevalence of anti-HCV (32%). Noteworthily, healthcare personnel did not have a different prevalence of anti-HCV antibodies from the population considered at low risk. Since the group of studies reporting on persons at high risk was heterogeneous with respect to the putative source of the infection and selection criteria for entering in studies, combined estimates on prevalence for these subgroups were not performed.

Confirmation of the Presence of Anti-HCV Antibodies and of HCV RNA in People at Low Risk

There were 5 studies reporting on confirmation of the presence of anti-HCV antibodies by recombinant immunoblot assay (RIBA) or the presence of HCV RNA by nucleic acid amplification testing (NAT) in people at low risk. RIBA turned out positive in 30–100% of the seroreactive cases to screening test (3 studies, WMP = 36.3%; 95% CI, 28.4–44.2%). The presence of viremia was ascertained in 16–80% of cases by NAT (4 studies, WMP = 29.9%; 95% CI, 22.3–37.4%). Among persons with a positive RIBA test, viremia was ascertained in 50–93% cases (2 studies, WMP = 91.5%; 95% CI, 83.3–99.7%).

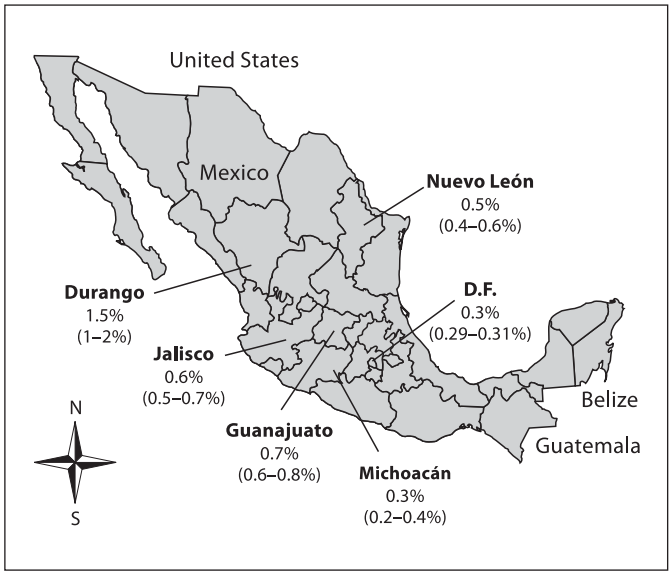

Fig. 1. Weighted mean prevalence (and 95% confidence interval) of anti-HCV antibodies determined by second- and third-generation immunoassay methods combined, calculated for each state of Mexico for which data were available (six states). D.F. stands for 'Distrito Federal' (Federal District).

HCV Genotypes

Our literature search yielded three reports on the frequency of HCV genotypes in cohorts including >50 persons. An early study from the West of Mexico reported on 90 patients with detectable HCV RNA [40]. In this report the frequency of HCV genotypes was as follows: 1a = 42%; 1b = 21%; 2a/2c = 20%; 4 = 16%, and 3 = 1%. In a multicenter study [41] reporting on 162 blood donors with detectable HCV RNA the genotype frequency was: 1b = 47%; 1a = 17%; 2b = 15%; 2a/2c = 12%; 3a = 6%;

Table 3. Independent risk factors for HCV infection in asymptomatic persons at low risk

Year of publication	City (state)	Population studied	Risk factors	Ref.
1994	Mexico City (D.F.)	Blood donors	Major surgery	9
1994	Guadalajara (Jalisco)	Pregnant women	Blood transfusion	12
1996	Durango (Durango)	Blood donors	Blood transfusion Sexual promiscuity	14
2002	Mexico City (D.F.)	Blood donors	Nasal cocaine use Dental procedures Sexual promiscuity Blood transfusion Household contact	24
2005	León (Guanajuato)	Blood donors	Blood transfusion Alcoholism Sexual promiscuity Hospitalizations	29

D.F. = Distrito Federal.

Only studies reporting odds ratios are included in this table. The risk factors are ranked in order of their contribution to predict anti-HCV seroreactivity, from the highest to the lowest odds ratios.

Table 4. Studies reporting on seroprevalence of anti-HCV in persons considered at high risk

Year of publication	City (state)	Population studied	Number	Seroprevalence % (95% CI)	Ref.
1994	Mexico City (D.F.)	Patients with elevated liver enzymes	450	14.8 (11.5–18.1)	31
1995	Mexico City (D.F.)	Healthcare personnel	289	2.1 (0.4–3.7)	32
1997	Guadalajara (Jalisco)	Healthcare personnel	62	1.6 (1.57–1.63)	33
2000	Mexico City (D.F.)	Patients with chronic renal failure	235	10.2 (6.3–14.1)	34
2000	Mexico City (D.F.)	Patients at emergency room	909	7.8 (6.1–9.5)	35
2001	Mexico City (D.F.)	Medical residents	89	1.1 (1.08–1.12)	36
2003	Mérida (Yucatán)	Patients with cirrhosis	153	32 (24.6–39.4)	37
2004	Mexico City (D.F.)	Patients with chronic renal failure	149	6.7 (2.7–10.7)	38
2004	Mexico City (D.F.)	Deferred blood donors according to medical history	1,057	1.3 (0.62–1.98)	27
2005	Durango (Durango)	Prison inmates	181	10 (5.6–14.4)	39

CI = Confidence interval; D.F. = Distrito Federal.

1a/1b = 2%, and other not classified = 1%. In another multicenter study [42] on 419 patients with detectable HCV RNA, the frequency of HCV genotypes was the following: 1b = 41%; 1a = 18%; 2a/2c = 13%; 1a/1b = 11%; 2b = 9%; 3a = 6%, and other genotypes (2a, 3b and 4) = 2%. Thus, genotype 1 had crude prevalence ranging from 63 to 70%, subtype 1b being the most frequent in the two multicenter studies.

Discussion

There is no single nation-wide study that describes the epidemiology of HCV infection in Mexico. In a remedial situation, but for exploratory purposes only, a systematic review offers the opportunity of gaining insight in this important issue, as well as planning comprehensive collaborative studies of a national scale. This strategy of

combining evidence on the frequency of HCV infection has been used [43–46]and has provided very useful information. Similar analyses can be undertaken in developing countries in which a large nation-wide study is, at the present time, unaffordable.

Our calculations on the prevalence of anti-HCV antibodies in Mexico yielded lower numbers than previously estimated [6, 7]. We found that the large majority of studies reported seroprevalence below 1%. These estimates on seroprevalence differed according to the laboratory method used. This may be due at least in part to inherent differences in the immunoassay methodology, as second-generation immunoassay is less sensitive and specific than third-generation [47], but also to the fact that when second-generation immunoassay was used, the smallest sample sizes were assessed. In these circumstances, we cannot definitively attribute the higher seroprevalence observed before 1999 compared with that seen after this year to a decrease in the frequency of HCV infection. Nonetheless, PP, MP and WMP for each immunoassay generation (or time period) were lower than 1–1.9%, which is one of the previously attributed prevalences of HCV infection in Mexico [7]. Assuming an overall seroprevalence of about 0.4% and since the total population size in Mexico is near 100 million [48], the number of persons seroreactive to anti-HCV antibodies in screening tests is supposed to be about 400,000. Furthermore, the true prevalence of HCV-infected people could be even lower, since a major part of the persons at low risk who resulted in being reactive to screening tests may be false positives [49–50]. Thus, extrapolating the scarce data on confirmation of anti-HCV by RIBA or HCV viremia by NAT, there would be 144,000 persons with specific anti-HCV antibodies and about 199,600 persons with viremia, respectively.

As expected, in this analysis, transfusion of blood products was found to be the main risk factor for HCV infection. As the use of illicit intravenous drugs is very infrequent in Mexico [51], a lower incidence of this infection can be expected in the future if the mode of transmission remains unchanged. Hence, even when marijuana and cocaine inhalation are the preferred forms of taking drugs among Mexican drug addicts [51], the use of illicit intravenous drugs should be prevented emphatically.

HCV genotype 1 appears to be the most prevalent in Mexico, subtype 1b being the most common genetic variant, as reported in the two largest multicenter studies. This distribution pattern of HCV genotypes is similar to that seen in Japan [52], South America [53] and some European countries [52], but different from that of the USA [52, 54], where subtype 1a is the most frequent. However, in the first study on HCV genotype distribution (in the West of Mexico) our group found that genotype 1a was the most frequent [40]. This could be explained at least in part with the analysis of migration patterns, since the West of Mexico is one of the country regions with the highest migration rates to the USA [48]. The reason of the differences in genotype distribution seen even in nearby countries is not clear; nevertheless, it might be due to different routes of infection, time of acquisition and, as has been suggested elsewhere [52], it may provide clues regarding the historical origin of HCV.

The information provided in this review should be taken with caution. Only 6 of the 32 states that conform to Mexico were analyzed. Other states may have data that have not reached publication. A special interest may be focused on the states from the Southeast of Mexico, where prevalence of hepatitis B is higher than in the rest of the country [55]. Also, the majority of persons included in our analysis, mainly blood donors, might not be representative of the general population.

In summary, the prevalence of anti-HCV antibodies in Mexico might be lower than previously thought. This and other epidemiological issues can only be fully addressed in a large nation-wide survey using immunoassay and molecular methodology. Hence, multicenter collaborative studies in Mexico are mandatory.

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