

Research article

## Prevalence of hepatitis B and C markers in high-risk hospitalised patients in Crete: a five-year observational study

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### Abstract

**Background:** So far the prevalence of viral hepatitis infection in hospitalized patients has not been extensively studied. Therefore we conducted the present five-year observational study to evaluate the prevalence of HBV and HCV infection in high-risk hospitalized patients of Crete, the largest Greek island, Due to the homogeneous population, epidemiological studies can be accurately done.

**Methods:** The study was carried out in two out of four District General Hospitals, and in the University Hospital of the island. Markers for HBV and HCV were studied and statistically evaluated according to age, sex and geographical area, in a well-defined hospitalized population.

**Results:** The total prevalence of HBsAg and anti-HCV in the three prefectures during the five-year study is 2.66% and 4.75% respectively. Overall the relative risks were higher in males than females for each hepatitis marker ( $p < 0.001$ ). Higher prevalence of HBcAb was found in the 41–60 years age group for both sexes (males 36.17%, females 27.38%). Peak HBsAg prevalence was found in the age group of 21–40 and 41–60 years for males (5.4%) and females (3.09%) respectively. Anti-HCV prevalence increases with age reaching the highest prevalence in the age group of 41–60 years for males (7.19%) and in the 61–90 years age group for females (7.16%). For both sexes significant differences between the three locations were identified. For HBsAg a higher prevalence in Heraklion (3.96%) compared to Chania (2.30%, males:  $p < 0.0001$ , females:  $p < 0.05$ ) and Rethymnon (1.45%, males:  $p < 0.01$ , females:  $p < 0.0001$ ) was detected. For HCV a significantly higher prevalence in Heraklion (6.54%) compared to Chania (2.39%, males:  $p < 0.001$ , females:  $p < 0.001$ ) but not in Rethymnon (5.15%, NS). A lower prevalence rate of HBcAb in Heraklion compared to Chania (20.07% versus 23.05%, males:  $p < 0.001$ , females:  $p < 0.001$ ) was found.

**Conclusions:** These results were possibly overestimated, but nevertheless reflect the situation of the general population within the island as shown by our previous publications in other study groups. Moreover they contribute to the mapping of viral hepatitis prevalence in a geographical area of Southern Europe and may be helpful in planning public health interventional strategies.

## Background

The problem of viral hepatitis in hospital populations around the world has not been adequately studied, although hospitalized patients overall and especially certain high risk groups among them, represent a possible source for viral hepatitis infection of medical, nursing and auxiliary personnel caring for them as well as for their relatives at home. Epidemiological studies concerning the prevalence of HBV and HCV markers in hospitalized patients have been published, in isolated groups of high-risk patients [1–4] or hospital workers [5] worldwide.

Crete, the third largest island of the Mediterranean Sea, has a very homogeneous population of 540,054 inhabitants (1991 census). This allows for epidemiological studies to be conducted with accuracy. Clinical studies have emphasized many differences between the island and mainland Greece, in both liver cell carcinoma characteristics and prevalence of viral markers [6]. A recent study in blood donors in northwest Greece reported an HBsAg prevalence of 0.85% [7] while a study of blood donors in Crete has shown a significantly lower prevalence of 0.40% for the same viral marker [8]. A survey of blood donors in mainland Greece reported a 0.4% prevalence of anti-HCV using a second generation enzyme linked immuno-assay (ELISA 2) [9] not different from the overall prevalence found with the same screening test in Crete (0.38%), but with marked differences among the prefectures of the island (Heraklion 0.52%, Rethymnon 0.52%, Chania 0.23%) [8].

Accepting that, high risk hospitalized patients are not the ideal population for epidemiological studies, overestimating the problem, nonetheless they contribute in the epidemiological mapping of a serious public health problem like viral hepatitis, in a certain geographical area. The aim of the present study was to investigate the prevalence of hepatitis B and C markers in high-risk patients admitted in two out of four District General Hospitals and in the University Hospital of the island, during a five-year period, in an attempt to assess the situation in the hospitals of the island.

## Methods

We retrospectively analyzed the results of virological examinations for HBV and HCV, done on patients admitted in the District General Hospitals of Chania and Rethymnon and in the University Hospital of Heraklion during a five-year period (1992–1996). All criteria for inclusion and exclusion of a patient in the study had been agreed upon, before starting the study in all three hospitals.

Chania and Rethymnon District General Hospitals serve the total population of the corresponding two western prefectures, while the University Hospital is the main hos-

pital, serving the two east prefectures of the island and it is also the referral center of Crete for liver diseases.

Virological tests were done in the Department of Virology, University Hospital and the Blood Banks of the other two Hospitals. HBsAg and anti-HCV were studied in all three hospitals while IgG-HBcAb was available only in Heraklion and Chania. Serum samples were tested by the micro-particle capture enzyme immunoassay according to the manufacturer's instructions, using kits from Abbott Laboratories (North Chicago, IL); IMx HBsAg (hepatitis B surface antigen), IMx CORE for IgG HBcAb and second and third generation enzymed linked immunosorbent assays (ELISA 2 and ELISA 3) for the detection of anti-HCV were used.

281 184 admissions (138 850 males) were recorded in the three hospitals during the study period of five years. Patients from day care hospital admissions were also included. In all three hospitals patients were considered as high-risk and included in the study if certain criteria applied upon admission were met. The criteria for screening those patients for hepatitis B and C were: Greek nationality, alcoholism, altered liver function tests or exposure of the patient to any risk factor;

Risk factors for HBV infection were: multiple sexual contacts, family history, professional risk, major or minor surgical or dental operations, iv drug abuse, tattooing or piercing, previous transfusion, chronic renal failure under dialysis and previous hospitalization over 5 days.

Risk factors for HCV infection were: homosexual contacts, family history, professional risk, major or minor surgical or dental operations, iv drug abuse, tattooing or piercing, previous transfusion, previous hospitalization over 5 days and chronic renal failure under dialysis.

Exclusion criteria for HBV testing was previous vaccination for hepatitis B with a recent proof of immunization.

A total of 46 901 patients (22 779 males) fulfilled the above criteria and were tested for HBsAg. In 21 981 of them (10 291 males), IgG-HBcAb was also studied. Anti-HCV was tested in 34 155 patients (16 919 males). Double tests were eliminated.

## Statistical analysis

For the statistical analysis the relative risks (RR) were calculated from the corresponding proportions. Simple binomial-based tests were used to test for differences in proportions between the sexes at different time periods and locations. Direct standardization was used in the comparison of positivity rates at the three locations for each of the sexes separately. Weighting was by the num-

bers investigated in each year under the assumption that different subjects were tested each year. The standard population used, was the population calculated so that the proportionate distribution was one third of the way between the three populations under study (Heraklion, Rethymnon and Chania). The Rethymnon and Chania populations were contrasted with the Heraklion population using a version of Cochran's test [10]. The rates calculated in Cochran's test were drawn only from the two years in which data were available for all three hospitals.

## Results

The crude prevalence rates of the markers during the time period considered are presented in Table 1.

Because of missing information in prevalence rates near the start of the study, information has been lost for statistical analysis. Data were not available yearly for Heraklion early in the study-period; therefore the rates calculated in Cochran's test, were drawn only from the two last years. On the other hand, because of these drawbacks in analysis, the extremely high and unexplained Rethymnon rates for anti-HCV, which were registered in 1992, were not included in the comparison between the three locations. However, certain conclusions can be drawn.

### Comparison between sexes and age groups

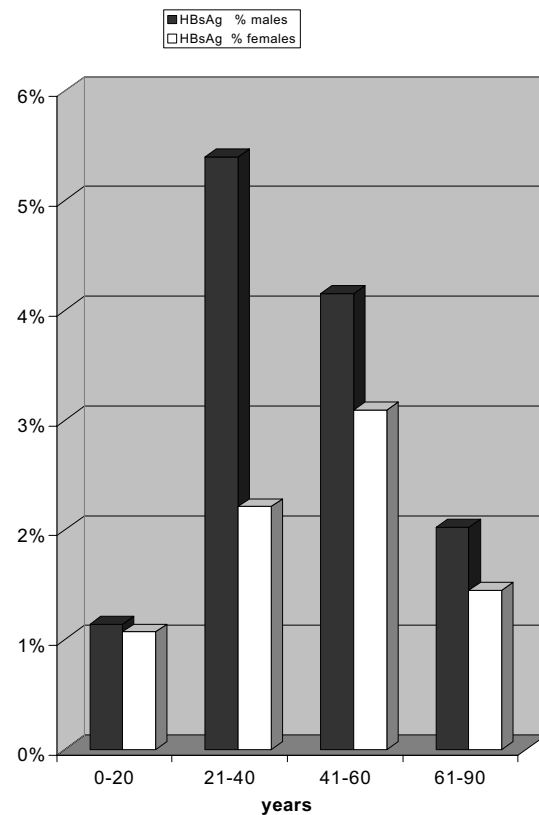
#### HBsAg

The proportion of males positive was overall significantly higher, than that of females in all three hospitals. Relative risks were 88%, >100% and 62% higher for males versus females in Heraklion, Rethymnon and Chania respectively, ( $p < 0.001$  for the test of differences in prevalence rates between males and females at each location). Considering each time period separately, there was no year in which the relative risk was significantly lower for males.

The prevalence of HBsAg in high-risk hospitalized patients of Crete, according to gender and age is shown in figure 1. The higher prevalence for males 5.4%, was detected in the 21–40 years age group, whether for females the peak HBsAg carrier rate (3.09%) was detected in the 41–60 years age group. The lower prevalence rate of HBsAg infection (1.1%) was found at the age group of 0–20 years for both sexes. This might be due to the fact that in Greece under the Guidelines of the Hellenic Society of Pediatricians, the HBV vaccination program of neonates has been going on since 1992, although it is only one year that this program became obligatory. It is therefore expected that the HBV infection rate in young people will further decline in the future.

#### HBcAb

the overall relative risks were 73% and 31% higher for males than females in Heraklion and Chania respectively



**Figure 1**  
Prevalence (%) of HBsAg in male and female high-risk hospitalized patients of Crete according to age.

(again  $p < 0.001$  in both Heraklion and Chania). The prevalence of HBcAb in high-risk hospitalized patients of Heraklion and Chania, according to gender and age is shown in figure 2. The peak exposure rates for both males (36.17%) and females (27.38%) detected in the 41–60 years age groups are much higher than the ones reported for blood donors (between 8% and 9.5% in different prefectures) and probably are due to the fact that in general, blood donors are younger than hospitalized patients. When blood donors of over 40 years of age are considered, the exposure rates are similar (23.32%) [8].

#### anti-HCV

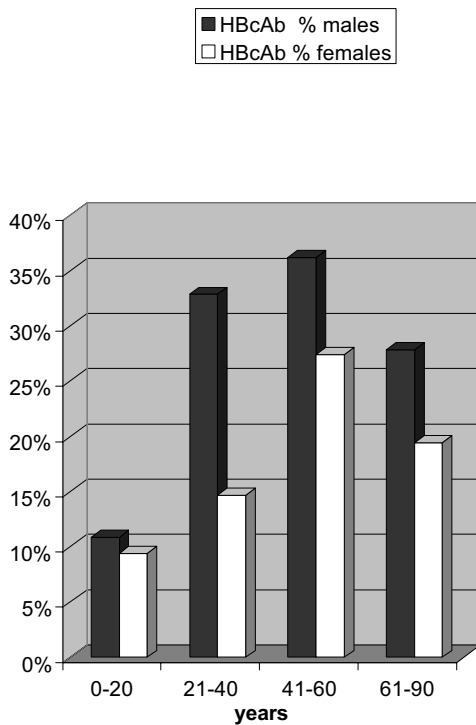
there were no overall differences between sexes in Rethymnon, but in Heraklion and Chania the relative risks were 23% and 39% higher for males as compared to females ( $p < 0.001$  and  $p < 0.01$  respectively).

The prevalence of anti-HCV in high-risk hospitalized patients of Crete, according to gender and age is shown in

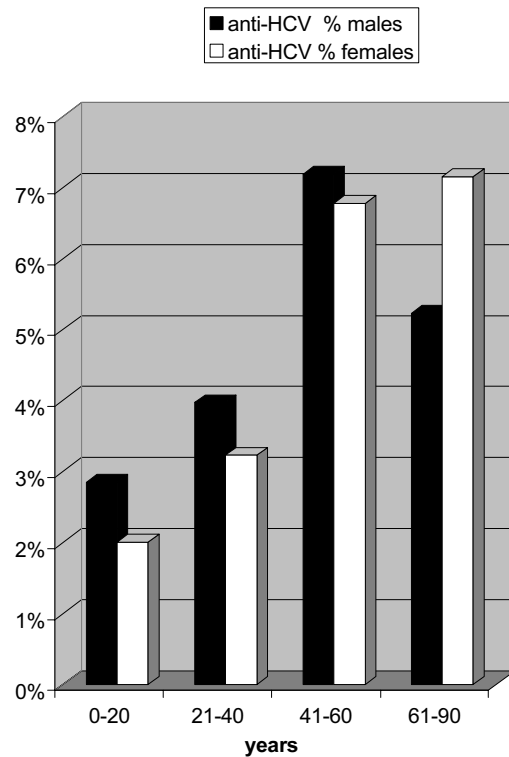
**Table 1: Prevalence rates (%) and relative risks (RR) of HBsAg, HBcAb and HCV in hospitalized patients over the 1992–1996 time period by sex.**

Marker	Location	Year	Males (m) tested	%	Females (f) tested	%	% (m+f)	RR (m vs f)		
HBsAg	Heraklion	1992–4	2979	6,11	3553	2,81	4,32	2,17	**	
		1995	1874	4,59	2534	2,57	3,43	1,79	**	
		1996	1741	5,11	2710	3,25	3,98	1,57	*	
		Overall		5,41		2,88	3,96	1,88	**	
	Hania	1992	1502	3,13	1381	1,38	2,29	2,27	*	
		1993	3016	2,39	2634	1,29	1,88	1,85	*	
		1994	2782	3,16	2497	1,88	2,56	1,68	*	
		1995	2156	2,41	1710	2,11	2,28	1,15		
		1996	1847	3,14	1760	2,10	2,63	1,49		
		Overall		2,80		1,73	2,30	1,62	**	
	Rethymnon	1992	697	3,01	915	0,77	1,74	3,94	*	
		1993	1369	1,39	912	0,66	1,10	2,11		
		1994	871	2,41	1154	1,21	1,73	1,99		
		1995	970	1,75	1115	0,81	1,25	2,17		
		1996	975	2,15	1247	1,12	1,58	1,92		
		Overall		2,03		0,94	1,45	2,17	**	
	HBcAb <sup>b</sup>	Heraklion	1992–4	2979	25,26	3553	17,69	21,14		
			1995	1874	24,76	2534	14,56	18,90	1,70	**
1996			1741	26,77	2710	15,09	19,66	1,77	**	
Overall				25,51		15,99	20,07	1,73	**	
Hania		1992	843	23,61	587	22,66	23,22	1,04		
		1993	919	22,63	712	24,16	23,30	0,94		
		1994	590	23,39	710	11,41	16,85	2,05	**	
		1995	816	34,80	424	28,30	32,58	1,23		
		1996	529	23,06	460	13,48	18,60	1,71	**	
		Overall		25,72		19,63	23,05	1,31	**	
HCV		Heraklion	1992–4	3319	8,44	3959	7,35	7,85	1,15	
			1995	1817	6,27	2361	5,12	5,62	1,22	
	1996		1713	6,25	2656	4,63	5,26	1,35		
	Overall			7,31		5,96	6,54	6,55	**	
	Hania	1992	739	1,49	903	0,78	1,10	1,92		
		1993	1323	2,34	901	2,11	2,25	1,11		
		1994	1928	4,15	1540	3,05	3,66	1,36		
		1995	1542	1,82	1075	2,23	1,99	0,81		
		1996	1794	2,79	1215	1,15	2,13	2,42	**	
		Overall		2,73		1,97	2,39	1,39	*	
	Rethymnon	1992	237	16,03	250	10,00	12,94	1,60		
		1993	763	3,93	452	7,52	5,27	0,52		
		1994	576	4,34	499	6,21	5,21	0,70		
		1995	573	2,27	618	3,72	3,02	0,61		
		1996	595	3,87	807	4,34	4,14	0,89		
		Overall		4,70		5,64	5,15	0,83		

\*Difference between sexes in the prevalence of the marker is significant at the 1% level, \*\* Difference between sexes in the prevalence of the marker is significant at the 0.1% level, <sup>b</sup>Not measured in Rethymnon



**Figure 2**  
Prevalence (%) of HBcAb in male and female high-risk hospitalized patients of Heraklion and Chania according to age.



**Figure 3**  
Prevalence (%) of anti-HCV in male and female high-risk hospitalized patients of Crete according to age.

figure 3. In accordance with our previous report on the general population [11] anti-HCV prevalence increases with age reaching the higher prevalence for males (7.19%) in the age group of 41–60 years and for females (7.16%) in the 61–90 years age group.

**Comparison between the locations**

For both sexes there was evidence of significant differences between the three locations, this evidence being more apparent in males than females (Table 1). More specifically, for both sexes, evidence was provided by Cochran s test, of significant differences in the three viral markers.

**HBsAg**

Higher prevalence in Heraklion (3.96%) than Chania (2.30%) (males:  $p < 0.0001$ , females:  $p < 0.05$ ), and Rethymnon (1.45%) (males:  $p < 0.01$ , females:  $p < 0.0001$ ).

**anti-HCV**

Higher prevalence in Heraklion (6.54%) than Chania (2.39%) (males:  $p < 0.001$ , females:  $p < 0.001$ ), but no significant difference between Heraklion and Rethymnon (5.15%) in males or females. It is interesting to note that, the Rethymnon prefecture with the lowest percentage of HBsAg, has a high prevalence of anti-HCV. A similar situation has been reported in volunteer blood donors on the island, where in the same prefecture with the lowest rate of HBsAg (0.27%) the highest rate of anti-HCV (0.52%) was found [8]. Moreover pockets of very high prevalence of anti-HCV have been discovered in the Rethymnon area [11]. These results are also in accordance with the higher prevalence of hepatocellular carcinoma due to HCV in the Rethymnon area [6].

**HBcAb**

Lower prevalence in Heraklion (20.07%) than Chania (23.05%) (males:  $p < 0.001$ , females:  $p < 0.001$ ). For similar exposure rates to HBV, there was a significant decrease

**Table 2: A comparison of crude prevalence rates (%) for the markers HBsAg and anti-HCV in Rethymnon and Hania over the 1992–6 period.**

	Rethymnon %		Hania %	Difference in prevalence	95%CI
Males	HBsAg	2.03	2.80	-0.008	(-0.013, -0.003)*
	anti-HCV	4.70	2.73	0.020	(0.011, 0.028)**
Females	HBsAg	0.94	1.73	-0.008	(-0.012, 0.004)**
	Anti-HCV	5.64	1.97	0.037	(0.027, 0.046)**

\*p < 0.001, \*\*p < 0.0001, CI : Confidence Interval

in carrier rate in Chania. This was true for practically every year and for both sexes. It was very clear in the year of 1995, when although the exposure rates were 32.58% in Chania versus 18.90% in Heraklion, carrier rates were 2.28% versus 3.43% respectively. Even on similar exposure rates, as during 1996, (Chania: 18.6% versus Heraklion: 19.66%) fewer people became carriers in Chania than in Heraklion (2.63% versus 3.96%). Since the population of these two prefectures is genetically homogeneous and the age groups of hospitalized patients were similar we suspect that the lower carrier rate in Chania might be related to an, as yet unidentified environmental factor.

In general the RR were higher in males for each hepatitis marker. This observation agrees with the earlier report in blood donors [8]. When results are analyzed according to sex and location, the male predominance is universal with one notable exception for anti-HCV in Rethymnon, which we call the Rethymnon female paradox. Females in Rethymnon have a higher HCV infection rate than males, a feature unique in the island, which we already reported in a study of general population in a rural area of Rethymnon (males: 2.4%, females: 3.7%) [11], and in the study of the volunteer blood donors (males: 0.37%, females: 0.49%) [8]. The reason for this discrepancy is not clear. Intravenous drugs cannot be the explanation since the same phenomenon appeared in an isolated community where no drugs exist [11]. Moreover, almost 90% of our HCV cases are of the sporadic type with no obvious source of infection. Medical and particularly midwifery malpractice of the recent past in the Rethymnon area, appears to be a rational explanation.

The University hospital of Heraklion is a referral center, with a much larger catchment area than the regional hospitals of Rethymnon and Chania that could be directly compared. Therefore the last two were compared in crude prevalence rates of the markers over the five-year period for males and females separately, using the binomial test for proportions. As can be seen in Table 2, for both the

male and female populations, evidence was provided of a significantly:

- Lower prevalence in Rethymnon than Chania for HBsAg (p < 0.001 and p < 0.0001 for males and females respectively).
- Higher prevalence of anti-HCV in Rethymnon than Chania (p < 0.0001 for both males and females).

The prevalence of HBV and HCV markers of patients, in the English publications during the past 10 years refers to isolated high-risk groups. Thus, a published survey of HBV and HCV infection markers from a referral center of Northern Greece among alcoholics with chronic liver disease, alcoholics without chronic liver disease, hospitalized non-alcoholic patients and healthy controls, reported an HBsAg prevalence rate of 10.8%, 7.4%, 1.4% and 2.1%, an HBcAb prevalence rate of 39.2%, 36.4%, 14.3% and 19.5% and an anti-HCV prevalence rate of 1.2%, 1.4% 0% and 0.6% respectively [12]. The prevalence rates of HBV viral markers in the non-alcoholic hospitalized patients are lower than ours while our figures come closer to the ones reported in their healthy control group. Furthermore our anti-HCV prevalence rates exceed theirs. The small number of patients included in the hospitalized non-alcoholic patients (70 patients) may be a problem for a direct comparison of the two studies but still we believe that these differences do reflect the different situation between Crete and mainland Greece. In another Greek study, the prevalence of anti-HCV of patients in haemodialysis was found to be 17.6% [13] while Romanian patients on dialysis since 1996 have an anti-HCV prevalence of 28.6% and an HBsAg prevalence of 21.6% [2]. High prevalence rates for HBsAg (15.3%) and anti-HCV (9.7%) were reported among non-intravenous-drug-using patients [1] attending clinics for sexually transmitted diseases that probably underline the importance of the sexual transmission of the viruses [14]. A recent report of Greek HIV-positive patients, reported prevalence rates of HBV extremely elevated at 67.4% rising to 90.9% in the blood

transfusion recipients, while anti-HCV were 13.8% rising to 45.5% in blood transfusion recipients [15]. Similarly in Italy HIV-positive patients have HBV infection markers prevalence rate of 82% and anti-HCV prevalence rate of 72% if they are drug addicts while the prevalence rate is 77% for HBV markers and 7% for anti-HCV if HIV-positive patients are homosexuals [4]. These extremely elevated figures apply to an even more selected high risk-group of patients, compared to our study. In a survey from mainland Greece HCV infection was responsible for 25% of chronic liver disease patients [16]. Higher figures than ours (18% anti-HCV, and 5% HBsAg) have been published concerning patients in an inner-city emergency department in a study that lasted for only six weeks [3].

It is obvious that due to the lack of homogeneity of the study groups mentioned before, direct comparisons of the present study with reports either from Greece or from other parts of the world may be illusive.

### Conclusions

In the present study we investigated the prevalence rates of HBV and HCV markers in high-risk hospitalized patients of Crete in a study period of five years. We consider important that similar studies are extended over a period of many years, since infection rates are not similar each year and a limited study period will not yield representative results. HBsAg had an overall prevalence rate of 2.66% with a significant difference between sexes (3.39% males, 1.97% females). A lower carrier rate was detected under the age of 20 years and peak carrier rates in middle age groups. HBcAb results showed an overall exposure rate to HBV virus of 20.96%, with the higher exposure rate for both sexes detected in the 41–60 years age group. anti-HCV had an overall prevalence rate of 4.75% with no significant differences between sexes (males: 4.90%, females: 4.60%), increasing with age and peaking in the 41–60 years age group for males and in the 61–90 years age group for females. This finding confirms our previous field studies reporting high anti-HCV prevalence (4.8%) in outpatients of primary health care centers in Crete [17].

In conclusion, we believe that, viral hepatitis markers prevalence rates of the high-risk hospitalized patients in Crete, overestimate but reflect the situation in the general population of the island. Our results also underline the differences between the island and mainland Greece, which is a country of intermediate prevalence of HBV and HCV infection. Additionally these data contribute to the mapping of viral hepatitis prevalence in this geographical area of Southern Europe and therefore may be helpful in planning public health interventional strategies.

### Abbreviations

HBV: Hepatitis B virus

HCV: Hepatitis C virus

HBsAg: Hepatitis B surface antigen

HBcAg: Hepatitis B core antigen

HBcAb: Hepatitis B core antibody

anti-HCV: antibody to hepatitis C virus

### Competing interests

None declared.

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