Epidemiology of viral hepatitis in the Mediterranean Basin

Tahan V, Ozdogan O, Tozun N

Marmara University, School of Medicine, Department of Gastroenterology, Istanbul, Turkey

Abstract

The prevalence of viral hepatitis is high and remains a serious public health challenge throughout the world. New molecular biology techniques provided a better understanding of the viruses over the last decades. Novel therapeutic options seem to be promising but preventing measures including donor screening, immunization against hepatitis A virus (HAV) and hepatitis B virus (HBV), universal use of disposable syringes and implementation of better hygienic conditions play a major role in the control of viral hepatitis. The Mediterranean basin has special demographic and socioeconomic features. We reviewed in this article the seroepidemiological features of viral hepatitis in this particular region.

Improving general conditions led to a tendency to be infected in older ages with HAV. Hepatitis B and C virus still remain to be the major causes of chronic hepatitis. The seroprevalence of hepatitis D virus, which was once endemic in the Mediterranean region seem to decrease nowadays whereas hepatitis E virus is still prevalent in some areas. Other viruses such as hepatitis G virus (HGV), TT virus (TTV) and SEN virus do not seem to be a major problem and their clinical importance remains to be determined in further studies.

Key words: epidemiology, hepatitis virus, Mediterranean.

ADDRESS FOR CORRESPONDENCE:
Nurdan Tözün MD, Professor of Gastroenterology
Marmara University, School of Medicine
Department of Gastroenterology,
Tophanelioglu Cad. No: 13-15,
Altunizade/Istanbul, Turkey
tel.: +90 216 3267073, fax: +90 216 3267073
e-mail: nurdantozun@marmara.edu.tr

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Introduction

Hippocrates was the first to use the term "epidemic jaundice" to describe a disease resembling outbreaks of viral hepatitis in the fifth century B.C. in Greece [1]. Despite considerable advances in medical technology and attempts to find "the magic bullet" to cure the disease, viral hepatitis still remains a major public health problem with its worldwide high morbidity and mortality. With new technologies over the last decade, there have been enormous advances in the understanding of viruses; their antigenic and constitutional features with particular focus on gene analyses and nucleotide sequences of the viral DNA/RNA.

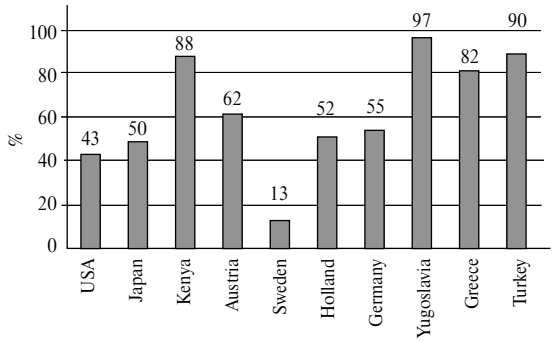
Development of sensitive assays, identification of new viral agents, safe and effective vaccines for hepatitis A virus (HAV) and hepatitis B virus (HBV) have been achieved. New nucleoside analogs have been found as effective alone or in combination with interferon in the therapy of viral hepatitis. Determination of viral genotypes and subtypes facilitated not only to track the epidemiological origin of these important pathogens but also to predict their future behavior and probability of response to antiviral treatment. Implementation of donor screening, effective inactivation of plasma derived products and widespread use of universal precautions vastly contributed to the prevention and control of viral hepatitis.

With its peculiar demographic and socioeconomic features, the Mediterranean basin has some specific significance in reference to seroepidemiology of viral hepatitis. In this article, we reviewed the present situation of the epidemiology of various forms of viral hepatitis in the Mediterranean basin.

Hepatitis A

HAV, an RNA virus classified in the Picorna virus family, is the cause of most common form of acute viral hepatitis in most parts of the world. The virus is strongly resistant to degradation by environmental conditions providing a very high rate of infectivity. Since the major mode of transmission is by person-to-

Figure 1. Seroprevalence of viral hepatitis A in various countries.



person contact via the fecal-oral route, the sanitation and the quality of water supply are highly related with the prevalence of infection. Nearly a third of patients acquire the infection from household or sexual contact with an infected person. Large families, poor education, inappropriate human-waste disposal system, crowded day-care centers and international travel have been linked to outbreaks and endemicity of HAV infection. Approximately, 50% of patients with hepatitis A do not have a recognized source of infection [2,3].

High-risk groups are cleaning personnel in hospitals, staff in day-care centers, pediatric nurses, IV drug users, homosexuals, patients with chronic liver disease, international travelers and consumers of high-risk foods (bivalve shellfish from stagnant water).

Epidemiology of HAV in the Mediterranean countries: The incidence of the virus varies with age, race, ethnicity and geographic region [4,5]. HAV is still endemic in the Mediterranean basin due to socio-economic, sanitary and hygienic conditions. *Fig. 1* shows seroprevalence of HAV in various countries including Mediterranean basin. Seroepidemiological studies of HAV were undertaken in various parts of Europe.

A multi center seroepidemiological study in 1977 showed, that anti-HAV seroprevalence rates were 95.3% in Israel and 96.9% in Yugoslavia [6]. Frösner et al. reported the rates of anti-HAV seropositivity as 75% in France and 82% in Greece in 1979 [7]. Other studies showed the rates as 95.9% (people >40 years old) in Crete [8], 59.1% in Spain [9], almost 10% in Northern and 40% in Southern regions of Italy [3,10]. In Egypt, anti-HAV seroprevalence was found to be higher than 95%, even in the youngest age group (in children <5 year old) [11]. Ungan et al. [12] notified the seropositivity as 68% in Western and 80% in Eastern regions of Turkey in 1998. Hepatitis A is mostly an asymptomatic infection of childhood. However, improving social conditions made a trend of getting infected in older ages resulting in an increase in morbidity and mortality of the disease in this specific age group. Anti-HAV positivity was 54.5% between the ages 3 to 10 and 100% over the age of 40 in Turkey [13]. By the age of 18, 30 to 40% of the Jewish population had anti-HAV antibodies in a study from Green et al. [14].

Prevention and vaccination strategies: HAV is vaccine preventable and the protective effect of the vaccine is 95% to 100% in healthy subjects [15]. A single dose of HAV vaccine was shown to provide 100 % of seroprotection within 2 weeks.

Table 1. Indications for HAV vaccine.

Travelers to endemic areas for more than 3 months
Military, diplomatic personnel
Patients with CLD (chronic liver disease)
Hemophiliacs receiving Factor Concentrates
IVDU (intravenous drug users)
Laboratory staff working with the virus
Homosexuals
Nursery home staff
Food handlers with poor hygiene

Active immunization can be done with inactivated (formaline), live attenuated or combined vaccines. There is no known contraindication and very few side effects related to HAV vaccine have been described. Combined HBV and HAV vaccine was found superior to monovalent vaccines regarding the tolerability, early antibody response, safety and cost [16]. Indications for active vaccination are summarized in *Tab. 1*.

Current recommendation is to give the vaccine at 12-24 months of age as two doses 6 months apart. In high endemicity area antibody test is recommended. Since universal vaccination for HBV is implemented in many countries both vaccines can be given in the same program. Cost-benefit analysis of outbreaks showed that HAV vaccination without screening anti-HAV antibodies is a cost-effective approach in the regions where anti-HAV rates are lower than 45% [17].

Hepatitis A vaccine may provide a protection of up to 30 years. Post-exposure administration of polyvalent immune globulin within 2 weeks of the exposure is recommended after suspicious contacts of household and sex partners. Passive immunization with Immune serum globulin should be applied at the doses of 0.02-0.06 ml/kg i.m., 2 weeks before and 2 weeks after exposure to virus and also to travelers to endemic areas, during epidemics of AVH, after a suspicious sexual intercourse and to consumers of high-risk foods for HAV. Current data support immediate immunization of young individuals against HAV in cases of dubious contacts with active HAV infection without screening for anti-HAV in the Mediterranean countries.

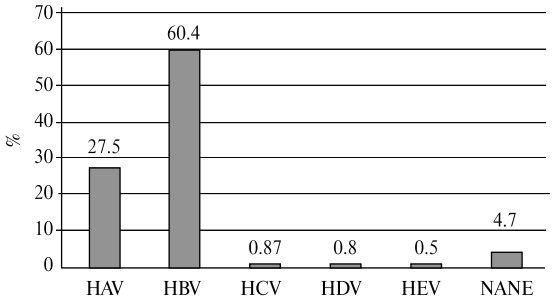
Hepatitis B

HBV, a DNA virus classified in the Hepadna virus family, is a devastating global healthcare issue. Around 1 million people die each year from HBV infection, making it the 9th leading cause of death worldwide [18].

Perinatal, vertical and horizontal transmissions occur during the birth or childhood in highly endemic populations such as Asians, whereas sexual, parenteral and horizontal transmissions are the major route of acquisition in low endemicity areas. In about 1/3 of cases the source of the infection is unknown. Seven genotypes of HBV were reported in the literature. Genotypes A and D are common in Western Europe whereas Genotype C is common in Asia [19]. Whether these genotypes have a role in the development and progression of chronic liver disease (CLD) or hepatocellular carcinoma (HCC) is still under investigation.

Epidemiology of HBV in the Mediterranean Countries: Hepatitis B infection has a wide range of seroprevalence in

Figure 2. Etiology of acute viral hepatitis in Turkey (pooled data of 4471 cases) [26].



HAV: Hepatitis A virus, HBV: Hepatitis B virus, HCV: Hepatitis C virus, HDV: Hepatitis D virus, HEV: Hepatitis E virus, NANE: Non-A-non-E virus.

Table 2. Preexposure application of HBV vaccines.

Health care personnel working with infected tissues or blood
Staff at institutions for disabled people
Hemophiliacs
Hemodialysis patients
Close family contacts of HBV infected individuals

Table 3. Postexposure application of HBV vaccines.

Infants born to HBsAg positive mothers or to mothers who had acute hepatitis B during pregnancy
Healthcare workers who had needle stick injury from a HBV positive patient
Sexual partners of individuals with HBV infection

the Mediterranean countries. In seroepidemiological studies, markers of hepatitis B infection (anti-HBs, anti-HBc or HBsAg) were observed in 11.7% (58/497) in healthy Spanish population [9]. HBsAg and anti-HBc prevalences were 3.7% and 34.2% in Italy respectively [20]. In Turkey, HBsAg prevalence was found as 1% in 1.377.688 blood donors while seroprevalence of HBV (HBsAg and/or anti-HBs) was between 25-60% [21]. Seroprevalence study of Greek warship personnel showed the rates of 1.1% in HBsAg and 17.7% in anti-HBs [22]. In another study from Greece, HBs Ag seroprevalence was found to be lower than 1% in the groups of military recruits, military personnel and family donors [23]. Roumeliotou et al. [24] found an increased prevalence of HBsAg carriers (6.9%) and HBV serologic markers (77.1%) among intravenous drug addicts. In a well-defined area in rural Crete, the levels of HBsAg and anti-HBs were reported as 1.2% and 24.57% respectively [8].

HBsAg positivity among Turkish children between the ages 2 to 12 was found to be 4.9% [25], while in adult age it was 7.1% together with 21.9% of anti-HBs seropositivity [21]. In other surveys from Turkey HBsAg seropositivity in various risk groups was found as 10% among healthcare staff, 40-60% among HCC patients, 40-80% in patients with chronic liver disease and 8.6% among pregnant woman [26]. *Fig. 2* shows etiology of acute viral hepatitis in Turkey [26].

HBe Ag negative mutants were reported most prevalent in Mediterranean countries as compared to Northern European countries and US. Funk et al. [27] reviewed that the median prevalence of HBe Ag negative chronic hepatitis was 33% in the Mediterranean basin and these patients had precore stop codon variants rate of 92%. The studies with the HBe Ag-negative phenotype in Turkish patients with chronic hepatitis B showed precore stop codon mutations (G to A change at nucleotide 1896) in 85% (29/34) but not core promoter mutation [28]. Actually, it is not clear if precore mutations directly cause detrimental effect on the course of chronic HBV infection. HBe Ag-negative patients who have 1896 stop codon mutation may subsequently develop precore translation initiation mutations, which seems to be related with enhanced HBV replication and severe liver disease [29].

Prevention and vaccination strategies: HBV infection can be prevented in non-infected individuals by vaccination with HBV vaccine. Series of 3 injections at 0, 1 and 6 months of vaccination is effective in over 90% of recipients [30]. The prevalence of HBsAg in general population has declined from 13.9 positive donations in 1986 per 10000 to 5.3 in 1991 in France [31] and 13.4% in 1978 to 3.7% in 1997 in Italy after the universal vaccination program [20]. European Consensus Group on Hepatitis B Immunity stated that booster vaccination after a successful primary vaccination series in healthy subjects is not required, because of the maintenance of HBsAg-specific memory expresses protection to clinically breakthrough infection even in the absence of detectable antibodies [32]. Only in the group of immune compromised individuals (hemodialysis, chronic renal failure, HIV positive patients, healthcare workers, travelers and others) booster doses are recommended Universal immunization can be the only strategy that will reduce the disease burden of HBV, as well as cirrhosis and hepatocellular carcinoma. The study of Chang et al. [33] has shown a significant decrease in the incidence of HCC among those who were vaccinated against HBV.

More than 116 countries included HBV vaccine into national immunization program since 1997. With regard to hepatitis vaccination in Spain and Italy, the coverage rate of immunization program increased to 90% and over [3]. Due to the successful vaccination programs most countries are in a transition from the high endemicity to the low endemicity status. *Tab. 2* and *3* show pre and post exposure prophylaxis in HBV infection.

Hepatitis B immune globulin is effective for passive immunization of the newborns to HBsAg-positive mothers, and in the individuals who had parenteral exposure and sexual contact with infected individuals.

Hepatitis C

Hepatitis C virus (HCV) is an RNA virus classified in the Flaviviridae virus family. Worldwide, one hundred and seventy millions of individuals worldwide are infected with HCV with an incidence rate of 3%.

Epidemiology of HCV in the Mediterranean countries: HCV has at least six genotypes from 1 to 6 and more than 80 subtypes. Genotypes 1a and 1b are the most common genotypes in Western Europe whilst genotype 4 is most prevalent in Egypt

(91.6%) [34]. In a study from Northern Spain, anti-HCV positivity was 1.6% and 80% of the patients had genotype 1b [35]. In Italy, 2 a/c genotype occurred in 60.9% of cases and HCV 1b genotype was found to be an independent risk factor for the development of cirrhosis [36]. HCV major genotypes in blood donors in France were 1b (34.3%), 3a (24%), 1a (19.5%), and 2 (11.4%) [37]. In the study of Diamantis et al. [38] genotype 3a was most prevalent in Greek patients (68% of all patients) and there was no significant difference regarding the genotypes among patients with different risk factors. Seroepidemiological studies from Turkey reported that the major genotype was 1b with a frequency of 70-98% [39].

World Health Organization estimated a prevalence rate for HCV infection of 4.6% in Eastern Mediterranean in 1999. Egypt had the largest scale of HCV infection prevalence ranging from 6% to 28% [30]. The prevalence rates reported from other Mediterranean countries were 2.9% (ages 20-61) [40], and 0.87% (ages 30-69) [41] in Italy; 0.6% (ages 6-75) in Spain [9], 1.8% (ages 12-55) in Turkey [42], 1.25% in Greek islands [43], 10.9% in Crete [8], 0.55-0.66 % in Israel [44] and 2.2% in the Gaza Strip of Israel [45].

In Egypt, history of antischistosomal injection therapy was found as a risk factor and was reported in 19% of anti-HCV positive individuals. Intravenous drug abuse is the most common risk factor identified with the rates of 71.1% in Spain [46], 67.5% in Italy [47] and 57% in Turkey [48]. The seropositivity rates among hemodialysis patients are 19.1% in Spain [49], 13.3% in Italy [50] and 14.4% in Turkey [49]. Transmission of HCV with blood or clotting factors diminished after implementation of routine donor screening and high seropositivity rates in hemophiliac patients were reported from various countries such as 63.9% in Spain [46], 100% in France [51] and 42% in Turkey [52].

Perinatal and intrafamilial transmission is uncommon in HCV as well as sexual transmission. In an epidemiological study from Turkey, Mert et al. [53] examined the spouses of the HCV carriers and the rate of seropositivity in this group was 0.64% (1/152). Nevertheless persons with multiple sexual partners were shown to be at greater risk for HCV transmission [54].

Prevention and vaccination strategies: There is no vaccine available for HCV and post exposure immune globulin prophylaxis is not effective to prevent it. In Mediterranean countries, screening for anti-HCV in blood / blood products has diminished the spread of HCV, but IV drug use, surgical interventions, dental treatment and hemodialysis still constitute a major route of transmission.

Hepatitis D

Hepatitis D virus (HDV) is a defective RNA virus that requires HBV to become infectious. Worldwide, 15 million people are infected with HDV which accounts for 5% of patients with HBV infection. Hepatitis D is endemic particularly in the Mediterranean basin. In other parts of the world, HDV infection occurs among intravenous drug addicts and persons who receive multiple blood transfusions. There are three genotypes of HDV. Genotype I predominates in Italy, Turkey and most of the other parts of the world. Genotype II is less aggressive while genotype III is one of the most aggressive ones. Italy and Eastern Europe are areas of highest prevalence for HDV [30]. Furthermore, IV drug addicts have higher prevalence of HDV in Greece and Italy [24,55].

Table 4. Peculiarities of HDV epidemiology.

Hepatitis Delta is declining in Europe / elsewhere
Precautions / vaccination for HBV are the major reasons for this decrease
Genotypes are important in determining the type of disease
Genotype I: Italy, Greece, Turkey and Africa
Genotype II: Japan, Taiwan-less aggressive
Genotype III: Peru-severe disease

Although HDV needs HBV for replication, the geographic distribution of HDV does not exactly match that of HBV distribution. Either as a superinfection or coinfection, hepatitis D is associated with more severe liver disease. In Southern Italy, HDV infection is high, appearing to have a more benign clinical course. In the absence of HBsAg, screening of blood donors for HDV is unnecessary. Sexual partners of the drug users with HDV infection were found to be infected in a rate of 33% [56] (*Tab. 4*).

The prevalence of HDV infection is decreasing due to HBV prevention programs and improvement in socio-economic conditions (*Tab. 4*). However for the individuals the prevention of HDV transmission depends on the behavior modifications and improvement of hygienic conditions.

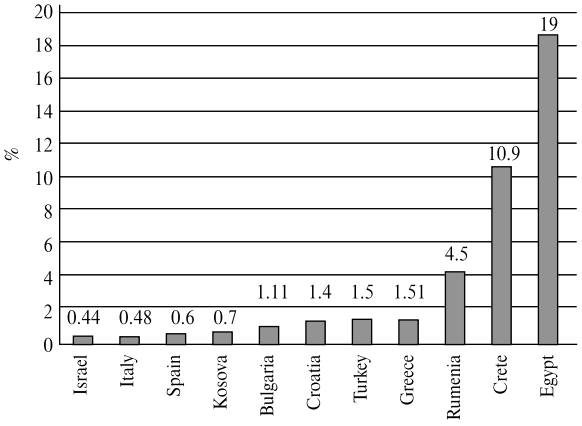
Hepatitis E

Hepatitis E virus (HEV), an RNA virus classified in the Caliciviridae virus family, is the most common cause of epidemic, enterally transmitted hepatitis. Ingestion of fecally contaminated water is the most common way, of transmission, which occurs most frequently during the rainy season that leads to outbreaks in endemic areas. Although the transmission is by the fecal-oral route, there is a low rate of clinical illness among household contacts of infected patients; an unexpected finding that may be related to the instability of the virus in the environment.

HEV accounts for as many as 50% of the cases of acute sporadic hepatitis in adults and children in some endemic areas [57]. Acute HEV infection is characterized by fluctuating aminotransferase levels and the overall case-fatality rate of 0.5% to 4%. However, pregnant women, especially when infected during the third trimester, have up to a 25% risk of mortality associated with acute HEV infection. HEV does not appear to cause chronic liver disease [58].

The seroprevalence of anti-HEV in Egypt is among the highest rate reported throughout the world, which exceeded 60% in the first decade of life, peaked at 76% in the second decade and remained above 60% until the eighth decade. In the Nile Delta, the seroprevalence of anti-HEV was 17.2% and increased by age [59]. Çetinkaya et al. [60] reported anti-HEV seropositivity as 7.6% in blood donors in Turkey. It is sporadic (2.1%) in Europe. In a survey covering 5 regions of Turkey the

Figure 3. Epidemiology of viral hepatitis C in various countries [76,77].



prevalence rate of anti-HEV in the general population was found to be 5.9%. The prevalence rates reported from other countries were 1.1% in Netherlands [61], 1.7% in Italy [62], 7.3% in Germany [63]. Immunoprophylaxis for HEV is not available and proper sanitation is the most important way of prevention. Boiling the water before consumption in doubtful situations appears to be effective in inactivating HEV.

Other viruses

GB virus / Hepatitis G

GB virus (GBV-C) and hepatitis G virus (HGV) are the minor variants of the same RNA virus in the Flaviviridae family. The virus can be transmitted parenterally, orally, vertically or by sexual intercourse. Clinical manifestations of HGV are not known, and the virus can persist in serum for many years. In Italy, high rates of GBV-C seropositivity of GBV-C were reported among blood donors (12.6%), hemodialysis patients (22%) and intravenous drug users (39%) [64]. In Greece, GBV-C/HGV RNA was found in 8.6%, 26.5%, 37.6% and 10% of patients with chronic hepatitis B, chronic hepatitis C, hemodialysis patients and normal subjects, respectively [65]. In Southern Italy GBV-C/HGV seroprevalence was 41.04% in HIV positive patients and 6.54% in healthy individuals [66]. In Egypt the prevalence was found to be 30% in chronic hemodialysis patients, 14% in patients with chronic hepatitis C, 12.2% in blood donors, 11.1% in chronic non-B non-C hepatitis, and 6.6% in health care personnel [67]. The contribution of HGV infection to chronic liver disease, HCC or other diseases of unknown origin is unclear. An association was investigated between HGV and non-Hodgkin lymphoma or GI cancer. Studies in various groups of diseases such as non-Hodgkin lymphoma [68], Behçet's disease [69] and ankylosing spondylitis [70] in Turkey have shown an associated a prevalence rate of 30%, 7.1% and 38.8% in HGV, respectively. More data is needed to achieve firm conclusions about the epidemiological and clinical importance of GBV-C/HGV infection.

TT virus

Hepatitis TT virus, or TTV is a parenterally transmitted DNA virus which has high prevalence among healthy population and chronic hepatitis patients. The virus can be transmitted both parenterally and orally. Seroprevalence of TTV in blood donors in France, Spain and Turkey were found as 2%, 14%, and 9.6-31% respectively [71]. In Turkey Avsar et al. [72] found TTV seropositivity of 43.5% in intravenous drug users and 20% in blood donors. In the study of Erensoy et al. [73] TTV DNA was found in 75% of hemodialysis patients, 80% of fulminant hepatitis patients, 61% of thalassemia patients and in 51.6% of volunteer blood donors. Among the sequenced isolates 35.9% belonged to genotype 1 and 64.1% belonged to genotype 2. In Egypt, the prevalence of TTV DNA did not differ among patients with chronic hepatitis B (46%), chronic hepatitis C (31%), schistosomal liver disease (36%) and blood donors (29%) [74]. TTV seems to be a worldwide pathogen with undetermined pathogenicity.

SEN virus

SEN virus, a DNA virus in the family of Circoviridae was discovered as a potential hepatitis virus, found in the blood of a HIV virus infected illicit drug user in 1999, in Italy. SEN virus can be transmitted parenterally. In a study coinfection of HCV with at least one of SEN D and H viruses correlated inversely with the effectiveness of the treatment with interferon and ribavirin [75]. The clinical data for this virus is far from being satisfactory and further studies are progressing to determine its role in liver disease.

Conclusions

The fact of globalization has made the propagation of diseases like viral hepatitis relatively easy throughout the world. Europe is a lively continent where thousands of people move to seek a job, to find new opportunities or simply for traveling purposes. Moreover wars, natural disasters or political instabilities make the trend for immigration even more justifiable. These events facilitate the spread of hepatitis viruses throughout the Mediterranean basin. The present cumulative data on the epidemiology of viral hepatitis C in various countries of this area is represented in *Fig. 3* [76,77].

At the other end of the spectrum morbidity and mortality rates related to viral hepatitis are progressively decreasing in this region of Europe. Better hygienic measures, widespread use of disposable syringes, definition of high risk groups, universal screening of blood donors and products for HBV and HCV, vaccination for HAV and particularly universal vaccination for HBV infection, demographic and behavioral factors may play a role in the reduced prevalence of viral hepatitides. Hepatitis E is a minor cause of viral hepatitis in the Mediterranean. Clinical importance of the other viruses remains to be determined by further studies.

The challenges to be faced in the next millennium involve the introduction of new and more antigenic vaccines for hepatitides as well as the development of safe and effective therapies for CLD. Mediterranean basin, well known for its exciting history, legends, natural beauties and healthy diet should get rid of the long standing assault of viral hepatitis and regain in the future its reputation as a healthy region, seat for eternal peace and felicity.

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