

# Recommendations for the better management of Hepatitis B in Spain\*

## Recommendations from the Hepatitis B Expert Group (GEsHeB)

### Hepatitis B Expert Group (GEsHeB):

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## PREFACE

### Dr. Rafael Esteban Mur

The European Union has been undertaking for several years now, different initiatives aimed at raising awareness on the importance of Hepatitis B as a transmissible disease capable of leading to irreversible chronic liver disease and responsible for a high number of deaths throughout the world. Experts have already drawn attention to this threat and claim that hepatitis B is a vaccine- preventable disease and that useful treatment options exist to avoid the progression of the disease in infected patients.

We must take into account that in Europe there are 1 million new infections per year due to HBV, almost 14 million people are infected with chronic disease and about 40,000 deaths are attributable to hepatitis B every year. Moreover, HBV is directly related to over 50% of liver cancer cases. On the other hand

the burden on the illness entails thousands of million-euro economic costs, which will exponentially increase until 2020 if appropriate therapeutic measures are not taken.

As far as the epidemiology is concerned, it is worth noting that migratory movements are greatly transforming the disease's scenario in the European Union. Thus, there is data revealing the increase of the incidence of new cases related to people who come from high endemicity areas.

Owing to its asymptomatic evolution, those infected and even healthcare providers themselves are frequently unaware of the condition and a precise diagnosis is only made when the consequences may be irreparable.

Different associations handle this problem in the European Union. Such is the case of the Viral Hepatitis Prevention Board (VHPB), drawing attention to the prevention of the disease. The European Association for the Study of the Liver (EASL) has released

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clinical practice guidelines for the management of the disease.

Recently, a group of experts headed by Dr. and MEP Thomas Ulmer has drawn up a report to be addressed in the different countries of the EU, which has been adapted to the Spanish context by the Hepatitis B Expert Group (GESH in Spanish). The recommendations herewith should be closely followed by social, political and healthcare stakeholders to ensure that Hepatitis B is managed in an appropriate and homogeneous way throughout the European Union.

## 1. INTRODUCTION

After the *Call for Action* was launched in 2006 and the *Orientation towards a better management of Hepatitis B in Europe* presented before the European Parliament in 2007, an initiative led by Dr. and MEP Thomas Ulmer and supported by experts from all over Europe, a group of Spanish experts decided to make a stride further and to adapt the contents herewith to the specific context of our country by means of the *Recommendations for the better management of Hepatitis B in Spain*.

As part of the Hepatitis B Expert Group (GESH), this multidisciplinary group of experts mainly aims at promoting the knowledge and awareness of the impact of Hepatitis B in Spain and the importance of its appropriate management as well as enhancing national integration of criteria regarding prevention, detection and treatment, involving the relevant stakeholders.

Therefore the Recommendations for the better management of Hepatitis B in Spain were drawn up; a document including guidelines which can be used in preparing comprehensive national and regional policies on the importance of this disease and hence raising awareness among all the people concerned to better manage hepatitis B within their range of action.

### What is Hepatitis B?

The hepatitis B virus (HBV) is one of many viruses (the others being A, C, D and E) that may cause hepatitis. Hepatitis B is a viral preventable infectious disease that can lead to cirrhosis (liver damage) and liver cancer.

The World Health organization (WHO) estimates that two thousand million people, five per cent of the world's population, is infected with the hepatitis B virus – twice as many as with hepatitis C and 7

times more than with the Human Immunodeficiency Virus (HIV) – out of which 350 million people are chronically infected.

The epidemiology of the disease varies significantly from one region to another and is affected greatly by immigration. In Europe, there are 1 million new infections per year due to HBV, and 14 million people are infected with chronic disease. Moreover, between 24,000 and 36,000 deaths are attributable to hepatitis B every year.

Traditionally, Spain has been among intermediate endemicity countries (between 2 and 7% of the general population). Some measures such as the introduction of the HBV vaccine in the NHS Vaccination Schedule in the 90s, systematic control of blood donations or serological screening of pregnant women during the third term have largely contributed to the decrease of Hepatitis B in Spain. Nevertheless, new social behaviors and immigration are currently increasing the number of people infected with HBV.

The natural history of Hepatitis is complex, in that it starts off as an acute disease that may then develop into a chronic condition (*see Figure 1*).

The risk of developing chronic disease depends on the age at which one becomes infected. Among adults, 1-5% of those infected will not be able to get rid of the virus and will develop chronic hepatitis B. Up to 1% will be exposed to fulminant hepatitis. By contrast, up to 95% of those infected as newborns and 10-30% of those infected before the age of 10 years will develop chronic disease. Moreover, one person in 20 infected by HBV becomes a carrier of the virus and may infect others without incurring any symptoms themselves.

If left untreated, chronic hepatitis B evolves into cirrhosis in 30% of patients and nearly half of these will die from liver failure or liver cancer. Hepatitis B is the most common cause of liver cancer worldwide and as such is the most common carcinogen after tobacco. Liver cancer is the fifth most common cancer in man.

### Burden of the illness

The economic cost associated with hepatitis B is considerable and costs escalate with the increasing severity of illness (Brooks et al., 2001). Costs include direct costs of treatment for hepatitis B as well as indirect costs linked to lost productivity and premature death of those affected. Studies on the direct medical costs for the management of different stages of chronic hepatitis B disease in France, Italy, Spain, UK (Brown et al., 2004), Germany (Dale et al., 2006), and Sweden

(De Cock et.al., 2006) showed a non-linear increase in average annual costs as the disease progressed from the early stages to later stages such as decompensated cirrhosis and liver cancer. For example, in Germany, the annual cost of chronic hepatitis B management increases from approximately €000 per patient at the stage of chronic active hepatitis, to approximately €5,000 at the liver cancer stage. In a South Korean study conducted in 1997, the authors found that direct costs of hepatitis B were the equivalent of 3.2% of national GDP and indirect costs represented over 20% of total costs (Yang et al, 2001).

In Spain, it is estimated that in 2005 approximately 115,000 people were infected with chronic hepatitis B. If left untreated, it has been calculated that in 2025 there would be 60,000 morbidity and mortality events and 40,000 deaths attributable to the disease. The health care economic cost associated with the disease would be of €1.84 thousand million. Using the appropriate treatment could save about €1,000 million (Idris B *et al.*)

### Routes of infection

Hepatitis B is a viral disease that is transmitted by contact with the blood or body fluids of an infected person. The main routes of infection are blood-borne and sexual. The virus is 100 times more infectious than HIV and 10 times more infectious than hepatitis C, thus the risk of infection upon exposure is very high.

### Main groups at risk for Hepatitis B

<https://www.hepatitisbforum.com/GEsHeB/>

- Men who have sex with men
- Heterosexual people with multiple sex partners
- Injecting drug users who share or have shared needles
- People with a history of sexually transmitted infections (STI)
- Household contacts of those infected with HBV
- Newborns of HBV-infected mothers
- Sex partners of those infected with HBV
- Inmates of long-term correctional facilities and prisons
- Patients undergoing hemodialysis
- Healthcare workers and public safety workers with frequent blood contact
- Clients and staff at institutions for the developmentally disabled
- Recipients of certain blood products and transfusions
- Travelers to areas of high HBV endemicity

### Management of hepatitis B

On one hand, management of hepatitis B consists of prevention, including vaccination, screening, detection and diagnosis; and on the other hand, it consists of treatment.

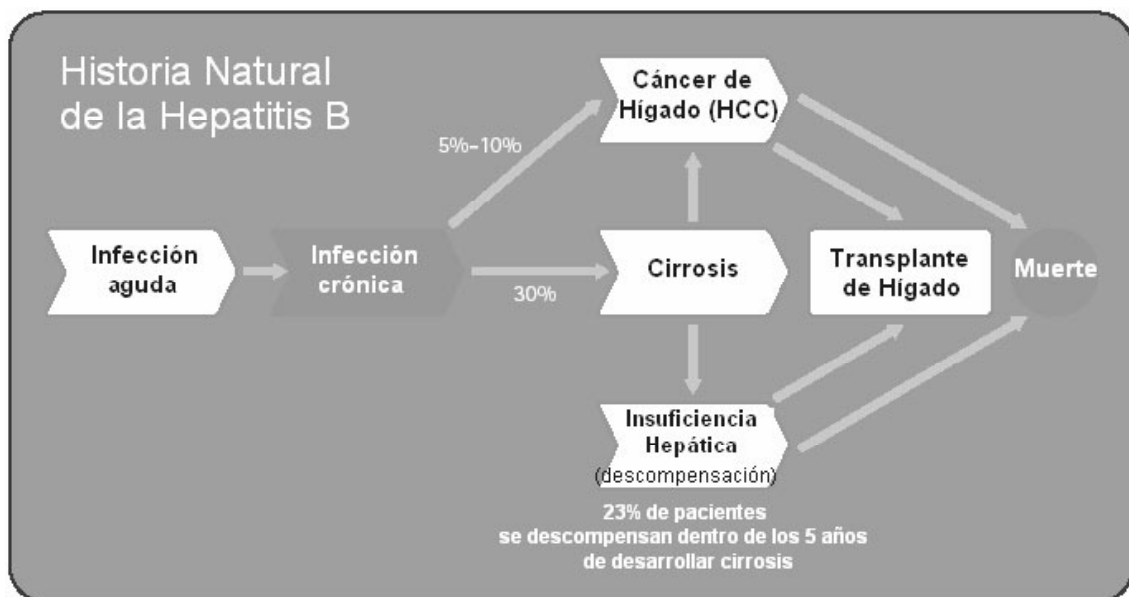


Figure 1. Adapted from Torresi *et al*, 2000 and Fattovich *et al*, 2003<sup>1,2</sup>.

*Vaccination* against hepatitis B has been shown to be 95% effective at preventing acute and chronic HBV and countries that have implemented widespread vaccination have seen incidence of HBV decrease significantly among children and adolescents. The WHO has recommended universal hepatitis B vaccination of all children and adolescents against hepatitis B as well as vaccination of risk groups since 1991. Vaccination policies differ across Europe, however, with countries such as the UK, the Netherlands and Nordic countries having opted not to include hepatitis B in their routine vaccination schedules. In Spain, universal vaccination among newborns and/or adolescents has been successfully implemented in all autonomous communities since the 90s.

It is important to consider that vaccination cannot prevent chronic hepatitis from occurring in already infected patients.

Hepatitis B is a silent disease in that symptoms are difficult to identify and may even be absent in up to 40% of cases. As a result, infected individuals may ignore that they are infected for years and health professionals often fail to diagnose the disease in its early stages. The absence and difficulty of identifying clear symptoms in acute hepatitis B makes screening of people at risk critical and diagnosis extremely important (Wong and Pomfret, 2007).

Indeed, *screening* of high-risk individuals for hepatitis B is essential for early identification and treatment of those infected. Screening allows guiding individuals infected with HBV to appropriate care and helping them prevent the infection of others. It also allows for household and sexual contacts of infected individuals to be offered vaccination (Valla *et al*, 2003).

*Diagnosis* of hepatitis B at an early stage may be critical in halting the progression of disease and limiting the risk of infection by affected individuals. Antiviral *treatment* has shown to slow the progression of the disease in those patients with chronic hepatitis B; it improves liver histology and prevents clinical decompensation of the disease.

## 2. RECOMMENDATIONS FOR A BETTER MANAGEMENT OF HEPATITIS B IN SPAIN

### FIRST RECOMMENDATION

**Europe must take the lead in recognizing Hepatitis B as one of the most significant public health issues and make it a priority area for the development of a cohesive strategy to ensure the appro-**

### **priate prevention, control and clinical management of the disease across Europe.**

Recent immigration trends in Europe have made it necessary to implement specific prevention measures in all European countries. Therefore, European organizations need to set out guidelines to be universally adopted in all EU countries and to update epidemiologic figures related to this disease.

### SECOND RECOMMENDATION

**Spain must adopt the European strategy promoting its common implementation across autonomous communities.**

Spain must support the EU documents and try to collaborate in order to lead the fight against the HBV infection.

National Health organizations from different communities must ensure the implementation of general recommendations to prevent hepatitis B.

Epidemiological data relating to the HBV infection should be used throughout the country.

### THIRD RECOMMENDATION

**Spain must keep its universal vaccination programs with current quality standards insisting on the coverage of foreign population.**

Currently vaccination policies differ across Europe. In fact, some countries do not include the HBV vaccine in their national vaccination schedules; such is the case of the United Kingdom, the Netherlands and Nordic countries.

Given the high levels of immigration within the EU, this lack of uniformity in vaccination policies threatens the potential to contain the spread of HBV. Epidemiological and cost-effectiveness based reports conclude that the best strategy in the fight against this disease is universal vaccination.

In our country, this was the measure adopted, thus including children and adults from risk groups in systematic vaccination programs, something which has greatly contributed to decrease the incidence of hepatitis B. Only universal vaccination among children, especially during preadolescence, can lead to the control of the disease in Spain.

A double strategy is recommended:

- 1) Selective vaccination of risk groups and newborns from mothers who are HBsAg positive.
- 2) Universal vaccination among children while breastfeeding.

All those communities which implemented pre-adolescent vaccination (12 years old) must maintain vaccination campaigns in schools until children vaccinated while breastfeeding reach that age. All those people younger than 22 years, who have not been previously vaccinated, will also be immunized.

Although protection antibodies may have been lost with time, the vaccine provides coverage of at least 15 years, probably due to the presence of immunological memory that allows a response upon exposure to the virus.

As far as the foreign population is concerned, both from developing and developed countries, special emphasis will be made on revealing their complete vaccination condition to ensure the highest safety level before viral preventable diseases included in Spanish vaccination schedules. The fact that these people may return home entails a specific risk that should be taken into account, since, apart from the individual risk, there is also a risk of transmission and infectious agent import.

Previous vaccination will only be considered if there is written evidence of appropriate dosage. The lack of such documentation will entail complete vaccination.

The determination of HB markers prior to vaccination is highly recommended for those people coming from endemic countries as well as for their sex partners and household contacts.

#### FOURTH RECOMMENDATION

**Improved information related to hepatitis B must be communicated to the general public specifically highlighting the possibility of prevention, detection and treatment.**

Increased disclosure of scientific findings related to the healing of the disease as well as detailed information targeted at the scientific community, the general public and health authorities need to be done.

Effective treatment options exist that may improve HB patients' outcomes, yet access to these treatments is restricted in our country and many other European countries.

Awareness and understanding of hepatitis B is low amongst health professionals due to the lack, up to recently, of therapeutic options. We can now say that specific antiretroviral therapies slow the progression of chronic hepatitis B and delay the onset of cirrhosis.

Awareness needs to be raised among all social sectors, especially amongst health policy makers pro-

moting their interest on hepatitis B as a potentially curable disease.

Wherever they access the health system, individuals should be offered the same complete information on prevention and treatment options for the HBV infection. Therefore, standards of training offered to all health professionals who may come into contact with individuals at risk of becoming infected with HBV or who are already infected by HBV need to be raised.

Clear and consistent messages related to hepatitis B must be communicated to the general public overturning misconceptions about Hepatitis B and its pathogenic capability.

#### FIFTH RECOMMENDATION

**Specific efforts need to be done to prevent the spread of Hepatitis B among prisoners and injection drug users.**

Injection drug users (IDUs) are at very high risk of contracting hepatitis B. Prisoners are also at high risk of doing so mainly due to the high prevalence of injection drug use, the marginal contexts from which they frequently come and because of risk behaviors.

In Spain, for 20 years now, serological screening is offered to all inmates on entry into prison and counseling on risk behaviors is provided. If indicated, vaccination is recommended.

The success of the program against HB developed in Spanish prisons along with the implementation of harm reduction strategies, have led to a HBV prevalence rate of 2.6% in Spanish prisons, according to the report *Prevahelp* carried out by the Group of Infectious Diseases of the Spanish Society of Prison Health (GEI-SESP). By contrast, the prevalence of hepatitis C is 22.7% and that of HIV is 10.8%. If we only consider the population within Spanish prisons who present complete HBV serology, 32.1% have postvaccinal immunization, 30.4% have natural immunization or the infection itself and 37.5% is susceptible to the infection with HBV. In our country, screening and vaccination are also offered in Addictive Behavior Units.

Programs for the prevention of blood-borne and sexually transmitted infectious diseases need to be supported within the penitentiary context and for injection drug users.

Moreover, awareness must be raised among health professionals in contact with prisoners or drug users on the importance of a complete diagnosis and an appropriate treatment for HBV patients not only as a means of preserving individual health conditions but also as a means of secondary prophylaxis.



## SIXTH RECOMMENDATION

**Immigrants from high HBV endemicity must be offered an appropriate screening as well as diagnosis and treatment options when required.**

Lately Spain has experienced an important immigration trend coming from high HBV endemicity areas (Sub-Saharan Africa) or intermediate HBV endemicity areas (Peru, Maghreb or former URSS).

Health education on this disease must be offered to all immigrants as part of a comprehensive care strategy and screening must be provided for those coming from HBV high prevalence countries.

Counseling must be provided for those who are already infected in order to prevent further infections and appropriate care and treatment must be offered if required.

As far as the immunization is concerned, all immigrant children and adults with the same indications as the national population must be vaccinated.

## SEVENTH RECOMMENDATION

**In Spain, the Epidemiologic Surveillance network for hepatitis B needs to be improved. Such system should be standardized among autonomous communities in accordance with the recommendations from the European Centre for Disease Prevention and Control.**

Spain has a Surveillance network which determines mandatory notification of some diseases (known as EDOs in Spanish), among which hepatitis B is included. Therefore, any practitioner both working in the public and private sector, must mandatorily notify the clinical suspicion of new cases of these diseases throughout the present week. This requirement is included in the *Real Decreto 2210/1995 of 28<sup>th</sup> December* (Regulation 2210/1995), which includes the creation of a National Surveillance Network and specific surveillance systems apart from the mandatory reporting of suspected cases of determined diseases. Such specific surveillance systems include case report systems, seroprevalence surveys, sentinel systems and others which could be applied to the surveillance of AIDS, HIV and other viral preventable diseases. Regarding viral hepatitis, such Regulation determines the creation of an annual report apart from weekly declarations.

In accordance with the Regulation 2210/1995, hepatitis B due to its viral preventable condition should count upon a specific surveillance system aimed at an appropriate assessment of the burden of the disease

in different geographical contexts so that the development of effective policies would be enhanced. Such surveillance system would need to follow the Recommendations from the European Centre for Disease Prevention and Control.

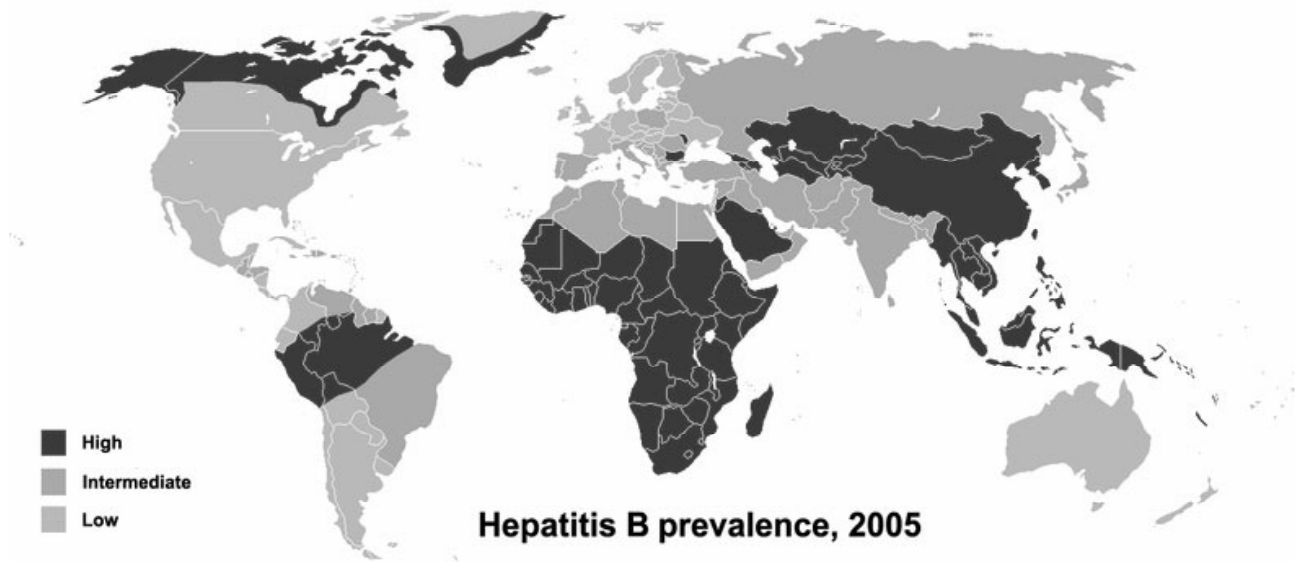
### Principles that should govern national surveillance systems on hepatitis B

- Develop a mandatory surveillance system that is able to distinguish cases of acute hepatitis B from chronic hepatitis B
- Develop an easily-applicable minimal dataset to ensure uniform data collection across all surveillance centers
- Measure the burden of illness posed by hepatitis B, including hospitalizations and sequelae
- Collect data on antiviral therapies to identify resistance patterns
- Collect a registry of hepatitis deaths and link these data to surveillance
- Record cases of liver transplantation and link these data (eg. through *EuroTransplant*) to surveillance systems for hepatitis B
- Perform 10-yearly seroprevalence studies, particularly in certain risk groups in countries with changing epidemiology
- Build in the ability to audit systems to ensure quality data collection

Source: EUROHEP.NET expert report

A recent European-wide report<sup>3</sup> concludes that there is major variability regarding hepatitis B surveillance systems (type of surveillance, case definition, data source, type of data collected, periodicity, etc.) and recommends its standardization and enhancement specially highlighting the difference between acute and chronic hepatitis B. It would also be important to report of the vaccinal history and the nationality of the patient.

In Spain, information regarding EDOs (Diseases that must be mandatorily notified) is included in the health related information from the National Statistics Institute ([www.ine.es](http://www.ine.es)). According to its latest references, between 2003 and 2007 the number of hepatitis B cases has ranged between 658 (2005) and 968 (2007). The quality of the EDO system is relative, due to the fact that an important under declaration has been concluded and therefore an underestimation of real cases is derived.



#### EIGHTH RECOMMENDATION

**Access to the best treatment options must be granted to all patients fulfilling clinical requirements.**

Currently there are effective and useful treatments for the evolution control of chronic hepatitis B. Access to such treatments must be enhanced for all those patients fulfilling clinical requirements collected in hospital protocols. These measures will reduce the morbidity related to chronic hepatitis B and the spread of the infection will be avoided as far as possible.

In our country, HBV chronic infection is still an important public health issue which could get worse due to the arrival of people from high prevalence countries for HBV. It is estimated that 350 million people worldwide are chronically infected with HBV, a disease that can lead to cirrhosis and liver cancer.

Recent advances have taken place concerning diagnosis methods and treatment options, both leading to an improvement of the quality of life and survival of those chronically infected.

The treatment of chronic hepatitis aims at delaying as much as possible the onset of cirrhosis and avoiding the development of complications such as hepatocellular carcinoma.

If we take into account the extent of the disease and the limited efficiency of therapeutic options, as well as the risk entailed by the appearance of resistant viral varieties, the decision to uptake treatment and

its duration must be carefully considered. If a patient decides to begin treatment it must be done in a personalized way between the patient and the practitioner, and taking into account features such as the age of the patient and his/her prognosis, adverse effect possibilities and the risk of appearance of resistant varieties.

#### Currently approved treatments for hepatitis B

##### Interferon:

- ✓ Standard Interferon alpha (IFN  $\alpha$ )
- ✓ Pegylated Interferon alpha (PEG-IFN  $\alpha$ )

##### Nucleotide and nucleoside analogues:

- ✓ Lamivudine
- ✓ Adefovir
- ✓ Entecavir
- ✓ Telvibudine
- ✓ Tenofovir

#### NINTH RECOMMENDATION

**Health professional's training on hepatitis B needs to be improved to ensure the best prevention, detection and treatment system.**

The evolution of knowledge in Medicine is continuous. The background of general hepatology and specifically of hepatitis B is permanently changing, with recent and relevant findings that can lead to a bet-

ter provision of health care. Being updated is always difficult, especially in specific areas of knowledge and relating to issues that, although prevalent in an important part of the population, do not affect non-specialized every day routines.

Several studies have identified lack of training and understanding of hepatitis B by general practitioners and non-hepatology specialists in the community and hospital settings as a key hurdle to early detection and appropriate management of hepatitis B<sup>4</sup>

In Spain an appropriate training needs to be offered to health professionals regarding hepatitis B and specifically aimed at practitioners developing their work in Primary Care services, penitentiary facilities, sexually transmitted diseases services, immigrant assistance and others. Training must aim at improving knowledge and skills related to the prevention, diagnosis and treatment of hepatitis B as well as at promoting a more active attitude towards patients diagnosed with the disease or at risk of having it.

As far as prevention is concerned, practitioners should encourage vaccination (appropriate coverage among children and less in adults at risk of being infected with HBV) and the evasion of risk behaviors. Regarding the diagnosis, aside from the clinical suspicion of symptoms and signs suggesting the disease, the availability of analytic tests confirming or refuting the disease and assessing its evolution must be enhanced. For the last years, new drugs have been in the therapeutic arsenal against hepatitis B improving patient outcomes, which must be prescribed by experienced physicians in the treatment and follow-up of these patients.

An appropriate coordination between different physicians capable of diagnosing hepatitis B and treatment units capable of providing quality treatment and follow-up should be established to enhance assistance continuity.

It is important to have an appropriate training and information regarding new therapeutic options leading to the improvement of the prognosis of hepatitis B, decreasing the possibility of it becoming chronic, leading to cirrhosis, liver cancer and death.

## TENTH RECOMMENDATION

**Research on hepatitis B to improve its assistance and develop innovative treatments must be enhanced.**

Both basic and clinical research must be enhanced

and funded to improve our knowledge of chronic hepatitis B, its natural history, its evolution and complications to improve current health care, to develop new treatments and determine as soon as possible the appearance of resistances.

Research on hepatitis B must be established on clinical and microbiological hospital backgrounds and a Primary Care context. From the scope of Primary Care emphasize must be done on research on the disease's epidemiology and the control of asymptomatic carriers.

Funding of such research must be led by both state and regional agencies from different autonomous communities.

The Spanish Department of health and Social Policies, by means of the *Health Institute Carlos III* (ISCIII) develops promotion and biomedical research coordination tasks within the National Health System.

ISCIII is a public research agency aiming at the enhancement and development of research and the provision of health related technical and scientific services by means of basic and applied research, assessment, accreditation, scientific and technical certification, health control scientific and technical counseling and biomedical and health science education and training. The National Plan on RTDI 2008-2011 appoints ISCIII as an administrator of such Plan and a key point of its role is represented by the guidelines regarding the sectorial strategic initiative of health research. (Official State Gazette BOE number 52. Friday 29<sup>th</sup> February 2008).

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