Public hearing
Paris, 9 November 2004

Vaccination against the Hepatitis B virus and multiple sclerosis
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Steering Committee

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Hearing Committee

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Speakers

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\(^1\) AFSSAPS: French Health Products Safety Agency

\(^2\) ANAES: French National Agency for Accreditation and Evaluation in Health

\(^3\) INSERM: French National Institute for medical Research

\(^4\) INVS: French National Institute for Public Health Surveillance

\(^5\) CNAMTS: National Health Insurance fund for salaried workers
A public hearing of experts on vaccination against the hepatitis B virus (HBV) and multiple sclerosis (MS) took place on 9 November 2004 at the request of Philippe Douste-Blazy, Minister of Health and Social Protection\(^6\). It was organised and financed by:

- the French Health Products Safety Agency (AFSSAPS)
- the French National Agency for Accreditation and Evaluation in Health (ANAES)
- the French Medical Research Institute (INSERM).

The hearing followed on from a consensus conference on "Vaccination against the hepatitis B virus" (Paris, 10-11 Sept. 2003) organised by ANAES and INSERM. The members of the hearing committee were appointed from members of the jury from that conference. Its aim was to re-examine the 2003 guidelines and to report on the latest data concerning:

- epidemiological studies and pharmacovigilance data on HBV vaccination and multiple sclerosis;
- clinical data on central nervous system (CNS) demyelinating disease;
- physiopathological data on vaccination and autoimmunity;
- clinical and epidemiological data on hepatitis B.

Special attention was paid to new data on CNS demyelinating disease in both adults and children, and its consequences. Recent studies were analysed, notably:

- the study by Hernan et al. published in September 2004 (only the abstract was available and discussed with the main author in a teleconference at the 2003 consensus conference),
- preliminary data from the Kidmus cohort study (a cohort of French children under 16 who have experienced a first acute episode of central demyelinisation).

The committee members re-examined the September 2003 guidelines on HBV vaccination in the light of the data presented at the hearing and invited readers to refer to these guidelines and the supporting evidence. They emphasised that further systems to collect and monitor data must be developed in France in order to measure public policy outcomes. This means developing models to assess the benefit/risk ratios of HBV vaccination strategies.

\(^6\) The hearing was held in accordance with two articles of the French Public Health Code (established by Law no. 2002-303 of March 4, 2002) relating to the rights of patients and the quality of the healthcare system (article L.1414-1 concerning ANAES and article L.5311-1 concerning AFSSAPS).
I. Introduction

The committee recalled the point made in the September 2003 report, that firm evidence is needed to demonstrate a causal relationship. The presence of a series or cluster of cases with the same recorded exposure is a factor to be taken into account but is not sufficient proof of a causal relationship. Observational and experimental studies are needed to demonstrate that a factor is the cause of a disease. Without a rigorous assessment, people may be misled by rumours, allegations or unproven hypotheses (about vaccination, and also about medicines, diet, environmental exposure, etc.).

In epidemiological studies, it is difficult to decide whether there is a causal relationship between a disease and a risk factor because:

(i) it is impossible to prove the absence of a causal relationship; even if no association is detected, the presence of a small risk cannot be excluded;
(ii) a relatively small association is difficult to detect particularly if it is not a common disease;

These points should be borne in mind when interpreting studies of any link between vaccination against HBV and possible side effects.

In addition,
- the hypotheses for CNS demyelinating disease have not changed since 2003,
- there have been no new clinical or experimental data on immunopathology; research results are too poor to support “biological plausibility” (Bradford Hill criteria),
- the models put forward at the 2003 consensus conference have not been developed,
- there has been no research into whether HBV vaccine may have a role in the onset of CNS demyelinating disease.

The committee renewed its recommendations that:
- research be carried out to study all the constituents of HBV vaccine and the differences between them (concentration and origin of the viral protein, combination with other valencies, etc.)
- experimental models be developed, in particular to explore any long-term effects of HBV vaccination on the CNS.

It also highlighted the inadequacy of the pharmacoepidemiological surveillance and research infrastructure in France.

II. Analysis of recent data

II.1 Case-control study by Hernan et al

The committee examined the data from this case-control study which demonstrate an association between HBV vaccination and onset of MS in adults aged 18 and over. The association reached statistical significance for vaccinations carried out during the 3 years

before onset of first symptoms of MS (odds ratio 3.1; 95% CI 1.5, 6.3). It was non-significant (odds ratio 1.8; 95% CI 0.5, 6.3) when the period of observation between HBV vaccination and the first symptoms of MS was limited to 12 months, in line with the results of most other similarly designed studies.

The committee was concerned about the possible impact on statistical significance of extending the observation period. Whenever possible, data from earlier studies should be reanalysed over a 3-year observation period, in order to confirm or invalidate Hernan et al’s results. According to the Bradford Hill criteria for causality, the strength of association would have to be the same on re-analysis at 3 years before a risk was considered to be present.

With regard to biological plausibility, the immunopathological data presented at the hearing provided no new information on either possible mechanisms or time to onset of MS after a causal event.

II.2 Kidmus French cohort study

This study included children with a first episode of acute CNS demyelinating disease before age 16 that might be a sign of MS onset. The aim of this study was to determine prognostic factors for relapse and progression to true MS after a first episode of acute CNS demyelinating disease. Children were included retrospectively between 1990 and 1998, and prospectively after 1998.

The vaccination status of children in this cohort is currently being analysed and validated. The preliminary analyses (presented at the hearing but not published) do not suggest that there is a link between HBV vaccination in infants, children or preadolescents and subsequent onset of a first episode of acute CNS demyelinating disease.

There was an increase in notifications of a first episode of acute CNS demyelinating disease before the age of 16 in this cohort between 1995 and 2001. There has also been an increase in co-payment exemptions for chronic disease granted for MS since 1996 (National Health Insurance fund for salaried workers (CNAMTS) data). Several factors, not necessarily the same ones, may explain these increases: bias due to increased awareness, better disease classification because of MRI, introduction of new and expensive forms of treatment, etc. They suggest that the number of new cases of MS should be monitored regularly.

The currently provisional results from the Kidmus cohort need to be confirmed by continued data collection and analysis. The results will have to be reviewed when they have been completed and published.

II.3 Age-related results

• Newborns and infants
The first analysis of data from the Kidmus cohort suggests that there is no risk of CNS demyelinating disease associated with HBV vaccination in newborns and infants. This is borne out by the absence of alerts in countries where vaccine coverage of newborns and infants is much higher than in France (approx. 95% since 1998 in Italy compared to 27% at age 2 in France in 2004).

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Vaccination against Hepatitis B virus and multiple sclerosis

- **Children and preadolescents**
  CNS demyelinating disease is rarely observed in children or preadolescents. The number of cases notified to pharmacovigilance authorities or recorded in the Kidmus cohort is small. There are no case-control studies in children. The committee therefore re-emphasized that at present there is no evidence to support any association between HBV vaccination in children and preadolescents, and CNS demyelinating disease.

- **Adults and adolescents**
  Worldwide epidemiological, physiopathological and immunological data do not exclude the possibility of a risk in adults, but the available evidence is insufficient to demonstrate a causal relationship between HBV vaccination and CNS demyelinating disease. Epidemiological data are lacking for adolescents. According to current knowledge of physiopathology, it is likely that any potential risk of CNS demyelinating disease after HBV vaccination in adolescents is similar to that in adults.

In conclusion, the data presented at the hearing did not call into question the positive benefit/risk ratio of HBV vaccination in newborns, infants, children and preadolescents. The benefit of vaccination for adults in an at-risk group appears to be higher than the risk, even for a greater than three-fold risk (as measured in the study by Hernan et al.)

### III. Strategies and actions

The committee confirmed that the actions recommended in September 2003 are still relevant. The information presented at the hearing did not call them into question.

- **Infants**
  Universal vaccination, i.e. vaccination of all infants, is strongly recommended because of the very probable long-term individual benefit (the duration of immune protection obtained by vaccinating at this age should protect against contracting the disease when older) and the anticipated benefit to the community through controlling the epidemic.

- **Children and preadolescents**
  A temporary programme to vaccinate unvaccinated children and preadolescents is strongly recommended. It should continue until infants who have been vaccinated under the universal vaccination programme have reached preadolescence (provided vaccine coverage level is satisfactory).

- **Persons at high risk of exposure to HBV**
  **Newborns of women who are seropositive for HBV.** Special care must be taken to ensure strict compliance with compulsory screening of all pregnant women for the HBSs antigen (AgHBs) because of the very high risk of vertical transmission of HBV and the high risk of progression to chronic hepatitis and complications if the newborn is infected with HBV. The committee recommended that routine serovaccination of newborns be compulsory if the mother is seropositive for HBV.

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

  **Individuals exposed because of at-risk situations or behaviour.** This concerns:
  - parenteral drug users (intravenous or intranasal use);
Vaccination against Hepatitis B virus and multiple sclerosis

- people who go in for tattoos or piercings;
- people in contact with an AgHBs carrier; the family and close contacts should be vaccinated after their individual HBV immunisation status has been verified;
- individuals infected with human immunodeficiency virus (HIV) or hepatitis C virus (HCV);
- chronic haemodialysis patients;
- chronic transfusion patients;
- patients and staff of centres caring 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.

These individuals are exposed to different levels of risk. Both collective and individual benefit need to be taken into account before they are vaccinated. The committee emphasised the need for data assessing the benefit of vaccination in each at-risk group.

The committee recommended that:
- special care be taken when assessing the benefit of vaccination in families with confirmed cases of MS because of familial susceptibility to MS;
- specific vaccination programmes be considered and assessed for each at-risk group. This recommendation should be included in public health programmes, particularly those aimed at vulnerable populations;
- measures aimed at migrant populations from high-endemic areas be considered. They should be offered access to HBV screening and vaccination.

The committee considered that there is insufficient benefit to justify promoting the vaccination of adults who do not belong to an at-risk group.

IV. Promoting a vaccination policy: a government responsibility

The committee regretted that the recommendations of the 2003 consensus conference jury have not yet been implemented a year after they were produced.

Information and public relations should be part of a global strategy that mobilises professionals nationally and locally, and covers all populations concerned without discrimination. The National Institute for Prevention and Health Education (INPES) could have a key role in this regard.

The committee renewed the urgent recommendation made in 2003 for setting up a strong coordination and monitoring body at national level (covering regional and local levels), in view of criticisms of the piloting and results of earlier HBV vaccination campaigns in France. This body should have the resources required to continuously coordinate, monitor and assess the vaccine strategy. Its powers should include:
- verifying the implementation and efficacy of measures (compliance with the complete vaccine schedule and level of coverage);
- assessing results including long-term results (both the epidemiological impact of vaccination and the possible onset in the long-term of serious adverse events, by following a cohort);
- remedying as early as possible any shortcomings of a vaccination programme.
IV.1. Public health measures to be taken

The committee took due note of progress in collecting data on side effects of vaccination and in granting vaccines a similar status to that of drugs, but called for the same standards of pharmacovigilance for vaccines as for other types of drugs. As a priority, it wanted a questionnaire for standardised and systematic collection of information about side effects reported after HBV vaccination, to complement the usual notification form.

The committee made the following recommendations:
- information on the progress of vaccination campaigns in infants and monitoring of vaccination coverage should be produced regularly by appropriate methods (e.g. through random sampling of health certificates);
- the Ministry of Health circular on compulsory screening for AgHBs in pregnant women at 6 months should be promoted, especially among obstetricians, anaesthetists and midwives, in order to prevent chronic infection by serovaccination at birth of newborns if their mothers are AgHBs carriers;
- HBV vaccination should be promoted among healthcare professionals. HBV vaccination is the only compulsory vaccination to protect both professionals and patients; the government must take responsibility for promoting and assessing this vaccination;
- a status report should be produced on the current state of vaccination promotion campaigns among all at-risk individuals and individuals from high-endemic regions;
- a study should be conducted on the type of temporary programme needed to make good missed vaccinations of children and preadolescents, and of its feasibility.

All this information should be used to update indicators for monitoring HBV vaccination, at least twice a year. A six-monthly report on actions undertaken was recommended. The members of the hearing committee proposed that they be involved with this report.

IV.2. Need for more data to assess the benefit/risk ratio of HBV vaccination

- Epidemiology
Data updates describing the situation among the general population and in at-risk populations are needed on:
  - hepatitis B (incidence of HBV infection, evolution of viral strains) and its complications (incidence of fulminant hepatitis, chronic hepatitis, cirrhosis and hepatocellular carcinoma, and mortality data);
  - CNS demyelinating disease (data based on strict, standardised and unchanged definitions), and its repercussions (time off work, incapacity, etc.).
Experts need these data to assess and monitor any changes in the benefit/risk ratio of HBV vaccination.

- Safety of vaccination among infants, children and preadolescents
Data are needed to confirm that HBV vaccination is safe in infants, children and preadolescents, as this is the basis for the current guidelines on vaccination in France:
  - the data from the Kidmus cohort have to be completed (vaccination status for all children, imaging data, etc.);
  - coordination within the Société française de neuropédiatrie (French Society of Neuropediatrics) and the Comité d'Interface INSERM–Pédiatrie (INSERM - Paediatrics Interface Committee) should be established as soon as possible and an epidemiological expert report should be produced;
- a well-designed case-control study should be carried out. Information must also be obtained on the safety profile of vaccination in infants and children in other European countries.

• Monitoring
A system needs to be introduced in France to monitor vaccination (cohort, registry, monitoring health insurance databases, etc.). There is also a more general need to find out about changes in the incidence of autoimmune disease in Europe (and also in North America), and to introduce the appropriate epidemiological surveillance systems.

• Research
Both physiopathological and epidemiological studies are needed to investigate any causal relationship between HBV vaccination and CNS demyelinating disease. It is necessary to set up:
- experimental research programmes (using existing models or designing new ones) and clinical research programmes on potential associations between HBV vaccination and CNS demyelinating disease;
- a national cohort of individuals with these diseases.

A relevant model of HBV vaccination and of its potential beneficial and undesirable effects is essential to compare vaccination strategies in quantitative terms, and assess the benefit/risk ratio for the community and for individuals (newborns with HBV-seropositive mothers; infants; children and preadolescents; adolescents and adults, both at-risk and not at-risk).

The committee suggested that the HBV vaccination monitoring body mentioned above should be in charge of implementing these proposals.

V. Legal implications

The committee emphasized that the general public perceives some ambivalence in the way post-vaccination events are viewed by French courts:
- on the one hand, there is a clear legal framework governing compulsory vaccination (for healthcare professionals) that can lead to recognition of the presumed causality of these events and allows them to be classed as work accidents;
- in all other cases, the burden of proof lies with the vaccinated individual. Legal precedent remains unclear on the admissibility of petitions for damages, which are generally refused by the courts and thus not satisfied.

This situation leads to a lack of understanding, to the extent that the committee felt that the implementation of any vaccination policy is currently much hindered by the debate about recognition and compensation for alleged side-effects. The confusion and uncertainty generated by this debate have affected both the general public and health professionals, and are an obstacle to the vaccination of individuals who should be vaccinated. Patients’ associations seem to be in two minds about vaccination. They recognise the benefits of vaccination, but at the same time they continue to press for a legal debate on the possible rare side effects.

In the interest of developing public health policies, the committee considered that the scientific and legal aspects should be separated. A causal association must be based on established scientific facts only, particularly epidemiological and physiopathological data.