VIRAL HEPATITIS

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This edition of *Viral Hepatitis* is based on material presented at the Viral Hepatitis Prevention Board meeting on the **Prevention and Control of Viral Hepatitis in Spain: Lessons Learnt and the Way Forward**
Madrid, Spain, November 23-24, 2006.

Editorial

This issue of *Viral Hepatitis* reviews topics covered at the VHPB's autumn meeting held on November 23-24, 2006 in Madrid, Spain. The overall objective of the meeting was to review the current situation relating to prevention and control of viral hepatitis in Spain. Main topics discussed among participants included the organization of healthcare system, the epidemiological situation, surveillance system, research activities, and current prevention and control measures of viral hepatitis. The meeting concluded with lessons learnt from the experience in Spain, the way forward and how to meet future challenges.

The 1978 Constitution established a new territorial structure, dividing Spain into 50 provinces, grouped into 17 Autonomous Communities (ACs) and 2 Autonomous Cities. Healthcare is organized in a two-level National Health System (primary healthcare, specialist care) whereby minimum health standards are guaranteed by a State consensus while additional health priorities may be adopted and entirely managed by the ACs of Spain. Primary healthcare is characterized by extensive accessibility and equity whereas the whole system poses the question of complexity versus flexibility of this type of constitutional framework. This question is of particular relevance in the light of similar devolved governmental or administrative entities in other European countries, such as, for example, the "cantons" in Switzerland, "Laender" in Germany, "regions" in Italy or "communities" in Belgium.

Within the epidemiological surveillance network for infectious diseases in Spain, a strengthened reporting system is needed as a basis for appropriate prevention and control policies. The importance of a well-functioning outbreak investigation programme, established for ten years, was further emphasized during the meeting. Outbreak information has been consolidated since 1987, thanks to the transfer of responsibilities to the ACs, further supported by increased human resources and staff training.

An update of the epidemiological situation on viral hepatitis in Spain showed that preventive measures have led to a significant decrease in the incidence of hepatitis A, B and C infections.

As a result of Spain's pioneering role in the implementation of successful universal mass vaccination programmes against hepatitis B (HBV) in the entire country starting already in 1992, the country has seen a steady decrease in annual HBV incidence.

Spain is an area of low hepatitis A (HAV) endemicity, with prevalence remaining under 15% in the up- to-19-year-old population (1996). Regional differences may be attributable to outbreaks in specific regions or to effective HAV vaccination programmes in some regions, as demonstrated in Catalonia. In terms of ongoing epidemiological research activities in Spain, molecular epidemiology studies investigate the presence of HAV in the environment, illustrating environmental circulation (sewage water, rivers, shellfish). A limited number of studies have investigated the epidemiology of hepatitis E (HEV) in Spain, with prevalence varying from 6 to 7%. Molecular techniques were used to investigate the presence of HEV in sewage water and the potential role of swine as animal reservoir. Interestingly, the data presented indicate that HAV and HEV may be more widespread than previously thought, representing a situation of sanitary risk. Based on these findings, the importance of including HEV testing in the routine diagnostics of acute and fulminant hepatitis was emphasized.

Discussions relating to current research activities also addressed the power of up-to-date molecular techniques used for the diagnosis of hepatitis in Spain. Substantial benefits gained from molecular epidemiology included the identification of the source of hepatitis C (HCV) infection and the establishment of its transmission mechanisms. Molecular diagnosis also led to the improvement of blood supply safety by reducing the residual risk of HBV transmission.

The frequency of HCV-HIV coinfection in Spain is one of the highest among European countries. It was concluded from the growing importance of HCV-related morbidity and mortality among the HIV positive population, that this large cohort of coinfected patients is expected to have an impact on the demand of health resources for clinical care.

While high coverage rates (> 95% in children) confirm the high performance of hepatitis vaccination programmes in Spain, specific recommendations were made during the meeting, relating to outstanding challenges to be faced.

Isabel Pachón and Daniel Shouval,
on behalf of the Viral Hepatitis Prevention Board

Prevention and Control of Viral Hepatitis in Spain: Lessons Learnt and the Way Forward
Madrid, Spain, November 23-24, 2006

Organization of healthcare system in Spain

National Health System: administrative and legal framework

The administrative organization in Spain is based on a parliamentary monarchy which has been in place since 1976. The 1978 Constitution established a new territorial structure, dividing Spain into 50 provinces, grouped into 17 ACs and 2 Autonomous Cities. ACs have wide legislative and executive autonomy, with their own parliaments and regional governments.

The public regime of the social security and the right for all citizens to enjoy health protection and healthcare are laid down in Articles 41 and 43 of the Spanish Constitution of 1978.

The main principles governing the exercise of this right are regulated by the *General Health Act 14/1986* and include:

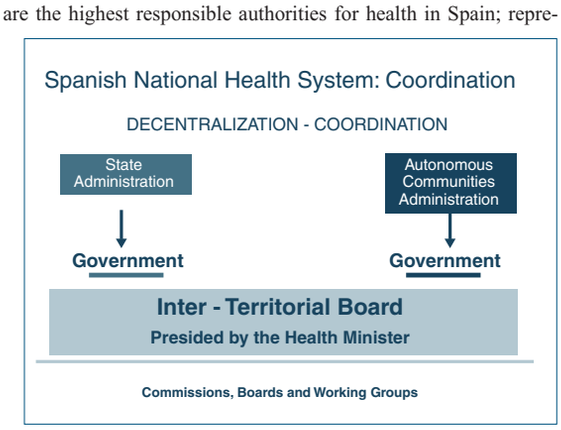
- public funding, with universal, free health services at the time of use;
- devolution of health affairs to the ACs;
- provision of holistic healthcare, aiming to achieve high quality, with proper evaluation and control;
- inclusion of the different public health structures and services in a National Health System (NHS).

Coordination of healthcare at national level is laid down in this Act which also identifies the tools for collaboration and establishes the NHS's Inter-Territorial Board as the coordinating body. The role of the board is further specified in the *Act 16/2003* on Cohesion and Quality in the NHS. Its main objective is to guarantee the right to health protection and ensure equity and quality through coordination and cooperation among the Public Health administrations of the decentralized NHS, as illustrated in the slide below. The board has an advisory role, making recommendations aiming at a consensus for national health policy while ACs are the decision-making bodies.

Members of the Inter-Territorial Board are the highest responsible authorities for health in Spain; representatives from both State and Regional Administrations are equally present.

The State Administration is represented by the Minister of Health who chairs the Board.

Each AC is represented by the member of the Regional Government in charge of health. The Spanish NHS includes both State and AC Health Departments and covers all health functions and services for which public authorities are legally responsible.



Healthcare in Spain is mainly provided within the public sector, in the form of a non-contributory benefit. It is paid for through taxation and is included in the general budget for each AC. Services offered by the Spanish NHS include:

- preventive care;
- diagnostic and therapeutic techniques;
- rehabilitation;
- health promotion and maintenance.

Pharmaceutical services cover drugs and health products. Unlike other services which are provided free of charge, pharmaceutical, orthopaedic and prosthetic services are cofinanced by users.

National Health System: State versus Autonomous Community powers

At national level, the Ministry of Health and Consumers' Affairs (MOH) is the body within the Central Administration which proposes and implements the main government guidelines on health policy, health planning and healthcare. State responsibilities include:

- **General organization and coordination of health matters** in terms of minimum requirements, aiming to achieve equal conditions of public health services; methods of information sharing, and technical standardization in specific areas; joint actions by State and AC authorities.
- **International health, and international health relations and agreements** relating to the surveillance and control of potential health risks in connection with the import, export or traffic of goods and international passenger traffic.
- **Legislation on pharmaceutical products**, in particular the evaluation, authorisation and registration of drugs and health products, as well as their public financing and pricing, and their purchase and distribution for international programmes; the deposit of drugs and health products for emergencies and catastrophes and the deposit of narcotics in accordance with international treaties; the importation of urgent, foreign medication.

Next to State powers, the ACs of Spain have devolved powers in the area of health. Such a decentralized structure allows for the management of healthcare to be brought closer to citizens, thus guaranteeing equity, quality and participation.

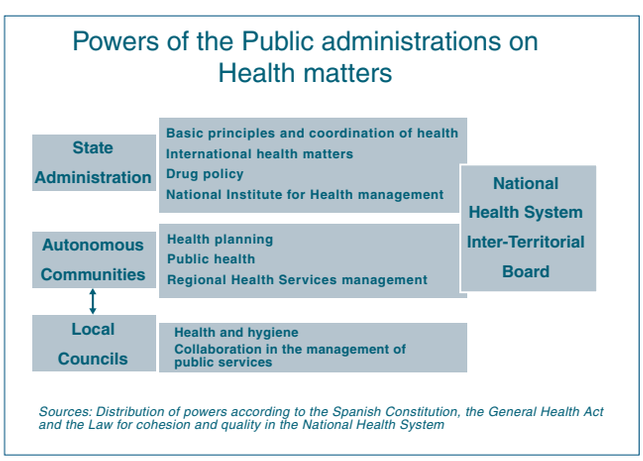
The devolution of public health powers began in 1979 and was completed in 1985 while devolution of healthcare powers began in 1981 and was completed in 2002, except for the autonomous cities of Ceuta and Melilla where the Central State Administration has kept the responsibility for health management.

Currently, the ACs hold powers for health planning, public health and healthcare. They have therefore taken on the functions and services, goods, rights and obligations relating to such powers, as well as the staff and budgets assigned to them.

The ACs should warrant minimum common health services within their territory and compliance with national public health and surveillance agreed protocols.

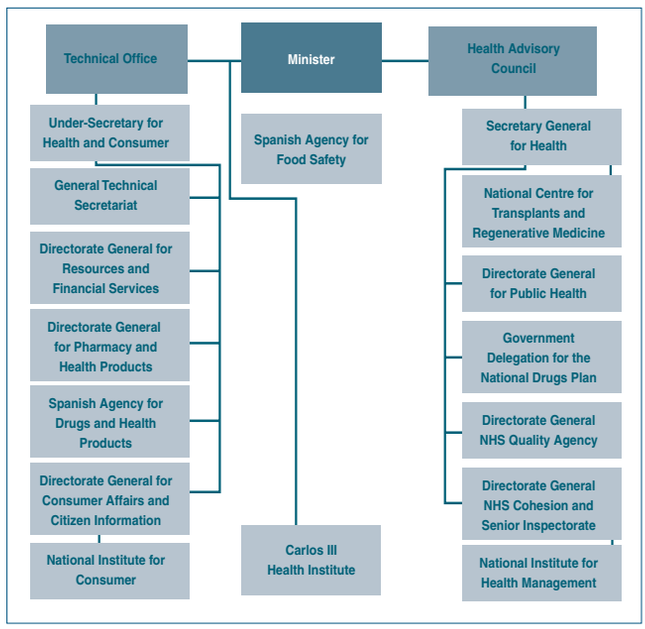
Their healthcare budget is allocated per capita and the ACs have the freedom to prioritize health matters within their own territory once minimum requirements set up by the State administration are satisfied.

Each AC has a Regional Health Service, which is the administrative and management body responsible for all the centres, services, and facilities in its own Community, whether these are organized by regional or town councils or other intra-Community Administrations.



The respective powers of the different public administrations, i.e. State Administration, ACs and Local Councils, in relation to health matters, are illustrated in the graph (bottom left of page), also showing the coordination role of the Inter-Territorial Board.

The overall structure and organization of Spanish MOH responsibilities is illustrated below.



Other basic functions within the MOH include public health, food safety and health research.

The Directorate General for Public Health leads actions to promote health and prevent illness, including environmental health and health at work while health research policy is essentially carried out at the Carlos III Health Institute, as well as other Ministry-run centres.

National Health System: Organization of Healthcare

Healthcare is organized at two levels within the Spanish NHS, including primary healthcare and specialist care.

Primary healthcare

Primary healthcare is characterized by extensive accessibility and sufficient technical resources to resolve the most frequent health problems. Primary healthcare aims to provide basic services within a 15-minute radius from any place of residence. The main facilities are the primary care centres which are staffed by multi-disciplinary teams comprising general practitioners, paediatricians, nurses and administrative staff and, in some cases, social workers, midwives and physiotherapists. Since these centres are located within the community, they also deal with health promotion and preventive healthcare. Maximum accessibility and equity means that primary healthcare also reaches homes when necessary.

Each AC establishes its own health areas according to demographic and geographic criteria. Health areas are then subdivided into basic health zones, which are the territorial framework for primary healthcare and the primary care centres.

Specialist care

Specialist care requires more complex and costly diagnostic and therapeutic resources. Access to specialist care is gained by referral from primary healthcare. Specialist care is provided in specialist centres and hospitals, for both in- and outpatients. Each health area has a general hospital for specialist care.

In terms of healthcare facilities, there were 2,702 primary care centres in the whole of Spain in 2004. In 2005, out of 779 hospitals, 37.6% (293 hospitals; 103,592 beds) belonged to the Public Health sector while 42.7% (333 hospitals; 31,075 beds) belonged to the private profit-sector. [Sources: Ministry of Health and Consumer Affairs, Regional Departments of Health of the Autonomous Communities and National Catalogue of hospitals]

In terms of human resources, the figures collected by the National Statistics Institute for 2004 are presented in the table on the right.

Based on a presentation by P Santa Olalla Peralta, Dirección General de Salud Pública, Ministerio de Sanidad y Consumo, Madrid, Spain.

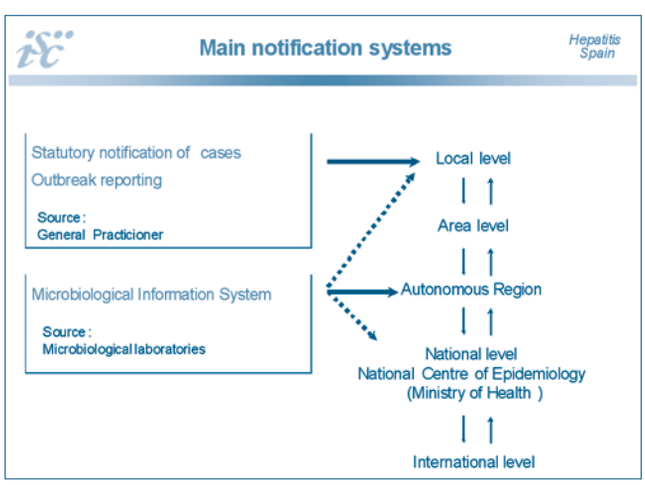
Registered health professionals, 2004			
	Total	% women	Registered health professionals per 1,000 inhabitants
Physicians	194,668	41.4	47
Dentists	21,055	40.5	0.5
Pharmacists	57,954	68.3	1.4
Veterinarians	25,604	35.1	0.6
Nurses	225,487	81.6	5.5

Source: National Statistics Institute INE

National Epidemiological Surveillance Network for Viral Hepatitis in Spain

A system of infectious disease surveillance has been in place in Spain since 1930 with a specific surveillance system for hepatitis -based on aggregated data of the numbers of suspected cases- since 1982. In 1995, the National Network of Epidemiological Surveillance was established by law, with wide powers allocated to ACs and national decisions taken by consensus. Protocols of statutory notifications of infectious diseases, such as hepatitis A and B, were approved and implemented in 1997, legally binding all practicing doctors to notify. Individual data started to be collected, based on minimal data sets. In addition, as of 1997, cases of viral hepatitis have been differentiated between hepatitis A, hepatitis B, as well as non-A, non-B hepatitis.

The surveillance network is structured according to the following notification systems:



Statutory notification of cases applies to diseases such as viral hepatitis A and B infections; it started in 1982, without differentiation between hepatitis A and B. The mandate was published in December 1995 to be implemented in 1996. The notification started in 1997. It is a passive surveillance system whereby all cases are notified by medical practitioners from the public and private sectors within the Spanish healthcare system. Standard case definitions are based on clinical criteria and can be suspected or probable while laboratory confirmation is occasionally provided at regional level only. Aggregated data are notified weekly while individual cases are notified on a yearly basis, whereby the following epidemiological data is communicated, including case classification (suspected/probable/confirmed); immunization status; as well as age, sex and week of notification.

The **Microbiological Information System** was put in place in 1989 for diseases such as hepatitis A, B and C; systematic implementation of this information system is still ongoing to date. It is a passive surveillance system based on voluntary notifications from microbiological laboratories, mainly in hospitals. The data include individual cases of confirmed recent infections, notified weekly. The information provided relates to age, sex and geographical location. Current coverage for the whole of Spain does not exceed 25%.

An **Outbreak Reporting System** is also part of the national epidemiological surveillance. It distinguishes between urgent notification of outbreaks defined as supra-communitary and therefore considered to be of national or international interest, and all other outbreaks which are reported on a quarterly basis. A common reporting format has been used in Spain with no major changes since 1983, based on the recommendations of the WHO Surveillance Programme for Control of Foodborne Infections and Intoxications in Europe. The information provided includes age, sex, symptoms, infectious agent, mode of transmission, geographical location, contributing factors and control measures applied.
Information on outbreaks has been consolidated since 1987 thanks to the transfer of responsibilities to ACs, coupled with increased human resources and staff training.

Complementary information systems include hospital discharge providing information on age, sex, geographical location, date and diagnosis; mortality surveillance providing information on age, sex, place, date and cause of death; further information systems include seroepidemiological surveys. There are no sentinel surveillance or registries for hepatitis at national level.

Based on a presentation by C Varela Martinez, National Centre of Epidemiology, Madrid, Spain.

Hepatitis A epidemiology in Spain, including molecular epidemiology and outbreak investigation

Surveillance data

Spain is considered an area of low endemicity for HAV virus infection and is characterized by a diminishing HAV seroprevalence in the population. The HAV epidemiological pattern in Spain is characterized by low prevalence in early ages increasing toward higher prevalence in older ages. This situation was confirmed for the whole of Spain in the 1996 National Seroprevalence Survey, as illustrated below:

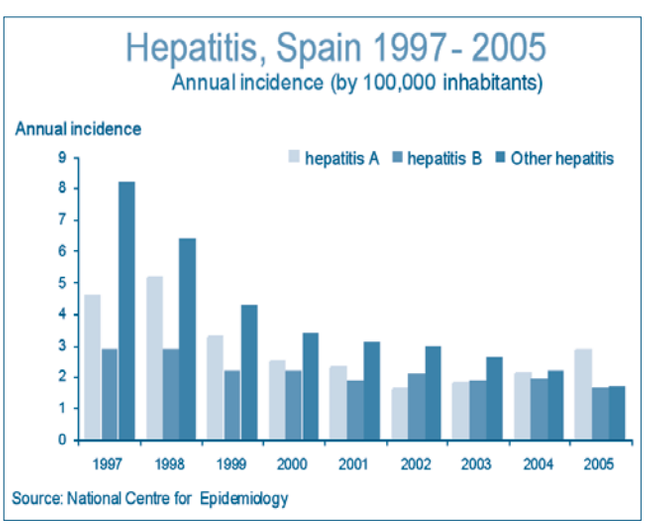
National Seroprevalence survey,1996

Hepatitis A: Immune population by age

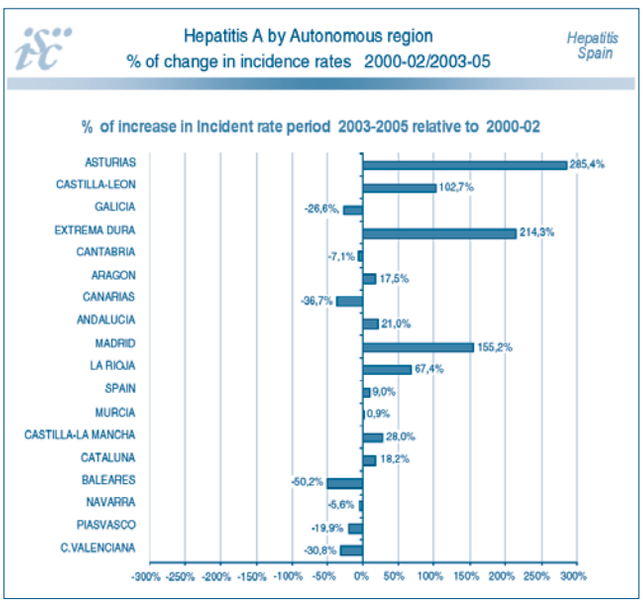
Age group	Sample size	HAV Ab Prevalence	95% CI
2-5	420	1.1	0 - 2.3
6-9	441	4	1.1 - 6.9
10-14	482	4.6	2.7 - 6.6
15-19	515	14.8	9.8 - 19.8
20-24	546	29.1	23 - 33.1
25-29	540	42	36.6 - 47.3
30-39	565	77.3	72.9 - 81.8

Within the specific area of Catalonia, a survey conducted before the introduction of HAV vaccination reported a seroprevalence of 67.8% in the general population, with less than 5% seropositivity rate reported in a group of subjects aged between 5 and 14 years [1].
These data indicate that a large percentage of the Spanish population under 30 years of age is not protected against HAV.

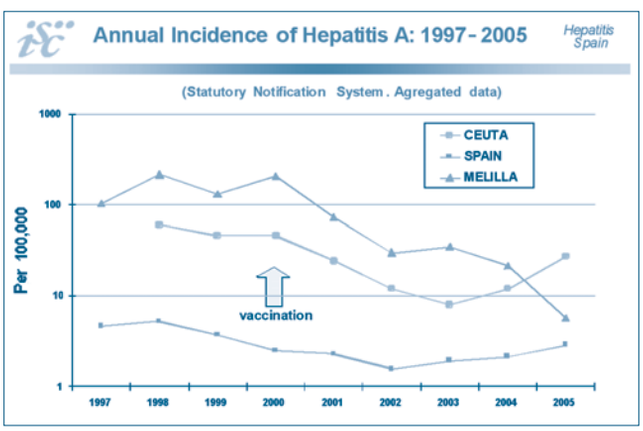
Over the period 1997-2005 a steady decrease of HAV annual incidence was observed in Spain over time, from 4.61/100,000 in 1997 to 1.60/100,000 persons-year in 2002, as reported by the National Centre for Epidemiology. However, as can be seen from graph below, the annual incidence most significantly decreased for non-A, non-B hepatitis. HBV incidence also decreased over time but to a lesser extent than the decrease in HAV incidence. The slight increase of HAV incidence which was observed between 2002 and 2005 is attributable to outbreaks.



Regional differences are illustrated in graph on top right, showing the percentage of increase or decrease in incidence rate per region over the period 2003-2005, compared to 2000-2002:



Taking a closer look at the aggregated data on the evolution of HAV annual incidence in Spain over the period 1997-2005 (see slide below), regional variations are observed, such as more important decreases observed in Catalonia, and the cities of Ceuta and Melilla, in 1998 and 2000, respectively corresponding to the introduction of HAV mass vaccination programmes in those regions.



These regional differences may be directly attributable to outbreaks in specific regions, i.e. the slight incidence increase observed in the overall data of Spain between 2002 and 2005 is not reflected in Catalonia where HAV incidence rather increased between 2001 and 2002 (a total of 19 outbreaks was reported for 2002 in Catalonia) while it decreased from 2002 to 2005. In the city of Melilla the incidence decreased from 2000 until 2005 whereas in the city of Ceuta an increase was observed between 2002 and 2005, in parallel to the situation for the whole of Spain.

Taking a closer look at the mean annual HAV incidence by sex and age over the whole period 1997-2005, the highest HAV incidence, about 8/100,000 was observed in 5-9 year-olds, and the incidence for women was lower than for men. Looking at the annual incidence by sex and age, an increase was observed in almost all age groups of both sexes between 2004 and 2005, while only a slight decrease was reported for 15-34- year-old men. In terms of regional differences, the incidences for the whole of Spain and Catalonia follow a similar pattern across age groups, except for a lower incidence observed in the 15-19-year-olds in Catalonia (1.67/100,000 compared to 3.51 /100,000 for the whole of Spain).

Data from hospital discharges also showed a slight HAV incidence increase from 2003 to 2004 while mortality was very low, with only one case per year between 2000 and 2002 (2 males, 1 female) and no deaths reported in 2003 and 2004.

Outbreak investigation

Outbreak investigation is, among other tasks related to Public Health, the remit of the National Centre of Epidemiology in Spain.
The importance of this activity is related to the current epidemiological pattern of HAV in Spain, which is characterized by low endemicity, low rate of illness, maximum age of infection in young adulthood, and main routes of transmission from person to person and outbreaks.
From the outbreak reporting system, a total of 375 viral hepatitis outbreaks were reported in the whole of Spain for the period 1996-2003, amounting to 2881 cases, however causing no mortality. The geographical distribution for these reported outbreaks was mainly concentrated in the areas of Catalonia, Andalucia, Valencian Community and Madrid.
The proportion of outbreaks caused by foodborne transmission was 15% over the whole period, with more than 2/3 of the foodborne outbreaks located in the regions of Catalonia, Andalucia, Valencian Community and Murcia. Half of foodborne outbreaks were caused by shellfish and mollusks, the other half being waterborne. Seventy percent of outbreaks were caused by direct transmission while the origin was unknown in almost 15%. Main outbreak locations included restaurants and hotels, schools and homes. The average duration of foodborne outbreaks was 44 days - which is typical for this type of outbreak- while outbreaks of other origin lasted longer, with an average of 56 days.

Control measures were communicated for 63% of outbreaks, among which 72% reported implementation of more than one method, in most cases sanitary education, and/or immunization (vaccination as a measure of outbreak control is a national recommendation in Spain but this decision is taken at the level of Community) and/or contact investigation. In one out of four outbreaks additional specific control measures were implemented.

Over the period 2003-2005, the annual number of hepatitis outbreaks was respectively 36, 44 and 38, with an average of 39 outbreaks per year; the total number of cases increased from 202 cases in 2003 to 309 cases in 2005. No death was reported over this period either. More detailed information relating to these outbreak reports is provided in the table below:

Hepatitis A

Hepatitis Spain

Outbreaks Reporting System

Year	N Outbreaks	Total cases	Mean cases per outbreak	Sd	Max number Cases	Minimum number Cases	Total cases hospitalized	% hospitalized	Sd % hospitalized	Maximum % hospitalized	Minimum % hospitalized
2003	36	202	5.6	6.3	28	2	15	7.4%	16.9%	60.0%	0.0%
2004	44	175	4.0	4.1	26	2	20	11.4%	19.8%	75.0%	0.0%
2005	38	309	8.1	10.1	45	2	52	16.8%	25.4%	100.0%	0.0%
Total general	118	686	5.8	7.3	45	2	87	12.7%	21.1%	100.0%	0.0%

Outbreak investigation activities conducted during the past ten years within the framework of the epidemiological training programme in Spain have focused on the development, evaluation and improvement of public health instruments.

To this purpose, a total of 12 hepatitis outbreaks were thoroughly investigated, among which 10 HAV outbreaks, one caused by HBV and one caused by HCV. Outbreaks occurred in numerous ACs of Spain and, in 70% of cases, the outbreaks took place at Community level. The main route of transmission was oral-faecal, but foodborne and waterborne outbreaks were also reported.

In terms of investigational procedures, the general criteria for outbreak investigation were applied, i.e. descriptive characterization of place, time and person in order to establish the relations between cases; case and control studies were also conducted. From these studies it could be established that the observations made were in line with similar studies on HAV disease worldwide.
Practically, the protocol questionnaire used for the notification of viral hepatitis in Spain was adapted to HAV investigation and information relating to general case notification, clinical symptoms, laboratory information, risk factors and control measures was obtained.

The objectives of these investigational activities include an assessment of the magnitude of the outbreak, the identification of source and vehicles, and risk factors for transmission.

The different types of studies conducted included case-finding by contacting clinicians and laboratories, descriptive studies, case-control studies (with case definition) among residents or communities, microbiological and environmental studies, etc.

Investigations performed within this programme included:

HAV outbreak due to contaminated food in Ceuta, February 2006: descriptive, case-control and environmental studies made it possible to characterize cases, locate the outbreak in place and time, as well as identifying the source of exposure. The laboratory information obtained also played an important role in this investigation.

HAV outbreak in Guadalajara, October 2000-May 2001: studies conducted have shown the epidemiological curve of the outbreak, i.e. the high number of cases observed among young adults at the beginning of the outbreak, increasing toward older age at a later stage of the outbreak. Also, the relation between primary case and secondary cases could be described thanks to a study of the geographical distribution of schools in the outbreak area.

HAV outbreak in Ibiza, September 2000-January 2001: because of the importance of Ibiza as a tourist destination in Spain, this study has shown the international implications of outbreak investigation with the simultaneous notification of HAV cases from Germany (German tourists in Ibiza) and the notification of outbreak situation in Ibiza. The primary case could be identified as a person working in a shop and restaurant in two distinct areas of the island where HAV cases were concentrated.

Current recommendations made by the National Centre of Epidemiology on the basis of results from the HAV outbreak investigation programme include the need for improved hygiene among food handlers; strengthened surveillance for foodborne diseases (in order to minimize underreporting) and enhanced cooperation at local and community level, as well as international cooperation when appropriate. At national level, vaccination is a recommended measure in outbreak control.

On the basis of information gathered from this programme, the National Centre of Epidemiology processes the following control instruments: protocols and guidelines, national databases and registries (including notifications and microbiological information), coordination, communication and follow-up of supra-regional investigations, international liaison with surveillance networks, and related publications (such as the Boletín Epidemiológico Nacional).

Molecular epidemiology: detection and identification of HAV strains

The epidemiology of water- and foodborne HAV in Spain was also investigated at molecular level. HAV strains recovered from clinical samples (anti-HAV IgM positive serum samples from patients with acute hepatitis) over the period 1990-2000 at the Hospital General Valle d'Hebron - Barcelona, Spain, as well as environmental water samples from urban

sewage and superficial water over the period 1994 to 2000 were analysed, using genetic amplification and characterization techniques [2]. Shellfish samples collected over an 18-month period from shellfish-growing areas in Spain -Western Mediterranean and the Spanish Atlantic Ocean- were also analyzed for HAV presence [3].

The data show that in the region of Catalonia over the period 1994-2000, HAV was circulating in the environment. HAV was frequently isolated from sewage water, rivers and occasionally in shellfish (see table below).

Presence of HAV in the environment and in food - Catalonia (1994-2000)

Type of sample	Positive samples detected by nested PCR
Sewage water	31/54 (57.4%)
Llobregat River	22/56 (39.2%)
Ter River	2/10 (20%)
Shellfish	4/104 (3.8%)

The presence of HAV was also assessed in clinical serum samples from patients with acute hepatitis, collected between 1990-2000. Among these samples, 26/74 (35.1%) of patients were positive for anti-HAV IgM and of these, 16/26 were positive for HAV-RNA.

The isolated HAV genomes were further characterized by direct sequencing. Results showed a 95% prevalence of HAV genotype 1 in the environment samples as well as in the clinical samples, with nearly 50% being either subgenotype 1A or subgenotype 1B. Various strains were found simultaneously in environmental and clinical samples. These strains appeared to be closely related to those described in distant geographical areas. Genotype 3A was also found but with a lower prevalence: 5% in sewage samples and 12.5% of serum samples. Strains belonging to a common endemic genotype were not identified. Also, both HAV and HEV isolates were occasionally identified in the same sewage samples (this is further developed in the section of this report relating to the epidemiology of HEV).

It was concluded from these molecular epidemiology data that the abundance of HAV in the environment, as tested in Catalonia, represents a situation of sanitary risk, especially considering the low seroprevalence of anti-HAV antibodies in the young population.

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HEV epidemiology in Spain and molecular diagnosis

HEV is transmitted primarily by the faecal-oral route. Faecally-contaminated drinking water is the most commonly documented route of transmission of HEV, person-to-person transmission appears to be uncommon.

Worldwide, two epidemiological forms have been described. HEV causes major outbreaks of acute hepatitis in endemic areas, especially in developing countries located in tropical and subtropical regions of the world where outbreaks are usually associated with faecal contamination of drinking water. In these countries, HEV is also responsible for sporadic acute hepatitis. In non-endemic, industrialized countries, isolated cases of hepatitis due to HEV have been reported, even in patients who were never linked to areas of HEV endemicity and had no contact with HEV-infected individuals. Reports of such autochthonous cases in non-endemic areas, defined as HEV in patients without history of travelling to endemic areas, raised the suspicion of an animal reservoir for HEV in industrialized countries.

Typical clinical signs and symptoms of acute HEV are similar to those of other types of viral hepatitis. Peak viremia and peak shedding of HEV into the faeces occurs during the incubation period and early acute phase of disease. Virus excretion in stools has been demonstrated up to 14 days after illness onset. Mortality is low (approximately 0.5 – 4.0% of patient population), except for pregnant women, where mortality rates can reach up to 20% [1].
In the last decade, many seroprevalence studies were carried out in industralized and developing countries to evaluate the presence of HEV in different animal species, such as rodents, poultry, cattle and swine. Swine appear to be the most important animal species involved in the spreading of HEV in the environment because of the great amount of manure generated, and the first HEV animal strain was of swine origin [2].

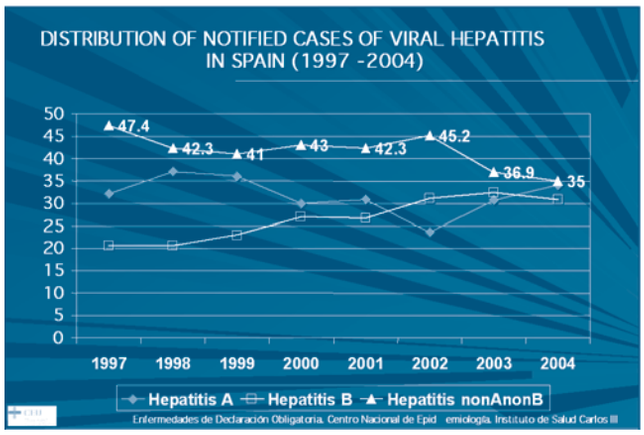
Diagnosis of HEV

Both IgM and IgG antibody to HEV (anti-HEV) are elicited following HEV infection. The titre of IgM anti-HEV declines rapidly during early convalescence; IgG anti-HEV persists and appears to provide at least short-term protection against disease.
Several diagnostic tests are available in research laboratories. Enzyme immunoassays and Western blot assays are used to detect anti-HEV IgM and IgG in serum. These can be complemented by polymerase chain reaction (PCR) tests to detect HEV RNA in serum and stool.

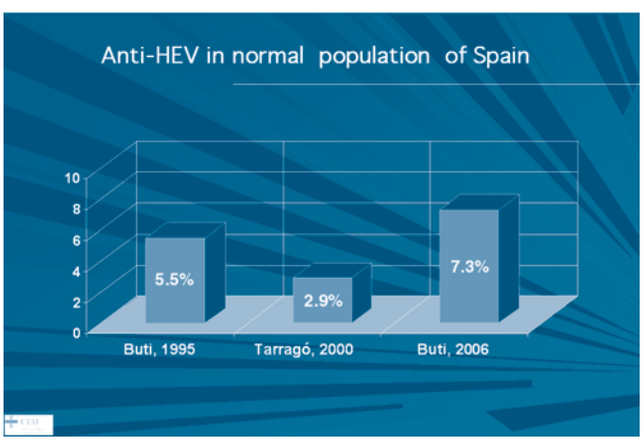
In industrialized countries, including Spain, lack of specificity of commercial ELISA test has been observed. Confirmation of HEV ELISA positivity by immunoblot is therefore extremely important for an accurate diagnosis of HEV.

HEV prevalence in the Spanish population

The distribution of viral hepatitis cases in Spain, notified by the National Centre of Epidemiology, shows that between 1997 and 2004 the proportion of non-A, non-B hepatitis cases decreased from 47.4% in 1997 to 35% in 2004 (next page). However, it should be noted that these non-A, non-B reports not only include HEV cases, but also HCV and hepatitis D cases, as well as hepatitis cases caused by other etiological agents.

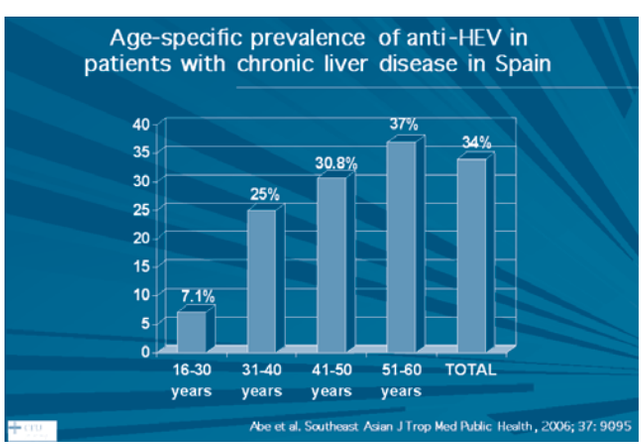


A limited number of studies have investigated the epidemiology of HEV in Spain and three reports on overall anti-HEV seroprevalence in the Spanish population have been published. In 1995 Buti *et al.* reported a 5.5% anti-HEV seroprevalence [3], whereas in 2000, Tarragó *et al.* reported a seroprevalence of 2.9% [4] (see below). More recently, Buti *et al.* (2006) found the prevalence of anti-HEV IgG antibodies in a population sample including both urban and rural areas of Catalonia to be 7.3% [5], compared to 3-20% in other industrialized, non-endemic countries.



Four studies reported HEV seroprevalence rates from 1994-2004 among Spanish patients with acute hepatitis, based on commercial ELISA data. In 1994 Buti did not detect any HEV positive patient on a total of 341 patients tested [6]. One year later, the same author reported a 5.6% seroprevalence [3]. In 2004 Pérez-Gracia *et al.* [7] reported a 7.7% seroprevalence by ELISA and confirmed by immunoblotting.

The prevalence of anti-HEV among patients with chronic liver disease has been reported by several studies to be significantly higher than that among persons with no apparent liver disease. Recently, Abe *et al.* [8] found 34% of Spanish patients with chronic liver disease to be seropositive for anti-HEV by ELISA. The prevalence of anti-HEV among this population increased with age, from 7.1% in the age class of 16 to 30 years up to 37% in patients aged 51 to 60 years.



HEV prevalence in the environment

The sporadic presence of clinical HEV strains in non-endemic areas has led to studies investigating the presence of the virus in the environment and the potential role of swine as an animal reservoir in acute hepatitis cases.

Several studies conducted in Spain were able to detect HEV in sewage water. A first study was published in 1998 by Pina *et al.* [9] who found one out of 37 (2.7%) urban sewage samples collected in Barcelona between 1994 and 1998 to be positive for the presence of an infectious HEV strain. In 2000, the authors [10] reported 8.3% HEV RNA presence in slaughterhouse samples and, in 2003, Clemente-Casares *et al.* [11] found 43.5% (20/46) of the urban sewage samples collected in Barcelona between 1994 and 2002 to be positive for HEV.

Additional work has been done in the detection of HEV in porcine serum and faeces samples. The results indicate that HEV is circulating in swine herds of Spain, in line with reports from other industrialized countries. Serum anti-HEV IgG antibodies were identified in 19% of swine tested in Catalonia (genotype 3). The presence of HEV RNA in up to 50% of porcine faeces samples [11,12,13] suggest that HEV could be more widespread than previously thought and raises concern about the use of manure as soil fertilizer.

Molecular epidemiology of HEV

Clinical and environmental samples were collected for PCR-analysis and identification of HEV strains infecting the population. An extensive genomic diversity has been observed among the different HEV strains isolated in Spain; in total 22 strains were identified. Six different HEV strains were isolated from clinical serum samples from Spanish patients with acute hepatitis (3 positive samples between 1989-99, and 3 in 2003). Of these, five human strains could be identified: one was isolated from a patient who had recently traveled to Ethiopia (genotype 1). The remaining strains (genotype 3) were from patients who had not traveled to endemic areas and were therefore considered as autochthonous HEV cases.

The majority (16/17) of sewage HEV strains belonged to genotype 3 and all swine HEV RNA isolates were also of genotype 3. Importantly, comparison of porcine and human HEV genome sequences revealed a close relationship between HEV strains isolated from sewage samples, human HEV strains causing acute hepatitis and the swine HEV strains identified in the same area. Of note, swine HEV strains appear to be more similar to the human HEV strains from the same area than to swine HEV strains from other areas. This indicates that swine might be a reservoir for HEV in Spain. In addition, both HAV and HEV strains were occasionally identified in the same sewage samples, indicating that HEV and HAV viral strains are circulating in the same location.

HEV should be considered as an environmental contaminant even in highly industrialized countries and the transmission routes of the infection must be further investigated. The dissemination of HEV genotypes that can cause outbreaks over the regions previously considered non-endemic (and where genotype 3 is the common genotype), should be monitored and evaluated.

These findings highlight the importance of including HEV testing in the routine diagnostics of acute and fulminant non-A, non-B, and non-C hepatitis even when no history of travel has been reported by the patient. The development of a reliable serological assay is crucial to estimate the real prevalence of HEV in non-endemic areas.

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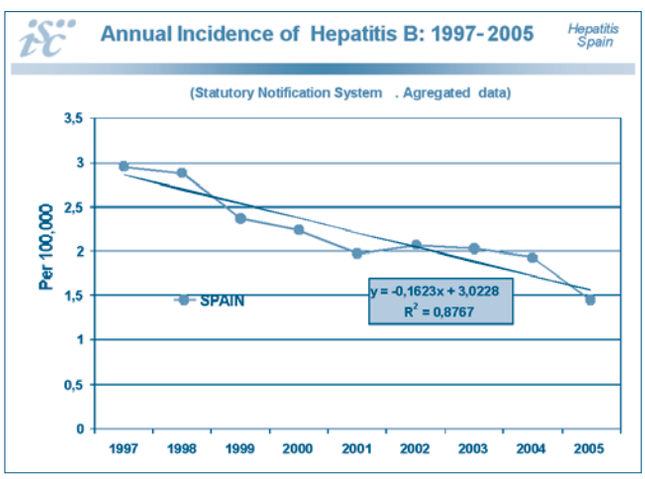
Based on presentations by R Gironès, University of Barcelona, Dpt. of Microbiology, Barcelona, Spain; MT Pérez-Gracia, University CEU Cardenal Herrera University, Dpt. Sanitary Attention, Public and Animal Health, Valencia, Spain.

Hepatitis B epidemiology in Spain, including molecular epidemiology and outbreak reporting

Surveillance data

Spain is a region of low HBV endemicity characterized by a steady decrease in the annual incidence. The statutory notification system reported a reduction of the incidence from 2.96 per 100,000 in 1997 to 1.45 per 100,000 in 2005, as illustrated in graph below.



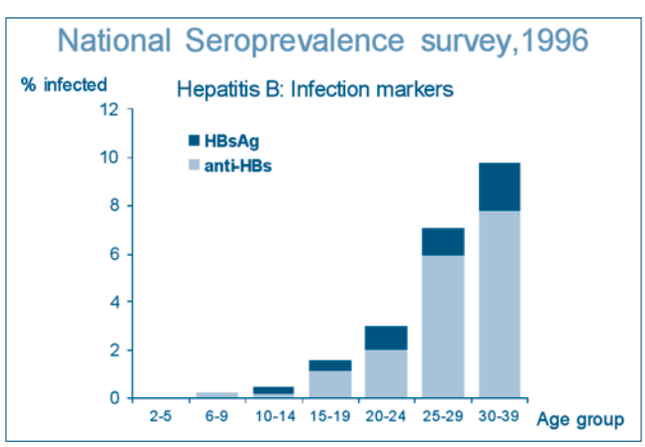
As appears from the 1996 survey, HBV infection marker, anti-HBc, starts to increase as of the age of 10-14 yrs / 15-19 yrs from <2% to reach >9% in the 30-39-year-olds (1.95% HBsAg positivity) (see table and graph on the right):

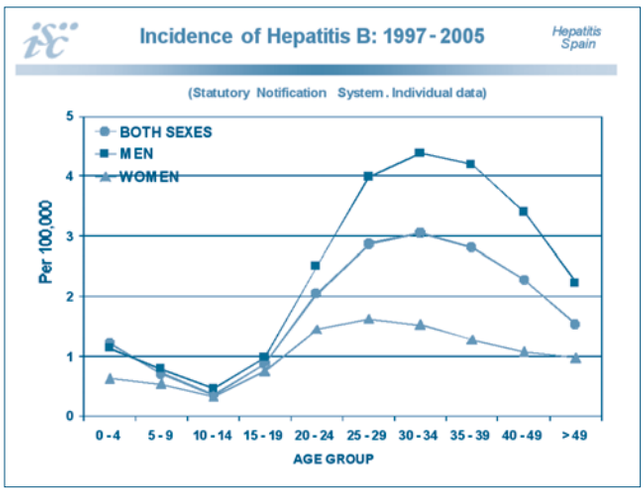
Looking at the mean annual HBV incidence data by sex and age over the period 1997-2005, the highest incidence was observed in the 20-49-year-olds while incidence in men was higher than in women across all age groups (see graph overleaf).

National Seroprevalence survey,1996

Anti-HBc Prevalence

Age group	Sample size	Prevalence	95%CI
2-5	418	0	0
6-9	439	0.3	0 - 0.9
10-14	481	0.6	0 - 1.7
15-19	513	1.3	0.4 - 2.2
20-24	545	3.7	1.9 - 5.5
25-29	539	7.4	3.6 - 11.3
30-39	564	9.8	6.7 - 12.9





A steady decrease was observed in the number of HBV hospital discharges from 1,661 to 1,219 over the period 1997-2003, however this trend was reversed from 2003 to 2004 with a rise to 1,324 discharges.

Mortality was more important in men than women over 1999-2004, with an increasing rate as of 25 years of age, rising from 7 cases among 25-34-year-olds to 32 cases among the 65-74-year-olds over the whole period.

Outbreak reporting

The number of hepatitis B outbreaks reported during 2003-2005 amounted to 13, with an average number of 2.5 cases per outbreak. No death was reported and the proportion of hospitalized cases was very low except for the 2005 outbreaks where 3 of the 15 cases were hospitalized.

Genetic diversity of HBV in the Spanish population

With respect to genetic diversity of HBV strains in Spain, a variety of genotypes, subtypes, and stable variants were observed in unselected DNA-positive HBV chronic carriers, with some geographic and temporal differences. In 2004, mutations previously reported to be associated with potential vaccine failure, immunoglobulin therapy resistance, or diagnostic test detection failure were identified in maximum 2.3%, 6.5% and 10.4% of the carriers respectively. The clinical significance of such mutants remains to be questioned; indeed this relatively high frequency of HBsAg mutants had only a minimal effect on the performance of diagnostic tests. The HBV mutants detected therefore do not seem to cause a measurable threat to current HBV vaccination policy. The frequency of amino acid substitutions in polymerase that are associated with antiviral resistance in chronic carriers also seemed to be low.

HBV in the blood transfusion setting in Spain

The seroprevalence of HBsAg in the Spanish population is <2%. In 2004, about 1.6 million blood donations were screened and the prevalence of HBsAg-positive blood donors was shown to be 0.04%, as detailed in the table below:

Spanish Blood Centers Statistics, 2004

	SPAIN		MADRID	N° Donations tested	Confirmed donations
	U x 100 000	prevalence	U x 100 000		
HIV-Ab	5.77	1/20,000	5.89	1,610,824	93
HCV-Ab	30.27	1/3,333	37.15	1,608,733	487
HBsAg	36.75(*)	(0.04%) 1/2,700	55.27	1,610,824	592
SIFILIS	16.82	1/5,900	16.76	1,610,826	271

(*) Range: 8,03 Vasque Country up to 56,20 Canary Islands

Safety testing of blood donations in Spain includes compulsory HBsAg assay and, of secondary importance, non-mandatory anti-HBc antibody and alanine aminotransferase (ALT) testing. Nucleic acid testing (NAT) is not mandatory but in 2006 it was used in 80% of blood donations.

Most blood donation centres in Spain decided not to implement anti-HBc antibody testing. The main reason is that the prevalence of anti-HBc-positive donors is quite high. In 1996, a 6.1% (130/2,161) prevalence of anti-HBc among blood donors was found and a more recent study conducted in blood centres in Catalonia found the rate to be 4.2% (651/15,545). Importantly, anti-HBc screening does not avoid transmission by blood donations during the window period of HBV infection.

The infection window period is an important issue in the setting of blood transfusions. Mathematical models predicted that in Spain, a significant number of blood units would be obtained during the window period of HBV infection (i.e. 1/100,000 donations).

By applying NAT-technology for HBV DNA screening in the blood bank setting, 30 days are gained in the window period for detecting HBsAg-positive donors, as compared to conventional serological enzyme immuno assay (EIA - Auszyme) or chemoluminescence assay (PRISM) [1].

In the four blood donation centres that started using HBV NAT-testing between 2004 and 2005, approximately 400,000 individual blood units were screened for HBV DNA up to December 2005. The methodology used was an initial screening for HBsAg (with EIA or chemoluminescence assay) and triplex NAT testing for the presence of 3 viruses (HBV, HCV, HIV). Initially reactive samples were re-tested and submitted to discriminatory testing to ascertain which of the 3 viruses was involved in the DNA signal. In addition, the donors were recalled for providing follow-up samples at different time points. The index donation and follow-up samples were submitted to an alternate NAT test and to extended HBV marker testing. The viral load of samples of positive cases was determined and for some cases, a fragment of HBsAg DNA was amplified for sequence analysis.
Among the yield cases detected up to December 2005, a total of 4 window period cases were identified, representing a rate of 1/98,600 donations. Of these, 3 were detected in a blood centre applying NAT testing of individual donations and 1 in a centre testing minipool samples (pool size of 8 donations). In addition to these 4 window cases, another occult phase donor positive for anti-HBc IgM antibodies was detected.
The results of this confirmatory testing and follow-up studies indicate that routine NAT testing of individual blood units would make a significant contribution to improving the safety of the blood supply in Spain by reducing the residual risk of HBV transmission. Moreover, a good correlation was found between the frequency of window phase cases found to be HBV DNA-positive by NAT and the frequency predicted by mathematical models (1/98,600 versus 1/100,000 donations, respectively).

Yield of HBV-DNA screening (Ultrio) (until December 2005)

Pool size	pre (post) HBsAg window phase infections	anti-HBc reactive occult HBV infections	Total yield HBV-NAT HBsAg negative	donations tested
MP-NAT (1:8)	1	5	6	237,357
yield rate	1:237,400	1: 47,500	1:39,600[a]	
ID-NAT	3 (1)	11	15	157,207
yield rate	1:52,402	1:14,300	1:10,500[a]	
total	4 (1)	16	21	394,564
yield rate	1:98,600	1:24,700	1:18,800	

[a] p<0.0001

MP: minipool
ID: individual donation

In silent, anti-HBc reactive but HBsAg-negative samples (i.e., samples from donors with so-called late phase or occult HBV infection), the yield of HBV identification using NAT technology was 1/24,000.

Individual donation testing by NAT was significantly more effective than NAT testing of mini-pools (pool size of 8 donations) in detecting low viral load in donations from donors in window phase as well as in donations from donors with occult HBV infection (see slide bottom right of page 10).

Individual donation-NAT testing was able to detect low viral load in donations from occult HBV infection carriers. The viral load in occult HBV infection samples ranged from values as low as 4.8 copies/ml to nearly 900 copies/ml. Of note, the question whether occult HBV infected individuals are really infectious by transfusion remains.

Among blood donations that were positive by HBV-NAT, HBV strains of genotype D were most prevalent. This was expected since HBV genotype D is the most prevalent type, overall in Spain. Apart from wild type HBV, numerous amino acid changes were identified in occult HBV infection cases; many of these mutations had not been previously described. Certain HBsAg mutants may be missed by some serological assays in blood donation testing.

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Based on presentations by E. Castro and R. Gonzalez, Red Cross Transfusion Centre (Serology Dpt.), Madrid, Spain; A. Avellón, National Centre of Microbiology, Spanish Hepatitis Reference Laboratory (Diagnostic Microbiology Service), Madrid, Spain; P Santa Olalla Peralta, General Directorate of Public Health, Spanish Ministry of Health, Madrid, Spain; C Varela Martinez, National Centre of Epidemiology, Madrid, Spain .

Hepatitis C epidemiology in Spain, including molecular diagnosis and prevalence in dialysis units

HCV epidemiology in the general population

No national data are available relating to HCV prevalence in Spain, however it is estimated that about 2% of the population has been infected with HCV (representing 800,000 to 1,000,000 persons) (see below). Several studies conducted in different parts of the country found prevalence rates in the general population ranging from 0.7% (Zamora, 2001) to 2.64% (Catalonia, 2002) [1-4]. The prevalence is higher in selected populations, such as immigrants (8.8%) [5] or drug users (up to 82%) [6].

Prevalence of Hepatitis C in Spain

Area	Population (n)	Prevalence*	Author	Year
Cataluña	General (2,154)	2.6%	Sola	2002
La Rioja	Urban (890)	2%	Sacristán	1996
Galicia	General (1,170)	1.6%	Riestra	2001
Murcia	General (2,203)	1%	García-Fulgueiras	1996
Zamora	General (675)	0.7%	Chimeno	2001
Alicante	Drug addicts (832)	82%	Esteban	1997
Madrid	Immigrants	8.8%	López-Velez	2003
Spain	Estimated	2%		

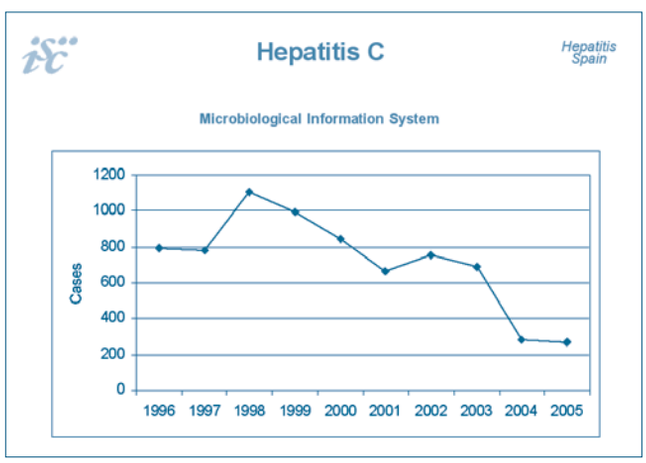
Around 70% of HCV-Ab positive are HCV-RNA positive

*according to HCV-Ab positivity

Preventive measures have led to a significant decrease in the incidence of HCV. Although HCV is not part of the mandatory notification system in Spain, it could be established from data collected via the microbiological information system -which covers 25% of Spain- that the number of new infections dropped significantly from 793 reported cases in 1996 to 265 reported cases in 2005 (see on right).

The data collected via the microbiological information system also showed that the total number of cases over from 1996 to 2005 was more important in men than women, in particular in the 25-44-years age group where the ratio male/female was 3 to 1. This age group accounted for more than half of the reported cases.

Data from hospital discharges have also shown a significant decrease in the number of diagnosed HCV cases from 4,131 in 1997 to 1,888 in 2004.



Over the period 1999-2004, for the 25-64-year-old group, a higher mortality rate was observed in men, whereas the trend was reversed as of 65 years of age. The majority of fatalities, more than 70 %, were reported from the 65-year-old group or older.

Two HCV outbreaks were notified over the period 2003-2005: one involving 8 cases in 2003 and one involving 17 cases (1 hospitalization) in 2004, with no death reported.

Transmission and molecular diagnosis of HCV

Up-to-date molecular techniques are used for the diagnosis and analysis of HCV infection in Spain. These techniques helped to establish transmission mechanisms and can be used to identify the source of infection by phylogenetic analysis of e.g. infected patients, and potential sources of nosocomial infection [7].

HCV is mostly transmitted via the following routes:

- parenteral transmission, mainly due to IV drug use and nosocomial infection (patient-to-patient, during haemodialysis, etc.)
- non-apparent parenteral transmission (e.g. healthcare workers)

In Spain, drug addiction is the most prevalent risk factor for HCV infection, followed by nosocomial infection due to normal clinical practice. Other mechanisms of transmission that may induce chronicity are residual.

Mother-to-infant transmission is only related to few special cases and is associated with high HCV viral load at delivery or human immunodeficiency virus (HIV) coinfection. Overall, sexual transmission appears to be very rare; only one case was reported in 1998. The use of barriers (condoms) may be recommended when there are sexual lesions.

The benefit of molecular epidemiology has not only been demonstrated by identification of the source of HCV infection and the establishment of its transmission mechanisms, it has also resulted in the modification of clinical procedures to prevent additional nosocomial infections. HCV transmission during clinical procedures has already been reported and investigated in several settings, e.g. patient-to-patient by using multi-dose vials, during haemodialysis, during Contrast-Enhanced Computer Tomography scanning by using multi-dose contrast medium, and by healthcare provider-to-patient transmission.

Results of molecular analysis can be used in matters as liability of healthcare providers, and compensation of nosocomially infected patients.

Epidemiology of HCV among dialysis patients

Dialysis patients are at high-risk for HCV infection, transmission in haemodialysis (HD) units has frequently been reported.

Since 1991 an epidemiological surveillance of HCV has been conducted in Spanish dialysis units. This survey collects an annual registry of HCV prevalence, together with the incidence in the different dialysis modalities. More than 50% of the Spanish dialysis population has been involved in this survey, with the number of participating centres increasing from 84 centres in 1991 to 135 centres in 2003, representing 5,218 to 10,597 participating dialysis patients, respectively.

The prevalence of HCV in Spanish dialysis patients was initially high, but decreased over time throughout the study, as illustrated on the right.

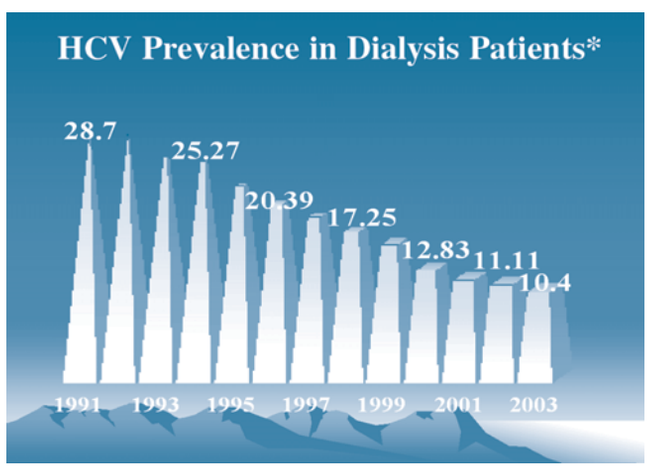
HCV prevalence was higher in HD patients than in peritoneal dialysis (PD) patients over the whole period. The prevalence of HCV among HD patients decreased from 36% in 1991 to 11.22% in 2003. In PD patients the prevalence was lower: 10.6% in 1991 and 7.5% in 2003.

Strict adherence to the universal infection control precautions [8] has been deemed adequate to prevent nosocomial transmission of HCV. However, in units with high prevalence of HCV infection, the implementation of universal precautionary measures may not suffice in order to decrease the incidence and prevalence of HCV. In this type of setting, strict isolation practices can be useful in order to achieve this goal.
Isolation measures to prevent nosocomial HCV infection in dialysis units were introduced in Spanish dialysis centres as of 1991 and since then, the number of dialysis centres adopting isolation measures increased over time, from 29.8% of centres in 1991 up to 96% of centres in 2003. The most frequently applied isolation measure is the use of dedicated monitors (HD-machine) and healthcare providers for HCV-positive patients in a defined sector of the unit. A few centers have specific HD sessions for HCV-positive patients or dialyze them in a separate unit.

The prevalence of HCV in Spanish dialysis units applying isolation measures appeared to be lower throughout the survey (1991-2003) than in centres not adopting specific isolation practices. Universal infection control precautions are the keystone in the prevention of nosocomial HCV transmission in HD units, but isolation measures have improved the results. Dialysis centres with high HCV prevalence appeared to represent a risk factor for patients becoming HCV-positive due to dialysis unit attendance. In these centres, isolation measures, in addition to the universal precautions, may be most critical to prevent patient seroconversion.

Accidents in HD units with blood from HCV-positive patients have been reported over the period 1991-2003. As detailed in the table below, some of these accidents led to seroconversion but the annual seroconversion rate due to accidents was low, with a maximum of 4 seroconversions noted in 1997. As of 2000, no seroconversions due to accident were noted.

A regular follow-up (at 6-month interval) of HCV prevalence in staff working in HD centres is performed. As shown in table at bottom of page, HCV prevalence is highest among nurses; however, their prevalence is in the same range as that reported for the general population in Spain.



* including haemodialysis and peritoneal dialysis patients

Number of accidents and seroconversions due to accidents in HD units

Year	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003
Accidents (N)	29	36	32	34	49	58	65	64	53	26	48	46	53
Sero-conversions (N)	2	1	0	1	1	3	4	0	1	0	0	0	0

N = annual number reported

HCV prevalence in HD staff

Year	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003
Physician	0.8	0	3.7	0.7	1.2	1.4	1.8	1.4	0.8	1.3	0.5	0.49	0.5
Nurse	4.7	1.5	3.6	2.8	3.2	2.5	3.2	2.8	3.7	2.5	1.8	1.8	2.2
Nurse Assistant	2.2	1.3	3.2	0	0	1.2	2.8	1.5	1.8	1.7	0.7	1	0.69
Nurse	0	0	0	0	0	2.2	0	0	3.5	0	0	0	0

In 2004, the Spanish Society of Nephrology published guidelines on HD-associated viral infections [9], emphasizing the need for the personnel of HD units to adhere to universal precautions. These guidelines describe minimal requirements and procedures for the most at-risk virus infections in dialysis units (HBV, HCV and HIV). The document provides an actualization of possibilities of virus treatment together with current legislation and implications of HCV infection for patients and staff. Actions to be taken in case of an epidemic outbreak or in case of an accident of staff with infected blood are described. The guidelines also consider conditions necessary for inclusion of these patients on the waiting list for kidney transplantation.

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Based on presentations by C. Varela Martinez, National Centre of Epidemiology, Mandatory Notifiable Diseases, Madrid, Spain; P. Barreiro, Service of Infectious Diseases, Hospital Carlos III, Madrid, Spain; J. Quer Sivila, Liver Unit, Hospital Vall d'Hebron, Barcelona, Spain; G. Barril, Unit of Hemodialysis, Hospital de la Princesa, Madrid, Spain.

Prevalence of viral hepatitis in HIV-infected individuals in Spain

Prevalence of HCV-HIV coinfection among HIV-positive mothers of newborn babies

Since the introduction of highly active antiretroviral treatment (HAART) in the mid 90's, less HIV-infected patients die from HIV-related or AIDS-indicative diseases but more die from other causes, many of them hepatic conditions.

HCV-positive end stage liver disease (ESLD) has become a leading cause for morbidity and mortality in HIV-positive patients and the liver damage caused by HCV disease progresses more rapidly in HIV-positive individuals. As illustrated in slide below, the percentage of hospital discharges among HIV-infected patients with the HCV diagnosis (as main reason for hospitalization or not) gradually increased from 17.6% in 1999 to 26.3% in 2002 in Spain while the same parameter has remained stable for other viral hepatitis infections (e.g. 3.6-4.1% for HBV over the same period). It is expected that the presence of this large cohort of HIV patients coinfected with HCV will have an impact on the demand of health resources for clinical care.

There was a dramatic decrease in the number of new AIDS cases among injection drug users (IDUs) in Spain between 1994 (about 5,000 cases) and 2005 (744). Still, IDUs, who are also at high risk for HCV infection, represent an important risk category for HIV/AIDS transmission in the country.

In the context of prevention of HIV infection and more specifically, mother-to-child transmission (MTCT) of HIV-HCV, an epidemiological information system was established to estimate the prevalence of HIV infection and HIV-HCV coinfection in unselected mothers of newborn babies. The system was initiated in 1996 in 8 autonomous regions of Spain and is based on anonymous testing in newborn babies. The testing is performed on residual dried blood spot samples from routine neonatal screening and the results are unlinked for identifiers. Samples that tested positive for HIV were subsequently tested for anti-HCV. In the period 1998-2004, the overall proportion of HIV-positive mothers with anti-HCV antibodies (data available for 5 regions) was 39.5%. The table below shows the aggregated data from 1998 until 2004.

SPNS

Hospital Discharges among HIV patients with a diagnosis of viral hepatitis[a] (N, %). 1999-2002

	1999 N(%)	2000 N(%)	2001 N(%)	2002 N(%)
Hepatitis C*	3,733 (17.6)	4,321 (21.0)	4,916 (24.6)	5,211 (26.3)
Hepatitis B	771 (3.6)	830 (4.0)	814 (4.1)	790 (4.0)
Other viral hepatitis				
Hepatitis A	12 (0.1)	12 (0.1)	4 (0)	16 (0.1)
Hepatitis Delta (wth hep B)	14 (0.1)	15 (0.1)	20 (0.1)	16 (0.1)
Hepatitis E	5 (0)	4 (0)	3 (0)	1 (0)
Other	17 (0.1)	14 (0.1)	17 (0.1)	6 (0.1)

[a] A patient can have more than one diagnosis
*p<0.05 in chi-square test for trend

Source: CMBD

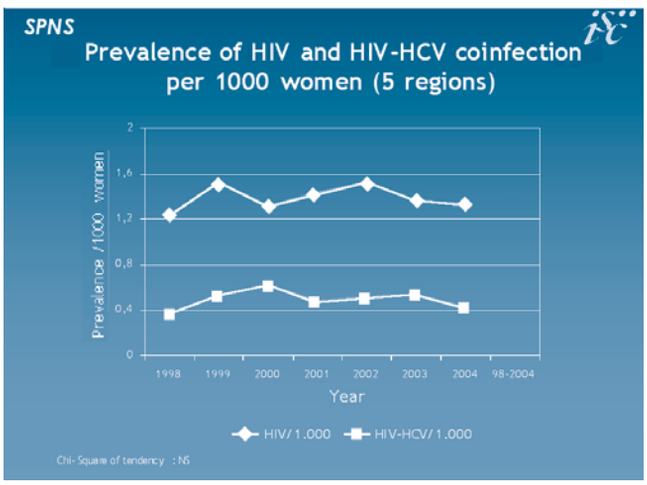
SPNS

HCV prevalence in HIV-infected mothers, 1998-2004 (5 autonomous regions)

Autonomous Region	Number Tested	HIV: Prev HIV + /1000 (95% CI)	HCV-HIV: HCV + (n)	HCV-HIV: Prev HIV-HCV + /1000 (95% CI)	HCV-HIV: Proportion HIV-HCV+ /HIV+
CANARY ISLANDS	102,743	1.59 (1.35-1.85)	49	0.48 (0.35-0.63)	31.61
CASTILLE - LEON	106,662	1.30 (1.10-1.54)	50	0.47 (0.35-0.62)	42.74
GALICE	125,984	1.56 (1.35-1.80)	88	0.70 (0.56-0.86)	45.83
MELILLA	7,468	0.94 (0.38-1.93)	1	0.13 (0.00-0.75)	14.29
MURCIA	101,635	1.10 (0.91-1.93)	34	0.33 (0.23-0.47)	37.36
TOTAL	444,492	1.39 (1.28-1.50)	222	0.50 (0.44-0.57)	39.50

HIV + (1998-2004): 618
HCV tested: 562 (90.9%)

The HIV prevalence was about 1.4/1,000 women and the prevalence of HIV-HCV was about 0.5/1,000 women. The prevalence was quite constant over this period (see slide below).



Based on the results obtained in this unselected population of pregnant women, it was concluded that the prevalence of HIV-HCV in Spain is high in comparison with other European countries and stable during 1998-2004. It is recommended that HCV testing should be done in HIV-positive pregnant women, as well as in all those with risk factors for HCV infection.

HIV coinfection in chronic viral hepatitis (HBV and HCV)

Overlapping routes of transmission of HBV or HCV viruses and of HIV result in a high frequency of HBV-HIV or HCV-HIV coinfection. In Spanish cohorts of HIV-infected people, the frequency of HCV-HIV coinfection is one of the highest among European countries while the prevalence of HBsAg-positive HIV patients is similar to that reported in other geographic areas around Europe (see table top right) [1-3].

PREVALENCE

Cohorts	N	Anti-HCV	HBsAg
VACH Cohort 2002[1]	4,709	69.2%	6.1%
GESIDA Cohort 29/02[2]	1,506	64%	4.8%
Hospital Interview 2003[3]	976	61.3%	9.5%
PISCIS COHORT[4]	2,035	36%	7%

*Patients included in the PISCIS cohort: 6,922 up to December 2004. 2035 patients started ART between 1998 and 2004.
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prevalence = % anti-HCV or HBsAg positive among a HIV+ cohort

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Based on presentations by M. Díez, Secretariat of the National Plan on AIDS, National Center of Epidemiology, Madrid, Spain; C. Tural, HIV Clinical Unit, Internal Medicine Department, University Hospital Germans Trias i Pujol.

Hepatitis vaccination policy, vaccine coverage and impact of immunization programmes in Spain

Vaccination policy: administrative framework

Spain has a Public Health System (PHS) with universal coverage and until recently, only few private health centres.

As detailed previously in this report, the establishment of the Spanish 1978 Constitution has led to a progressive transfer of central health competencies to the ACs; this process was completed in 2002.

National consensus on basic health policies and priorities on healthcare issues are established by the Inter-Territorial Board formed by National and Regional Ministries of Health (representatives from each AC); implementation of such policies and priorities is ensured via a Public Health Commission, attached to the Council.

The need for coordination of health programmes and vaccination policies among ACs led to the creation of the Permanent Commission for the Follow up of Health Programmes in 1988.

In 1991, this Commission created, in turn, the Programmes and Vaccine Registration Board in order to deal with specific vaccine issues. This board is coordinated by the general sub-directorate of Health Promotion & Epidemiology and consists of representatives from the vaccination programmes of each AC and several State institutions with relation to vaccines.

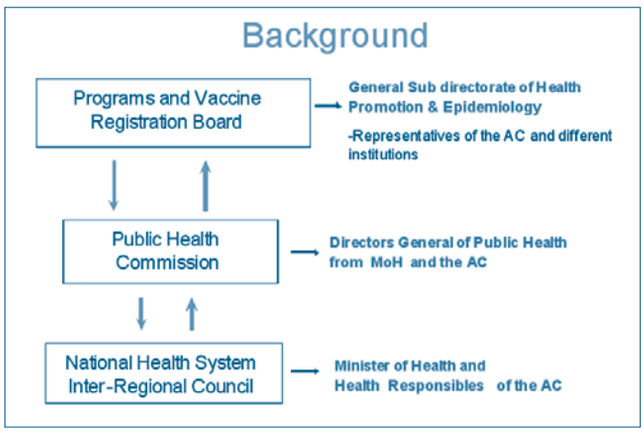
The Public Health Commission created in 1992 is composed of the Directors General from the Ministry of Health and ACs. Several boards, commissions and working groups are accountable to this Commission.

The administrative process regulating the establishment and implementation of the national immunization schedule in Spain is illustrated on page 15, whereby the Programmes and Vaccine Registration Board of the Ministry of Health -composed of representatives from the ACs and different institutions such as the Spanish Drug Agency, the National Centre for Epidemiology, as well as invited experts- makes recommendations on vaccine issues and immunization schedules. Such proposals are sent for approval to the Public Health Commission before reaching the Inter-Territorial Board. Once vaccine recommendations are approved by the Council in the form of a consensus, they are incorporated into the National Immunization Schedule (NIS).

In addition, the following State institutions are involved with immunization matters:

- **Spanish Drug Agency** responsible for the evaluation, authorization and registration of vaccines.
- **Directorate General of Pharmacy and Health Products** responsible for authorizations relating to public financing and pricing; and for the maintenance of a strategic, State-run deposit.
- **Directorate General of Public Health** responsible for recommenda-

tions, coordination of immunization schedules, coverage analysis, and evaluation of routine immunization schedules.



State powers in relation to vaccines include the regulation of conditions and minimum requirements aiming to maintain confluence, harmonization, coordination and cohesion across initiatives and vaccination guidelines from individual ACs. The State is also the focal point on vaccines for international institutions and organizations.

Implementation of immunization programmes

Despite all vaccines included in the NIS being voluntary, very high coverage levels are reported in all ACs of Spain. Most vaccines included in the primary immunization series are administered by paediatricians. However, some vaccines may be given in schools, by a public health physician and/or nurse.

The NIS is implemented in almost all ACs. It is very rare for a Community not to supply a recommended vaccine. In a couple of Communities, additional vaccines which are not included in the NIS are provided e.g., hepatitis A vaccine. Depending on the Community, there might also be slight differences on targeted high risk groups, e.g. in the case of HAV vaccine, or recommended ages for a specific vaccine, e.g. influenza vaccine.

Each AC is responsible for purchasing the vaccines for their region with, as a result, potential price variations for the same vaccine across Communities, depending on regional tender terms. All recommended vaccines are free of charge and paid by AC government. No earmarked national funds are provided to the Communities to purchase vaccines. Therefore, based on their existing budget, a Community might, in theory, not agree to support a new vaccine recommended by the Programmes and Vaccine Registration Board of the Ministry of Health or by the Public Health Commission of the Inter-Territorial Board if it could not afford the expenses.

HAV vaccination policy in Spain

In 1993 HAV vaccination was only recommended to travelers to endemic areas and hemophiliacs.

In 1997 HAV vaccination was recommended for the following high-risk groups:

- travelers to HAV endemic areas
- men who have sex with men and several sexual partners
- injection drug users
- household contacts or care givers of persons with hepatitis A
- staff in contact with untreated waste water
- healthcare staff of hospitals and health institutions
- nurseries staff
- hemophiliacs
- staff frequently involved in situations of disasters

In 2004 HAV vaccination recommendations for adults were reviewed to include the following categories of high-risk groups:

- food handlers
- transplantation patients
- HIV-infected individuals
- CLD patients

However, some divergence regarding the recommended high-risk groups is observed in some ACs.

Three ACs have routine HAV immunization programmes:

- routine immunization of children < 2 years old in the cities of Ceuta and Melilla, two Spanish cities in North Africa, which are characterized by specific epidemiological patterns;
- pilot programme of pre-adolescent immunization with combined hepatitis A+B vaccine in Catalonia, started in 1998 .

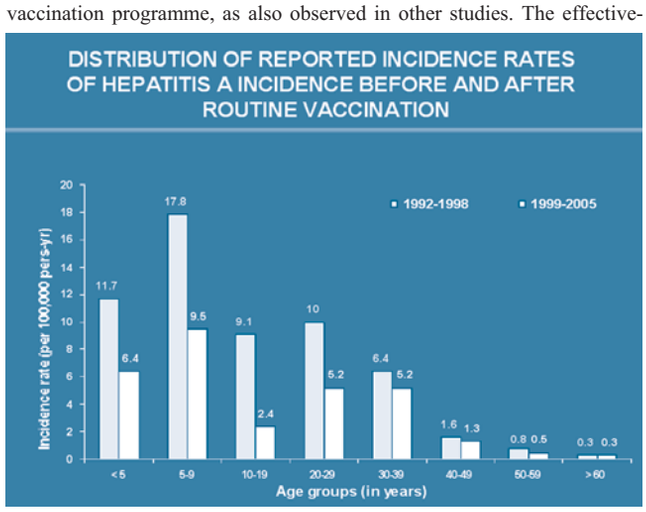
HAV immunization programme in Catalonia

Catalonia started its HAV risk-group vaccination programme in 1995 but, as it became obvious that no reduction was observed, either in the number of HAV morbidity reports: 2.79/100,000 in 1995 versus 8.10/100,000 persons-year in 1998, or in the number of yearly HAV cases: 279 in 1995 versus 493 in 1998, a programme of mass hepatitis A+B vaccination in pre-adolescents (12 year-olds) in schools was begun in the last quarter of 1998.

The rationale for this universal vaccination programme included:

- limited impact of selective vaccination of risk groups
- immediate impact of universal vaccination on clinical cases
- potential of mass vaccination to eliminate the disease
- combined hepatitis A+B vaccine available
- well-established HBV vaccination programme of pre-adolescents in schools
- low cost of the programme
- acceptable cost-effectiveness and cost-benefit ratios of the programme [1]

As shown in graph below, seven years following the implementation of the mass vaccination programme, the HAV incidence rate in the general population of Catalonia has fallen by 47.3%, in comparison with the previous seven years. The greatest fall (73.6%) occurred in the 10-19-year-olds group (corresponding to the vaccinated cohorts) followed by the 20-29-year-olds group (48%), as shown in graph below. The reduction in the incidence in non-vaccinated age groups supports the indirect effects of the vaccination programme, as also observed in other studies. The effective-



ness of the vaccination programme was estimated at 98% and the prevented fraction of HAV in children (6-19-year-olds) was estimated at 89% of the seven-year period [1,2].

HBV vaccination policy in Spain

Historical

HBV vaccination has had an unusual progressive implementation pattern in Spain, which may be due to the ongoing devolution process when the vaccine was introduced. Another factor which may have contributed to this gradual process are the costs linked to the simultaneous vaccination of two target groups (children and adolescents) and the changing evidence as to the best age group to vaccinate.

HBV vaccination was implemented in 1983 with a Royal Decree 3179/1983 from the Ministry of Health relating to recommendations of vaccination for the following high-risk groups:

- haemodialyzed or blood transfusion patients
- healthcare staff from haemodialysis units, laboratories, surgical and dental services
- institutionalized mentally disabled inpatients and staff working at these institutions
- household members and sex partners of persons with chronic HBV infection
- persons with frequent skin punctures not controlled by a health professional (e.g. intravenous drug users)
- specific cases where particular circumstances may warrant use of the HBV vaccine

In 1990, on the basis of an Inter-Territorial Council Agreement, the following high-risk groups were added to the 1983 existing list:

- newborns to chronically infected mothers (pregnant women screened; no HBIg administered)
- recipients of certain blood products (e.g., haemophiliacs)
- healthcare workers or others with occupational exposure to blood or blood products
- inmates and staff of long-term correctional facilities
- persons with several sex partners
- international travelers who will live or work for six months or longer in areas with high levels of chronic HBV infection
- frequent travelers to highly endemic areas who are at risk of having sexual contacts

Subsequent steps in the evolution of HBV vaccination policy were made on the basis of Inter-Territorial Council Agreements in 1992, 1996, and 2003 respectively, with recommendations focusing on:

1992

- intensified efforts toward higher coverage of HBV vaccination of newborns to chronically infected mothers
- development of HBV vaccination programmes for 12-13-yr-old pre-adolescents in all ACs within their resources and in a reasonable timeline
- continued and increased HBV vaccination in high-risk groups

Inter-Territorial Council of National Health System
Recommended Vaccination Schedule (2006)
Approved by the Inter-Territorial Council on 29 March 2006

VACCINATION	AGE													
	2 months	4 months	6 months	12 months	15 months	18 months	3 years	4 years	6 years	10 years	11 years	13 years	14 years	16 years
Poliomyelitis	IPV1	IPV2	IPV3		IPV4									
Diphtheria-Tetanus-Pertussis	DTPa1	DTPa2	DTPa3		DTPa4			DTPa5 or DT					Td	
Haemophilus Influenzae B	Hib1	Hib2	Hib3		Hib4									
Measles-Mumps-Rubella				MMR1			MMR2[a]							
Hepatitis B	HepB 3 doses 0; 1-2; 6 months									Hep 3 doses[b]				
Meningococcal Meningitis C	MenC1 MenC2[c]				MenC3[d]									
Varicella										VZV[e]				

a Children not vaccinated at this age will receive the second dose between 10-13 years of age

b Children who did not receive primary vaccination during infancy

c Children will be administrated two doses of MenC vaccine between 2 and 6 months of age, at least 2 months apart

d Booster dose administration is recommended as of 2 months of age

e Vaccination only for children with no history of varicella zoster virus (VZV) disease or vaccination

Source: adapted from http://www.msc.es/ciudadanos/proteccionSalud/infancia/docs/c2006.pdf

1996

- HBV pre-adolescent vaccination programme included in the immunization schedule of all ACs
- HBV newborn vaccination included in some ACs

2003

- HBV newborn vaccination included in all ACs, at either 0, 1, 6 or 2, 4, 6 months
- HBV vaccination at 0, 1, 6 months for newborns to chronically infected mothers

2004

- revised recommendations for high-risk groups to include transplantation patients, HIV-infected individuals and CLD patients

Vaccine coverage and impact of HBV immunization programmes

As already mentioned earlier, very high levels of vaccine coverage are reported in Spain, e.g. >84% HBV vaccine coverage was reported among adolescents in the year 1997-1998 following the 1996 recommendation; subsequent coverage figures in this population were maintained around 80% up to 2005. Of note, the lowest figure reported over the period 1997-2005 (<78%) refers to school year 2003-2004 and may be explained by the growing number of adolescents already vaccinated as part of children immunization programmes.

It should also be noted that these figures may be underestimated due to school population used as denominator and because of adolescents who may have already been vaccinated as newborns.

Average figures for HBV vaccine coverage in children across all ACs were 97.6%, 96.9% and 96.1% for the years 2003, 2004 and 2005, respectively (see table below). These figures are similar to those reported for other primary immunization vaccines.

The implementation of HBV immunization programmes in Spain has contributed to the steady decrease of hepatitis annual incidence over time (as illustrated in the graph presented on page 9 .)

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Based on presentations by P Santa Olalla Peralta, Dirección General de Salud Pública, Ministerio de Sanidad y Consumo, Madrid, Spain and Ángela Dominguez, Directorate of Public Health, Generalitat of Catalonia, Spain.

Hepatitis B Vaccine Coverage, in Children by AC (2003-2005)

COMUNIDADES AUTÓNOMAS	2003	2004	2005
Andalucía	93,8	97,9	92,8
Aragón	97,7	100	100
Asturias	98,3	98,5	97,6
Baleares	96,7	96,4	91,8
Canarias	92,9	94,1	94,1
Cantabria	94,6	92,1	98,1
Castilla La Mancha	95,9	96,9	98,8
Castilla Y léon	97,8	98,2	96,9
Cataluña	94,7	98,8	98,6
C. Valenciana	97,6	98,1	96,5
Extremadura	96,2	97,1	94,8
Galicia	96,5	98,7	98,7
Madrid	97,7	96,4	94,4
Murcia	98,4	98,0	99,3
Navarra	94,6	95,7	98,3
País Vasco	96,1	95,3	95,2
Rioja	97,9	96,8	97,4
Ceuta	100	**	**
Melilla	100	98,5	100
TOTAL NACIONAL	**97,6**	**96,9**	**96,1**

Conclusions of the Meeting

Organization of healthcare system in Spain

- The Spanish National Health System is:
  - based on public funding with universal free health services;
  - divided between State and Autonomous Community (AC) Health Departments (devolution);
  - coordinated by the Inter-Territorial Board.
- The Inter-Territorial Board makes recommendations in the form of a MOH national consensus that guarantees equal minimum healthcare standards.
- ACs make decisions regarding health policies and vaccines procurement.
- Healthcare budget is allocated per capita to each AC; individual ACs may decide on additional priorities within the budget.
- Healthcare is organized at two levels within the Spanish National Health System, including primary healthcare (in primary care centres) and specialist care (in specialist centres and hospitals).

Hepatitis epidemiological surveillance in Spain

- Since 1995, epidemiological surveillance is based on 3 main information systems, including:
  - statutory notification by general practitioners, for hepatitis A and B infections (Note: 5-10 times underreporting observed for hepatitis A in Catalonia);
  - microbiological information for hepatitis A, B and C (25% reporting coverage, overall);
  - outbreak reporting for hepatitis A, B and C.
- Complementary information systems include hospital discharges, mortality surveillance, seroepidemiological surveys, sentinel surveillance and special registries.
- Surveillance and reporting systems for viral hepatitis should be further strengthened in terms of:
  - timely and complete case-based reporting for all variables, including laboratory confirmation;
  - data analysis allowing identification of well-defined high-risk groups and, more generally, appropriate policy decisions and actions to further strengthen prevention and control efforts.

Hepatitis outbreak investigation in Spain

- Outbreak investigation is part of national surveillance and a specific training programme run by the National Centre of Epidemiology has been in place for 10 years.
- Objectives of the outbreak reporting programme are to assess and confirm the magnitude of reported outbreaks, to identify its source/vehicles, and to identify risk factors/source of transmission.
- Over the period 1996-2003 a total of 375 viral hepatitis outbreaks were reported, involving 2881 cases (107 reported outbreaks in Catalonia):
  - 15% foodborne (50% water/50% shellfish);
  - 70% caused by direct transmission (numerous cases in schools);
  - control measures reported for 63% outbreaks.
- Recommended outbreak control measures include improved hygiene, enhanced surveillance, enhanced international cooperation, as well as the use of vaccines. [Note: the decision to vaccinate is made at the level of each AC].

Epidemiology of hepatitis A in Spain

- Spain is characterized by low HAV endemicity, with low rates of disease and very low mortality.
- A high percentage of <30-yr-olds are not protected (<5% of 5-14yr-olds are seropositive in Catalonia).
- HAV incidence has decreased from 1997 until 2005, however a rise was observed between 2002-2005, possibly due to immigration (study in Catalonia), with some regional variations observed.
- Highest HAV incidence was observed among 5-9-year-olds.
- In the two autonomous cities of Melilla and Ceuta, previously characterized by exceptionally high HAV incidence rates, a significant decline has been observed following implementation of immunization programmes.

Molecular epidemiology of hepatitis A in Spain

- In the region of Catalonia, HAV was detected in sewage, rivers and occasionally shellfish.
- Most HAV isolates were of subgenotypes 1A or 1B.
- It was concluded from molecular epidemiology data that the abundance of HAV in the environment, as tested in Catalonia, represents a situation of sanitary risk, especially considering the low seroprevalence of anti-HAV antibodies in the young population.

Hepatitis E epidemiology in Spain, including molecular diagnosis

- In 2000, HEV seroprevalence in the whole of Spain was 2.9% while it was 7.3% in Catalonia in 2006, compared to 3-20% in other industrialized countries.
- Six HEV strains were isolated from serum samples of patients with acute HEV. Among the five human strains that could be identified, four were autochthonous and one was imported (1989-2003).
- HEV-RNA was identified in 44% of sewage samples from Barcelona (genotype 3).
- Anti-HEV (IgG) antibodies were identified in 19% of pigs in Catalonia (genotype 3).
- The close relationship between HEV strains isolated from sewage samples, human HEV strains causing acute hepatitis and the swine HEV strains identified, indicates that swine might be a reservoir for HEV in Spain.
- HEV virus strains detected in pigs could also be a source of infection for humans.
- Both HAV and HEV isolates were occasionally identified in the same sewage samples.

Diagnosis of HEV

- Several diagnostic tests are available: enzyme immunoassays and Western blot assays are used to detect anti-HEV IgM and IgG in serum; these can be complemented by PCR tests to detect HEV RNA in serum and stool samples.
- Lack of specificity of commercial ELISA test has been observed. Confirmation of HEV ELISA positivity by immunoblot is extremely important for an accurate diagnosis of HEV and the development of a reliable serological assay is crucial to estimate the real prevalence of HEV in "non-endemic" areas.
- HEV should be considered as an environmental contaminant, therefore HEV-RNA testing should be included in investigation of acute/fulminant non-A, non-B, and non-C hepatitis, even in the absence of travel history.

Epidemiology of Hepatitis B in Spain

- Spain is a region of low HBV endemicity, characterized by a progressive decline (47.3% fall) in incidence of acute hepatitis B between 1997-2005.
- High HBV seroprevalence is observed among 30-39 year-olds (1.95% HBsAg positivity).

Use of molecular techniques for hepatitis B diagnosis

- A variety of HBsAg mutants have been detected among HBsAg carriers but these do not cause a measurable threat to the current vaccination policy.
- Safety testing of blood donations in Spain includes compulsory HBsAg assay and of secondary importance anti-HBc Ab and ALT. Nucleic acid testing (NAT) technology is used in 80% of blood donations.
- When applying NAT-technology for HBV DNA screening in the blood bank setting, the yield of HBV identification ranges from 1:98.000 in the window phase, and 1:24.000 for silent HBsAg-negative samples.
- Some HBsAg mutants may be missed by some serological assay in blood donation testing.

Epidemiology of hepatitis C in Spain

- HCV prevalence ranges from 1.5-2.5% in the general population of Spain, with a rapid drop of the number of new infections observed between 1996 and 2005.
- Major routes of transmission include parenteral transmission -mainly due to IVDU, nosocomial infection and percutaneous transmission- and non-apparent parenteral transmission, e.g. healthcare workers, tattooing, and acupuncture.
- The number of HCV cases is highest among 25-44 year-old men and drug addiction is the most important risk factor.
- HCV prevalence is high in haemodialyzed patients but universal precaution and isolation measures have led to the decrease of HCV infections.

Use of molecular techniques in nosocomial HCV outbreaks

- HCV transmission during clinical procedures was reported and investigated in several settings.
- The benefit of molecular epidemiology was demonstrated in:
  - identifying the source of HCV infection;
  - establishing HCV transmission mechanisms;
  - implementing modified clinical procedures in order to prevent additional nosocomial infections.
- In Spain, molecular HCV epidemiology has legal, economical and medial practice implications.

Prevalence of viral hepatitis in HIV-infected individuals

- In Spain, the frequency of HCV-HIV coinfection is one of the highest among European countries, while prevalence of HBsAg-positive patients with HIV is similar to that in other geographic areas around Europe.
- The percentage of hospitalizations due to HCV among HIV patients has gradually increased over the period 1999-2002. HCV-positive cirrhosis of the liver has become a major cause for morbidity and mortality in HIV-positive patients in Spain.
- The presence of the large cohort of HIV patients coinfected with HCV is expected to have an impact on the demand of health resources for clinical care.
- The consequences of HCV or HBV chronic infections in HIV-positive patients are:
  - faster liver fibrosis progression rate;
  - increased liver-related mortality and overall mortality rates;
  - increased rate of hepatotoxicity to antiretroviral agents which limits future therapeutic options;
  - poorer CD4+ cell gain with an effective antiretroviral scheme in HCV coinfected patients.

Hepatitis vaccination policy in Spain

- Spanish National Immunization (NIS) guidelines are generally implemented in all ACs.
- Recommended vaccines are free of charge and paid by ACs.
- Universal HBV vaccination is recommended in the entire country.
- Universal HAV vaccination is recommended in 3 ACs, and HAV vaccination for high-risk groups in the entire country.
- Most vaccines are administered by paediatricians or in schools.
- Some ACs provide additional vaccines (e.g. HAV vaccine).
- High performance of immunization programmes needs to be sustained, prioritizing high-risk groups, including immigrants.
- Specific recommendations for revising of future vaccination policy include:
  - is vaccination of healthcare workers needed?
  - adolescent immunization with combined hepatitis A+B vaccine will become less needed as children are immunized via HBV universal programmes;
  - should 18-month-olds be vaccinated against HAV?
  - confounding effect of immigrants will need to be considered for future vaccination policies.

Hepatitis A vaccination in Spain

- 1993: high-risk group vaccination is recommended.
- 1997: extended high-risk group vaccination.
- 1998: routine adolescent vaccination in Catalonia with combined hepatitis A+B vaccine, with estimated 98% effectiveness in 2005.
- 2000: routine vaccination of children <2yrs in Ceuta and Melilla (based on specific epidemiology).
- 2004: revision of adult HAV vaccination recommendations to include additional high-risk groups.

Hepatitis B vaccination in Spain

- 1983: high risk-group vaccination is recommended in the entire country.
- 1990: extended high-risk group list, including newborns of HBsAg-positive mothers.
- 1992: efforts toward adolescent vaccination programmes.
- 1996: adolescent (12-13yrs) vaccination in all ACs + newborn vaccination in some ACs.
- 2003:
  - infant vaccination in all ACs at 0,1,6 or 2,4,6-month schedule;
  - passive/active vaccination of newborns to HBsAg-positive mothers at 0,1,6-month schedule;
  - adolescent vaccination continued until children immunized reach adolescence.
- 2004: revision of adult HBV vaccination recommendations to include additional high-risk groups.
- 2005: >95% vaccination coverage for primary immunization series in all ACs.

Adapted from a presentation by Prof. Daniel Shouval, Liver Unit, Hadassah University Hospital, Jerusalem, Israel.

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