



# VIRAL HEPATITIS

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This edition of *Viral Hepatitis* is based on material presented at the Viral Hepatitis Prevention Board meeting on **Prevention and control of viral hepatitis in France**. Veyrier-du-Lac, France, November 18-19, 2004.

## Editorial

This issue of *Viral Hepatitis* takes a look at prevention and control of viral hepatitis in France, based on conclusions that were reached during the VHPB meeting that was held November 18-19, 2004 in Veyrier-du-Lac, France.

### *Achievements of France's national hepatitis programmes*

Since the early 1990s, prevention and control of viral hepatitis was already considered a public health priority in France. During the last decade, much progress has been made in reducing morbidity and mortality due to viral hepatitis. France's national hepatitis programmes have resulted in more effective screening campaigns, enhanced hepatitis surveillance systems, an improved network of thirty-one hepatology reference centres, and excellent hepatitis research programmes that are funded by a wide range of sources, some of which include the ANRS / ANRH, the European Commission, and external grants and scholarships. Some of the most successful achievements of France's viral hepatitis programmes are the newly enhanced capacity for diagnosing larger numbers of patients and the currently easy access to therapy with costs to patients that are fully reimbursed.

### *France's new public health policy law*

A new public health law, enacted in August 2004, will help to reinforce coordination and synergy among institutions and other key players, with prevention programmes that will also be implemented at regional level. The aims of this new law are to improve public health through prevention of avoidable and premature morbidity and mortality, maintaining quality of life among the disabled, and reducing disparities and inequalities within the healthcare sector.

### *Hepatitis B in France*

Although hepatitis B incidence is low in France, it remains an important public health concern. Universal hepatitis B immunisation has been recommended in France since 1994; current recommendations target all children under thirteen years of age (preferably in infancy), and all risk groups. In terms of new surveillance capacity, France's previous reporting system based on passive reporting by physicians participating in a national sentinel network, has now been replaced by a new mandatory hepatitis B notification system that was first implemented in March 2003. During the first year of mandatory notification, data show that two-thirds of all cases of HBV infections could have been prevented had systematic hepatitis B vaccination been carried out, and that prevention strategies need to be reinforced to protect newborns of HBV-infected mothers.

### *Hepatitis C in France*

New estimates based on preliminary data for 2004 show that HCV prevalence in France is 0.86%. Although HCV infections have declined dramatically within the general population, HCV incidence among injecting drug users (IDUs) remains high. Thus far, France's risk-reduction policies within the drug-using population have had an insufficient impact on HCV transmission, and new strategies for prevention and case identification will need to be devised.

Nosocomial HCV infections continue to occur, despite mandatory notification since 2001, mainly due to breaches in hygiene. An official recommendation in France is that HCV-positive healthcare workers carry out less invasive procedures to minimise risk.

### *Safety of hepatitis B vaccination*

There have been no changes in France's immunisation schedule for hepatitis B since 1998. The French national advisory board and the technical committee on vaccination (CTV - *Comité Technique des Vaccinations*), the French Ministry of Health, the Global Advisory Committee on Vaccine Safety of the World Health Organization, expert committees and current scientific data continue to support the safety and efficacy of the hepatitis B vaccine.

Further support for hepatitis B immunisation comes from the Viral Hepatitis Prevention Board, which remains fully committed to the current WHO recommendations for hepatitis B vaccination. The VHPB continues its advocacy for universal and risk-group immunisation programmes to eliminate hepatitis B virus infections.

*Nicole Guérin and Françoise Roudot-Thoraval,  
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## Prevention and control of viral hepatitis in France - a VHPB Symposium Report - Veyrier-du-Lac, France, November 18-19, 2004

### The healthcare system in France

#### Structure of the healthcare system

The French healthcare system is complex, with administration mainly centralised at national level for France's twenty-six regions, one hundred local authorities (*Départements*), and 36,679 municipalities.

The French Ministry of Health has four main areas of responsibility comprising (1) a general health directorate that defines health policy; (2) a directorate of hospitals and healthcare management, responsible for managing all health resources in both public and private sectors; (3) a social security directorate, responsible for financial matters and for supervising social security organisations, including health insurance funds; and (4) a social policy directorate, responsible for the social aspects of some special segments of the population (e.g., disabled, elderly).

#### The financial burdens of longevity, unemployment, and new therapies

France, like many other Western countries, is facing difficulties in sustaining a healthcare infrastructure that is under growing pressure from increasing expenditures, with no guarantees of additional funding. Approximately ten million persons in France are sixty-five years or older, representing a growing segment of the population that often requires long-term healthcare. In contrast, the total birth rate in France is comparatively low [1]. Additional burdens on the healthcare system are increasing levels of unemployment and increased health costs for new therapies.

Since 1945, France's healthcare system has been widely funded by statutory insurance. Under this system, individual benefits have been independent of personal contributions with the result that private insurance and its ensuing costs are on the rise. In 2000, France adopted a universal coverage act that provides healthcare to all French citizens, with employers and employees sharing the costs.

#### French demographic data – a healthy population?

France, with a population of nearly sixty million people, has a high health ranking by the World Health Organization, taking into account healthy life expectancy (without disability or incapacity), child and adult mortality rates, among other indicators [2]. Although some of the data show a relatively healthy population in France, other core health indicators reveal a high rate of premature mortality, primarily among males, as a result of tobacco and alcohol consumption and accidental deaths.

Health data by region show higher mortality and morbidity rates in areas of the country with high levels of unemployment (e.g., Pas de Calais in the North) where high-risk behaviour, such as consumption of alcohol and tobacco, is also frequent.

Among the leading causes of death in France are cardiovascular disease (31.1%), cancer (27.7%), accidents (8.3%), and respiratory disease (8.1%). Infectious diseases (1.4%) are ranked as the tenth cause of death in France.

#### Prevention

France's entire expenditure for healthcare in 2003 was 168,084 million euros, of which only 2.3% comprised prevention programmes covering the following areas:

- Occupational health
- School health
- Mother-and-child health
- Immunisation
- Public-health programmes

In August 2004, the Public Health Policy Law was enacted. The objectives of this new law are to improve the health of the French population through prevention of premature morbidity and mortality, maintaining quality of life for the disabled, and reducing health inequalities. This health policy law allows for better coordination among institutions and other key players, particularly at regional level where prevention programmes can be implemented.

The public health law also includes an annex that describes the following objectives in the field of prevention for the next five years:

- Behavioural risks: alcohol and tobacco consumption, drug addiction, unhealthy dietary habits;
- Environmental risks, including occupational risks;
- Chronic diseases;
- Cancer;
- Infectious diseases policy, including immunisation policy, chronic infectious diseases such as viral hepatitis, HIV/AIDS, nosocomial infections, antibiotic resistance.

The French Ministry of Health has also developed five strategic priority plans relating to cancers, environmental health, risk behaviour linked to or leading to violence, uncommon or orphan diseases, and the quality of life of chronically ill patients.

### Immunisation

Immunisation policies are defined at national level, but may be adapted at regional level according to epidemiological situations as well as to specific immunisation programmes developed for various regions. For example, mandatory immunisation policies

are decided and implemented at national level. However, strategies to administer recommended vaccines may be taken at regional level, which accounts for geographical differences in vaccination coverage levels throughout the country.

### Conclusions

There is, indeed, a huge imbalance between expenditures for prevention and those for treatment. This is all the more reason to continue to carry out a wide range of programmes, studies, and other activities whose results will help to demonstrate the cost-effectiveness of prevention measures in France's healthcare system. To remedy this imbalance, much work still needs to be done to achieve better coordination and synergy among the various players, and to improve the quality and accessibility of prevention activities in France. The 2004 public health act will, hopefully, open up new channels that will allow France to achieve its public health objectives for the next five years and beyond.

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*Based on a presentation by Dr Martine Le Quellec-Nathan, Direction Générale de la Santé, Ministère de la Santé et de la Protection Sociale, Paris, France.*

## National strategy for prevention and control of viral hepatitis infection in France

During the early 1990s, preventing and controlling hepatitis C virus (HCV) infection was already considered a public health priority in France. Recognising that additional epidemiological data would be needed on hepatitis C before developing a national prevention and control plan, France's Institute of Health Surveillance (InVS - *Institut de Veille Sanitaire*) conducted a series of epidemiological surveys in 1994. Results showed HCV prevalence in France between 1.1% and 1.2% in the adult population (20-59 years old), and chronic infection between 0.9% and 1.0% (between 400,000 and 500,000 persons). Seventy-five percent of HCV-infected patients were unaware of their seropositivity. The main routes of transmission were identified as injecting drug use and administration of blood products in at least 60% of the cases. In 1997, the number of HCV-related deaths in France was estimated at 1,837.

These data led to a ministerial decision in January 1999 to launch a national hepatitis C programme [1]. The objectives of this first programme, which covered the period 1999 to 2001, were:

- Screening to detect 75% of seropositive persons (compared with only 25% who were aware of their status in 1994); and
- Providing anti-viral treatment to 80% of eligible patients.

Six strategies were developed to achieve the programme's objectives (shown below). These strategies would be implemented by the central administration together with specific committees, and by regional and local authorities allowed to adapt the plan according to their specific epidemiological situations. The specific budget allocated to private and public hospitals for this first programme was 227 million euros.

### Main components of France's first hepatitis C programme (1999-2001)

- Reinforcing primary prevention of HCV infection;
- Enhancing HCV testing and increasing public awareness of HCV infection through repeated media campaigns;
- Reinforcing access to care and treatment of hepatitis C;
- Creating a surveillance system;
- Centralising HCV clinical research;
- Evaluating programme results.

The programme also brought about the creation of thirty-one reference centres located within regional university hospitals, which were progressively set up beginning in 1995. The role of these reference centres is to determine clinical and therapeutic protocols, conduct clinical trials, and provide treatment for difficult cases, including complications. Regional networks are made up of general practitioners and specialists who can prescribe treatment. In addition, there are specialised networks for risk groups (e.g., injecting drug users, alcohol-dependent, HIV/AIDS patients). Coordination of all reference centres within the networks is done by a national network [2], a non-governmental organisation that also provides guidelines and teaching, and participates in the surveillance network implemented by InVS.

A second hepatitis C programme was put into action for 2002-2005 that also included prevention and control of hepatitis B [1], and was based on updated epidemiological data [3]. The general principle guiding the strategy for this updated plan was to combine

the programme with other activities and services relating to drug addiction, HIV infection, health protection for vulnerable segments of the population, illegal drugs, tobacco and alcohol, and safety of health products.

This second programme was based on a common strategy of reducing the risk of HCV and HBV transmission, updating and reinforcing hepatitis C prevention and control measures, and implementing new and specific measures for hepatitis B.

The goals of this new programme were:

- Screening to identify 100% of infected persons;
- Reducing mortality attributable to chronic hepatitis B and hepatitis C by 30%;
- Reducing the proportion of patients with chronic hepatitis B / C from 10-20% to 7-14% by 2008, according to the objective of the recent law concerning the policy of Public Health [4].

Some of the achievements of these first two programmes included state financial support for risk reduction material to *drug users* and for dissemination of information brochures and leaflets. This strategy, while effective for HIV-infected persons, was less successful among injecting drug users where there is a persistence of HCV transmission (estimated incidence: 2,700-4,400 new cases per year). For *prison inmates*, HCV prevalence is much higher than in the general population. Although recommendations have been made to reinforce prevention, the results have not yet been evaluated. Notification of *nosocomial infections* has been mandatory in France since 2001. However, due to the persistence of unsafe procedures in these settings, recommendations and guidelines were set up to reduce nosocomial transmission.

Media campaigns were carried out between 2000 and 2001 to help raise awareness of at-risk situations and to promote *HCV screening* [5-6]. This information campaign included mailings of leaflets and brochures to 67,000 general practitioners and specialists. Reimbursements were also made available for HCV diagnostic testing carried out in private laboratories. The success of this campaign was demonstrated by the 26% increase in testing between 2000 and 2002, with over 1.2 million tests conducted each year.

*Improvements in access to care and treatment in hospital services* was another achievement of the 1999-2002 plan, which saw an increase in the number of persons consulting in hospitals and in the number of patients being treated:

- Year 2000: 23,000 new consultants vs 6,000 / year (1994)
- Year 2001: 10,400 patients treated vs 8,000 in 1998 and 4,000 in 1995

Other positive developments of the programme included delivery of medicines by hospitals and liberal pharmacies and, in 2003, the possibility for a first treatment prescription to be given by a private specialist without a hospital visit.

Mathematical modelling of the complications and deaths related to hepatitis C in France in the next 50 years as well as data on the risks associated with nosocomial transmission were provided by INSERM (*Institut National de la Santé et de la Recherche Médicale*) in 2003.

Except for the area of basic *research* in INSERM, research on hepatitis C was given to France's national agency for research on SIDA/AIDS (ANRS) 1999. In 2004, ANRS activities were extended to hepatitis B and fundamental and vaccine-related research on hepatitis B and C.

A *surveillance system* was also introduced, which first takes into account viral serology results collected in anonymous and free screening centres and on blood donations. In 2000, two specific hepatitis C networks were set up, one on HCV serology activity carried out within 257 private and hospital laboratories and the other based on the characteristics of newly referred patients through 26 reference centres. Notification of acute HBV infection became mandatory in 2003. Mortality data will also become available (InVS/INSERM).

A national survey carried out between 2002 and 2003 on HBV and HCV prevalence will provide data on the proportions of screened persons and patients with access to healthcare. These data will contribute to assessment of the impact of France's HBV / HCV prevention and control plan.

A strategic committee has been established with the following priorities:

- Programme evaluation and definition of follow-up actions;
- Submit proposals to reinforce primary prevention of viral hepatitis;
- Submit proposals to reinforce specific prevention measures and access to screening, information, multi-disciplinary care, and anti-viral treatment for drug users;
- Submit proposals to optimise care in and out of hospitals by providing access to medical care with or without treatment, including psychiatric care and management of undesirable effects of treatment.

What the future holds for France's viral hepatitis prevention and control programme may depend, in part, on how new strategies will be adapted to the new prevalence data from the national survey. Also crucial to how this programme will evolve are the conclusions of experts and patient support groups from a November 2004 meeting on hepatitis B vaccination. The next steps will involve a decision by the Minister of Health that will result in reinforcement of prevention and control of hepatitis B and C in the coming years.

### Conclusions

Some of the challenges still facing France's healthcare system are the ongoing epidemics of HCV infections among injecting drug users – a situation that places a tremendous burden on the already-saturated reference centres. There has also been relatively slow development of networks outside of the specialised centres due to the reluctance of practitioners to participate in these networks. Treatment for the most severely affected patients (with, e.g., cirrhosis, hepatocellular carcinoma) remains insufficient. More research capacity and strategic planning are also needed in terms of carrying out long-term projects, cohort studies, and large-scale trials.

Some of the major achievements that resulted from France's national prevention and control plan against HBV and HCV can be attributed directly to an active national programme that provided effective screening campaigns, an effective network of reference centres, and excellent research programmes. One of the most important achievements that resulted from France's new prevention programmes is the current easy access to therapy with costs to patients fully covered, and the new capacity for diagnosing large numbers of patients.

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Based on presentations by Dr Anne-Marie Jullien-Depradeux, Direction Générale de la Santé, Ministère de la Santé et de la Protection Sociale, Paris, France; and Dr Patrick Marcellin, Service d'Hépatologie and INSERM U481, Hôpital Beaujon, Clichy, France and Fédération Nationale des Pôles de Référence et Réseaux Hépatites (FNPRRH).

## Hepatitis A in France

Hepatitis A is not a reportable disease in France – the only country in the European Union which has no surveillance of acute HAV infection. French data on HAV infection therefore offer few possibilities for monitoring epidemiological trends, assessing risk factors, and identifying sources of outbreaks.

### Increase of susceptible adults in France

France is a low-endemic area for hepatitis A. During the last twenty years France has seen a decrease in hepatitis A seroprevalence mainly due to improved hygiene and housing conditions. Seroprevalence data showed a decrease in prevalence of anti-HAV antibodies among French military recruits between 1978 and 1997 (a group which is representative of the French male population), corresponding to increased numbers of susceptible adults in the general population.

Local hepatitis A outbreaks still occur in day-care centres, health-care institutions for children with developmental disabilities, small communities due to person-to-person transmission and food contamination, as well as among men who have sex with men (MSM).

### Hepatitis A immunisation recommendations

Current hepatitis A immunisation recommendations in France are targeted to the following risk groups:

Occupational exposure to HAV	Other risk groups
<ul style="list-style-type: none"> <li>• Staff in day-care centres</li> <li>• Staff in healthcare institutions for children with developmental disabilities</li> <li>• Food handlers and restaurant workers</li> <li>• Workers exposed to raw sewage</li> </ul>	<ul style="list-style-type: none"> <li>• Non-immune travelers (over one year old) to endemic countries</li> <li>• Children with developmental disabilities in healthcare institutions</li> <li>• Persons with chronic liver disease</li> <li>• Men who have sex with men</li> </ul>

### Mandatory notification – proposal for change

A sentinel surveillance system (*réseau sentinelle*) has been in place in France since 1991. However, only a limited number of cases of

HAV infection, based on notifications by participating general practitioners, have been reported. A further limitation of the sentinel system is that it is not designed to detect outbreaks.

In order to enhance hepatitis A outbreak detection and to document incidence and HAV exposure, a pilot study was carried out between 1999 and 2000, based on the notification of confirmed cases by biologists, who participated in the study on a voluntary basis, to the district medical officer. The clinician in charge completed clinical details and information on exposure. The study demonstrated that although it was possible to determine HAV incidence by age and gender, the main objective (i.e., outbreak detection) had not been achieved due primarily to the limited number of participating laboratories and to the lack of capacity to identify clusters of cases at the district level. A positive aspect was the apparent willingness on the part of the biologists to take part in this type of study.

Following the results of the pilot study, a working group was set up in 2004, which concluded that the primary objectives of a hepatitis A surveillance system in France should be to detect outbreaks and to monitor incidence. On November 11, 2004, a proposal was submitted to the *Conseil Supérieur d'Hygiène Publique de France* for mandatory notification of hepatitis A by biologists to district medical officers. The proposal, if adopted, would also allow for identification of clusters. Complementary collection of data on exposures would be organised periodically (once every 3 years) or in case clusters occurred. A decision on this proposal, accepting the principle of mandatory notification of hepatitis A, has been taken on November 26, 2004.

Based on presentations by Dr Elisabeth Delarocque-Astagneau, Institut de Veille Sanitaire, Département des Maladies Infectieuses, Saint-Maurice, France; Dr Jean-Claude Desenclos, Institut de Veille Sanitaire, Département des Maladies Infectieuses, Saint-Maurice, France; and Dr Elisabeth Nicand, National Reference Centre for Enterically-transmitted Viral Hepatitis (HEV), Military Hospital Val de Grâce, Paris, France.

## Hepatitis B in France

### Epidemiology of hepatitis B in France

Although hepatitis B has a low incidence in France, it remains an important public health concern. Strengthening current strategies of prevention and vaccination are needed to reduce further the number of acute cases of HBV infection, including a reduction of maternal HBV transmission to newborns. Prior to 2004, much of the epidemiological data for hepatitis B virus infection in France were limited, dating back to the 1990s. However, with new surveillance tools that were implemented in 2003, new data are now being generated to monitor hepatitis B prevalence and incidence trends in France.

### Hepatitis B surveillance

A working group on hepatitis B surveillance proposed mandatory notification of acute hepatitis B cases in 1998. The proposal was implemented in March 2003 in order to enhance collection of epidemiological data that were previously derived from a sample of physicians participating in a national sentinel surveillance network (*Réseaux sentinelles*, INSERM U444). The new surveillance system involves mandatory reporting by biologists and clinicians to their district health office, which reports to the national *Institut de Veille Sanitaire* (InVS).

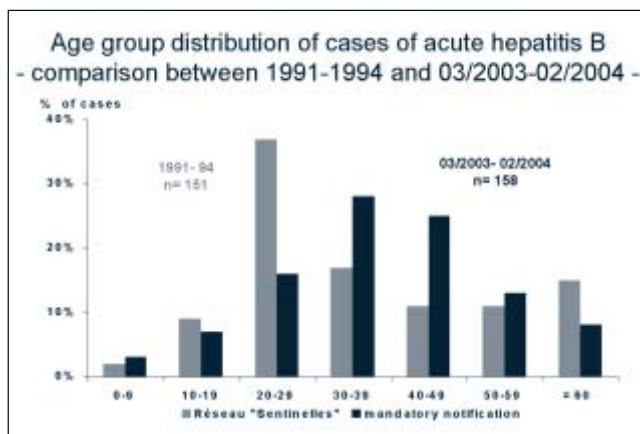
During the first year of mandatory notification (March 2003 to March 2004), 158 acute hepatitis B cases were reported:

- 58% of cases occurred among hospital doctors;
- Sex ratio M / F: 2.95 (118 / 40);
- Median age: 37 years for males; 36 years for females;
- 69% of cases resulted in jaundice;
- 46% of cases resulted in hospitalisation;
- Fulminant hepatitis occurred in three cases, two of which resulted in death (one of the fatalities occurred in an infant born to an HBsAg-positive mother).

Mandatory notification data (2003-2004), showing the reported exposures in a period of six months prior to the onset of symptoms (n = 145), are shown below. Among the 145 patients, 91 (63%) belonged to high-risk groups and had an indication of vaccination (for partners or family members it is not known whether HBsAg positivity was known prior to the onset of acute hepatitis B).

Risk factor	Number of cases	% of cases
Sexual contact ( <i>multiple sexual partners, men who have sex with men, positive partner</i> )	59	40.6
Injecting drug use	9	6.2
Invasive treatment	15	10.3
Tattoo, piercing	5	3.4
Family contact	14	9.7
Perinatal transmission	2	1.4
Live-in institution	11	7.6
Travel in endemic areas	21	14.5
No known risk factor	43	29.6
More than one risk factor	38	26.3

In the figure shown below, there is a shift in acute cases from the twenty- to twenty nine-year age group (1991-1994) to the thirty- to thirty nine-year age group (March 2003-March 2004). This trend may reflect the positive impact of the hepatitis B vaccination strategy for pre-teenagers and adolescents implemented in France in 1994.



Two thirds of all of the cases could have been prevented had hepatitis B vaccination of risk groups been systematically carried out. It is clear from the above data that hepatitis B prevention strategies in newborns of infected mothers should be reinforced.

One limitation of the new reporting system is under-reporting by private practitioners. However, it is expected that lack of notification will decrease over time as the new surveillance system develops.

France's new surveillance system is further strengthened by national reference centres for hepatitis A, B, and C. For hepatitis B and C, the centres provide a regulatory basis for molecular epidemiological research (including molecular typing, collection of strains) and for surveillance in blood donors.

Nevertheless, there is a need to improve epidemiological data through enhanced surveillance for acute cases and for HBV prevalence within the general population and at-risk groups. A nationwide survey on prevalence of hepatitis B and C chronic infection has been carried out in France in 2004 (sample size: 15,000). The results of this survey are pending.

#### Hepatitis B immunisation policy

France's immunisation policy is reviewed every year, taking into account newly available vaccines and an assessment of the benefit / risk balance of vaccination. Once the immunisation schedule is agreed upon, it is published in France's *Official Bulletin (Bulletin officiel)*, in the *Weekly Epidemiological Bulletin (Bulletin Épidémiologique Hebdomadaire - BEH)* and on the website of the French Ministry of Health ([www.sante.gouv.fr](http://www.sante.gouv.fr)).

Vaccines against diphtheria, tetanus, tuberculosis, and polio are compulsory in France for the general population. Healthcare workers must be vaccinated against diphtheria, tetanus, polio, and hepatitis B.

Compulsory vaccines are available free of charge when administered through the public sector. For vaccines administered to patients on a private basis, 65% of the cost of an officially recommended vaccine is refunded by the social security system. Most private insurance companies cover the remaining 35%.

A chronology of France's HBV screening and hepatitis B immunisation recommendations is shown in the table below:

Date	Event
December 1971	Screening of HBsAg in blood donors
June 1982	Recommendation of hepatitis B vaccination for workers exposed to HBV and other persons at risk of HBV infection
October 1988	Anti-HBc screening in blood donors
January 1991	Compulsory hepatitis B vaccination for healthcare workers
February 1992	HBsAg screening during 6th month of pregnancy
October 1994	Recommendation of hepatitis B vaccination for pre-adolescents (i.e., 10-12 years of age)
January 1995	Recommendation of hepatitis B vaccination for infants

Universal hepatitis B vaccination has been recommended by the CSHPF (*Conseil Supérieur d'Hygiène Publique de France*) since 1994; the latest immunisation recommendations were made in March 2002.

For 2004, France recommends systematic hepatitis B vaccination of all children under thirteen years of age, preferably as infants, and of all risk groups.

#### Definition of high-risk groups:

- Infants born to HBsAg-positive mothers;
- Children in residential institutions for the handicapped;
- Persons in residential psychiatric institutions;
- Children in day-care centres;
- Persons engaging in sexual intercourse with multiple partners;
- Injecting drug users;
- Persons travelling to areas of intermediate or high hepatitis B endemicity;
- Persons planning to reside in areas of intermediate or high hepatitis B endemicity;
- Persons with potential exposure to patients, or exposed to blood or biological products, either directly or indirectly, e.g.:
  - Potential recipients of massive or multiple blood transfusions;
  - Family or close contacts of HBV-infected patients or chronic HBsAg carriers;
  - Sexual partners of HBV-infected patients or chronic HBsAg carriers.

The 2004 immunisation calendar in France is based on a three-dose schedule, with the third dose administered between five and twelve months after the second dose, with no booster dose. Booster doses may be recommended in certain circumstances among persons at professional risk of HBV infection.

Two licensed hexavalent vaccines have only been used on a limited basis in France. These vaccines are not reimbursed and, therefore, are costly for some parents of young children.

There appears to be a general view among some doctors and parents of young children in France that children should not be vaccinated against hepatitis B at a young age if they are not at risk – a view that has also been influenced by the hepatitis B vaccination multiple sclerosis (MS) “scare” in 1997-1998. The impact of this view is illustrated by vaccination coverage data showing that although twenty six million people were immunised in France in 1998 (42% of the population), each year only 25 to 30% of infants receive the hepatitis B vaccine.

In contrast with the relatively low infant coverage, the hepatitis B immunisation campaign targeted to pre-adolescents was a great success, according to national immunisation data for 1998, with 80% coverage for this age group.

In October 1998, following allegations of an association between the hepatitis B vaccine and MS, France temporarily suspended its school-based hepatitis B immunisation programmes for adolescents. Although no scientific evidence has been established of a causal link between hepatitis B vaccination and MS, hepatitis B immunisation coverage in France has not recovered to its previous levels. A population survey conducted in 2002 revealed an overall vaccination coverage rate of 21.7% and very low three-dose coverage rates among infants (19.8%), children (23.3%), and adolescents (46.2%) [1].

Today, one of the main public health challenges facing France is re-establishing public confidence in the overall safety and benefits of hepatitis B vaccination. It will be through political commitment at the highest levels, however, before socially acceptable strategies are implemented to achieve this goal. Further, licensed hexavalent vaccines are available in France but are not being used to achieve optimum immunisation coverage among infants. Political will is also clearly needed to support reimbursement of these vaccines within the French healthcare system.

### Prevention and residual risk of HBV infection following blood transfusions

Assessment of blood safety depends on monitoring trends in residual risks of viral infections that are transmitted by transfusions. In France, these trends were analysed during consecutive three-year-study periods between 1992 and 2003. As risk is mostly associated with the window period, residual risk is estimated by multiplying incidence rates by the duration of this period.

HBV blood screening in France, which first began in 1971 with HBsAg enzyme immunosorbent assays, is one of the most successful aspects of France’s national health programme. Nucleic acid testing (NAT) was first introduced in France in 2001 for HIV-1 and HCV RNA to minimise risk in blood and blood products. Some of the benefits of NAT include achievement of a high level of blood component safety as well as improved diagnosis of infection in blood donors.

An extension of NAT technology application to HBV testing in France has been considered. It was finally decided, however, not to implement HBV-NAT, based on the conclusions shown in the following table.

• Before the introduction of NAT
✓ Residual risk for the three viruses (HIV, HBV, and HCV) combined was 1/235 000 donations in 1999-2001, compared with 1/65 000 donations in 1992-1994.
✓ This 4-fold decrease was linked to the decline of both HBV and HCV incidence because of:
• Improved donor selection
• Preventive measures taken to avoid nosocomial infections
• Hepatitis B vaccination campaign
• After the introduction of NAT
The current overall residual risk is 1/350 000 donations and the main part of this risk is related to HBV infection

Other data that led to this decision showed that NAT would have had a limited impact on further reducing residual risk in France based on the following factors:

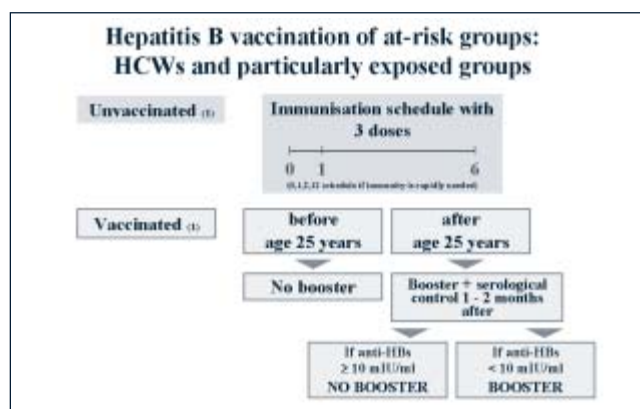
- extremely low risk of a blood recipient becoming infected with a retrovirus or a hepatitis virus;
- high sensitivity of HBsAg assays;
- single nucleic acid testing still not available in France;
- 22% of the population in France received a complete course of HBV vaccination.

### Preventive measures against HBV infection in healthcare workers

Since June 1982, hepatitis B vaccination has been recommended for workers exposed to the hepatitis B virus and for other persons considered at high risk of HBV infection. For healthcare workers, particularly vulnerable through potential exposure to HBV, hepatitis B vaccination has been mandatory since 1991.

Although hepatitis B vaccination coverage levels have increased among healthcare workers in Paris hospitals from 72% in 1990 to 91% in 1993, they remain less than optimal. Similarly, among surgeons practicing in France, only 79% had been vaccinated against HBV in 1997 [2].

For healthcare workers and other persons at risk, the hepatitis B immunisation schedule is as follows:



Five to ten percent of healthcare workers vaccinated against HBV have anti-HBs levels lower than 10 mIU/ml after six doses of HBV vaccine.

For HBV-infected healthcare workers, three antiviral agents for the treatment of chronic hepatitis B have been approved: interferon, lamivudine, adefovir (+ tenofovir and emtricitabine in HIV-infected patients). Currently under consideration in France, is the issue of whether or not to allow healthcare workers on long-term monotherapy, in remission of HBV DNA, to return to performing invasive procedures.

[Editorial note: The topic of HBV, HCV and HIV-infected healthcare workers will be discussed further in the next issue of *Viral Hepatitis*.]

### Preventive measures for prisoners

Among the many characteristics that are shared among prisons are that they often comprise young, adult males, living in overcrowded conditions, with access to unauthorised drugs. These conditions contribute to a relatively easy means of transmission of HBV, HCV, and HIV among prisoners.

Some of the preventive measures that have been taken in France to help reduce high-risk behaviour that contributes to HBV, HCV, and HIV transmission in prisons include:

- 1989 mandatory delivery of a condom upon release from prison;
- 1993 setting up anonymous testing centres in prisons;
- 1994 reorganisation of the French healthcare system in prison with increased emphasis upon prevention;
- 1996 providing harm reduction tools to prisoners (e.g., opiate maintenance therapy, bleach, condoms);
- 1997 French Ministry of Health and Ministry of Justice: new mission (*mission santé-justice* / Health-Justice mission) to propose a specific strategy for prevention of viral hepatitis in French prisons;
- 2000 recommendations of the mission, which also include hepatitis B vaccination [3].

### Hepatitis B vaccination – French prison data

In 1998, a survey was carried out by the *Observatoire Régional de la Santé Provence-Alpes-Côtes d'Azur* (ORS PACA), upon request of the French Ministries of Health and Justice. According to the results of this study, a relatively low percentage (14–28%) of inmates had received a complete HBV immunisation course. The survey also revealed contradictions of opinion between staff and inmates, with 69% of prisoners reporting that they would accept immunisation if it were offered to them, and prison medical teams reporting that inmates had refused the proposed immunisation.

Data from the anonymous testing centre at the Baumettes prison in Marseille revealed decreasing post-immunisation status in 2003, with 24% of incoming inmates anti-HBs positive in 2003 compared with approximately 33% in 2002.

The Baumettes data also reveal a serious lack of knowledge among new inmates regarding their immunisation status: two-thirds of the inmates with a post-immune serological status did not know if they had been previously vaccinated.

### Screening policy

France's screening policy is based on strict anonymity of data provided by inmates upon admission to prison. New inmates are offered testing for HIV and HBV, and HCV in case of an identified risk factor. The results are then transmitted to inmates to whom counselling is offered.

### Main risk factors among prison inmates

The ORS PACA survey showed that among the participants who had ever injected drugs, 30% had injected drugs in prison, 5% reported injecting drugs for the first time in prison, and 21% had shared injecting material.

Other survey data showed that 1.4% of the survey respondents had practiced homosexual intercourse in prison, 8% had practiced heterosexual intercourse in prison, and 66% reported not having used a condom during their last sexual contact. In 2004, only one

prison in France (Baumettes in Marseille) was offering a condom distributor within the institution. In other prisons, access to condoms is provided only through medical units.

Tattooing was reported by 21% of the respondents.

### Syringe exchange programmes not allowed in France

While syringe exchange programmes have worked successfully in several countries (e.g., the United Kingdom, Spain, Switzerland, Germany, USA), in 2000 the French Health-Justice mission recommended not to implement an experimental syringe exchange programme in French prisons. This issue has not been re-examined since then, despite a proposal to distribute syringes pre-filled with injectable buprenorphine or methadone.

The situation reflects an inherent contradiction in allowing injecting drug use in French prisons which, at the same time, is prohibited within a legislative context.

### Challenges in prison prevention programmes

France's penal system will need to undergo further innovative changes in providing greater and more homogenous access to opiate maintenance treatments, pilot programmes, and enhancement of prisoner information services.

One of the major goals to be achieved within the committal population is to ensure that an inmate who is seronegative upon admission to prison remains seronegative upon release.

Preventive measures within the prison environment will need to focus more on behavioural change among inmates that will contribute to higher uptake levels of hepatitis B vaccine as well as on additional harm-reduction measures such as needle-exchange programmes. Public debate on legislative aspects of prevention strategies in prisons will be necessary to achieve such goals.

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## Hepatitis C in France

### Epidemiology of hepatitis C in France

Over 170 million people are infected with the hepatitis C virus (HCV) worldwide. In 1994, prevalence of anti-HCV positivity in France was estimated at 1.05% (550,000 to 600,000 persons) and the number of chronic (HCV-RNA-positive) infections estimated at 400,000 to 500,000 persons. Preliminary results of a survey performed in 2004 show prevalence estimated at 0.86% (95% confidence interval: 0.66-1.10%).

#### *HCV incidence and routes of transmission*

HCV infection began as an essentially transfusion-transmitted / nosocomial disease during the 1950s. At present, the number of HCV infections in France remains high among injecting drug users (IDUs), with an incidence density ranging from ten to forty percent person-years.

Data showing various routes of HCV transmission among more than six thousand patients enrolled in a nationwide survey of chronic hepatitis C, who were referred to thirty hospitals in France for the periods 1991-1993 and 2000-2002, are shown below [1,2]:

Route of transmission	1991-1993	2000-2002
Transfusion before 1991	37.0%	31.5%
Injecting drug use*	24.7%	45.6%
Nosocomial**	14.9%	17.8%
Not identified	20.4%	13.1%

\* *In men, drug use now represents 60% of cases.*  
 \*\* *Potential, unproven route of transmission.*

HCV-HIV co-infections occur mostly through drug use. While HCV incidence has dramatically decreased in the general population in France, the incidence of HCV among IDUs is an uncontrolled issue that will require new strategies for prevention.

Data from a large-scale French survey [3] show mother-to-infant transmission at 3.8% (95% CI: 0.8-6.8%) in mono-infected mothers, and 10.9% of mothers (95% CI: 4.1-22.3%) who were co-infected with HIV.

There are no large-scale studies available in France on HCV transmission in sexual partners. Although sexual transmission of HCV is rare in France in heterosexual and regular partners, there have been recent cases of acute hepatitis C among homosexual men co-infected with HIV [4].

#### *HCV genotypes*

Six HCV genotypes have been identified, each having various subtypes. Quasispecies co-exist in an infected person. In France [5], the dominant HCV genotypes identified in IDUs are 3 and 1a, for blood recipients and nosocomial sources genotypes 1b and 2. HCV genotype 4 is emerging in France, recently infecting IDUs and immigrants from Egypt and sub-Saharan Africa.

#### *HCV infection among older patients*

Older HCV-infected patients present special challenges to health-care treatment in terms of treatment failure, the risk of developing cancer and end-stage liver disease in cirrhotics, and the need for transplantation – all of which place a great burden on the reference centres which are already operating under heavy work loads.

### Hepatitis C surveillance

The *Institut de Veille Sanitaire* (InVS) and the *Fédération Nationale des Pôles de Référence et Réseaux Hépatites* (FNPRRH) are

responsible for the administration and coordination of a national hepatitis surveillance network. This network is based on twenty-six hepatology reference centres and monitors changes in epidemiological and clinical characteristics of HCV patients at first referral [2].

Data derived from HCV surveillance systems in France are also complemented by various research studies that provide additional information on HCV-infected patients from mandatory notification data on nosocomial-related hepatitis B or C [6], from blood donors (residual risk) [7], and surveillance of HCV serology screening activities based on 257 participating laboratories [8].

The surveillance system, implemented in 2000, is based on newly referred HCV-infected outpatients in 26 hepatology reference centres. A case is defined as a newly referred (first contact) anti-HCV-positive patient in any of the participating reference centres. Epidemiological and clinical data are derived from standardised notification forms.

Some of the more specific information or data collected by the hepatology reference centres are shown below:

- Circumstances of HCV antibody testing and date of diagnosis;
- Risk factors for HCV transmission;
- Suspected year of infection;
- Assessment of severity of disease through clinical-biological-morphological stages (already completed for 87% of patients);
- ALT value, HCV genotype;
- Liver biopsy results (documented for less than 40% of patients);
- Alcohol consumption.

The total number of newly referred HCV-positive patients in the hepatology reference centres has increased from 2,063 in the year 2000 to 4,259 in 2002. (The system was set up in April 2000.) Ten percent of the patients have cirrhosis at first referral [2]. Patients' characteristics were compared for those with and without cirrhosis; the results underscore the important role of past excessive alcohol consumption in the development of cirrhosis for HCV patients [9].

### Screening

Screening has become a very successful achievement of France's viral hepatitis prevention and control programme. It is estimated that by the year 2002, approximately 60% of new hepatitis C patients had been diagnosed following HCV screening. The latest programme objective is to diagnose 100% of HCV-infected patients by 2005.

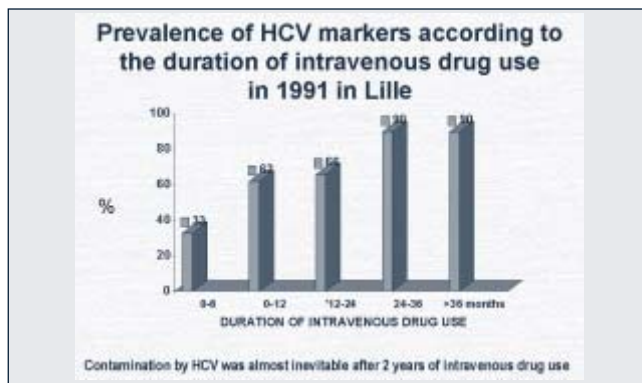
Some of the measures that have led to enhanced screening in France during the last several years are:

- Setting up centres for anonymous, cost-free screening (CDAG - *Consultations de dépistage anonyme et gratuit*);
- Testing of 76,000 persons in 2001, of whom 1.6% tested HCV positive;
- 20% of screening took place in hospitals; 80% in cities;
- Increased testing by approximately 20% per year between 1998 and 2002.

Although many high-risk groups are being reached, diagnosis of low-risk patients will need to be increased.

### Preventive measures for injecting drug users (IDUs)

Injecting drug use has become the main route of HCV transmission. Europe, the USA and Australia report high prevalence among IDUs ranging between 50% and 90%. French data are shown in the following slide [10].



In order to prevent HIV and HCV transmission among injecting drug users in France, health authorities implemented a national risk-reduction programme in 1993 with measures aimed at providing IDUs with easy access to syringes, opiate substitution, HIV and HCV screening, and counselling for infected patients.

Between March 1999 and July 2001, a survey [11] was conducted to determine incidence and risk factors of HCV and HIV infections in a prospective cohort of injecting drug users in the North and East of France. Of the 231 HCV-seronegative IDUs who were enrolled in the study, sixty-six were excluded from the analysis – three (1.3%) died and sixty-three (27.3%) did not undergo a final serum test.

The study results showed that:

- 165 participants (71.4%) underwent a final HCV serum test.
- Among the 165 enrollees, 16 seroconverted for HCV during follow-up.
- No HIV seroconversion was detected.
- The crude incidence density for HCV infection is, therefore, nine percent person-years.

The incidence of HCV infection among IDUs in France remains rather high. The main risk factors are sharing injection and preparation equipment and ongoing, regular injecting practices. Among the factors that are likely to contribute to sharing are cocaine use as well as sporadic and unplanned injections.

One may conclude that France's risk-reduction policies have had an insufficient impact on hepatitis C transmission in the drug-user population. There is still much that remains to be done to reduce HCV incidence among IDUs that could be achieved by implementing the following measures:

- Prevent syringe use, particularly among the youngest drug users;
- Improve accessibility to injection equipment that aims to prevent re-use behaviour and sharing (e.g., by needle exchange programmes);
- Continue opiate substitution policy taking into account its limitations;
- Reinforce screening of HCV infection in IDUs;
- Reinforce accessibility of treatment to IDUs.

### Nosocomial HCV infections

Notification of nosocomial HCV infection has been mandatory in France since July 2001. Although cases still occur in France, frequency is rare. Since 2001, there have been thirteen notifications of hospital-acquired cases of HCV infection.

The three possible modes of HCV transmission are (1) patient to patient; (2) patient to healthcare worker (HCW); and (3) healthcare worker to patient.

#### Patient-to-patient transmission

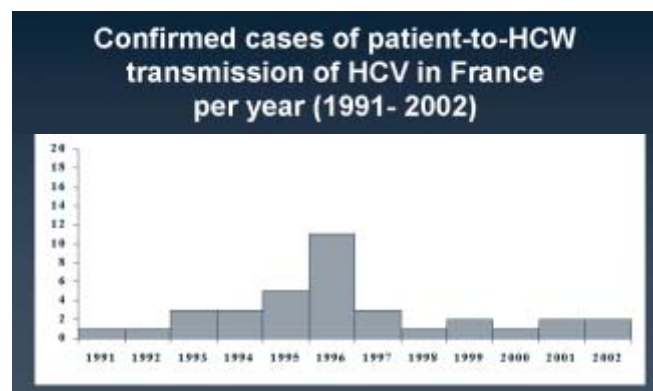
The mechanisms for HCV transmission from patient to patient are often unknown and can occur in various settings: haemodialysis,

digestive endoscopy, contact with diabetic children, anaesthesiology, transplantation and surgery. Some of the well-known mechanisms of HCV transmission include sharing injection material and products, as well as breaches in barrier precautions and in material disinfection.

Some of the control measures in nosocomial settings in France are the introduction of single-dose vials, disposable needles and syringes, no re-use of multi-dose vials, and use of peripheral venous catheters with an anti-reflux system.

#### Patient-to-HCW transmission

In France, the case definition for occupational HCV infection in a healthcare worker requires (1) documented occupational exposure to blood or infectious body fluids from an anti-HCV-positive source; (2) the HCW was anti-HCV negative at the time of exposure; and (3) the HCW had HCV seroconversion that was temporally associated with the exposure. A table showing the number of confirmed cases of HCV transmission in healthcare workers in France between 1991 and 2002 is shown below [12]:



Evidence from multiple case reports shows percutaneous exposure to infected patients' blood, but few case reports show conjunctival splashes of blood to healthcare workers [13,14].

In 1998, a study was carried out in France to estimate the annual number of cases of HCV transmission from infected patients to uninfected surgeons or nurses due to percutaneous injury during invasive procedures [15]. The risk of transmission was estimated using a model based on three probabilities: (a) that a healthcare worker sustains at least one percutaneous injury during a procedure; (b) that 1-10% of patients are HCV-seropositive; and (c) that transmission of the virus to the healthcare worker occurred after such exposure. The data showed the following estimates for surgeons and nurses in France at risk of acquiring occupationally-related HCV infection:

- between 2 and 21 surgeons / year (out of a total of 20,000)
- between 16 and 167 nurses / year (out of a total of 300,000)

The study concluded that these estimates highly justify the introduction of preventive measures in France to protect healthcare workers from blood-borne infection during medical care. New devices, safer suturing techniques, and alternative procedures to prevent parenteral exposure should be considered for surgical procedures at risk. Campaigns against recapping needles must be reinforced, and organisational models promoting decentralisation and professional autonomy must be considered to lower the risk of percutaneous injury to nurses [15].

#### HCW-to-patient transmission

HCV transmission from a healthcare worker to a patient occurs mostly through blood exposure during orthopaedic and cardio-

thoracic surgery and other procedures involving gynaecology and anaesthesiology.

For healthcare workers in France, recent national recommendations require that they know their HCV status. A healthcare worker who is aware of being HCV infected must undergo a group evaluation during which time he / she is advised to consider using less exposure-prone procedures; also discussed are the risks of continuing employment in a medical setting.

#### Conclusions

Despite recommendations on prevention and control of HCV infection in healthcare settings, breaches in medical practices associated with HCV transmission still occur in France. Further efforts on preventing blood-borne virus infections are needed and should be based on the recommendations of expert steering groups. One official recommendation is that HCV-infected healthcare workers should carry out less invasive procedures to minimise risk.

#### Prevention and residual risk of HCV infection following blood transfusions

HCV screening was first carried out in France in 1990 for anti-HCV using enzyme immunosorbent assays (EIA). Since 2001, nucleic acid testing (NAT) has been used for HCV screening in France as a means of minimising risk in blood and blood products.

Data (1998-2003) for HCV infection risk factors in first-time blood donors show significant gender differences. The main risk factor among HCV-infected men was injecting drug use (37.8%), while for HCV-infected women the main risk factor was nosocomial transmission (31.2%). Data for the same time period showing risk factors for HCV seroconverters among repeat blood donors also revealed gender differences: among HCV-infected men, the main known risk factor was injecting drug use (25%) compared with women for whom the main risk factor was sexual contact with an HCV-infected partner (17%).

These data suggest that improvements are still needed in hepatitis C prevention and control measures among IDUs and that the risk for nosocomial transmission of HCV needs to be reduced still further.

There has been a four-fold decrease in residual risk for HBV, HCV, and HIV infection combined (1 / 235,000 donations in 1999-2001 versus 1 / 65 000 donations in 1992-1994). This decrease is linked to the decline of both HCV and HBV incidence, and can be attributed to:

- improved donor selection;
- preventive measures taken to avoid nosocomial infections;
- hepatitis B vaccination campaigns.

Since implementation of NAT, the residual risk of transfusion-transmitted viral infections in France is estimated at 1 in 3,150,000 donations for HIV and 1 in 10,000,000 for HCV. Currently, the risk of a blood recipient becoming infected with a hepatitis virus in France is extremely low.

#### Preventive measures for prisoners

In 1997, the French Ministry of Health and Justice requested that a survey be carried out to evaluate the transmission of hepatitis virus in French prisons. Data from the ORS (*Observatoire Régional de la Santé*) PACA (*Provence-Alpes-Côtes d'Azur*) survey [16] showed that among the 155 inmates who ever injected drugs (out of 1212 respondents), 30 % injected drugs in prison, 5% injected drugs for the first time in prison, and 21% had shared injecting material in prison. Homosexual intercourse was mentioned by 1.4% of respondents, heterosexual intercourse by 8%, and 66% reported

not having used a condom during their last intercourse.

More recent data from a 2000 national survey [17] among prison medical units (based on 81/172 questionnaires returned in a prison population of 24,045 inmates) reveal that HCV seroprevalence was 6.3%.

Harm-reduction tools in French prisons include opiate substitution, material disinfection with bleach (in use in French prisons since 1997, but poorly promoted in terms of its preventive action), condom use, and, more recently, experimental units for family visits. The French Health-Justice mission recommended in 2000 not to implement experimental syringe exchange in French prisons. This issue has not been re-examined despite proposals such as distributing syringes pre-filled with injectable buprenorphin or methadone.

Education measures rely on prison medical and social teams who are investing heavily in providing information on risk and prevention of viral infections as well as counselling to inmates. Partnerships are also forged among associations and institutions. For the PACA region, there has been co-funding with the DRSP (*Direction Régionale des Services Pénitentiaires*) where education measures have doubled since 2000. In 2004, nine different educational initiatives were carried out relating to HIV, HBV, and HCV.

#### Conclusions

The most urgent and minimal goal to achieve is that a seronegative inmate upon admission must remain seronegative upon release. From a qualitative perspective, efforts to improve the working relationships between staff and inmates, and to promote existing tools will contribute to decreasing risk behaviour. Promoting peer education via peer training programmes will also help to achieve these goals.

#### Prediction of HCV-related morbidity and mortality burden in France

Determining the burden of hepatitis C depends on the number of subjects who are infected with HCV, the stage of the patient's disease, and the natural history of hepatitis C with, or without, treatment. Because of the difficulty in measuring these variables directly, and because epidemiological data are limited, mathematical modeling [18,19] based on back-calculation of past HCV infections is a useful tool in allowing prediction of disease burden in a given population as well as for the economic evaluation of hepatitis C treatment programmes.

A back-calculation approach is used to reconstruct the history of HCV infection in France and to predict mortality due to hepatocellular carcinoma (HCC) related to HCV.

The model is based on information about the natural history of the disease, epidemiological data about the HCV-infected patients in three French cohorts, and mortality data from national statistics. It takes into account that: age at disease diagnosis = age of infection + time to disease development.

Using the back-calculation model, the HCV epidemic in France was traced back to the 1940s and resulted in the prediction that HCV-related annual mortality (deaths from liver failure and HCC), due to pre-1999 infections would rise from 3,000 (2,000-4,400) in 2002 to 4,500 (3,500-6,900) in 2022, unless effective anti-HCV treatment reaches at least 50% of the HCV-infected French population [19,20]. The model shows that improvements in HCV therapy have been too recent and too few patients diagnosed and deemed treatable to induce a decrease or even a stabilisation of HCV-related mortality.

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## Hepatitis B and C registries

Specialised registries have been created in France in order to determine the epidemiological status of hepatitis B and C in the general population. Population-based registries record all new cases of a disease in a well-defined geographical area. They are also instrumental in organising research studies based on their recorded data.

A specialised registry was set up in January 1994 in the Côte-d'Or and in January 1995 in the Doubs administrative areas.

Data that were compiled between January 1994 and December 1999 were obtained from three sources:

- biological and virological analysis laboratories that reported all new HBsAg-positive and anti-HCV-positive cases to the registry;
- specialists in gastroenterology, hepatology, infectious diseases, and internal medicine; and
- general practitioners who prescribed the serology examination.

Initial results showed that the yearly incidence of HBsAg and anti-HCV antibodies in the general population of the Côte-d'Or and Doubs areas is high. Data based on annual detection rates suggest that there are approximately 6,000 HBV carriers in France, and approximately 18,000 acute cases of hepatitis C. This is represented

in more detail in the table below.

Incidence of diagnosed cases	
Annual HBsAg detection rates / 100 000	
- males:	10.1 ± 0.7
- females:	8.2 ± 0.6
~ 6,000 new cases in France	
Annual anti-HCV detection rates / 100 000	
- males:	33.1 ± 0.9
- females:	22.6 ± 0.7
~ 18,000 new cases in France	

In addition to enhancing epidemiological knowledge of viral hepatitis, population-based registries are necessary in the fight against hepatitis B and C to allow the:

- evaluation of the impact of screening campaigns and guidelines;
- evaluation of health networks and treatment of patients; and
- examination of the natural history of hepatitis, on a long-term basis, in the general population.

*Based on a presentation by Dr Patrick Hillon, Département d'Hépatogastroentérologie, Hôpital du Bocage, Dijon, France.*

## Hepatitis E in France

### Epidemiology of hepatitis E in France

Epidemics of hepatitis E have been reported in high-endemic areas such as Africa and Asia. Although there is a correlation between poor sanitary conditions and endemicity for hepatitis E infection in developing parts of the world, sporadic cases of acute hepatitis E have also occurred in industrialised countries (e.g., in Europe, North America, Australia). Most of these HEV infections are considered to be imported, although some cases have been described among patients without a recent travel history in endemic areas.

In Europe, anti-HEV seroprevalence among blood donors is estimated between 1 and 5%, dependent on their age group and possible occupation close to animals. In France, hepatitis E infections have also been reported in persons who had not recently visited a high-endemic area.

Between 2001 and 2002, sera of 431 patients from the Midi-Pyrénées area diagnosed with acute hepatitis with unknown aetiology, were tested for anti-HEV IgG [1] and HEV RNA by realtime Taqman PCR. Forty-six (10.7%) samples tested positive for anti-HEV IgG and HEV RNA was amplified in 16 of them. Nine of the patients had not recently visited endemic areas and three of them had visited Spain. Sequencing of these HEV strains showed they belonged to genotype 3, well distributed in industrialised countries.

Data collected by the French National Reference Centre for Enterically-transmitted Viral Hepatitis equally shows circulation

of hepatitis E virus in France in cases without any evidence of recent travel in endemic areas.

Serological data on domestic animals (swine, cattle, rodents) suggest a potential animal reservoir. Moreover, swine HEV sequences are closely related to those of human HEV strains [2]. However, the possible transmission route between humans and animal reservoir is not yet clear.

### Prevention and control of hepatitis E

Hepatitis E virus is transmitted mainly through the faecal / oral route. Outbreaks are often associated with massive contamination of water supplies. General prevention measures are based on improving sanitary conditions (e.g., safe water through boiling and proper disposal of sanitary waste). An effective hepatitis E vaccine is under evaluation in Nepal.

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*Based on a presentation by Dr Elisabeth Nicand, National Reference Centre for Enterically-transmitted Viral Hepatitis, Military Hospital Val de Grâce, Paris, France.*

## Viral hepatitis research in France

France has a long tradition of excellence in clinical research and today is still one of the leading countries conducting basic research. Funding for viral hepatitis research comes from a wide range of sources, which include institutions, hepatitis-targeted funds, external grants, and additional types of scholarships. Both fund raising and writing grant proposals represent huge investments in time for investigators and must be taken into account in managing the financial as well as the scientific aspects of their research activities.

At the institutional level, research funding comes from the following sources:

- public hospitals;
- universities;
- CNRS (*Centre National de la Recherche Scientifique*), France's national centre for scientific research, a public research organisation active in all areas of science; and
- INSERM (*Institut Nationale de la Santé et de la Recherche Médicale*), France's national institute for health and medical research.

These institutions not only provide the basic infrastructure but also the funding for salaries and research budgets.

### ANRS / ANRH – a major source of viral hepatitis research funding

France's national agency for research on AIDS - ANRS (*Agence Nationale de Recherches sur le SIDA*) was created in July 1992 as an organisation specifically dedicated to research on AIDS. In January 1999, ANRS extended its research activities by providing funding for clinical, therapeutic, and public health research into hepatitis C, and since January 2004, research funding for hepatitis

B. Today, ANRS / ANRH (*Agence Nationale de Recherches sur le SIDA et les Hépatites Virales*) represents a major source of non-structural funding for hepatitis research in France.

ANRS operates under the auspices of the French government – i.e., the Minister of Research, the Minister of Health, and the Minister of Foreign Affairs. Other ANRS / ANRH partners and stakeholders are CNRS, INSERM, IRD - France's institute for research and development (*Institut pour la Recherche et le Développement*), and the Pasteur Institute.

The aims of ANRS are to:

- Develop closer interaction among various areas of research;
- Coordinate AIDS and viral hepatitis research;
- Promote closer collaboration among research teams;
- Identify new research teams that have a potentially important role to play in conducting AIDS and viral hepatitis research;
- Provide funding to support research.

While ANRS funding for viral hepatitis research has increased somewhat, the budget is still lower than what had originally been requested, representing approximately ten percent of the total ANRS budget (i.e., 4.5 million out of approximately 42 million euros). It is hoped that the budget for viral hepatitis will be increased in the future to at least fifteen percent of the total ANRS budget. In 2004, the viral hepatitis research funding was distributed as follows:

- |   |        |
|---|--------|
| • Clinical research                     | 74.0 % |
| • Basic research                        | 20.3 % |
| • Research in human and social sciences | 3.5 %  |
| • Research in developing countries      | 2.2 %  |

Since 1999, ANRS has provided funding within the following areas:

- Conception and performance of 18 therapeutic trials involving 70 research centres;
- Funding of 76 research laboratory projects
- Funding of 43 pre- and post-doctoral fellowships and 12 clinical study monitors; and
- Funding of the French national cohort of patients with HCV- and HBV-related cirrhosis.

Due to the low incidence of hepatitis B in France, there are relatively few hepatitis B projects being carried out, with more research targeted to hepatitis C. There is a need, therefore, to increase the number of hepatitis B projects in ANRS, particularly epidemiological research on HBV infection including data on chronic carriers.

### European Commission funding: Fifth and Sixth Framework Programmes

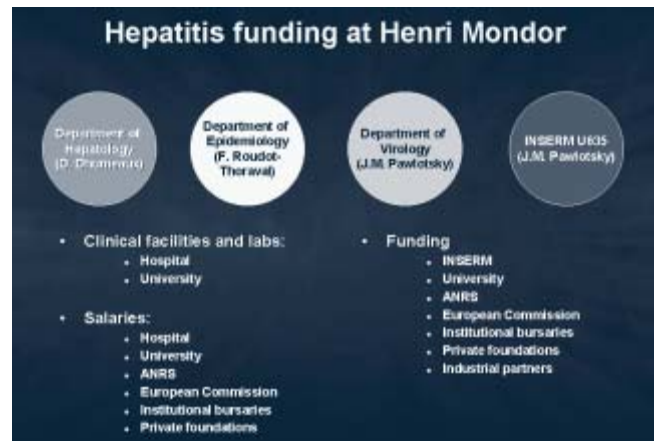
At European level, hepatitis-targeted research has been funded through the Fifth Framework Programme (1998-2002) of the European Commission [1], where a number of projects on hepatitis B and hepatitis C have been carried out. Although the Sixth Framework Programme (2002-2006) [2] represents a good potential source of funding, viral hepatitis research projects need to be added. Indeed, only one project, the ViRgil (antiviral resistance) Network of Excellence, is focusing explicitly on viral hepatitis. Of the sixty centres that comprise ViRgil, only three French centres are participating in the network in the viral hepatitis programme. Viral research projects could clearly benefit from additional lobbying at European level to help increase funding within the Sixth Framework Programme.

### Other sources of funding

France's national cancer organisation (*Ligue Nationale contre le Cancer*), the Foundation for Medical Research (*Fondation pour la Recherche Médicale*), local institutions, and private foundations also contribute to research funding.

At the Henri Mondor University Hospital, one of the leading institutions in France conducting viral hepatitis research, funding for the various research projects comes from a wide range of sources,

as shown below:



Additional research funding is available through the following sources:

- Regional or local administrations
- International grants (e.g., NIH, HHMI)
- Private foundations
- Industrial sponsors

Within industry, diagnostic and pharmaceutical companies are major partners in research funding, particularly for individuals who are doing post-doctoral research.

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## Hepatitis B vaccine safety issues

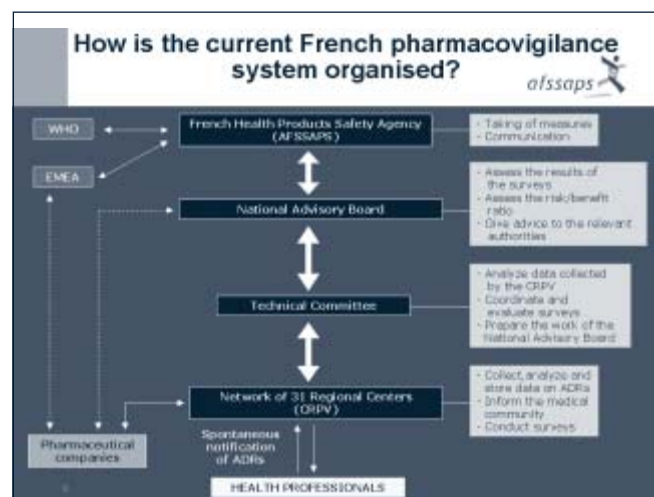
### Pharmacovigilance in France

Pharmacovigilance is the process of evaluating and monitoring human medical products in order to identify previously unrecognised changes in the patterns of adverse drug reactions (ADRs). In contrast to drugs, which are used in treating people who are already ill, vaccines are given to individuals (especially young children) who are usually healthy, as a preventive measure against disease. Despite these fundamental differences, in France vaccines are considered medical products and hence there is no specific vaccine pharmacovigilance.

As in other countries, pharmacovigilance in France is based on a passive surveillance system that relies on spontaneous reporting by healthcare professionals who voluntarily report any ADR they believe may be attributable to a drug. As is the case with many systems that rely on passive reporting, there is inevitably substantial under-reporting. Consumer reports of ADRs are taken into account only when they have been medically confirmed.

The French system of pharmacovigilance is based on a decentralised collection and validation of safety data through regional centres,

and a centralised evaluation and decision-making process at the French Health Products Safety Agency (AFSSAPS – *Agence Française de Sécurité Sanitaire des Produits de Santé*).



All prescribers (general practitioners, dentists, mid-wives) and pharmacists must report all serious or unexpected suspected ADRs. Pharmaceutical companies must report:

- All serious suspected ADRs that have occurred in France;
- All serious ADRs reported in the European Union when France is a Rapporteur or a Reference Member State;
- All serious and unexpected ADRs reported outside of the European Union.

France's pharmacovigilance database was set up in 1985. Since then, the database has received and entered over 250,000 medically-confirmed case reports with:

- Causality score;
- Data used for pharmaco-epidemiological studies (e.g., age, time to onset of disease, outcome).

### History of hepatitis B vaccination strategies in France

Hepatitis B vaccination in France began in 1982. At that time, it was targeted only to risk groups. In December 1993, France recommended hepatitis B vaccination in the infant immunisation schedule. This was followed by a school-based vaccination campaign for eleven-year olds, initiated by the French Ministry of Health during the 1994-1995 school year, for a ten-year period.

Since 1994, hepatitis B vaccination coverage has been low for infants (less than 40%) but between 1994 and 1998 relatively high among pre-adolescents (approximately 7.5 million vaccine recipients vs a total of 10 million vaccinated to date).

In September 1998, AFSSAPS convened a meeting to review the safety profile of hepatitis B vaccine. Updated information on cases of central demyelinating disorders reported up to March 1998 were reviewed, as well as the results of case-control studies about the risk of central demyelinating disease following hepatitis B immunisation. Based on these data, the conclusions of the meeting were that no relationship was demonstrated between a risk of central demyelinating events and hepatitis B vaccination. However, a low risk was not totally excluded.

Based on an analysis of the French pharmacovigilance data and on a review of the results of the specific pharmaco-epidemiological studies, the *Institut de Veille Sanitaire* (InVS) concluded the following:

- Infants – there is no reason to question infant hepatitis B vaccination since there has been no notification of neurological events following immunisation in this group;
- Adults – while international data do not favour a causal association, French data do not disallow a small excess risk. However, if a neurological risk exists, it appears negligible for high-risk individuals in comparison with the benefits of hepatitis B vaccination.
- Pre-adolescents – even in the worst-case scenario (i.e., existence of a causal relationship, with an odds ratio of 2, which is very unlikely according to the data available), the benefit / risk analysis remains in favour of continuing hepatitis B vaccination [1].

Following the cautionary principle, the Ministry of Health temporarily suspended the hepatitis B school-based immunisation programme for pre-adolescents in October 1998. However, taking into account the benefits of the vaccine, French authorities continued to support infant and adolescent vaccination through primary care physicians.

Since the 1998 decision of the Health Ministry, hepatitis B vaccination coverage has declined sharply. Despite the fact that there have been no changes in the immunisation schedule since 1995 and that hepatitis B vaccination remains recommended in

infants, adolescents and high-risk adults, hepatitis B immunisation has not recovered to its previous coverage levels.

### Hepatitis B vaccine safety concern confined to France

Almost half of the population in France (approximately 30 million inhabitants, of whom 20 million are adults) were vaccinated against hepatitis B virus infection between 1984 and 2003. Between 1994 and 1998, there was high hepatitis B vaccination coverage among school children as well as among low-risk adults. The discontinuation of the school-based campaigns was, to a certain extent, interpreted as France's recognition of a safety issue and, therefore, created some confusion in the media, the general public, and the medical community. The vaccine "scare" has also been taken up by anti-vaccination groups, supported by some media, in order to advance their agenda.

Following a case-control study [1] that was published in September 2004 on the risk of multiple sclerosis in adults associated with recombinant hepatitis B vaccine, The Global Advisory Committee on Vaccine Safety (GACVS) of the World Health Organization issued its findings [2] that the "...argument submitted by Hernán et al [the authors of the study] are insufficient to support the hypothesis of a link between hepatitis B vaccination and MS [multiple sclerosis], and do not justify discontinuation or modification of immunisation programmes with HBV. The latter have had a demonstrated profound beneficial public health benefit worldwide." [3]

### Position of various public stakeholders and expert committees

- In September 2004, the national advisory board and the technical committee on vaccination (CTV – *Comité Technique des Vaccinations*) reviewed the data on hepatitis B vaccine, and consistently advised the Ministry of Health to maintain the vaccination strategy (i.e., infants, adolescents, high-risk adults, and mandatory vaccination of health professionals). Similar statements conclude that there is no indication to change this advice.
- The same conclusions have been reached by a special ad hoc expert committee that was set up by the Ministry of Health (Commission Dartigues, 2001).
- The same conclusions were given by the jury of the International Consensus Conference in September 2003 that included some of the best expertise available in the world on this topic [4].
- There is continual support and commitment in favour of hepatitis B vaccination from the professional societies of hepatology in France.

### Conclusions

To date, there is no risk of central demyelinating events following hepatitis B immunisation among infants – to date, no cases reported in this group.

The National Advisory Board, the CTV, and the WHO do not recommend changes in the current universal immunisation schedules worldwide.

It would appear that until there is a firm political commitment on the part of the French authorities affirming the safety of hepatitis B vaccination, this issue will remain unresolved in the view of the general public and in certain parts of the medical community, putting into jeopardy France's well-established immunisation programmes.

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Based on presentations by Dr Nicole Guérin, Comité Technique Vaccinations, Antony, France; Dr Alexis Jacquet, Pharmacovigilance Unit, AFSSAPS, Saint-Denis, France; and Dr Daniel Lévy-Bruhl, Département des Maladies Infectieuses, Institut de Veille Sanitaire (InVS), Saint-Maurice, France.

## What still needs to be done

### Achievements and challenges

The prevalence of *hepatitis C virus* antibody in France in 1994 has been estimated at approximately 1% in the general population. Newly released figures for 2004 indicate an HCV antibody prevalence of 0.86% in the 20-80 year age group. Risk factors for HCV infection are now well known and prevention programmes are in place to reduce incidence. However, HCV incidence has remained very high among injecting drug users. Harm-reduction measures had a limited impact and new strategies will be needed to reduce HCV incidence further in this high-risk group. HCV prevalence among prisoners is much higher than in the general population. Although recommendations have been made to reinforce prevention in the prison population, the results have not yet been evaluated.

Since 2001, cases of nosocomial HCV infection must be notified through the French mandatory nosocomial infection reporting system. This system indicates that nosocomial HCV transmission is still occurring, but could be reduced further by a strict implementation of standard precautions.

The national viral hepatitis prevention programme will need to be evaluated in terms of short-term indicators, the incidence of end-stage liver disease, and its overall effectiveness for HCV prevention and control. Several surveillance systems have been implemented in the last five years to monitor the progress of the French national hepatitis B and C prevention programme. Screening of HCV has been advocated. Treatment of HBV and HCV chronic infections is available, and managed by hepatologists, hepatology referral centres, and general practitioners. However, problems remain, such as the treatment of non-responders or patients with end-stage liver diseases (cirrhosis, HCC). Additional efforts and new strategies will need to be designed to improve treatment compliance and for treating non-responders.

Epidemiological knowledge of *hepatitis B virus* in France still needs to be improved:

- The recently introduced mandatory reporting system for acute HBV infection needs to be improved in terms of its completeness in notifications of cases.
- Data on prevalence of HBV infection in the general population and in risk groups will be available soon (early 2005).

Improvements are also needed for prenatal screening and prevention of perinatal HBV transmission to newborns.

France has still not recovered from the 1998 hepatitis B vaccination crisis. Despite scientific data supporting the safety and efficacy of hepatitis B vaccine, and official statements by the World Health Organization and expert committees supporting the current French immunisation strategy, hepatitis B vaccination coverage has not improved. In order to help re-establish confidence in the vaccine,

there is a need for:

- political commitment at the highest level that supports and promotes the safety and benefits of hepatitis B vaccine;
- the design of socially acceptable strategies to reinforce vaccine uptake;
- promotion of the safety, benefits, and use of the hexavalent vaccine.

Data on *hepatitis A virus* in France are quite limited. France is the only country in the European Union without HAV surveillance. Therefore, epidemiological trends, risk factors, outbreak detection, and evaluation of vaccination coverage among risk groups in France are difficult to assess. Mandatory notification of hepatitis A for surveillance purposes is being considered. Hepatitis A vaccine, however, is available and recommended for high-risk groups.

For *co-infected patients*, screening and treatment should be carried out as early as possible in order to prevent severe morbidity from HBV and HCV infections. There is still a need for better management of patients with addiction, for more clinical research, and for new treatment strategies.

While a passive reporting system is necessary for surveillance of *adverse events*, data need to be reinforced through active surveillance and supported by pharmaco-epidemiological databases. A key priority will be to re-establish the public health balance between the unproven risk of multiple sclerosis and the long-term benefits of immunisation.

Hepatitis research in France is organised, promoted, and funded by public institutions within the *Agence Nationale de Recherches sur le SIDA et les hépatites B et C* (ANRS). More hepatitis B and C research projects, particularly for hepatitis B, are needed. Such research should include:

- Multi-disciplinary projects;
- Clinical trials carried out independently of industry; and
- Public health research into epidemiology, social sciences, and quality of life.

### Conclusions

#### What went wrong

- Response to the hepatitis B immunisation crisis in France by authorities, industry, and media that led to decreased public confidence in hepatitis B vaccination and the resulting lower coverage.

#### What has been done that still needs to be improved

- prevention of mother-to-child transmission;
- surveillance of hepatitis B;
- prevention of HCV infection among injecting drug users;
- viral hepatitis prevention and care in prisons;
- earlier management of co-infections;
- management of alcohol consumption in the management of hepatitis;
- short-term evaluation of national prevention programmes.



*What still needs to be done*

- restore confidence in HBV immunisation;
- hepatitis A surveillance;
- long-term evaluation of end-stage liver disease
  - its impact on long-term morbidity / mortality;
  - from a health-economic perspective.
- unresolved questions for which further data / research / policies are needed:
  - new strategies for HCV prevention among injecting drug users;
  - specific strategies for inmates;
  - reducing barriers to access of care and treatment;

- better understanding of the hepatitis B immunisation crisis;
- defining and implementing socially acceptable immunisation strategies;
- devising new treatment strategies for co-infected patients, and non-responders;
- long-term evaluation of programmes.

*Based on a presentation by Dr Jean-Claude Desenclos, Département des Maladies Infectieuses, Institut de Veille Sanitaire, Saint-Maurice, France.*

## Conclusions of the meeting

The Viral Hepatitis Prevention Board held its autumn meeting November 18-19, 2004, in Veyrier-du-Lac, France. The objectives of the meeting were to provide an overview of viral hepatitis in France, and reviewing, evaluating and providing updates on:

- The epidemiology of viral hepatitis;
- Surveillance systems for infectious diseases and adverse events following vaccination;
- France's viral hepatitis research activities;
- Viral hepatitis prevention and control measures;
- Lessons learned from the French experience: achievements, challenges, and the way forward.

### The healthcare system in France

- France is facing difficulties similar to other countries in sustaining high levels of health expenditures, with no guarantees of increased funding. This is due to an increasing ageing population (approximately ten million people in France are sixty-five years or older), relatively low birth rates, increasing levels of unemployment, and increased health costs for new therapies.
- Despite indicators showing a relatively healthy population in France, other core indicators show a high rate of premature mortality due to high-risk behaviour, such as high consumption of alcohol and tobacco, and to accidental deaths. Higher mortality and morbidity rates are also found in areas of the country with high levels of unemployment, where high-risk behaviour is frequent.
- Decision-making within France's healthcare administration is centralised at national level. However, the recently enacted Public Health Policy law of August 2004 provides for implementation of strategies at a decentralised level. While mandatory immunisation policies are decided and implemented at national level, strategies to administer recommended vaccines may be taken at regional level, which accounts for disparities in vaccination coverage levels by geographical area.
- In order to address the huge imbalance between France's healthcare expenditures for prevention, (only 2.3% spent on prevention programmes in 2003) and for treatment, further studies will need to be carried out to help demonstrate the cost-effectiveness of prevention in the healthcare system.

### National strategy for prevention and control of viral hepatitis

France's viral hepatitis prevention and control programmes are based on strategies to reduce the risk of HBV and HCV transmission through updating and reinforcing hepatitis C prevention and control measures, and implementing new measures for hepatitis B prevention.

France's national prevention and control plan for hepatitis B and C have led to enhanced screening campaigns, an effective network of reference centres, and excellent research programmes. Major achievements of these programmes have led to:

- Primary prevention measures aimed at populations at highest risk of viral hepatitis infections;

- Mandatory notification of nosocomial HCV infection;
- Effective screening campaigns and increased HCV testing;
- Improvement of access to care and treatment, particularly in hospital services;
- Improved and easy patient access to therapy with costs fully reimbursed; and
- New capacities for diagnosing large numbers of patients.

Challenges facing France's healthcare system are the continuing hepatitis C epidemics among injecting drug users, the relatively low participation of general practitioners in networks that are outside of the specialised reference centres, and the need for more research capacity and strategic planning for long-term projects, cohort studies and large-scale trials. Evaluation of the viral hepatitis programme, in terms of short-term indicators, is also needed.

### Hepatitis A in France

#### *Epidemiology*

Hepatitis A is not a reportable disease in France, where endemicity is low. The prevalence of anti-HAV antibodies in French military recruits decreased from 1978 to 1997. As this group is representative of the male population in France, these data show an increasing number of susceptible adults in the general population. Outbreaks still occur due to person-to-person transmission and food contamination among groups living in close contact, and among men who have sex with men.

#### *Immunisation*

France's hepatitis A immunisation recommendations are targeted to groups considered at increased risk of HAV infection.

#### *Surveillance*

As France has no surveillance of acute HAV infection, the possibilities are limited for monitoring epidemiological trends, assessing risk factors, identifying outbreak sources, and assessing risk-group vaccination coverage of outbreaks. France has a sentinel surveillance system that has been in place since 1991, but the system is limited by under-reporting by participating general practitioners, and is not designed to detect outbreaks.

A pilot study was conducted between 1999 and 2000 to detect hepatitis A outbreaks, to document incidence and HAV exposures. Participation of clinical laboratories was voluntary; at the same time, there was an insufficient number of participating laboratories, and a lack of capacity to identify clusters at district level. One positive aspect of this study was the willingness of the biologists to participate.

A proposal has been submitted to France's Upper Council for Public Health (CSHPF - *Conseil Supérieur d'Hygiène Publique*

*de France*) for mandatory notification of hepatitis A by biologists to district medical officers. A decision on this proposal, accepting the principle of mandatory notification of hepatitis A, has been taken on November 26, 2004.

### **Hepatitis B in France**

#### *Epidemiology*

Incidence of hepatitis B infection in France is low. Nevertheless, there is a need to optimise the current strategy of prevention and vaccination to reduce further the number of acute cases of HBV infection. Measures to improve prenatal screening need to be reinforced to prevent perinatal HBV transmission to newborns.

There has been a shift in acute cases of hepatitis B from younger people in the 20 to 29-year age group (1991-1994) to those in the 30 to 39-year age group (March 2003-March 2004), a trend which may reflect the positive impact of France's hepatitis B vaccination strategy targeted to pre-teenagers and adolescents in 1994.

There is a need for further epidemiological studies on HBV prevalence within the general population and risk groups. A nationwide survey is being carried out on prevalence of chronic hepatitis B and C infections (results are pending). A new surveillance system was set up in 2003 and is now producing new data to monitor hepatitis B prevalence and incidence trends in France.

#### *Surveillance*

Notification of hepatitis B has been mandatory in France since March 2003, when France's new health surveillance system was put into place. Since then, all acute cases of hepatitis B must be reported by biologists and clinicians to their district health office, which reports to the national Institute of Health Surveillance (InVS - *Institut de Veille Sanitaire*). However, the system needs to be improved in terms of its completeness in notification of cases.

Preliminary results show that during the first year of mandatory notification (March 2003 to March 2004) two-thirds of all acute HBV cases could have been prevented had hepatitis B vaccination of risk groups been systematically carried out. These data highlight the need for reinforced prevention strategies to protect newborns of HBV-infected mothers.

National reference centres for hepatitis A, B, and C are contributing to the new surveillance system by providing a regulatory basis for molecular epidemiological research and for surveillance in blood donors.

#### *Immunisation*

France has recommended hepatitis B vaccination since 1982 for all workers exposed to HBV and other persons at risk of HBV infection. Since 1991 hepatitis B vaccination has been compulsory for healthcare workers. Universal hepatitis B vaccination in France has been recommended by the CSHPF since 1994. The latest recommendations were made in March 2002. The 2004 schedule recommends systematic immunisation of all children under 13 years of age, preferably during infancy, and of all risk groups. The immunisation policy is reviewed every year and takes into account newly available vaccines in France and the benefit / risk assessment of vaccination. Although vaccination policies have been agreed, infant and child vaccinations are not adequately implemented. Two hexavalent vaccines, while available, are only used on a limited basis in France as they are not reimbursed through the healthcare system.

#### *Prevention and control measures*

1. Residual risk of HBV infection following blood transfusions:

Blood screening in France for HBV began in 1971 using HBsAg enzyme immunoabsorbent assays (ELISA), and is one of the most successful aspects of France's national health programme. Nucleic acid testing (NAT) had been considered for HBV testing in 2001 but it was decided not to implement this technology in France due to its estimated limited impact on minimising residual risk in blood and blood products.

2. Healthcare workers:

Hepatitis B coverage levels remain less than optimal among certain groups of healthcare workers. According to 1997 data, only 79% of surgeons practicing in France had been vaccinated against HBV. There are also ongoing discussions of whether to allow healthcare workers who are in remission of HBV DNA and on long-term monotherapy, to perform invasive procedures.

3. Prisoners:

One of the major goals within France's committal population is to ensure that HBV-seronegative inmates upon admission to prison remain seronegative throughout their prison term.

Harm-reduction measures to help reduce high-risk behaviour in French prisons still need to be reinforced. Syringe-exchange programmes are not allowed in France despite proposals that would require distribution of syringes that are pre-filled with injectable buprenorphine or methadone. While injecting drug use is allowed within French prisons, syringe exchange is prohibited within a legislative context.

Further innovative measures need to be introduced within the prison environment to allow for more homogenous access to opiate maintenance treatments, pilot programmes, and enhancement of prisoner information services. Prevention strategies will need to be devised to encourage behavioural change among inmates that will lead to higher uptake levels of hepatitis B vaccination. Further clinical research is needed as well as new treatment strategies to improve management of patients with addictions.

### **Hepatitis C in France**

#### *Epidemiology*

In 1994, the prevalence of anti-HCV positivity in France was estimated at 1.05%, a figure which represents approximately half a million HCV-infected persons. Between 400,000 and 500,000 persons are estimated to have chronic (HCV-RNA-positive) infections. Preliminary survey data (2004) indicate a prevalence of 0.86%. HCV incidence remains a problem among IDUs, with current values estimated at 10-40% person-years.

HCV genotypes 3 and 1a are dominant in injecting drug users (IDUs) in France; for blood recipients and nosocomial sources, genotypes 1b and 2 are dominant. HCV genotype 4 has emerged in France infecting IDUs and immigrants from Egypt and sub-Saharan Africa.

Older HCV-infected patients represent a great burden for reference centres that are operating under heavy work loads. These patients present special healthcare challenges in terms of treatment failure, the risks of developing cancer and end-stage liver disease, and the need for transplantation. Strategies for improved treatment compliance and treatment for non-responders will need to be devised.

#### *Surveillance*

The aims of a hepatitis C surveillance programme are to provide data that allow evaluation of the national viral hepatitis

prevention programme and to adapt public health actions accordingly. Such surveillance programmes also serve as alerting mechanisms for intervention, and provide hypotheses for research. In general, surveillance systems should be regarded as intelligence tools that allow rapid interaction with coordinating networks and partners.

Surveillance systems in France are administered and coordinated by the *Institut National de Veille Sanitaire* (InVS) and France's national federation of reference centres and hepatitis networks (*Fédération Nationale des Pôles de Référence et Réseaux Hépatites* - FNPRRH). These surveillance systems are based on the following:

- Laboratory-based surveillance of HCV serology (screening);
- Newly referred HCV-infected patients in hepatology reference centres;
- Mandatory notification of nosocomial-related hepatitis C (or B);
- Surveillance of residual risk in blood donors.

#### *Prevention and control measures*

Sixty percent of new hepatitis C patients were diagnosed in 2002; the latest programme objective is to diagnose 100% of HCV-infected patients by 2005. Although many risk groups are being reached, there needs to be improvement in diagnosing patients at low risk of HCV infection. Screening and treatment should be carried out as early as possible for co-infected patients to prevent severe morbidity from HBV and HCV infections.

#### *Prevention and control of nosocomial infections*

Notification of HCV nosocomial infection has been mandatory in France since July 2001. Although frequency is low, cases still occur (13 notifications in France since 2001). More efforts are needed to prevent blood-borne virus infections based on the findings of expert steering groups, and stricter compliance with standard hygiene precautions.

- The mechanism of *patient-to-patient transmission* is very often unknown, occurring in various settings such as haemodialysis, digestive endoscopy, contacts with diabetic children, anaesthesiology, transplantation, and surgery. Some well-known mechanisms are sharing injection material and products, and breaches in barrier precautions and material disinfection.
- To reduce *patient-to-healthcare worker (HCW) transmission*, preventive measures need to be introduced in France to protect HCWs from blood-borne infection during medical care. For at-risk surgical procedures, safer suturing techniques and alternatives to prevent parenteral exposure should be considered, as well as reinforcing campaigns against recapping needles to lower risk of percutaneous injury.
- *HCW-to-patient transmission* mostly occurs through blood exposure during orthopaedic and cardiothoracic surgery and other procedures involving gynaecology and anaesthesiology. Recent recommendations in France require that HCWs know their HCV status. HCWs aware of being HCV-infected must undergo a group evaluation during which time the HCW is advised to consider using less exposure-prone procedures; also discussed are the risks in continuing employment in a medical setting. An official French recommendation is that HCV-infected HCWs carry out less invasive procedures to minimise risk.

#### *Residual risk of HCV infection following blood transfusions*

Nucleic acid testing (NAT) for HCV screening has been used in France since 2001 in order to minimise the risk in blood and blood products. The benefits of NAT include the introduction of new methods in blood screening, a high level of blood component safety, and improvement in diagnosing infection in blood donors. Since implementation of NAT, the risk of a blood recipient in France becoming infected with a hepatitis virus is extremely low (1 in 10,000,000 blood donations for HCV).

#### *Prisoners*

Harm-reduction measures need to be strengthened. For example, material disinfection with bleach, used in French prisons since 1997, is not adequately promoted in terms of its preventive action. Syringe-exchange programmes, although recommended by the French Health-Justice mission in 2000, are still not allowed, despite proposals to distribute syringes pre-filled with injectable buprenorphin or methadone.

Improving the working relationships between staff and inmates and promoting existing harm-reduction tools will contribute to decreasing risk behaviour within the committal population.

#### *Prediction of HCV-related morbidity and mortality burden in France*

Using mathematical modeling, based on a back-calculation approach of past HCV infections, is a useful tool in allowing prediction of disease burden in a given population and economic evaluation of hepatitis C treatment programmes.

The model shows that improvements in hepatitis C therapy have been too recent and too few patients diagnosed and deemed treatable to induce a decrease or even a stabilisation of HCV-related mortality.

#### **Hepatitis B and C registries**

A population-based registry is a structure that continuously records all new cases of a disease in a well-defined population. Recorded data from registries are also useful as a basis for research studies. Population-based registries in France contribute to enhanced epidemiological knowledge of HBV and HCV, allowing:

- Evaluation of the impact of screening campaigns and guidelines;
- Evaluation of health networks and their effectiveness;
- Examination of the natural history of hepatitis, on a long-term basis, in the general population.

#### **Hepatitis E in France**

Hepatitis E outbreaks occur in high-endemic areas (e.g., Africa, Asia). Sporadic cases have also occurred in low-endemic areas (e.g., in Europe, North America). Data from the French national reference centre for enterically transmitted hepatitis show decreasing anti-HEV seroprevalence and circulation of HEV in France among persons without any recent travel history to endemic areas.

There is a potential animal reservoir of HEV (e.g., swine HEV sequences are closely related to those of human HEV strains) but the transmission route between humans and the animal reservoir is not yet clear.

#### **Viral hepatitis research in France**

France is one of the leading countries conducting fundamental research, with a long tradition of excellence in clinical research. Diverse sources of funding come from institutions, hepatitis-targeted projects, external grants, scholarships, and industry.

At the institutional level, institutions such as CNRS (*Centre National de la Recherche Scientifique*), and INSERM (*Institut National de la Santé et de la Recherche Médicale*) provide the basic infrastructure for research as well as funding for salaries and research budgets.

The ANRS / ANRH (*Agence Nationale de Recherches sur le SIDA et les Hépatites Virales*), France's national agency for

research on AIDS and viral hepatitis, operates under the auspices of the French government. Currently there is more research targeted to hepatitis C than to hepatitis B due, in part, to the low incidence of hepatitis B in France. More hepatitis B projects need to be carried out, particularly multi-disciplinary projects, clinical trials independent of industry, and public health studies targeted to epidemiological research on HBV infection and data on chronic carriers and, more generally, research into the social sciences and quality of life.

Henri Mondor University Hospital is one of France's leading institutions conducting viral hepatitis research.

At European level, hepatitis-targeted projects are funded through the Fifth and Sixth Framework Programmes of the European Commission. Although these programmes represent a good potential source of funding, more viral hepatitis research projects need to be added and could clearly benefit from additional lobbying at European level to help increase funding within the Sixth Framework Programme (2002-2006).

Other funding sources are available through regional or local administrations, international grants, private foundations and industrial sponsors such as diagnostic and pharmaceutical companies partnering with post-doctoral research fellows.

### Hepatitis B vaccine safety issues

In France, there is no specific pharmacovigilance for vaccines, which are considered medical products. The current French pharmacovigilance system is a passive surveillance system, based on a decentralised collection and validation of safety data through regional centres and a centralised evaluation and decision-making process at the French Health Products Safety Agency (AFSSAPS - *Agence Française de Sécurité Sanitaire des Produits de Santé*). Reporting of suspected adverse drug reactions is mandatory for prescribers and pharmacists. The methodology is based on medically-confirmed case reports.

There have been no changes in France's hepatitis B vaccination schedule since 1998. Hepatitis B vaccination remains recommended in infants and adolescents, and adults who are at increased risk of HBV infection. Nevertheless, hepatitis B coverage has not recovered to its previous levels since France's 1998 hepatitis B vaccination crisis.

Scientific data support the safety and efficacy of hepatitis B vaccine, and expert committees and the VHPB continue to support WHO's recommendations on hepatitis B immunisation. However, there is still a need for firm political commitment from French authorities to affirm the safety of hepatitis B vaccination to help re-establish confidence in the vaccine.

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