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Hepatitis C in the three main health institutions in Mexico: a 13-year mortality and hospitalization analysis

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ABSTRACT

There are no studies in Mexico comparing Hepatitis C virus (HCV) epidemiology among Health Institutions. In this report, we described the deaths and hospitalizations due to HCV in the three main Health Institutions in Mexico: the Mexican Institute of Social Security, the Institute of Social Security for State Workers and the Ministry of Health, during the period 2004-2017. A secondary analysis was carried out across the country using hospital administrative death databases. Adult deaths and hospitalizations rates were calculated in reference to the total affiliated population and all-cause in-hospital mortality risk were also evaluated. There were 7,914 deaths and 9,002 hospitalizations due to HCV. Mortality and hospitalization rates of these three institutions together showed a continuous decrease over the analyzed time: the mortality rate dropped from 1.25 to 0.41 per 100,000 affiliates during 2004 and 2017, respectively (66.9% of change), and the hospitalization rate dropped from 2.19 to 0.39 per 100,000 affiliates (81.9% of change). All-cause in-hospital survival accounted for 89.6%. Older age groups and Ministry of Health hospitalizations were associated with higher all-cause in-hospital death rates. In conclusion, the mortality and hospitalizations rates found in this study reflect a decrease in the burden of HCV in Mexico.

KEYWORDS: Hepatitis C virus. Hospitalization. Mortality. Survival.

INTRODUCTION

Hepatitis C is a blood-transmitted infection caused by the Hepatitis C virus (HCV), which can lead to chronic liver disease, cirrhosis, hepatocellular carcinoma and death[1]. Hepatitis C is a global public health problem that affects 71 million people worldwide and causes about 400,000 deaths annually[2].

Epidemiological studies in Mexico have estimated a prevalence of HCV infection between 0.5% and 1.5%[3], however, to our knowledge, there are no studies describing hospitalizations and mortality caused by HCV and comparing these outcomes among Health Institutions.

In Mexico, above 90% of the population has medical coverage and is served by the three main Health Institutions: the Mexican Institute of Social Security (IMSS), the Institute of Social Security for State Workers (ISSSTE) and the Ministry of Health (MoH), with about 60, 13 and 53 million affiliates, respectively. The first two institutions are social security systems bringing health care and socioeconomic benefits to formal sector workers as well as government employees and their families. In contrast, MoH provides health services to social security unaffiliated Mexicans, many of whom have been incorporated to the "Popular Insurance" health program[4-7].

Given the lack of recent reports quantifying the epidemiological burden of HCV in our country among Health Institutions, we aimed to describe the deaths

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and hospitalizations due to HCV, in affiliates to the three main Health Institutions in Mexico during a 13-year period (2004-2017). In this report, we have also described the in-hospital survival in the hospitalizations due to HCV as well.

MATERIALS AND METHODS

Study design and population

A national-wide data analysis was carried out using death and hospital discharge information from the Mexican Epidemiological and Statistical Deaths Subsystem and the Hospital Discharge Database System. These database systems integrate information from all the health institutions annually, providing data from the 32 States that encompass the Mexican territory.

HCV registers in adults aged 20 and over in the years 2004-2017 were identified by using the B17.1, B18.2 and B19.2 codes of the International Classification of Diseases, 10th revision. Those codes corresponded to acute, chronic and unspecified viral hepatitis C respectively, and were identified as the main cause of death and hospitalization. Data on sex, age and geographical region were obtained for each register.

Statistical analysis

Characteristics of the deaths and hospitalizations were compared in the IMSS, ISSSTE and the MoH groups by the chi-square and the one-way ANOVA tests.

Crude and adjusted HCV death and hospitalization rates were expressed per 100,000 affiliates aged 20 and over for the IMSS, the ISSSTE, the MoH, and for the three Health Institutions together. Adjusted rates were standardized using the World Health Organization World Standard Population 2000-2025[8], in order to control variations in the population age distributions among Health Institutions.

To evaluate all-cause in-hospital survival, we estimated survival curves with 95% Confidence Intervals (95% CI) by means of the Kaplan-Meier method. We have also conducted a multivariate Cox proportional hazard model to calculate adjusted hazard ratios (HR) with 95% CI, in order to assess the association between hospitalization characteristics and all-cause in-hospital mortality risk.

Mortality rates, hospitalization rates and all-cause in-hospital survival were estimated by sex, age group, health institution (IMSS, ISSSTE and MoH) and geographical region. For the last variable, the 32 States were grouped into three regions, as follows: West (Aguascalientes, Baja California, Baja California Sur, Chihuahua, Colima, Durango, Guanajuato, Jalisco, Michoacan, Nayarit, Sinaloa and Sonora), Central (Mexico City, Hidalgo, Mexico, Morelos, Queretaro and Tlaxcala), and East (Campeche, Chiapas, Coahuila, Guerrero, Nuevo Leon, Oaxaca, Puebla, Quintana Roo, San Luis Potosi, Tabasco, Tamaulipas, Veracruz, Yucatan and Zacatecas). In all the analyses, the deaths, hospitalizations and population for the MoH corresponded to the Popular Insurance affiliates only. The R software v.3.0.1 was used to carry out the statistical analysis.

Ethical statement

All the procedures were carried out in accordance with ethical standards of the institutional guidelines and the national laws, and also according to the 1964 Helsinki declaration and its later amendments.

Given that this study was based on the use of public available databases with no personal identifiers, neither the Institutional Review Board approbation, nor the formal informed consent were required.

RESULTS

Deaths due to Hepatitis C virus and mortality rates

A total of 7,914 deaths due to HCV from 2004-2017 were included in our study (5,157 from the IMSS, 1,269 from the ISSSTE and 1,488 from the MoH). The mean age at death was 60.4 years old and most deaths occurred in females from the West region of Mexico. Significant differences regarding sex, age and geographical region were observed among Health Institutions (Table 1). The 20-years-old adult and over affiliated population increased in the three health institutions: for IMSS from 28.5 in 2004 to 47.4 million in 2017; for ISSSTE from 5.8 to 7.6 million and for MoH adult affiliates incremented from 2.6 to 29.1 million (Supplementary Figure 1) in the study period. Mortality rates of the three institutions together showed a continuous decrease over the time (from 1.25 in 2004 to 0.41 per 100,000 affiliates in 2017 – a 66.9% of change) (Figure 1). This decrease has also been observed in all the three Health Institutions, both, in males and females, in each of the age groups and in the three geographical regions, as well (Supplementary Figure 2).

Hospitalizations due to Hepatitis C virus and hospitalization rates

As outlined in Table 2, we included 9,002 hospitalizations due to HCV (6,838 in the IMSS, 1,380 in the ISSSTE and

Table 1 - Characteristics of the deaths due to hepatitis C virus[a].

Characteristic	Mexican Institute of Social Security	Institute of Social Security for State Workers	Ministry of Health	All the three Institutions	P-value[b]
No. of deaths	5,157	1,269	1,488	7,914	
Sex (%)					
Male	32.3	27.4	48.4	34.5	
Female	67.7	72.6	51.6	65.5	<0.001
Age at death, years (mean ± SD)	60.7 ± 12.3	63.4 ± 11.3	56.5 ± 13.3	60.4 ± 12.5	<0.001
Age at death (%)					
20-39 years	5.1	2.4	10.1	5.6	
40-59 years	40.1	34.7	50.9	41.3	
≥60 years	54.8	63.0	39.0	53.1	<0.001
Geographical region (%)					
West	51.7	33.6	59.2	50.2	
East	15.9	19.9	18.3	17.0	
Central	32.4	46.5	22.4	32.8	<0.001

Data are presented as mean ± SD or percentages. [a]The study included deaths due to hepatitis C virus during the period 2004–2017. [b]The p-value was calculated with the Chi-square and the one-way ANOVA tests, with the null hypothesis being no differences among the three health institutions.

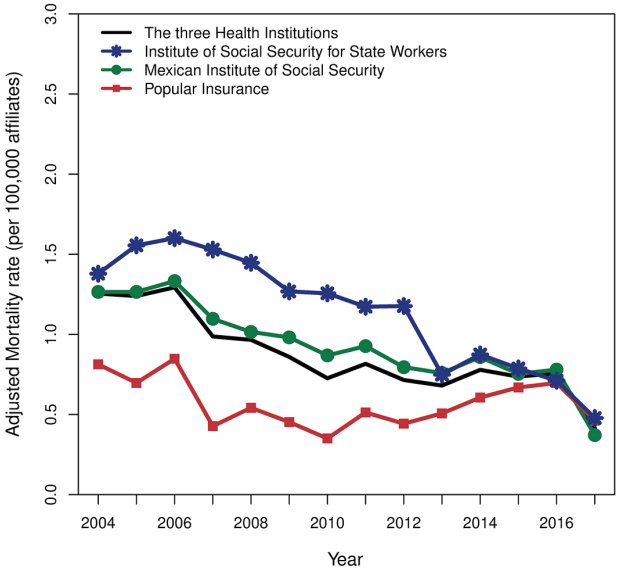

Figure 1 - Mortality due to hepatitis C virus in adults aged 20 and over, according to the Health Institution (Mexican Institute of Social Security, Institute of Social Security for State Workers, Ministry of Health, or all the three Health Institutions) from 2004 to 2017. Adjusted mortality rates per 100,000 affiliates are shown. The Ministry of Health included the Popular Insurance affiliates only.

784 in the MoH), the average length of hospital stay was 5.3 days and the mean age at hospitalization was 52.3 years old. Similar to death results, most hospitalizations occurred in females and in the West region of Mexico, with significant differences among Health Institutions.

Hospitalization rates combining the three institutions together showed a continuous decrease during the study period (from 2.19 in 2004 to 0.39 per 100,000 affiliates in 2017 – a 81.9% of change) (Figure 2). This rate decrement was observed in the IMSS and in the ISSSTE, in both, males and females, in all age groups and in the three geographical regions. However, an important increment in hospitalization rates was found among MoH affiliates (Supplementary Figure 3).

Hepatitis C virus in-hospital survival

In the survival analysis, 966 all-cause in-hospital deaths and 47,472 in-hospital person-days were examined. During the study period, 10.7% of hospitalizations reported death at discharge (overall survival of 89.3%). The Kaplan-Meier's survival analysis and the multivariate Cox proportional hazard model, all-cause in-hospital mortality rates were significantly higher in older age groups, in the West and East regions and in the MoH hospitalizations (Table 3, Figure 3 and Supplementary Figure 4).

DISCUSSION

HCV is a world-wide public health problem with a global prevalence around 1% and important regional variations even in different areas of the same country[2].

Several studies suggest that HCV incidence and

Table 2 - Characteristics of the hospitalizations due to hepatitis C virus[a].

Characteristic	Mexican Institute of Social Security	Institute of Social Security for State Workers	Ministry of Health	All the three Institutions	P-value[b]
No. of hospitalizations	6,838	1,380	784	9,002	
Sex (%)					
Male	41.1	31.6	57.0	41.0	
Female	58.9	68.4	43.0	59.0	<0.001
Age at hospitalization, years (mean ± SD)	52 ± 13.4	55.3 ± 13.1	49.4 ± 14	52.3 ± 13.5	<0.001
Age at hospitalization (%)					
20-39 years	18.2	9.9	25.8	17.6	
40-59 years	53.0	52.5	51.7	52.8	
≥60 years	28.8	37.7	22.6	29.6	<0.001
Geographical region (%)					
West	39.4	29.6	67.3	40.3	
East	19.9	16.1	26.4	19.9	
Central	40.8	54.3	6.3	39.8	<0.001
Length of hospital stay, days (mean ± SD)	5 ± 6.1	5.7 ± 6.7	6.5 ± 6.5	5.3 ± 6.2	<0.001

Data are presented as mean ± SD or percentages. [a]The study included hospitalizations due to hepatitis C virus during the period 2004–2017. [b]The p-value was calculated with the Chi-square and the one-way ANOVA tests, with the null hypothesis being no difference among the three Health Institutions.

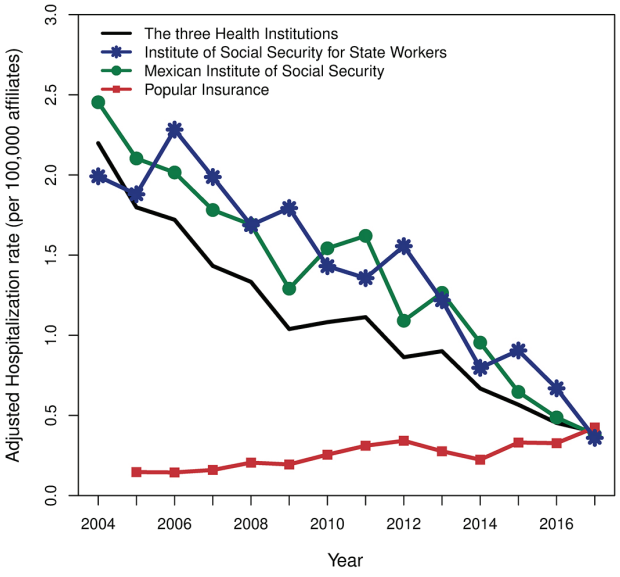

Figure 2 - Hospitalization due to hepatitis C virus rate in adults aged 20 and over, according to the Health Institution from 2004 to 2017. Adjusted hospitalization rates per 100,000 affiliates are shown. The Ministry of Health included the Popular Insurance affiliates only.

mortality have been decreasing in the last decades due to improvements in the health care safety[9,10]. However, in many middle and low-income countries, the existence of a large amount of cases that acquired HCV due to unsafe health-care procedures or due to intravenous drugs use and contamination that took place by the end of the 20th century, may increase the HCV complications and mortality in the coming years[11].

Previous studies in Mexico have shown that blood transfusion is the most frequent HCV transmission mechanism[3,12] and that HCV incidence and mortality rates had a mild increment in the past[13,14]. In this study, using administrative registers of the three main Health Institutions, which covers about 90% of the Mexican population with an overlapping coverage below 2%[15]; we found a continuous decrease of HCV mortality and hospitalization rates during the 13-year period. We have also found that rates were higher in women, in older age groups and in the West and Central regions of the country. In addition, in-hospital survival was 89.3%; older age groups and Ministry of Health hospitalizations showed lower all-cause in-hospital survival.

Consistent with our results, a previous study of viral hepatitis in Mexico conducted by Mendez, found higher mortality rates in females, in the North, Central and West regions and in more aged groups[14]. This report has also observed an increase in overall mortality rates with a similar mortality rate curve during the period 2004-2007.

Table 3 - Hazard ratios for all-cause in hospital mortality[a].

Characteristic	No. of hospitalizations	No. of in hospital deaths	Person-days of hospital stay	All-cause mortality rate (95% CI)[b]	HR (95% CI)	Adjusted HR (95% CI)
No. of hospitalizations	9,002	966	47,472	20.35 (0.65-19.07)		
Sex						
Female	5,312	557	27,612	20.17 (0.85-18.52)	1.00	1.00
Male	3,690	409	19,860	20.59 (1.02-18.64)	1.02 (0.90-1.16)	1.11 (0.97-1.27)
Age at hospitalization						
20-39 years	1,585	81	7,347	11.02 (1.22-8.75)	1.00	1.00
40-59 years	4,753	422	24,486	17.23 (0.84-15.61)	1.56 (1.23-1.98)	1.67 (1.31-2.12)
≥60 years	2,664	463	15,639	29.61 (1.38-26.94)	2.69 (2.12-3.40)	3.02 (2.37-3.84)
Geographical region						
Central	3,587	297	18,774	15.82 (0.92-14.06)	1.00	1.00
West	3,628	439	19,714	22.27 (1.06-20.22)	1.41 (1.21-1.63)	1.34 (1.15-1.56)
East	1,787	230	8,984	25.60 (1.69-22.38)	1.62 (1.36-1.92)	1.57 (1.31-1.87)
Health Institution						
Mexican Institute of Social Security	6,838	639	34,477	18.53 (0.73-17.11)	1.00	1.00
Institute of Social Security for State Workers	1,380	163	7,922	20.58 (1.61-17.53)	1.11 (0.93-1.32)	1.06 (0.89-1.27)
Ministry of Health	784	164	5,073	32.33 (2.52-27.54)	1.74 (1.47-2.07)	1.69 (1.41-2.02)

[a]Hazard ratios (HR) were adjusted using a Cox proportional hazard model. [b]All-cause mortality rates are expressed as number of in-hospital deaths/1,000 person-days of hospital stay. CI indicates the confidence interval.

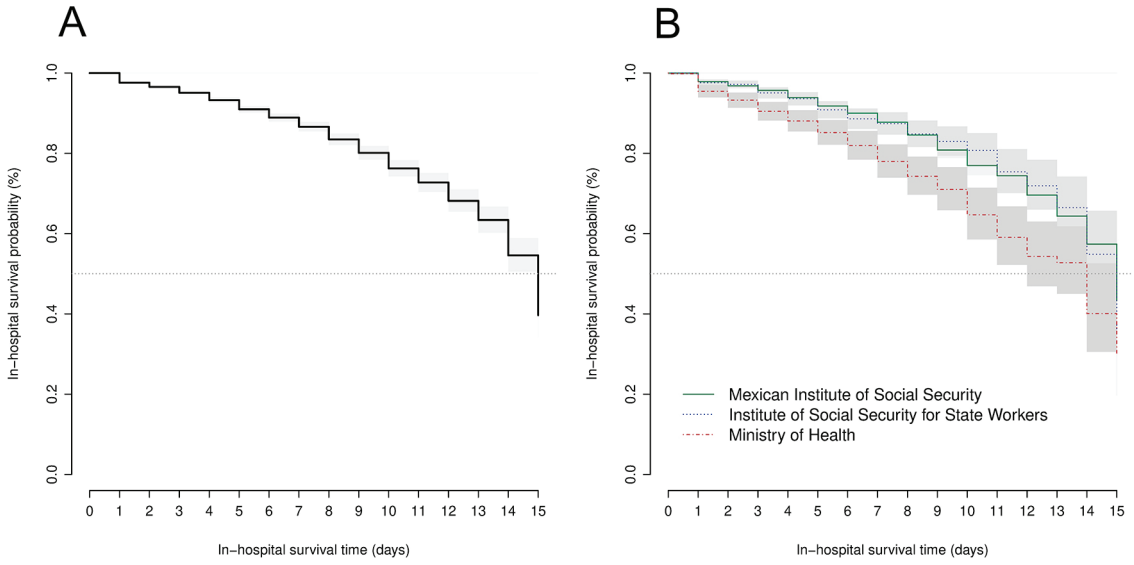

Figure 3 - Hospitalization due to hepatitis C virus survival according to the Health Institution from 2004 to 2017 (log-rank test $p = 5.0 \times 10^{-9}$). Survival curves and their 95% Confidence Interval (CI) are shown. The Ministry of Health included the Popular Insurance affiliates only.

Contrary to these agreements, the mortality rates observed in our report were lower compared to those from some other studies carried out outside of Mexico, which reported stable or increasing trends, and higher mortality rates in males[16-18]. As previously mentioned, most HCV cases in Mexico occurred in women infected by blood transfusions, so that differences regarding mortality rates and the male predominance could be explained by transmission through

unsafe intravenous drugs injections, which tends to increase and affect the male group predominantly[19,20].

Only a few studies have focused on hospitalizations due to HCV. Similar to our results, a report from Poland found considerable differences among provinces and a slightly decrease in the percentage of hospitalized cases[21]. A second study from England, reported higher hospitalization rates in males during the 1989-2003 period[22]. In relation to in-hospital survival, the death frequency in our study (10.7%) was almost double the mortality reported in HCV patients without sustained viral response[23]. This important difference could be attributed to a more advanced stage and complexity of hospitalized HCV patients compared to those of HCV out-patients. One of the notorious findings of our study was the higher mortality and hospitalization rates among women (Supplementary Figures 2A and 3B). This finding could be explained by a female predominance among the HCV-infected patients included in the present study. However, the similarity of in-hospital mortality showed by our results between the sex groups might indicate that there are no differences between treatment and severity of HCV in females compared to males. This last finding is an interesting topic that could be addressed by future investigations.

Our study found a decrease in HCV death and hospitalization rates and differences in sex and age distributions among Health Institutions. In this regard, it is important to remark that blood screening in Mexico started in 1993 and nowadays about 95% of blood products are screened for HCV[24]. The control of this historical key factor in Mexico could explain the important reduction in both, the HCV prevalence among blood donors (from 0.72 in 2000 to 0.48 in 2015)[25,26] and in the HCV death and hospitalization rates. It is also important to note that the decrease in the HCV rates was inversely correlated with the increase in the affiliated population. The Mexican population growth and the increment in the health insurance coverage have caused a continuous rise in the number of affiliates to the Mexican Health Institutions in the last years[27]. Despite these findings, MoH affiliates showed a male predominance with lower age of disease presentation, and even an increase in HCV hospitalization rates compared to those of the other Health Institution. This last situation could suggest that different transmission mechanisms other than the traditional blood transfusion are affecting MoH affiliates.

As the study was based on the analysis of administrative databases, the main limitation of this report was the absence of relevant clinical information such as the diagnosis of hepatitis B virus/HIV coinfections, HCV treatment, liver functional condition or hepatic causes related to in-hospital mortality. Moreover, the presence of a single cause of hospitalization/death in the available registers could lead to underestimation of the HCV burden, because HCV usually appears as a contributing cause rather than the main reason of death or hospitalization.

Despite the above mentioned limitations, the available administrative data allowed us to perform a significant sample-size national-wide HCV mortality and hospitalization analysis including the three main Health Institutions and all the regions of Mexico, over a 13-years period.

To our knowledge, this is the first analysis examining hospitalizations and mortality due to HCV that compared the three main healthcare institutions in Mexico. In spite of the decrease of HCV burden showed by our study, it is important to strength preventive and medical control interventions in order to eliminate viral hepatitis C as a public health threat in the near future.

CONCLUSION

In conclusion, the mortality and hospitalizations rates found in our study reflect a decrease in the burden of HCV in Mexico.

ACKNOWLEDGMENTS

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CONFLICT OF INTERESTS

None

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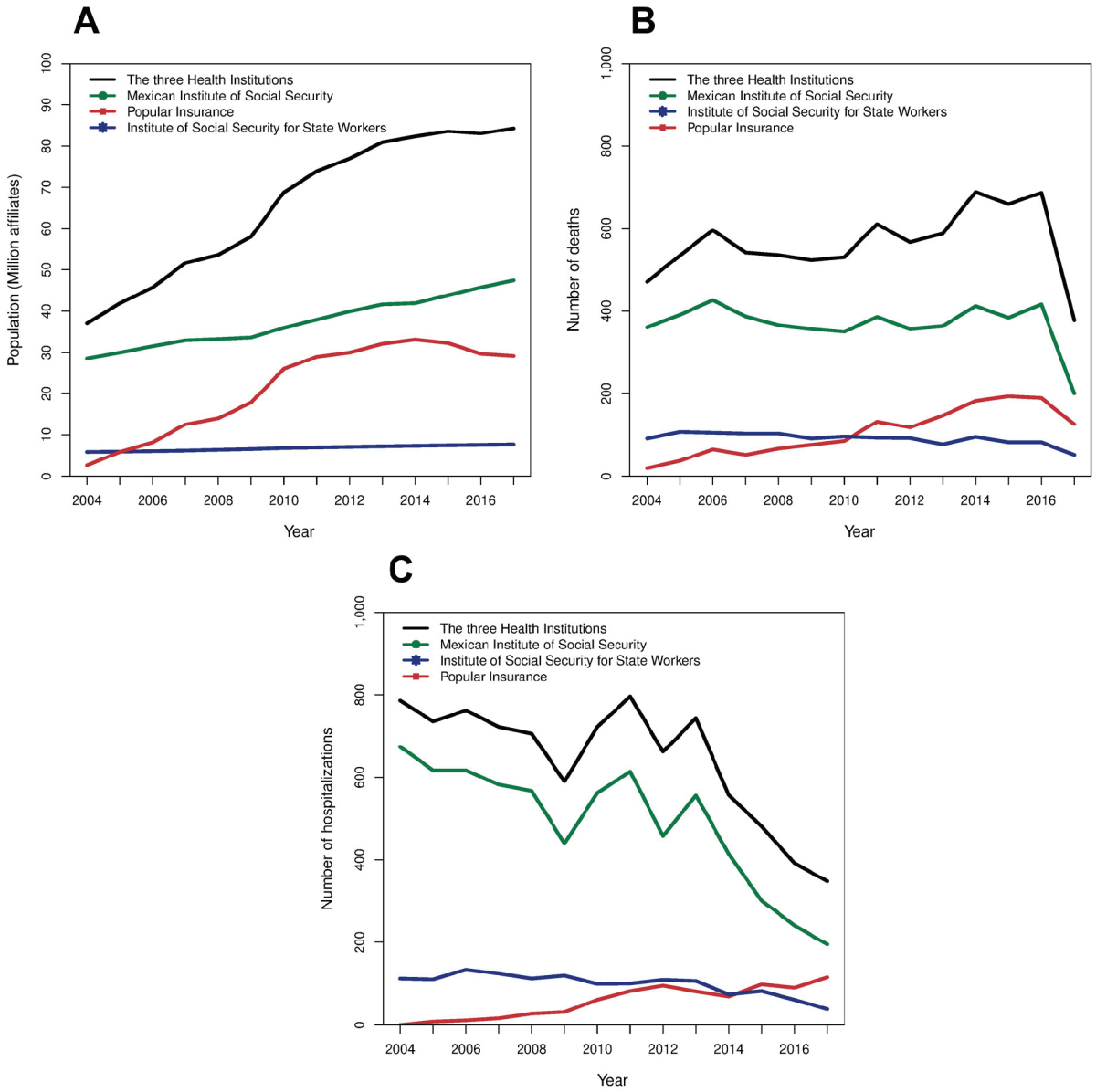
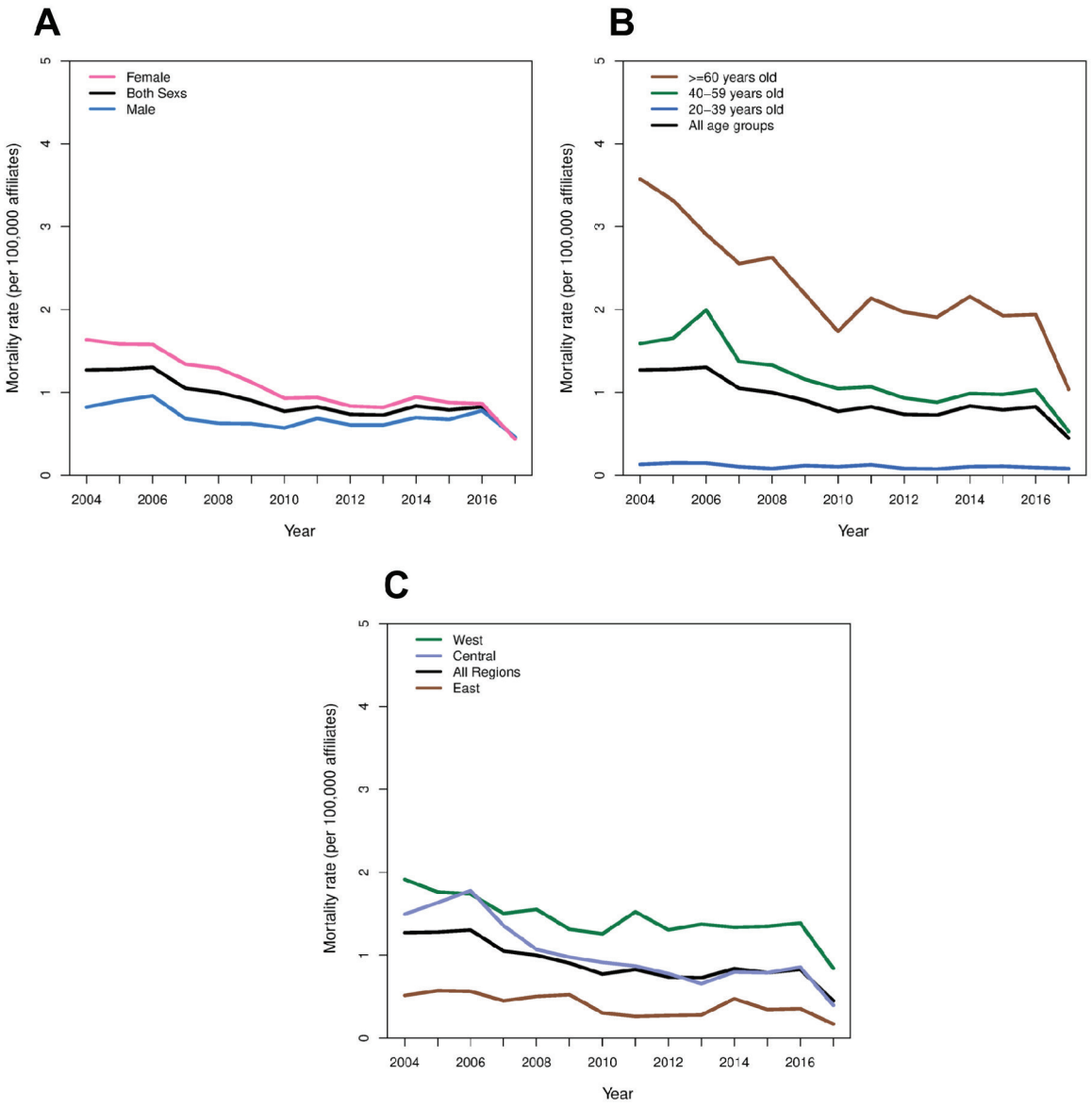
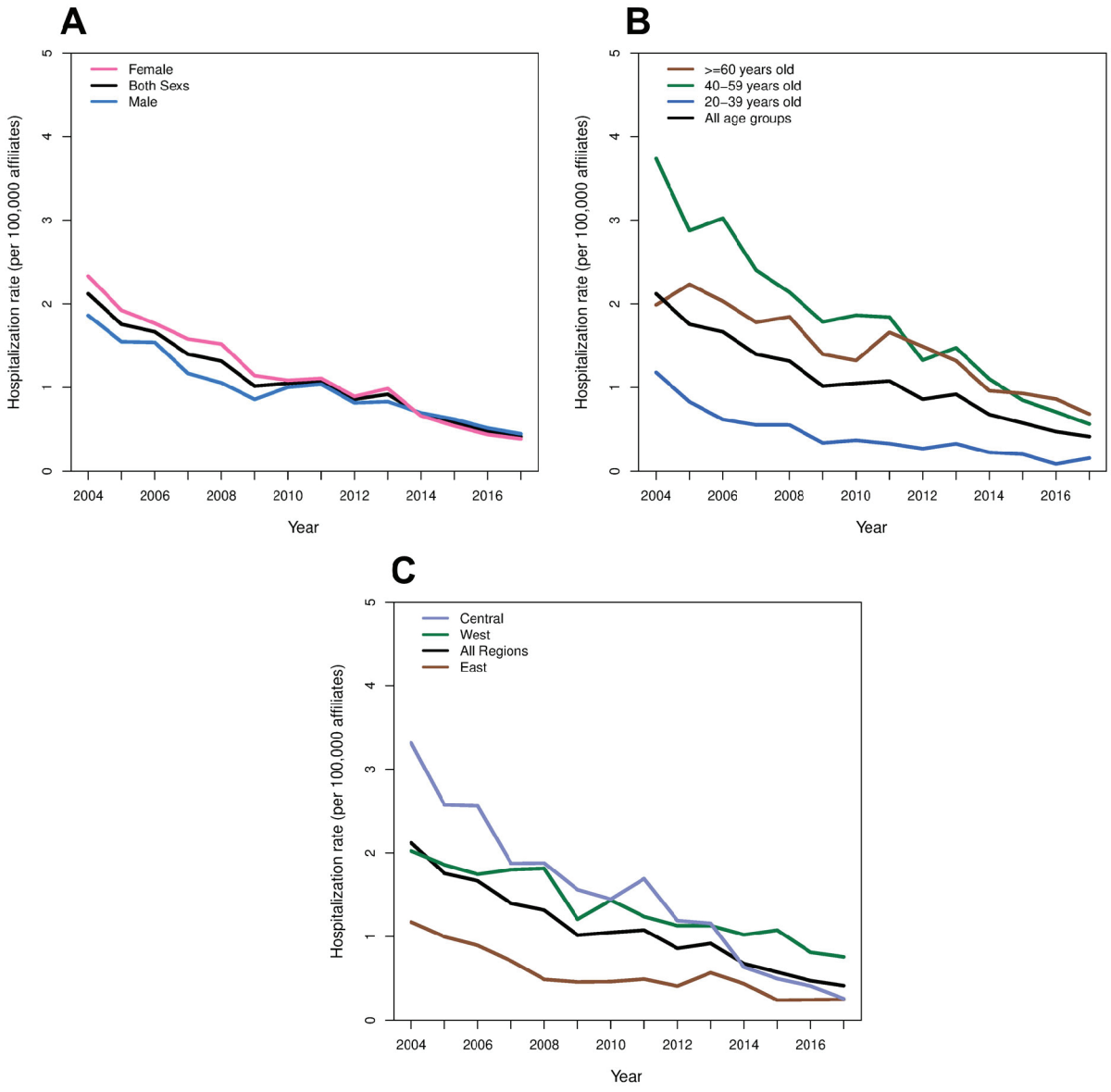
SUPPLEMENTARY MATERIAL



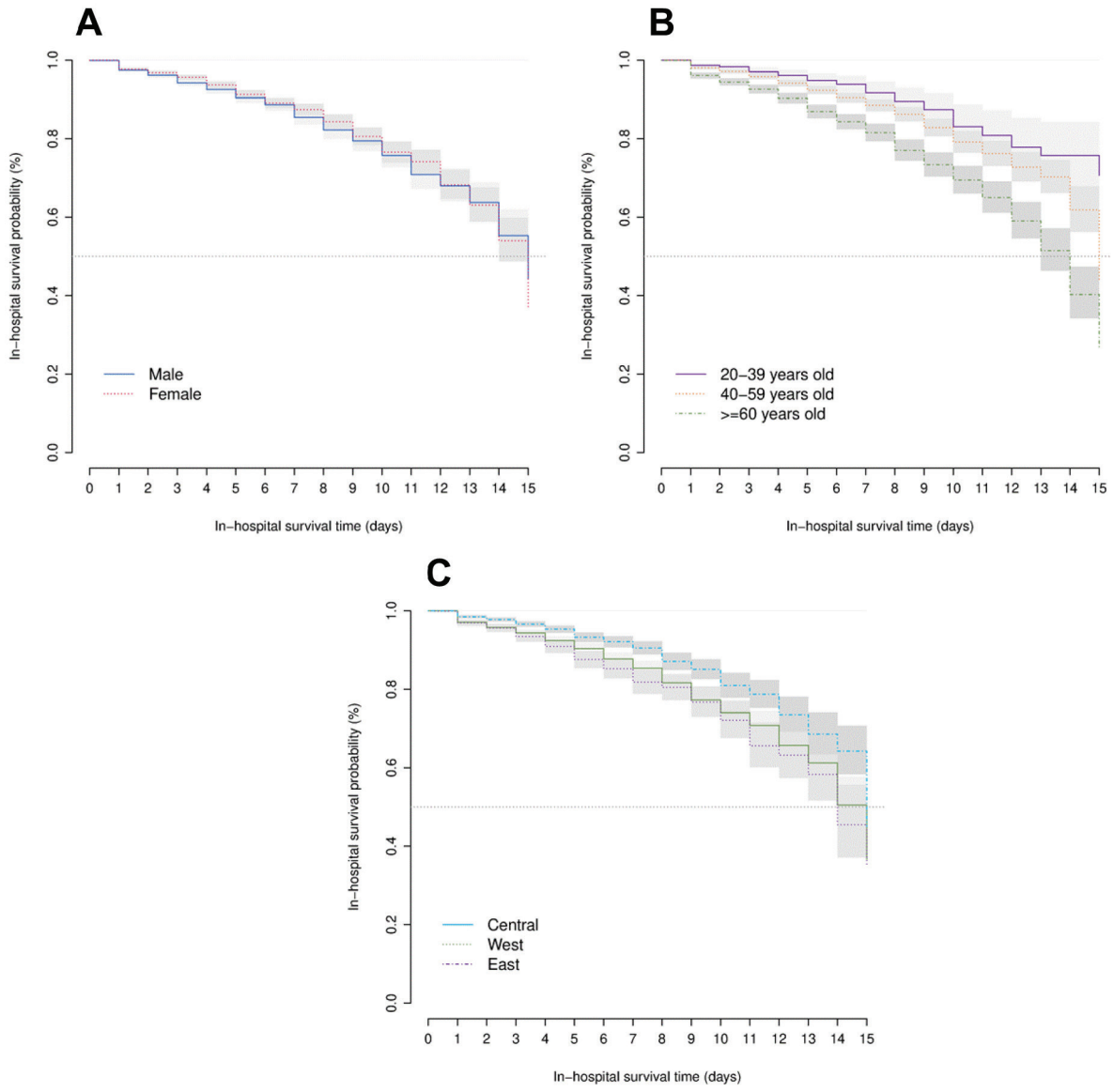
Supplementary Figure 1 - Hepatitis C virus mortality and hospitalization analysis in adults aged 20 and over, according to the Health Institution (Mexican Institute of Social Security, Ministry of Health, Institute of Social Security for State Workers and the three Health Institutions) from 2004 to 2017: A) Affiliated population; B) Number of deaths due to hepatitis C; C) Number of hospitalizations due to hepatitis C. The Ministry of Health included the Popular Insurance affiliates only.



Supplementary Figure 2 - Hepatitis C virus mortality rate in adults aged 20 and over according to the death's characteristics: A) Sex; B) Age group; C) Geographical region. Mortality rates (per 100,000 affiliates) are shown.



Supplementary Figure 3 - Hepatitis C virus hospitalization rates in adults aged 20 and over according to the hospitalization's characteristics: A) Sex; B) Age group; C) Geographical region. Hospitalization rates (per 100,000 affiliates) are shown.



Supplementary Figure 4 - Hepatitis C virus in-hospital survival in adults aged 20 and over according to the hospitalization's characteristics: A) Sex (log-rank test p = 1.00); B) Age group (log-rank test p $<2.0 \times 10^{-16}$); C) Geographical region (log-rank test p = 8.0×10^{-9}). Survival curves and their 95% Confidence Intervals (CI) are shown.