Gastroenterología y Hepatología 46 (2023) 116–123

Gastroenterología y Hepatología

www.elsevier.es/gastroenterologia

ORIGINAL ARTICLE

Changes in the epidemiology of hepatitis A: Clinical and preventive implications

Nora Mariela Martínez Ramírez[a,*], **Alejandro González Praetorius**[a], **Yolanda Martínez Benito**[b], **María Victoria García Rivera**[c], **Begoña Caballero López**[a], **Miguel Torralba González de Suso**[d]

[a] *Sección de Microbiología, Hospital General Universitario de Guadalajara, Guadalajara, Spain*
[b] *Delegación Provincial Consejería Sanidad Guadalajara, Guadalajara, Spain*
[c] *Consejería de Sanidad Castilla-La Mancha, Spain*
[d] *Servicio de Medicina Interna, Hospital General Universitario de Guadalajara, Guadalajara, Spain*

Received 2 August 2021; accepted 19 July 2022
Available online 11 March 2023

KEYWORDS
Hepatitis A;
Epidemiology;
Outbreaks;
Risk groups

Abstract
Introduction and objectives: Hepatitis A Virus Infection (HAI) has been related to the hygienic-sanitary situation of an area, the changes in the epidemiology of HAI in the province of Guadalajara between 1991 and 2017 are analyzed.
Materials and Methods: Cases of HAI declared between 1991 and 2017 in Guadalajara were included. The variables analyzed were age, sex, environment, risk factors for HAI and need for hospitalization. The incidence was compared in 3 periods: 1991—1999, 2000—2008 and 2009—2017.
Results: 233 cases of HAI were declared, the average incidence rate was 4.27 cases/100,000 inhabitants, highest between 1991—1999 (6.93) and lowest between 2009—2017 (1.92), with an increment in 2017 (5.5). The median age was 16 years (IR: 8.5–28.5 years), 58.4% were male, and the highest incidence occurred between 5—14 years in both sexes. The most frequent risk factors were family and non-family contact and trips to endemic areas (18.6%, 17.3% and 18.2%, respectively). The last risk factor increased after 2000 ($p = 0.001$), as did the incidence in urban areas. The MSM group showed an increase in the last period ($p < 0.001$). Hospital admissions increased progressively from the first to the third period studied ($p = 0.001$).
Conclusions: HAI has a low incidence in our area. More cases related to travel or sexual practices are observed. This should be considered when establishing prevention policies, including vaccination of the most exposed people.
© 2022 Elsevier España, S.L.U. All rights reserved.

* Corresponding author.
E-mail address: nmmartinezr@sescam.jccm.es (N.M. Martínez Ramírez).

2444-3824/© 2022 Elsevier España, S.L.U. All rights reserved.

PALABRAS CLAVE
Hepatitis A;
Epidemiología;
Brotes;
Grupos de riesgo

Cambios en la epidemiología de la hepatitis A: repercusiones clínicas y preventivas

Resumen
Introducción y objetivo: La infección por el Virus de la Hepatitis A (IVHA) está relacionada con la situación higiénico-sanitaria de una zona, se analizan los cambios en la epidemiología de IVHA en la provincia de Guadalajara entre 1991 y 2017.
Materiales y Métodos: Se incluyeron los casos de IVHA declarados entre 1991 y 2017 en Guadalajara. Las variables analizadas fueron edad, sexo, ámbito, factores de riesgo para IVHA y necesidad de hospitalización. La incidencia se comparó en 3 períodos: 1991—1999, 2000—2008 y 2009—2017.
Resultados: Se declararon 233 casos de IVHA, la tasa de incidencia media fue 4.27 casos/100.000 habitantes, más elevada entre 1991—1999 (6.93) y más baja entre 2009—2017 (1.92), con un repunte en 2017 (5.5). La mediana de edad fue 16 años (RI: 8,5–28,5 años), el 58.4% fueron varones, y la mayor incidencia se dio entre 5—14 años en ambos sexos. Los factores de riesgo más frecuentes fueron contacto familiar y no familiar y viajes a zonas endémicas (18.6%, 17.3% y 18.2%, respectivamente). Estos últimos aumentaron a partir del 2000 ($p = 0.001$), así como la incidencia en zonas urbana s. El grupo HSH mostró un incremento en el último período ($p < 0.001$). Los ingresos hospitalarios aumentaron de forma progresiva desde el primer al tercer período estudiado ($p = 0.001$).
Conclusiones: La IVHA tiene baja incidencia en nuestra zona. Se observan más casos relacionados con viajes o prácticas sexuales. Esto debe considerarse a la hora de establecer políticas de prevención incluyendo la vacunación en las personas más expuestas.
© 2022 Elsevier España, S.L.U. Todos los derechos reservados.

Introduction

Hepatitis A is an acute, self-limiting disease caused by the hepatitis A virus (HAV), an RNA virus belonging to the *Picornaviridae* family. The infection is characterised by a benign course in most cases, with a low mortality rate (2 per 1000 cases with jaundice), and does not lead to chronic hepatitis or a carrier state[1].

The infection can be asymptomatic (especially in children), have a subclinical course, or present a typical clinical picture of acute hepatitis[1].

The form of contagion of HAV is the faecal-oral route, and it is a highly contagious virus that spreads rapidly to close contacts[2]. For this reason, HAV infection is directly related to the hygiene and sanitation situation of an area, classifying them as areas of very low, low, intermediate or high endemicity. Spain is in an area of low endemicity, along with the rest of the countries of Western Europe, North America and Australia[3].

The available vaccines are from inactivated viruses and can be monocomponent or combined with other antigens such as the hepatitis B virus (HBV + HAV vaccine) or typhoid fever. In Spain, vaccination is recommended in all autonomous communities in risk groups and as a post-exposure measure to prevent infection in contacts[4].

The objective of this study was to analyse the changes in the incidence and epidemiological characteristics of HAV infection in the province of Guadalajara occurring between 1991 and 2017.

Patients and methods

The study included all cases of HAV infection diagnosed between January 1991 and December 2017 at the Clinical Microbiology Laboratory of the Hospital General Universitario de Guadalajara [General University Hospital de Guadalajara], which serves the population of the entire province, approximately 250,000 inhabitants. The samples came from the emergency department, from hospitalised patients or from different primary care centres throughout the province.

Cases were defined as patients in whom HAV IgM was detected, based on the Hepatitis A Surveillance Protocol of the Red Nacional de Vigilancia Epidemiológica del Instituto de Salud Carlos III [National Epidemiological Surveillance Network of the Carlos III Health Institute] [5]. Detection of HAV IgM was performed by chemiluminescence immunoassay (CLIA) (Architect, Abbott Laboratories, USA).

For the clinical epidemiological study, the following patient data was collected: age (stratified into the following groups: 0—4, 5—14, 15—24, 25—34, 35—44 and >45 years), sex, risk factors for acquiring the infection, need for hospitalisation, and complications, as well as being included in large outbreaks. The clinical-epidemiological data from all the patients were collected from the information provided by the Epidemiology Department of the Delegación de Sanidad y Asuntos Sociales de Guadalajara [Office for Health and Social Affairs of Guadalajara].

The patient was considered to come from an urban or rural area if they lived in a town of more or less than 10,000

Table 1 Mean annual rate of hepatitis A by age groups and sex in Guadalajara, periods 1991–1999, 2000–2008 and 2009–2017.

Age	No. of cases in period/100,000 inhabitants			Total
	1991—1999	2000—2008	2009—2017	
Males				
0—4	0	6.50	7.40	5.37
5—14	31.88	16.64	1.59	14.44
15—24	16.65	7.37	4.43	9.27
25—34	9.45	10.68	4.48	7.92
35—44	2.01	5.02	3.12	3.52
>45	0.37	0	0.22	0.17
Total	8.06	5.64	2.40	4.90
Females				
0—4	3	20.52	3.13	8.51
5—14	32.91	19.79	4.29	20.82
15—24	7.45	2.98	3.69	4.62
25—34	3.70	4.84	1.19	3.09
35—44	2.24	3.55	0.94	2.03
>45	0.34	0	0.22	0.18
Total	5.78	4.72	1.43	3.62
Both sexes				
0—4	1.46	13.33	5.32	6.90
5—14	30.47	18.18	2.88	17.19
15—24	12.25	5.26	4.07	7.02
25—34	6.68	7.90	2.88	5.6
35—44	2.12	4.33	2.01	2.81
>45	0.35	0.35	0.22	0.17
Total	6.93	5.19	1.92	4.27

inhabitants, respectively. The provincial number of inhabitants by age groups and sex was calculated by inter-census estimates (1991–2011) and by the average of the population census (2012–2017), from the National Institute of Statistics[6].

For the comparison of the incidence of HAV infection between the time periods, the cases were divided into three periods: 1991—1999, 2000—2008 and 2009—2017.

The data relating to the period 1991—1999 have already been previously published[7].

Statistical analysis

For the description of events, frequencies and percentages were calculated. For the description of quantitative variables, the mean and standard deviation or the median and interquartile range (IQR) were used. Mean annual incidence rates were calculated based on age, sex, analysis periods in the study, and various risk factors for HAV infection. Logistic regression was performed using the different periods, and how they were associated with various epidemiological and clinical variables, as the independent variable. Odds ratios were calculated with their 95% confidence interval as a measure of risk. The comparison of quantitative variables was carried out with the Student's t test, ANOVA test and the Jonckheere-Terpstra non-parametric test of linear trend for the study of quantitative variables. All contrasts were bilateral and statistical significance was considered if the p-value was less than 0.05. The software package used for the analysis was STATA® v.16.0

Results

In the period between 1991 and 2017, 233 cases of HAV infection were declared in the province of Guadalajara, which represents an average incidence rate of 4.27 cases/100,000 inhabitants throughout the period, being higher in the years between 1991—1999 (6.93) and very low in the period 2009—2017 (1.92) (Table 1), highlighting a rebound in 2017, with an incidence rate of 5.5 cases/100,000 inhabitants (Fig. 1). The highest number of cases occurred in 1992 with 26.2 cases/100,000 inhabitants, followed by 2001 with 23.9 cases/100,000 inhabitants, in both cases due to outbreaks that occurred in Molina de Aragón in 1992–1993 and in the city of Guadalajara in 2001. The second one affected a Roma community and primary schools. In 2016, no cases of HAV infection were detected in the province of Guadalajara (Fig. 1).

In the period studied (1991–2017), the median age was 16 years (IQR: 8.5–28.5 years), and 136 (58.4%) were male, with incidence rates in males of 4.90/100,000 inhabitants and in females of 3.72/100,000 inhabitants) (rate ratio: 1.32; 95% CI: 0.34–5.07; $p = 0.754$). Table 1 shows the incidence rates according to age and gender in the three periods, and Fig. 2 shows the incidence rates according to age in the different periods, in both sexes. The 5—14 years age group was the

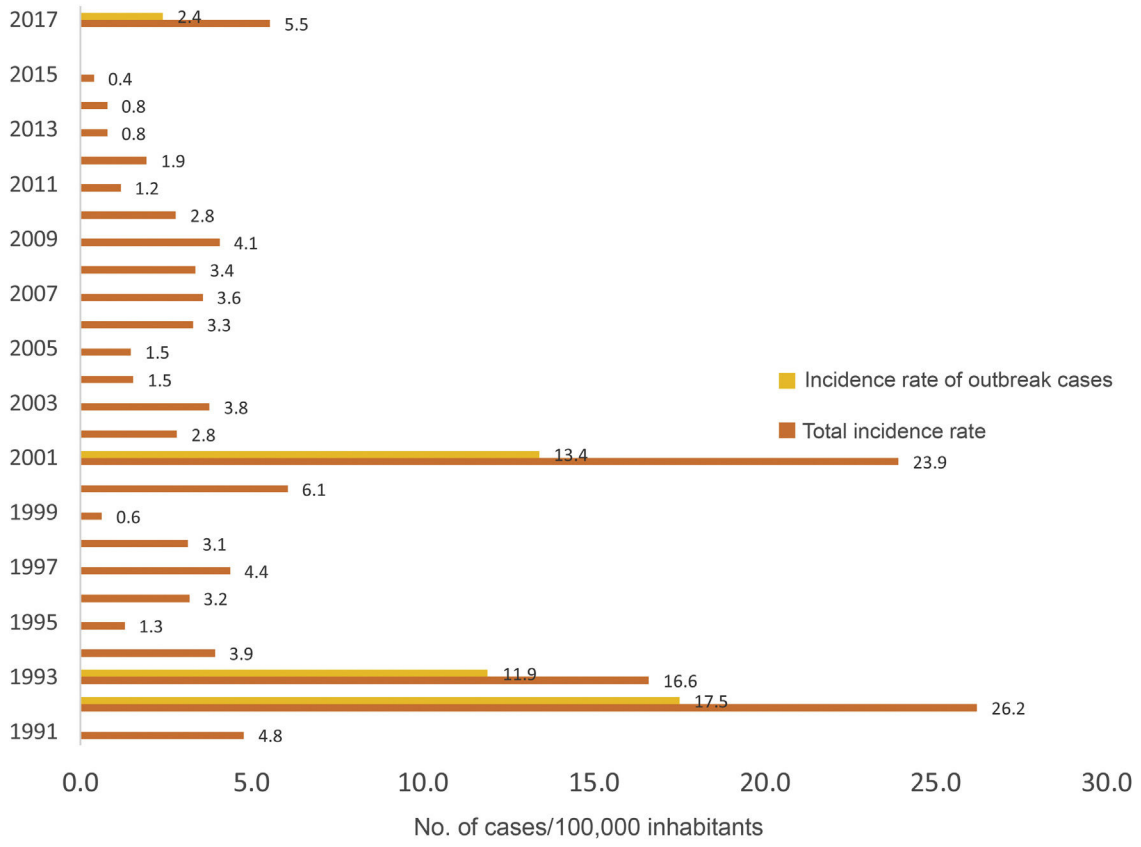

Figure 1 Annual incidence rates (No. of cases/100,000 inhabitants) of total cases and of cases belonging to large outbreaks.

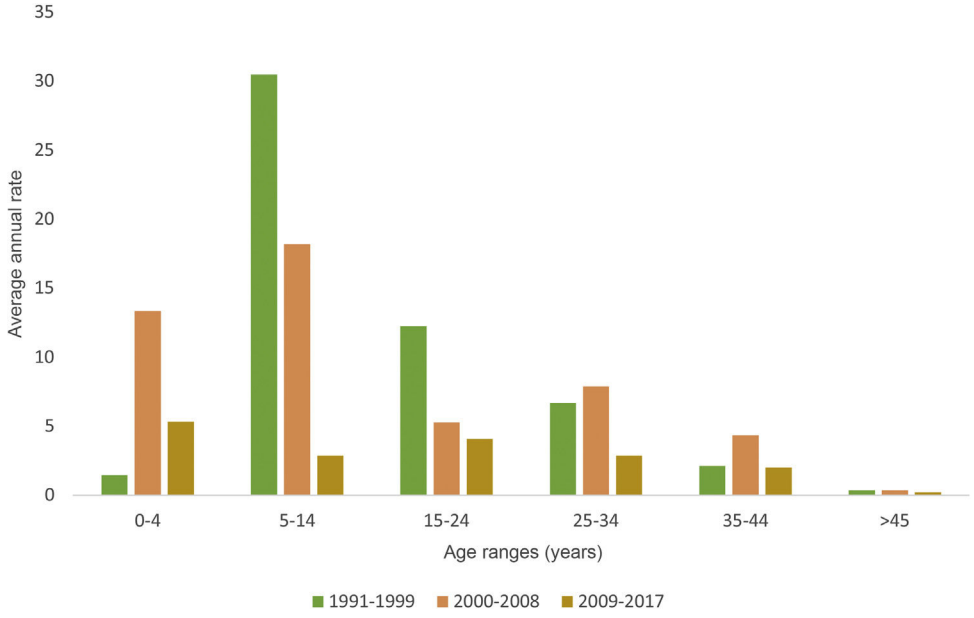

Figure 2 Average annual rate of hepatitis A by age groups in Guadalajara, periods 1991–1999, 2000–2008 and 2009–2017.

group with the highest incidence rate in the overall period in both sexes. However, in the third period, this trend was not respected in males, where a higher incidence rate was observed in boys aged 0—4 years.

It is noteworthy that in the last period the increase in cases of HAV infection in 2017 occurred mostly in men aged 18–43 years with an annual incidence rate of 19.2 cases/100,000. This trend was also seen in 2009, although to a lesser extent, with an incidence of 9.8 cases/100,000 inhabitants in this same group (data not shown in the table).

Depending on the area of residence, the average incidence rate in the rural, urban and Guadalajara capital

Table 2 Clinical-epidemiological characteristics of HAV infection in the periods 1991–1999, 2000–2008 and 2009–2017.

Variables	1991—1999 Period 1	2000—2008 Period 2	2009—2017 Period 3	Total	Period 2 vs. 1 OR (95% CI) p-value	Period 3 vs. 1 OR (95% CI) p-value	Period 3 vs. 2 OR (95% CI) p-value	p-value linear trend
Male sex (%)	58.8	51.1	64.7	56.5	0.73 (0.41—1.30) $p = 0.289$	1.29 (0.57—2.90) $p = 0.542$	1.76 (0.78—3.96) $p = 0.173$	$p = 0.91$
Median age years (IQR)	13.5 (10.5—23)	18 (7.5—31.5)	21 (8.75—33.25)	15.5 (9.5—28.5)	$p = 0.315$	$p = 0.195$	$p = 0.418$	$p = 0.302$[a]
Urban area (average incidence rate)	5.1	7.0	1.9	4.3	1.37 (95% CI: 0.917—2.057; $p = 0.127$)	0.382 (95% CI: 0.228—0.629; $p < 0.001$)	0.279 (95% CI: 0.173—0.441; $p < 0.001$)	N/A
Guadalajara (mean incidence rate)	5.9	9.0	2.6	5.7	1.52 (95% CI: 1.013—2.333; $p = 0.043$)	0.449 (95% CI: 0.255—0.771; $p = 0.003$)	0.293 (95% CI: 0.173—2.333; $p = 0.043$)	N/A
Rural area (average incidence rate)	9.2	3.4	1.9	4.2	0.367 (95% CI: 0.235—0.565; $p < 0.001$)	0.201 95% CI: 0.117—0.333; $p < 0.001$)	0.588 95% CI: 0.304—0.967; $p = 0.038$)	N/A
Urban/rural ratio	0.6	2.0	1.0	1.0	N/A	N/A	N/A	N/A
Hospitalisation	20.6%	42.2%	55.9%	35.2%	2.81 (1.50—5.27); $p = 0.001$	4.88 (2.11—11.26); $p < 0.001$	1.74 (0.80—3.80); $p = 0.164$	$p < 0.001$

N/A: not applicable; IQR: interquartile range.
[a] Jonckheere-Terpstra test.

Table 3 Mean age of hospitalised and non-hospitalised patients with HAV infection in the periods 1991–1999, 2000–2008 and 2009–2017.

	Hospitalised	Not hospitalised	p-value
Age 1991—1999 (IQR)	13 (7.25—24.5)	14 (10—22)	0.432
Age 2000—2008 (IQR)	26 (9—34)	12 (6—27)	0.006
Age 2009—2017 (IQR)	26 (20—35)	9 (2—16)	0.038

IQR: interquartile range; HAV: hepatitis A virus.

population was 4.2, 4.3, and 5.7 cases/100,000 inhabitants, respectively, throughout the period studied. Table 2 shows an increase in the incidence rate in urban areas in the period after the year 2000, with no differences in the incidence rate of HAV infection between the two areas in the last period.

Hospital admissions of cases diagnosed with acute HAV infection represented 35.2% and increased progressively from the first to the third period studied ($p = 0.001$) (Table 2). Table 3 shows that hospitalised patients from the year 2000 were older than those not hospitalised ($p < 0.05$). Throughout the entire period analysed, only four cases presented severe hepatitis (6.4%), defined by a prothrombin time <50%, and in no case was it fulminant hepatitis.

Table 4 describes the risk factors for infection acquisition. Considering the global data, the most common known risk factors were family and non-family contact with known cases and travel to endemic areas (18.6, 17.3, and 18.2%, respectively). Of note was the decrease in non-family contacts in the periods after 2000 ($p = 0.001$). In this sense, it is important to highlight that 100% of the cases with a risk factor for non-family contact before 2000 were affected by an outbreak in Molina de Aragón (rural area). Cases related to travel to endemic areas suffered a marked increase in the period after 2000 ($p = 0.001$) and mainly affected children up to 14 years of age (61.7%) who had travelled to their parents' countries of origin (data not shown in the table). These endemic areas corresponded to North Africa (62.5%), as well as different countries in South America (25%), Eastern Europe (10%) and Asia (2.5%). The risk of infection related to the group of men who have sex with men (MSM) showed a significant increase in the last period (linear trend $p < 0.001$), highlighting 27.3% in the period 2009—2017, representing 40% of the total cases in 2009 and 42.8% in 2017. In men between 18 and 46 years of age, the MSM risk factor rose to 67% and 60% in 2009 and 2017, respectively.

Discussion

In recent years, HAV infection has had a very low incidence in the province of Guadalajara, as has been observed in the rest of the country and in Europe[8], most probably due to better quality hygiene and sanitation conditions in recent years. The autonomous community of Castile-La Mancha does not include the hepatitis A vaccine in the vaccination schedule for the general population, so it cannot be attributed to greater serological protection, unlike other communities with established vaccination programmes[9].

The usual epidemiological pattern of hepatitis A with the highest incidence in childhood seems to have changed in the last period from 2009 to 2017, since in the paediatric population it was not higher than in those over 15 years of age. This decrease in the incidence of HAV infection in childhood leads to a consequent increase in the susceptible adult population (as seroprevalence studies have already shown[10]), a population exposed to suffering from a disease with greater symptoms and, consequently, a greater need for hospitalisation, as was observed in our study. The Comité Asesor de Vacunas (CAV) [Vaccine Advisory Committee] of the Asociación Española de Pediatría (AEP) [Spanish Association of Paediatrics] continues to recommend vaccinating risk groups against hepatitis A, but also indicates that universal vaccination of all children could be the optimal strategy for eventual eradication and control of this disease[11].

Despite the global data with very low average incidence rates, in 2009 and, above all, in 2017, a striking increase in the number of cases of HAV infection was observed in the province, which mainly affected men aged between 18 and 46 years old, of whom 67% and 60%, respectively, recognised having risky sexual relations with other men. This increase in cases in this group of young MSM has also been described in the rest of Spain[12,13] and at a European level, with outbreaks in numerous countries of the European Union from the end of 2016[8]. Organisations such as the WHO recommend hepatitis A vaccination in the MSM population as a measure to prevent outbreaks and virus circulation[14].

In HAV infection, small outbreaks in families or schools are common[15]. During the study period, three epidemic waves occurred that had a more or less significant influence on the incidence: in 1992–1993 (Molina de Aragón), in 2001 (Guadalajara capital) and in 2017 (the international epidemic wave related to the MSM collective). It is essential to stress the importance of the measures recommended to prevent the spread of outbreaks, such as rapid diagnosis and prompt notification to epidemiology departments[16], as well as the establishment of hygiene measures such as enteric isolation[5]. Post-exposure prophylaxis through vaccination or administration of immunoglobulins can be considered for close contacts of an HAV case, while in outbreaks in closed communities or social groups with a higher risk of infection, the vaccine is recommended as a control measure[5].

With respect to acquisition risk factors, the global data continue to support family contacts as the first factor, as previously described[7], but since 2000 the acquisition of infection due to travel to highly endemic areas has become more important. It mainly affects children who travel to their parents' country of origin, a situation that could be avoided with vaccination for international travel.

The CAV-AEP currently maintains the recommendation to vaccinate people with an increased risk of infection against hepatitis A, while considering that, ideally, universal vaccination of all children could be the optimal strategy for the eventual eradication and control of this disease.

Table 4 Risk factors for acquiring HAV infection.

Acquisition risk factor	1991–1999 Period 1	2000–2008 Period 2	2009–2017 Period 3	Total	Period 2 vs. 1 (OR 95% CI) p-value	Period 3 vs. 1 (OR 95% CI) p-value	Period 3 vs. 2 (OR 95% CI) p-value	p-value linear trend
Family contact	19.6%	18.8%	15.2%	18.6%	0.95 (0.47–1.93) $p = 0.89$	0.93 (0.74–1.18) $p = 0.570$	0.77 (0.26–2.26) $p = 0.634$	$p = 0.614$
Non-family contact	34.0%	6.9%	0.0%	17.3%	0.144 (0.06–0.35) $p < 0.001$	$p < 0.001$	$p = 0.193$[a]	$p < 0.001$
Travel	8.2%	21.8%	36.4%	18.2%	3.10 (1.31–7.35) $p = 0.008$	6.36 (2.31–17.51) $p < 0.001$	2.05 (0.88–4.81) $p = 0.095$	$p < 0.001$
School	4.1%	13.9%	0.0%	7.8%	3.74 (1.19–11.80) $p = 0.017$	$p = 0.572$[a]	$p = 0.021$[a]	$p = 0.729$
MSM	0.0%	8.7%	27.3%	8.0%	$p = 0.037$	$p < 0.001$	3.93 (0.98–15.81) $p = 0.066$[a]	$p < 0.001$
Roma ethnic group	1.0%	9.9%	0.0%	4.8%	10.55 (1.32–84.07) $p = 0.006$	$p = 1.0$[a]	$p = 0.119$[a]	$p = 0.365$
Food	3.1%	3.0%	6.1%	3.5%	0.959 (0.19–4.87) $p = 1.0$[a]	2.02 (0.32–12.67) $p = 0.601$[a]	2.11 (0.24–13.20) $p = 0.416$	$p = 0.531$
Nursery school	0.0%	5.0%	6.1%	3.0%	$p = 0.060$	$p = 0.063$[a]	1.24 (0.23–6.71) $p = 1.0$[a]	$p = 0.030$
IVDU	1.0%	1.0%	0.0%	0.9%	0.96 (0.06–15.57) $p = 1.0$[a]	$p = 1.0$[a]	$p = 1.0$[a]	$p = 0.650$
RF not known	28.9%	9.9%	18.2%	19.0%	0.27 (0.12–0.60) $p = 0.001$	0.55 (0.20–1.47) $p = 0.228$	2.02 (0.67–6.07) $p = 0.222$[a]	$p = 0.019$

IVDU: intravenous drug users; HAV: hepatitis A virus; MSM: men who have sex with men; RF: risk factor.
[a] Fisher's exact test.

This study has a series of limitations. Due to the evolution of HAV infection itself, and dividing the study into three periods, epidemic waves can alter the incidence in a period of time due to the increase in cases within outbreaks. It is possible that there were cases of HAV infection that were diagnosed in private clinics or hospitals in neighbouring provinces and have not been included in this study. It is probable that not all the cases of risky MSM behaviour in the group of men between 18 and 50 years of age have been collected, and, finally, as it is such a long period that begins in an era prior to computerised medical records, there are details such as the days of admission or the characteristics of the hospitalised patients to which we currently do not have access to be able to complete the study.

Conclusions

In recent years, a change has been observed in the epidemiological characteristics of HAV infection in the province of Guadalajara. From being an infection mainly in children with the appearance of outbreaks due to direct contact typical in areas of medium incidence, where the adult population is progressively more immunised, we have become an area of low incidence. In these areas, and like the countries around us, more and more cases are observed in the adult population, with more hospitalisations that are related to travel or sexual practices. This should be considered when establishing prevention policies, including vaccination of the most exposed people.

Conflicts of interest

The authors declare that they have no conflicts of interest.

References

1. Mandell, Douglas, Bennett. Enfermedad es infecciosas. In: Principios y práctica. 8 ed. Bennett: Dolin & Blaser; 2015.
2. Cuthbert J. Hepatitis A: Old and New. Clinical Microbiology Reviews. 2001;14:38–58.
3. Centro Nacional de Epidemiología. Instituto de Salud Carlos III. Red Nacional de Vigilancia Epidemiológica. Protocolos de enfermedades de declaración obligatoria. Madrid, 2013.
4. Ministerio de Sanidad y Consumo. Vacunas y programas de vacunación. [Accessed 14 February 2021]. Available in: https://www.mscbs.gob.es/profesionales/saludPublica/prevPromocion/vacunaciones/vacunas/profesionales/hepatitisA.htm; 2021.
5. Centro Nacional de Epidemiología. Instituto de Salud Carlos III. Red Nacional de Vigilancia Epidemiológica. Protocolos de la Red Nacional de Vigilancia Epidemiológica. Madrid, 2013. [Revised 22 May 2022]. Available in: https://www.isciii.es/QueHacemos/Servicios/VigilanciaSaludPublicaRENAVE/EnfermedadesTransmisibles/Documents/PROTOCOLOS/PROTOCOLOS%20EN%20BLOQUE/PROTOCOLOS_RENAVE-ciber.pdf.
6. Instituto Nacional de Estadística. Cifras de población y censos demográficos. [Revised 03 June 2022]. Available in: http://www.ine.es/.
7. González Praetorius A, Rodríguez-Avial C, Fernández C, Pérez Pomata MT, Gimeno C, Bisquert J. Incidencia y factores de riesgo de hepatitis A en la provincia de Guadalajara. Gastroenterol Hepatol. 2002;25:230–4.
8. European Centre for Disease Prevention and Control. Hepatitis A. In: ECDC. Annual epidemiological report for 2016. Stockholm: ECDC; 2019.
9. Domínguez A, Oviedo M, Carmona G, Jansá JM, Borrá E, Salleras L, Plasencia A. Epidemiology of hepatitis A before and after the introduction of a universal vaccination programme in Catalonia, Spain. J Viral Hepat. 2008;15:51–6.
10. Estudio poblacional de seroprevalencia de anticuerpos frente al virus de la hepatitis A en la Comunidad de Madrid, 2008-2009. Enferm Infecc Microbiol Clin. 2016;34:33–8.
11. Manual de vacunas en línea de la Asociación Española de Pediatría. Publicado en Comité Asesor de Vacunas de la AEP (https://vacunasaep.org). [Revised 30 July 2021]. Available in: https://vacunasaep.org/documentos/manual/cap-28.
12. Vigilancia de la Hepatitis A Castilla la Mancha. Año 2018. Consejería de Sanidad. Dirección General de Salud Pública y Consumo Boletín epidemiológico de la Comunidad de Madrid N(6. Volumen 24. Jun 2018.
13. Lorenzo Ortega R, O'Donnell Cortés B, Ortiz González Serna R, Gallardo García V, López Hernández B. Cambios en el patrón epidemiológico de la Hepatitis A en Andalucía: 2007-2017. Rev Esp Salud Pública. 2018;92.
14. World Health Organization WHO position paper on hepatitis a vaccines: June 2012 -recommendations. Vaccine. 2013;31:285–6.
15. Venczel LV, Desai MM, Vertz PD, England B, Hutin YH, Shapiro CN, Bell BP. The role of Child Care in a Community-Wide Outbreak of Hepatitis A. Pediatrics. 2001;108:E78, http://dx.doi.org/10.1542/peds.108.5.e78.
16. Torner N, Broner S, Martinez A, Tortajada C, Garcia de Olalla P, Barrabeig I, et al. Factors Associated to Duration of Hepatitis A Outbreaks: Implications for Control. PLoS One. 2012;7:e31339, http://dx.doi.org/10.1371/journal.pone.0031339.