

Prevalence and undiagnosed fraction of hepatitis C infection in 2018 in Spain: results from a national population-based survey

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[†]See [Supplementary Appendix 1](#).

Background: A national strategy against hepatitis C virus (HCV) was implemented in Spain in 2015 with the aim of reducing associated morbidity and mortality. In order to improve our understanding of the epidemiology of HCV, we analysed the prevalence of HCV antibodies and active infection overall and by age and sex in the general population aged 20–80 years. We also aimed to report the undiagnosed fraction. **Methods:** A national population-based seroprevalence survey was conducted in 2017–2018. A representative sample from the general population was selected using two-stage sampling. The prevalence of total HCV antibodies and of HCV RNA was calculated using inverse probability weighting based on bootstrapping. **Results:** Overall, we approached 17 496 persons; 9103 agreed to participate and met the eligibility criteria and 7675 were aged 20–80. We obtained a prevalence of HCV antibodies of 0.85% [95% confidence interval (CI): 0.64–1.08%] and of active infection of 0.22% (95% CI: 0.12–0.32%). The prevalence of active HCV infection was highest in men aged 50–59 (0.86%; 95% CI: 0.28–1.57%) and in men aged 60–69 years (0.72%; 95% CI: 0.27–1.28%). Prevalence was below 0.20% in the remaining age groups. The undiagnosed fraction for active HCV infection was 29.4%. **Conclusion:** This study shows that prevalence of HCV in the general population in Spain is low and reflects the impact of scaling up treatment with direct acting antivirals, together with other prevention strategies, from 2015 onwards. The data reported can guide subsequent public health actions.

Introduction

Elimination of viral hepatitis by 2030 is one of the United Nations Sustainable Development Goals.¹ Spain is fully committed to this goal, and our national hepatitis C virus (HCV) strategy was implemented in 2015 to reduce HCV-related morbidity and mortality.² An extrapolation of studies published in 2014 yielded an estimated national prevalence of HCV antibodies and active infection of 1.7% and 1.2%, respectively,³ although a considerably higher prevalence of HCV has been reported in high-risk groups,^{4–9} such as people who inject drugs (PID),^{4,5} people living with human immunodeficiency virus (HIV),^{6,7} migrant populations from endemic areas⁸ and persons in prison settings.⁹

A deeper understanding of the epidemiology of HCV infection in Spain was established as one of the objectives of the national strategy against Hepatitis C to guide public health policy. Most studies on the prevalence of HCV in the general population until 2017 were not representative at national level and lacked information on HCV viraemia. This article describes the prevalence of HCV antibodies and active HCV infection in Spain in 2017–2018 overall and by age and sex in a representative sample of the general population aged 20–80 years. We also report the undiagnosed fraction of HCV infection.

Methods

Study design, setting and participants

Data from the second Seroprevalence Study in Spain, a national population-based, cross-sectional study, were used to assess

seroprevalence against vaccine-preventable diseases and other infections that are relevant for public health. We selected participants from the general population aged 20–80 years living in Spain and entitled to a health card granting access to primary health care. Eligible individuals were those who did not report any condition and/or treatment leading to immunodeficiency (which included AIDS but not HIV). The fieldwork was conducted between May 2017 and May 2018. A detailed description of the methodology was published elsewhere.^{10,11}

Sampling strategy and sample size

A representative sample of 8800 individuals was considered based on previous estimates of prevalence of HCV antibodies and HCV active infection (1.7% and 1.2%, respectively),³ precision ranging from 0.3% to 0.4%, alpha error of 5% and a design effect of 1.5. We developed a two-stage sampling strategy, taking into account the size of the population ascribed to primary health centres throughout Spain. The first-stage sampling units were 220 randomly selected primary health centres with blood collection facilities. The probability of selection was proportional to the size of the population registered. The second-stage sampling units were 40 individuals per facility in the blood collection queue for testing. Participants were approached by a trained interviewer and invited to answer a 10-minute questionnaire on sociodemographic and clinical variables and risk factors for HCV infection (except injection drug use and sexual behaviours). They were also asked for permission to test blood samples for hepatitis A, B and C and HIV infection, as well as other diseases. The proportion of men and women and the age

distribution were previously established, and, when necessary, random telephone calls to the eligible population ascribed to a given health centre were made to complete the number of people for each age group. The number of persons born outside Spain was monitored so that this did not exceed the proportion within the general population.

Laboratory methods

Analytical determinations were conducted at the National Centre for Microbiology (NCM) of the Carlos III Institute of Health, as follows: (i) presence of total antibodies against HCV (anti-HCV) using the LIAISON[®] XL MUREX HCV Ab chemiluminescence assay (DIASORIN) (accredited by ENAC); (ii) HCV RNA detection using nested PCR of the 5' NC region (method developed by the NCM, with an estimated sensitivity of 1000 IU/ml); (iii) determination of HCV genotype in RNA-positive samples by amplification of NS5B region followed by Sanger sequencing (method developed by NCM, estimated sensitivity 10 000 IU/ml); and (iv) confirmatory HCV antibody tests using Western blot [HCV Blot 3.0 MP (DIASORIN) and INNO-LIA (FUJIREBIO)].

Outcome definitions

HCV-infected respondents (both active and past infection) had detectable HCV antibodies, including cases with total reactive antibodies in the chemiluminescence assay and HCV RNA detection and cases with total reactive antibodies in the chemiluminescence assay and one or both positive confirmatory tests. HCV infection was considered active when HCV RNA was detectable.

Non-HCV-infected respondents did not have reactive total antibodies in the chemiluminescence assay or had reactive antibodies but negative HCV RNA, as well as negative results in both confirmatory HCV antibody tests.

HCV infection was considered indeterminate when the respondent had total reactive antibodies in the chemiluminescence assay, a negative HCV RNA result and indeterminate results in both confirmatory antibody tests. Indeterminate results could correspond to residual HCV antibodies or false positives, although only rarely to active HCV infection.¹² For the purpose of these analyses, these respondents were considered negative cases.

Other measurements

The explanatory variables were sex (male and female), age group/birth cohort [20–29 years (1997–1988), 30–39 years (1987–1978), 40–49 years (1977–1968), 50–59 years (1967–1958), 60–69 years (1957–1948) and 70–80 years (1947–1937)], educational level (first grade or lower, second grade first cycle, second grade second cycle, third grade), social class [I (privileged), II (middle), III (under-privileged)],¹³ country of birth (further grouped as Spain or outside Spain), size of the city of residence (fewer than 10 000 inhabitants, 10 000–50 000 inhabitants, 50 000–100 000 inhabitants, 100 000–500 000 inhabitants, more than 500 000 inhabitants) and risk factors for HCV infection, such as past history of blood transfusion (and whether this was before 1992) and clotting factor concentrates for haemophilia, tattoos, acupuncture, infiltrations and other invasive procedures such as catheterization and dialysis. Participants were asked if they lived with someone with HCV. The questionnaire is freely available.¹¹

For confirmed cases of HCV infection, further information was extracted from clinical records at a second stage. This included whether HCV infection was previously known, together with information regarding linkage to care and treatment with DAAs.

Statistical analysis

The adjusted prevalence of HCV antibodies and active HCV infection was obtained using inverse probability weighting based on

bootstrapping. 95% confidence intervals (95% CIs) were calculated to estimate prevalence. Data were analysed using Stata vs. 11 and SPSS vs. 21.

Ethics approval

The study was approved by the Ethics Committee of the Carlos III Institute of Health. Participants signed an informed consent document, which gave permission for their general practitioner to be informed if a blood test yielded a result that would require a subsequent health intervention.

Results

We approached 17 496 persons, of whom 9103 agreed to participate, met the eligibility criteria for the HCV study and of which 7675 were aged 20–80. The global response rate was 52%; this was higher in women (54.9%) than in men (49.5%) and lower in people aged over 60 years. Response rates were lower in large cities (64.1%) than in smaller municipalities and were higher in participants with lower than primary studies (66.9%) than in those with secondary (53.2%) and university studies (50.8%). Response rates were higher among people born outside Spain (75.1%) than among Spanish-born people (51.3%). The main reason for non-participation was lack of time (34.3%) and lack of interest (27.9%).

The sociodemographic characteristics of the 7675 participants are summarized in [table 1](#). Overall, 101 samples were reactive to HCV antibodies in the chemiluminescence assay. After confirmation, HCV-positive results were reported for 66 patients, 17 of whom had detectable RNA and, therefore, active HCV infection. The prevalence of HCV antibodies was of 0.85% (95% CI: 0.64–1.08%) and of active infection of 0.22% (95% CI: 0.12–0.32%). The most frequent genotype was 1b (41.2%), followed by 1a (23.5%), 3a (11.8%), 2c (5.9%), 4a (5.9%) and indeterminate (11.8%).

The prevalence of HCV-positive antibodies and of active HCV infection was higher in men aged between 50 and 59 years and in under-privileged social classes ([table 1](#)). A clear pattern by age and sex was identified, with the highest prevalence of HCV antibodies among men older than 50 and women older than 70 years. The highest prevalence of active HCV infection was seen in men aged 50–59 and 60–69 years, with figures of 0.86% and 0.72%, respectively; the prevalence in the remaining groups was under 0.20% ([figures 1](#) and [2](#)). A higher prevalence for both HCV antibodies and active infection was also observed in persons with lower educational level and under-privileged social class ([table 1](#)). There were no remarkable differences according to the size of the municipality of residence, and differences between Spanish and non-Spanish patients were not statistically significant ([table 1](#)).

The prevalence of HCV antibodies and active infection was, overall, higher among participants who reported any risk factor for parenteral transmission ([table 2](#)). However, after disentangling risk factors individually, not all of them were associated with an increased prevalence of HCV infection ([table 2](#)).

The undiagnosed fraction of HCV infection was determined by cross-checking the clinical histories of the 66 cases with confirmed past or active HCV infection. Information was located for 59: all 17 cases with active infection were traced back; the HCV status was unknown in 5 (29.4%). Out of the 42 cases with past HCV infection, only 6 (14.3%) were not previously known. Out of all the cases where active infection by HCV was previously known by the national health system, 50% were verified to have started treatment with DAA; no DAA treatment was confirmed in 17%, and no information was available for the remaining 33%.

Table 1 Prevalence of HCV antibodies and active HCV infection according to socio-demographic variables

	N	Antibodies				Active infection			
		n	%	95% CI LL	95% CI UL	n	%	95% CI LL	95% CI UL
Sex									
Men	3670	48	1.24	0.92	1.58	14	0.35	0.17	0.53
Women	4005	18	0.46	0.28	0.66	3	0.08	0.01	0.18
Age group (birth cohort)									
20–29 (1997–1988)	1207	1	0.07	0.00	0.15	0	0.00	0.00	0.00
30–39 (1987–1978)	1202	1	0.09	0.01	0.17	1	0.09	0.01	0.17
40–49 (1977–1968)	1432	14	0.99	0.57	1.48	2	0.14	0.00	0.28
50–59 (1967–1958)	1417	22	1.56	0.99	2.27	7	0.50	0.22	0.85
60–69 (1957–1948)	1426	12	0.83	0.48	1.25	5	0.34	0.06	0.69
70–80 (1947–1937)	991	16	1.63	0.87	2.49	2	0.19	0.00	0.39
Country of birth									
Spain	7186	59	0.81	0.61	1.03	15	0.20	0.10	0.30
Other	489	7	1.30	0.44	2.44	2	0.34	0.00	0.96
Area of residence									
Lower than 10 000	1535	17	1.04	0.59	1.53	3	0.18	0.00	0.38
10 000/50 000	1986	13	0.71	0.41	1.07	5	0.26	0.06	0.49
50 000/100 000	984	8	0.82	0.32	1.35	1	0.08	0.00	0.29
100 000/500 000	1860	18	0.94	0.57	1.33	4	0.24	0.08	0.45
More than 500 000	1310	10	0.70	0.27	1.19	4	0.24	0.01	0.52
Level of education									
1st grade or lower	2340	38	1.71	1.22	2.24	12	0.54	0.28	0.84
2nd grade 1st cycle	1478	9	0.62	0.28	1.05	1	0.07	0.00	0.21
2nd grade 2nd cycle	1756	13	0.66	0.27	1.10	3	0.14	0.00	0.36
3rd grade	1888	5	0.27	0.06	0.49	1	0.05	0.00	0.15
Social class									
I (privileged)	1717	7	0.40	0.16	0.71	2	0.12	0.00	0.29
II (middle)	1459	8	0.50	0.16	0.85	2	0.10	0.00	0.30
III (under-privileged)	4246	51	1.20	0.91	1.53	13	0.31	0.17	0.48
Total	7675	66	0.85	0.64	1.08	17	0.22	0.13	0.31

Population aged between 20 and 80 years.
95% CI, confidence interval at 95%; LL, lower limit; UL, upper limit.

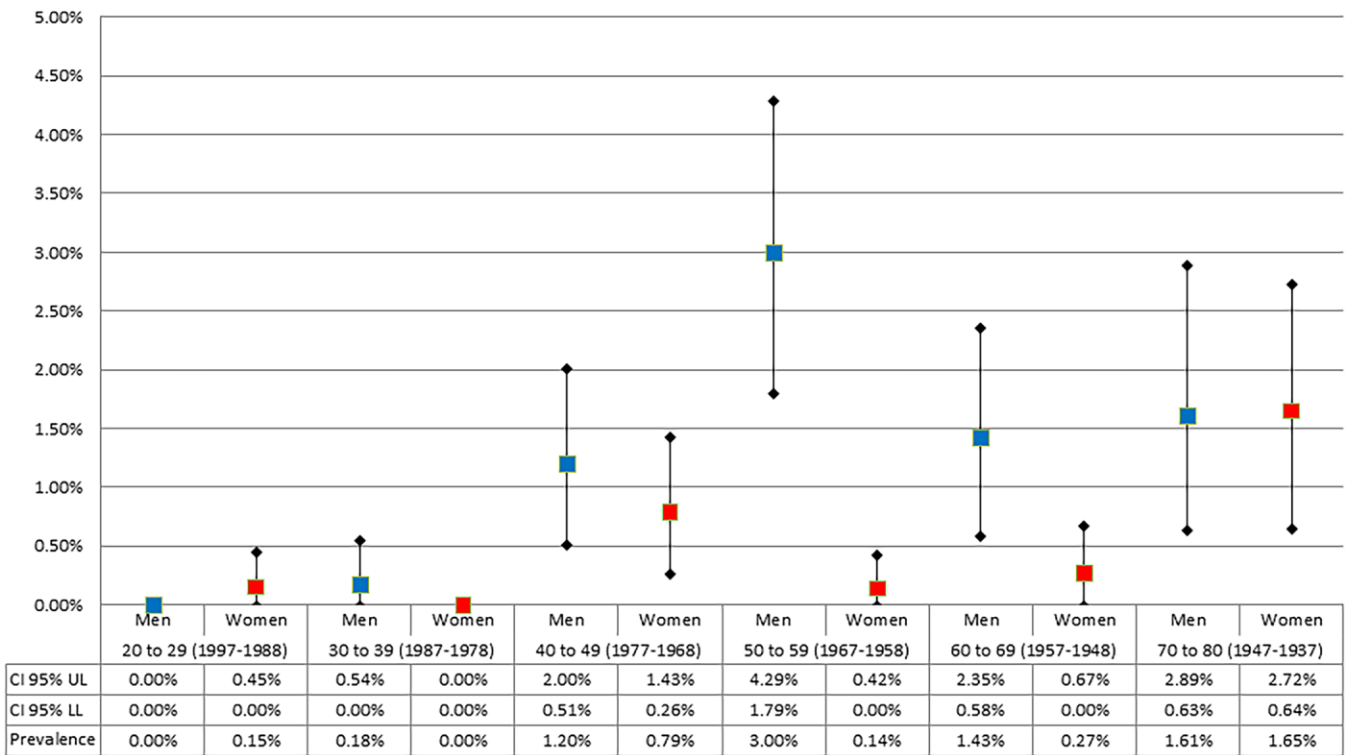


Figure 1 HCV antibody prevalence by age group (20–80 years) and sex. Second Seroprevalence Study in Spain: Hepatitis C 2017–2018

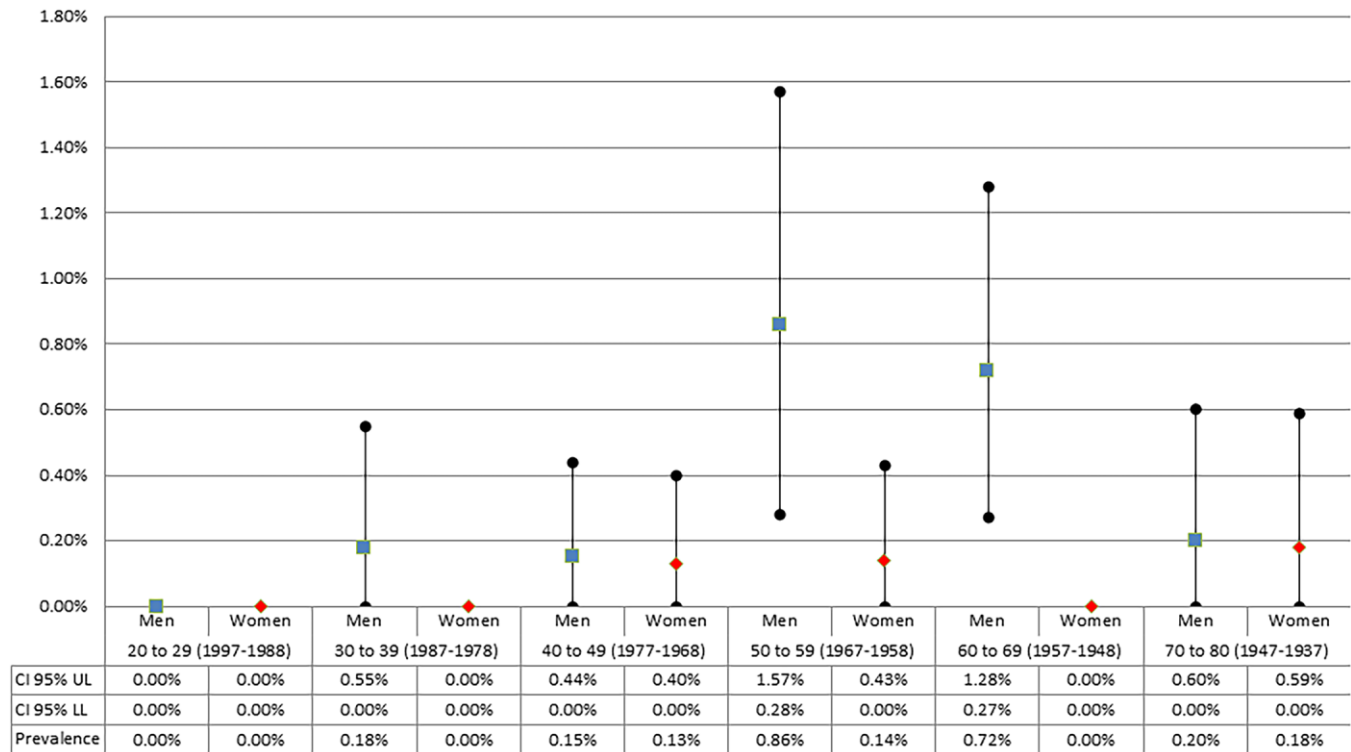


Figure 2 Active HCV infection prevalence by age group (20–80 years) and sex. Second study of Seroprevalence in Spain: Hepatitis C 2017–2018

Table 2 Prevalence of HCV antibodies and active HCV infection according to risk factor for HCV transmission

	N	Antibodies				Active infection			
		n	%	95% CI LL	95% CI UL	n	%	95% CI LL	95% CI UL
Any parenteral transmission risk factor									
Yes	4804	51	1.08	0.82	1.36	14	0.29	0.15	0.43
No	2754	15	0.48	0.32	0.67	3	0.09	0.01	0.17
Acupuncture, tattoos and infiltrations									
Yes	2416	20	0.88	0.56	1.22	7	0.31	0.11	0.52
No	5142	46	0.85	0.65	1.06	10	0.17	0.08	0.28
Blood transfusion									
Yes	639	21	3.42	2.20	4.73	7	1.09	0.35	1.85
No	6919	45	0.63	0.48	0.80	10	0.14	0.07	0.22
Invasive procedure									
Yes	3413	39	1.16	0.85	1.47	8	0.22	0.08	0.38
No	4145	27	0.62	0.43	0.81	9	0.21	0.12	0.33
Dialysis									
Yes	60	1	1.96	0.40	4.94	0	0.0	0.00	0.00
No	7498	65	0.85	0.67	1.03	17	0.22	0.00	0.31
Haemophilia									
Yes	29	0	0.00	0.00	0.00	0	0.0	0.00	0.00
No	7529	66	0.86	0.69	1.06	17	0.22	0.15	0.30
Lived with someone with HCV infection									
Yes	210	8	4.12	1.85	6.78	3	1.59	0.00	3.36
No	7348	58	0.16	0.00	0.33	14	0.18	0.10	0.27
Total	7675	66	0.85	0.64	1.08	17	0.22	0.13	0.31

Population aged between 20 and 80 years.

Discussion

The prevalence of HCV antibodies and active HCV infection in the general population aged 20–80 years attending primary health care centres in Spain in 2017–2018 was 0.85% (95% CI: 0.64–1.08%) and 0.22% (95% CI: 0.12–0.32%), respectively. A clear sex and birth cohort pattern can be identified, with a higher prevalence of HCV antibodies in men over 50 years of age and women over 70. The prevalence of active HCV infection was highest in men aged 50–59

and 60–69 years: 0.86% (95% CI: 0.28–1.57%) and 0.72% (95% CI: 0.27–1.28%), respectively. Prevalence was below 0.20% in the remaining age groups. The undiagnosed fraction for active HCV infection was 29.4%.

The prevalence of HCV antibody found in this study is lower than that reported in the EU/EEA: 1.1% (95% CI: 0.9–1.4%) in the general population, blood donors and pregnant women between 2005 and 2015.¹³ It is also lower than the estimates reported by Gower et al.³ and data reported from previous studies conducted in Spain

before 2017.^{14–25} As expected, prevalence was lower than in the first seroprevalence study in Spain performed in 1996 (1.4%).²² By contrast, our estimates were closer to those of population-based studies from more recent periods.^{26,27} A population-based study within three Spanish regions in 2015–2017 identified a prevalence of HCV antibodies and active infection of 1.2% and 0.31%, respectively.²⁷

By the time the field work of this study had been completed (May 2018), close to 120 000 persons with active HCV infection had been treated with DAA in Spain²; this figure has since increased to close to 135 000 in 2020.² Therefore, the estimates for HCV active infection in 2017–2018 shown in this study reflect our on-going national strategy against hepatitis C initiated in 2015. Whereas the population effectiveness of DAAs is the most likely explanation for the striking differences with previous studies regarding the prevalence of active HCV infection, additional aspects should be taken into account. Sampling strategies, whether population-based or hospital-based, and the national or regional scope of these studies may also account for some variations. The handling of undetermined HCV results, which in this study were classified as negative cases, may explain some of the differences in antibody prevalence, as they may be related to residual antibodies in respondents with past infection.¹² It should be noted that the prevalence of active HCV infection may have been slightly underestimated in our study owing to the sensitivity of molecular-based laboratory techniques. However, it is well established that active HCV infections in the absence of antiviral treatment exhibit HCV RNA viral loads above 1000 IU/ml.^{28–30} Therefore, the misclassification of a small proportion of patients (estimated to be 3–5% of all HCV antibody positive patients in the absence of treatment) has no real public health implications and does not affect the main conclusions or their public health implications.

The most prevalent genotypes in this study, as previously reported in Spain, were 1b and 1a.^{12,27,31,32} The sex and birth cohort patterns of the current HCV epidemic are consistent with those of previous publications.^{19–27} The highest HCV antibody prevalence in the oldest age groups has been linked with the use of unsterile procedures (largely injections with unsterile syringes) before 1975, as well as with blood and blood product transfusions before 1990.^{14,15,18,20,22,23,26,27,31} The peak HCV prevalence in men born in the 1960s is closely associated with the injected heroin epidemic that affected Spain from the 1980s till the mid-1990s and led to extremely high HIV/HCV coinfection rates.^{6,7,33}

Consistent with the literature, an inverse socioeconomic gradient was associated with HCV infection,^{14,15,18,23} the prevalence of which was higher in foreign-born persons than in Spanish-born persons, as previously reported.^{8,27,34} However, the difference was not statistically significant. The present study did not find differences according to the size of the municipality of residence. Some studies have found higher rates in urban settings,^{14,19} whereas others have not.¹⁸ HCV was moderately more frequent among persons reporting at least one risk factor for parenteral transmission, as widely published elsewhere.^{13–15,18,20,23,26,27,31} As many as 63.5% of the study participants reported at least one of the risk factors for HCV infection collected in the study; however, unfortunately, the questionnaire was not designed to identify, beyond blood transfusions prior to 1992, the present-day risk for HCV transmission in Spain. As the main objective of this study was not to identify well-established risk factors for HCV infection in Spain, we consider this limitation has a restricted scope.

The undiagnosed fraction of positive antibodies to HCV was 14.3% and that of active HCV infection was 29.4%. Since previous HCV tests performed in private practice or in sexually transmitted infection (STI) clinics may have gone unrecorded, we anticipate that these undiagnosed fractions may be overestimated. The undiagnosed fraction for HCV infection in the few studies which have measured it in Spain in recent years ranges from 3% in a hospital-based study that linked a higher number of health information sources²⁵ to 40%

in a population-based study.²⁷ These differences could also be explained by differences in HCV testing policies implemented at regional level in recent years.

In absolute terms, of the population of 34 753 283 individuals aged 20–80 years at the end of 2017 in Spain,³⁵ 337 107 were estimated to have HCV antibodies and 76 839 active HCV infection; of the latter, 22 478 remained undiagnosed. These inferences are associated with the population attending primary health care centres and largely exclude PID, people living with HIV, and persons in prison. Therefore, initiatives targeting these populations need to be delivered at drug rehabilitation centres, STI clinics, HIV hospital units and prison hospitals.

The methodology used in this study made it possible to obtain estimates based on the general population attending primary health care centres. However, potential selection and information biases warrant discussion. One limitation of this study is that of the setting interviews were conducted in, which hampered questions regarding drug and sexual behaviour. At the time of the field work for this study, undocumented migrants (except pregnant women and minors under 18 years) were not entitled to universal health care, thus potentially leading to underrepresentation of the foreign-born population and an underestimation of the prevalence of HCV.

In conclusion, our study provides the most accurate description to date of the current epidemiology of HCV infection in the adult general population in Spain, indicating that prevalence is low. It also provides key information for public health policy regarding HCV screening that will enable us to fulfil our commitment to eliminating HCV in Spain by 2030.

Supplementary data

Supplementary data are available at *EURPUB* online.

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Conflicts of interest: None declared.

Key points

- This study provides the most accurate description to date of the current epidemiology of hepatitis C virus (HCV) infection in the general population in Spain, where the prevalence of HCV infection can now be considered low.
- A clear sex and birth cohort pattern can be identified, with a higher prevalence of HCV antibodies in men over 50 years of age and women over 70. The undiagnosed fraction for active HCV infection was 29.4%.
- These findings will inform public health policy and HCV screening guidelines in order to achieve the Sustained Development Goals for the elimination of HCV infection by 2030.

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