



**Consensus conference**

**Vaccination against the hepatitis B virus**

**10-11 September 2003**

**Xavier-Bichat Medical School - Paris**

**Guidelines**

The conference was organised

at the request of:

Jean-François Mattei, Minister of Health, the Family and the Disabled

by:

- the French Agency for Accreditation and Evaluation in Health (ANAES)
- the French Medical Research Institute (INSERM)

with the participation of:

- the French Agency for the Safety of Health Products (AFSSAPS)
- the French Agency for AIDS Research (ANRS)
- the French Institute for Health Monitoring (InVS)
- the French Institute for Prevention and Education in Healthcare (INPES).

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## **STEERING COMMITTEE**

É. Alimi, INSERM, Paris  
P. Arwidson, INPES, Vanves  
P. Blanchard, ANAES, Saint-Denis  
M. Brodin, Xavier-Bichat Faculty of Medicine, Paris  
A. Castot, AFSSAPS, Saint-Denis  
P. Dosquet, ANAES, Saint-Denis  
N. Dumarcet, AFSSAPS, Saint-Denis  
J. Étiemble, INSERM, Paris  
C. Grillot-Courvalin, ANRS, Paris  
D. Lévy-Bruhl, InVS, Saint-Maurice  
I. Morer, AFSSAPS, Saint-Denis  
C. Paindavoine, ANAES, Saint-Denis

## **EXPERTS**

P. Bégué, paediatrician, Paris  
R. Chen, pharmacoepidemiologist, Atlanta  
D. Costagliola, epidemiologist, Paris  
É. Delarocque-Astagneau, epidemiologist, Saint-Maurice  
F. Denis, virologist, Limoges  
P. Duclos, medical officer, WHO, Geneva  
A. Flahaut, epidemiologist, Paris  
A. Fourrier, pharmacoepidemiologist, Bordeaux  
T. Hanslik, specialist in internal medicine, Paris  
JL. Imbs, pharmacologist, Strasbourg  
R. Liblau, immunologist, Toulouse  
C. Lubetzki, neurologist, Paris  
P. Marcellin, hepatologist, Clichy  
CA. Siegrist, immunologist, Geneva  
P. Van Damme, epidemiologist, Anvers

## **JURY**

M. Brodin, chairman, doctor specialising in public health, Paris

J. Bénichou, biostatistician, Rouen  
M. Boelaert, epidemiologist, Anvers  
JP. Boissel, pharmacologist, Lyon  
M. Desvarieux, epidemiologist, Minneapolis  
B. Fallissard, biostatistician, Villejuif  
M. Goldberg, epidemiologist, doctor specialising in public health, Paris  
P. Gressens, neuropaediatrician, Paris  
JG. Guillet, immunologist, Paris  
C. Maitrot, school doctor, Rennes  
G. Orth, virologist, Paris  
M. Royez, general secretary, French National Federation for People Injured at Work and the Disabled (FNATH), Paris  
J. Siemiatycki, epidemiologist, Montreal  
F. Vialla, legal expert, Montpellier

## INTRODUCTION

The conference took place in the wake of a massive vaccination campaign which was carried out in France between 1994 and 1998 as part of a worldwide campaign launched by the World Health Organisation to control hepatitis B.

The jury tackled questions by focusing on key areas:

- analysis of epidemiological data and of changes resulting from vaccination,
- vaccine efficacy,
- assessment of side effects and benefit/risk ratios.

It proposed areas in which action might be taken, using as a basis the written evidence submitted by the experts and the data presented and analysed.

These guidelines chiefly concern the vaccination of neonates, infants, children and adolescents. Particular attention was given to high-risk situations, especially in adults, which need to be managed by screening and preventive vaccination.

## INCIDENCE AND PREVALENCE DATA FOR FRANCE

Owing to a paucity of epidemiological data on the hepatitis B virus (HBV) in France, incidence and prevalence figures are subject to caution. The jury made the following observations on the basis of the available data.

**Low level of endemic HBV in metropolitan France.** The estimated prevalence of chronic HBV carriers determined from cross-sectional studies in the early 1990s in metropolitan France is between 0.2 % and 0.5 % (at least 100,000 chronic carriers). However, prevalence may be very high in certain population subgroups (immigrants from countries where HBV is highly endemic, individuals with multiple sexual partners, parenteral drug users, individuals infected with the human immunodeficiency virus (HIV), etc.). The figures for the French overseas departments and territories are higher than for metropolitan France.

**Monitoring systems.** It is difficult to measure HBV incidence, i.e. the number of new cases of infection with HBV per inhabitant and per year, as current monitoring systems identify only new cases of acute symptomatic hepatitis, which represent only 30–50% of all new cases of infection with HBV.

Compulsory notification of acute viral hepatitis was suspended in France in 1985. Incidence data was obtained from two monitoring systems:

- the Lyon Urban Community (Courly) network of laboratories,
- the INSERM “sentinel” network of general practitioners.

The INSERM estimates were higher than those from Courly, but there were differences in method and in how cases were defined.

INSERM reported a mean incidence level for symptomatic acute hepatitis B in France in 1991-94 of 14.5 new cases per 100,000 inhabitants per year (i.e. approx. 8,000 new cases/year). Extrapolation gives some idea of infection rates at the time: approximately 20,000 new cases of infection with HBV every year and an estimated 1,000 to 2,000 new chronic HBV carriers a year. All monitoring data, although fragmentary, have indicated a marked decrease in incidence of hepatitis B over the last ten years, but the INSERM sentinel network no longer seems able to indicate national incidence. Rough estimates could be close to 2,000 to 3,000 new cases of acute

symptomatic hepatitis per year, with a marked decrease in incidence of fulminant hepatitis compared with figures for the period before vaccination was introduced. Fulminant hepatitis is often fatal, and occurs in between 0.1% and 1% of cases of acute hepatitis B. The reduction in fulminant hepatitis is corroborated by a fall in the annual number of liver transplants for fulminant hepatitis B, from 20 in 1990 to 6 in 2000.

**Chronic complications.** The major problem with HBV infection lies in its chronic complications. Approximately 5–10% of infected immunocompetent adults become chronic carriers. This proportion is much higher in neonates (nearly 90%) and infants. Half of all chronic carriers develop cirrhosis or hepatocellular carcinoma; 30-50% of these will die as a result of HBV infection. In 1999, the French centre recording the causes of death, CépiDc, reported a total of 7,477 deaths from cirrhosis and/or hepatocellular carcinoma, taking all causes together. Clinical experience suggests that between 15 and 20% of these will be attributable to HBV. The treatment currently prescribed to chronic carriers to avoid progression to complications is still very ineffective. In addition, treatment is taxing, often poorly tolerated, and frequently leads to resistance.

**Transmission modes.** In France, data from the sentinel network for 1991-96 show that the predominant modes of HBV transmission were sexual (35%) and parenteral drug use (20%), broadly as for HIV transmission. The mode of transmission was unknown in 35% of cases. This means that it is difficult to identify high risk groups and provide protection to all individuals likely to be affected. Healthcare professionals have a high risk of transmission.

Extrapolation based on a French regional retrospective study suggested that, in view of the number of pregnant women infected with HBV, slightly more than 3,000 neonates a year could become chronic HBV carriers if they did not receive serum and were not vaccinated within 12–24 hours of birth. Despite a policy of routine screening for HBs antigen (HBsAg) during pregnancy, 20% of pregnant women are not screened. In addition, 2 neonates out of every 5 born to screened mothers do not receive serum and are not vaccinated.

**Lifetime risk.** In order to evaluate how an HBV vaccination strategy might benefit an individual, it is important to assess his/her lifetime risk of contracting the infection if no such strategy is in place. In France, this risk has not been calculated. In Belgium, which also has a low endemic level of infection, it is about 2% for children aged between 5 and 9 years.

## VACCINE EFFICACY

The efficacy of vaccination against HBV can be measured by the protection or benefit in terms of reduction in incidence of chronic carriers, as well as by the clinical benefit, i.e. the reduction in incidence of morbidity and mortality attributable to HBV.

Studies in countries with a high endemic level of HBV infection have shown a marked difference in prevalence of HBsAg carriers before and after vaccination. Clearly, the vaccine reduces the rate of chronic carriage and thus the virus reservoir. This leads to a decreased risk of disease transmission. Humans being the only reservoir for the virus, effective control of HBV infection can be envisaged.

The vaccine is also effective in preventing acute hepatitis. Moreover, reduced chronic carriage has an impact on clinical complications of infection (cirrhosis and hepatocellular carcinoma), as observed in countries with a high level of endemic infection. The vaccination programme in Taiwan led to a reduction from 0.70 to 0.36 cases of hepatocellular carcinoma per 100,000 children aged between 6 and 14 within 10 years of the start of the programme.

However, the vaccine's efficacy in terms of morbidity and mortality has not been measured in countries, such as France, with a low endemic level of disease. The results of simulations produced with mathematical models designed to assess the benefit of a vaccination strategy need to be analysed with caution. Several of the models have shown how immigration from countries with high endemic HBV levels could impact on vaccination strategies, by sustaining the reservoir of chronic carriers of HbsAg.

## **POTENTIAL SIDE EFFECTS OF VACCINATION AGAINST HBV**

### **Limitations in the interpretation of epidemiological results**

The jury drew attention to the evidence needed to demonstrate a causal relationship. A series or cluster of cases with the same recorded exposure warrants attention but does not alone constitute adequate proof of a causal relationship. Observational studies and trials are needed to provide evidence for the assumption that a factor is indeed the cause of a disease. Without such rigorous studies, people may be misled by rumours, allegations or unproven hypotheses (which may concern not only vaccination but also medicines, diet, environmental exposure, etc).

The evaluation of a causal relationship between a disease and a risk factor in epidemiology poses two problems: (i) The absence of a causal relationship cannot be proven, (ii) An epidemiological tool has a limited resolution capacity for detecting relatively small effects, in particular for rarer diseases. These points should be borne in mind when interpreting studies of any association between vaccination against HBV and the onset of possible side effects.

### **Diseases other than demyelinating disease**

***In children:*** A very large number of children have been vaccinated against HBV in many countries. There is no evidence for a link between vaccination and non-demyelinating disease in children.

***In adults:*** Macrophagic myofasciitis is a histological lesion that has very recently been described in adults and which, to date, has been almost exclusively reported in France. A case series has established a relationship between the lesion and a vaccine against HBV containing aluminium hydroxide, an adjuvant that has been very widely used for many decades in different vaccines. However, there is no convincing epidemiological evidence to support a relationship between vaccination and the presence of any disease related to this lesion. Nor is there any evidence for a relationship between vaccination and other non-demyelinating conditions.

### **Demyelinating disease**

***In children:*** There have been no pharmacovigilance notifications and there is no evidence to support any relationship between vaccination against HBV and demyelinating disease.

***In adults:*** Data from case series and French pharmacovigilance system reports have generated an alert but are not sound enough to establish a causal relationship between vaccination and demyelinating disease. Sounder, epidemiological studies have not established any convincing link either but cannot exclude a weak link. Their designs have some limitations and their results are often contradictory. They do not always study the same diseases nor cover the same time periods (period between vaccination and onset of disease, which varies considerably depending on the study). The study conditions preclude comparisons and pooling of results. A recent study from Great Britain has shown a statistically significant association but the results need to be re-examined once published in full. Furthermore, there is no epidemiological evidence to support the hypothesis

that HBV vaccination can cause exacerbations in individuals with multiple sclerosis nor that there is a risk in the event of a family history of multiple sclerosis.

### **Physiopathological mechanisms of potential side-effects**

***Demyelinating disease:*** Current theories and speculation based on published data have led to hypotheses on the possible mechanisms of autoimmune disease and, in particular, for demyelinating disease (molecular mimicry, bystander effect and autoreactive cells, polyclonal activation, involvement of regulating T cells, etc.). However, they are not backed up by experimental evidence either from animal studies (available or possible experimental models, e.g. humanised mice in models of multiple sclerosis, predisposed mice, etc.) or from human studies (pathophysiological studies, e.g. investigation of cellular immunity in infected and vaccinated individuals, investigation of cellular immunity in people with multiple sclerosis, etc.). Studies on genetic predisposition also need to be carried out.

***Macrophagic myofasciitis:*** Animal studies have demonstrated that the adjuvant (aluminium hydroxide) plays a key role in the mechanism. A nosological classification for this histological lesion and its relationship with autoimmune disease have yet to be established.

***Non-demyelinating diseases:*** A critical review of the epidemiological data did not suggest that these diseases are related to vaccination. Should new data arise, the use of animal models has to be considered.

In conclusion, current hypotheses on the mechanism of side-effects are not supported by any experimental data from animal or human studies. The formulation of new hypotheses might also do well to take account of the heterogeneous composition of the vaccines (concentration of antigen, origin of recombinant antigen, adjuvant, preservative) and toxicology data.

### **Assessment of benefit/risk ratio**

It may seem paradoxical to determine a benefit/risk ratio for vaccination against HBV not knowing for certain whether the vaccine has any side effects. Two studies have been carried out, one in France (preadolescents), the other in Italy (preadolescents and young adults). Both have established a ratio in favour of vaccination.

If the estimated risks of vaccine use change, the benefit/risk ratio and, in its wake, the public health decision must be reassessed.

## **STRATEGIES AND ACTION**

The populations targeted by vaccination guidelines (neonates, children, preadolescents, various high-risk groups) have not yet been sufficiently covered, while the unexposed adult population has undergone unwarranted vaccination. This raises the question whether the procedures used to implement previous vaccination programmes were appropriate.

In its recommendations on vaccination policy, the jury therefore emphasised the need for strict measures supporting the implementation of these guidelines and the importance of not ignoring the prevailing lack of support for (or even resistance to) the benefits of vaccination. In addition, the following points were made:

- vaccination does not exclude other existing or future preventive measures, particularly as they prevent other diseases as well as risks in the workplace. In particular, the use of condoms should continue to be promoted, along with compliance with all the control measures relating to sexually transmitted disease;

- measures to control HBV are closely linked to measures aimed at, amongst others, the hepatitis C virus (HCV) and HIV, particularly for patients infected by multiple viruses or likely to be so;
- in view of current epidemiological data, there needs to be a special focus on screening individuals and on preventing high risk exposure to HBV, particularly among immigrants from countries with a high level of endemic infection, individuals engaging in high-risk sexual practices, parenteral drug users and individuals exposed through their work.

### **Recommendations on vaccination policy in neonates**

*Universal vaccination of neonates is strongly recommended* for the following reasons:

- anticipated benefits to the community: controlling, even eliminating hepatitis B;
- long-term benefits to the individual: avoiding disease in the event of future high risk practices (sexual transmission, intravenous drug use and other parenteral modes of contamination);
- quality of response and duration of immune protection from vaccination at this age, when the protocol is fully complied with;
- absence of current data establishing that there is any risk of serious side effects;
- potential ease of implementation within the French health system.

*Promoting universal vaccination of neonates is a government responsibility*, which implies:

- allocating adequate resources to meet the objectives set before, during and after vaccination; to implement the strategy, the public bodies responsible for the protection of infants and the healthcare professionals working in independent practice need to harmonise their actions;
- informing the populations concerned through a publicity campaign, and training all the healthcare professionals involved;
- checking the implementation of measures undertaken and their efficacy, both in terms of compliance with the full vaccine schedule and coverage levels;
- assessing the results, including long-term results, of the efficacy of vaccination and the absence of serious long-term side effects by monitoring a cohort.

The jury suggested the use of a vaccination monitoring system in neonates, in particular to assess its application, its impact in terms of vaccination cover and its clinical consequences.

### **Recommendations on vaccination policy in children and adolescents**

*A temporary programme to vaccinate children and adolescents who have been missed is strongly recommended.* It should be continued until the neonates covered by the universal vaccination campaign have reached preadolescence, provided coverage was satisfactory. The reasons for this recommendation are:

- anticipated benefits to the community in terms of control or even, ultimately, elimination of hepatitis B;
- anticipated short- and medium-term benefit to the individual depending upon their age, in view of the possibility of high-risk behaviour or exposure (sexual behaviour, drug use, high-risk profession, etc.);
- the negative results of the epidemiological study published to date seeking to establish a relationship between vaccination and serious side effects for this age range.

## **Recommendations on vaccination policy in the event of high risk of exposure to HBV**

- ***Neonates born to women who are HBV seropositive***

*Strict compliance with compulsory screening of all pregnant women for HBsAg must be ensured because of:*

- the very high risk of vertical transmission of HBV to the neonate;
- the high risk of progression to chronic hepatitis, with its complications, in neonates.

*The jury recommended that vaccination of neonates be compulsory if the mother is HBV seropositive. Permanent monitoring measures need to be introduced throughout France (including overseas departments and territories) to ensure that compulsory screening of pregnant women and vaccination of neonates are put into practice.*

- ***Healthcare professionals***

*French legislation requires healthcare professionals (including independent healthcare professionals) to be immunised against hepatitis B. This measure is not only for their own protection, but also to prevent transmission of HBV to patients.*

- ***Subjects exposed because of a high-risk situation or behaviour***

This concerns:

- parenteral drug users (intravenous or intranasal use);
- people who have tattoos or piercings;
- people in contact with an individual carrier of HBsAg (in the family or community);
- people infected with HIV or HCV;
- chronic haemodialysis patients;
- chronic transfusion patients;
- patients and staff of institutions for the mentally handicapped;
- heterosexual or homosexual individuals with multiple sexual partners and/or a recent sexually transmitted disease;
- travellers to countries with high levels of endemic infection;
- prisoners;
- transplant candidates.

*Vaccination is particularly recommended for these individuals because of the variety of high-risk situations and the often ill-determined levels of risk. Specific programmes with adequate resources (including a permanent assessment system) should be implemented for each category of high-risk behaviour or situation. This recommendation should be included in public health programmes, in particular those aimed at vulnerable populations.*

- ***Special situations***

The jury drew attention to the need for measures designed for migrant populations from areas with high endemic infection levels. They should be offered screening for and vaccination against HBV.

In view of the risk of horizontal contamination,

- a family with an HBV carrier should be vaccinated after checking each family member's immunisation status with regard to HBV,

- vaccination of the contact population in a community of children with an HBV carrier should be considered, again after checking each individual's immunisation status with regard to HBV.

**Recommendations on vaccination policy: Information and publicity strategies**

These strategies must be incorporated into a national and local system which involves healthcare professionals and indiscriminately covers all the populations concerned. The French Institute for Prevention and Education in Healthcare (INPES) could play a key role in this regard.

Because of criticism of the organisation of previous HBV vaccination campaigns and their results, the jury put a strong emphasis on the absolute need for a powerful monitoring and coordination body at national level (including regional and local units). It should be adequately resourced and given the mission of permanently coordinating, monitoring and evaluating the vaccine strategy. It should also have the power to correct any problems as rapidly as possible.

