

Surveillance of adverse events following immunization

Viral Hepatitis Prevention Board Meeting

Veyrier du Lac, France, November 18-19, 2004

*Agence française
de sécurité sanitaire
des produits de santé*



What is the aim of pharmacovigilance ?



- To identify and analyze adverse drug reactions (ADRs) resulting from the use of human medical products in order to detect a safety signal.
- But, are the vaccines considered as a medical product despite its well-known particularities ?



VACCINE = MEDICATION :

- with a preventative target
- used in healthy subjects often young
- individual benefits deferred and unknown
- immediate risk

In France, a vaccine is considered as a medical product.



NO SPECIFIC PHARMACOVIGILANCE FOR THE VACCINES

Are there legal basis concerning pharmacovigilance in France ?



- **The decree of March 13, 1995 (updated on January 29, 2004) concerning pharmacovigilance of the drugs for human use defined :**
 - **the aim of pharmacovigilance**
 - **the organization of the national pharmacovigilance system**
 - **the missions and mandatories of all those involved in pharmacovigilance programme.**

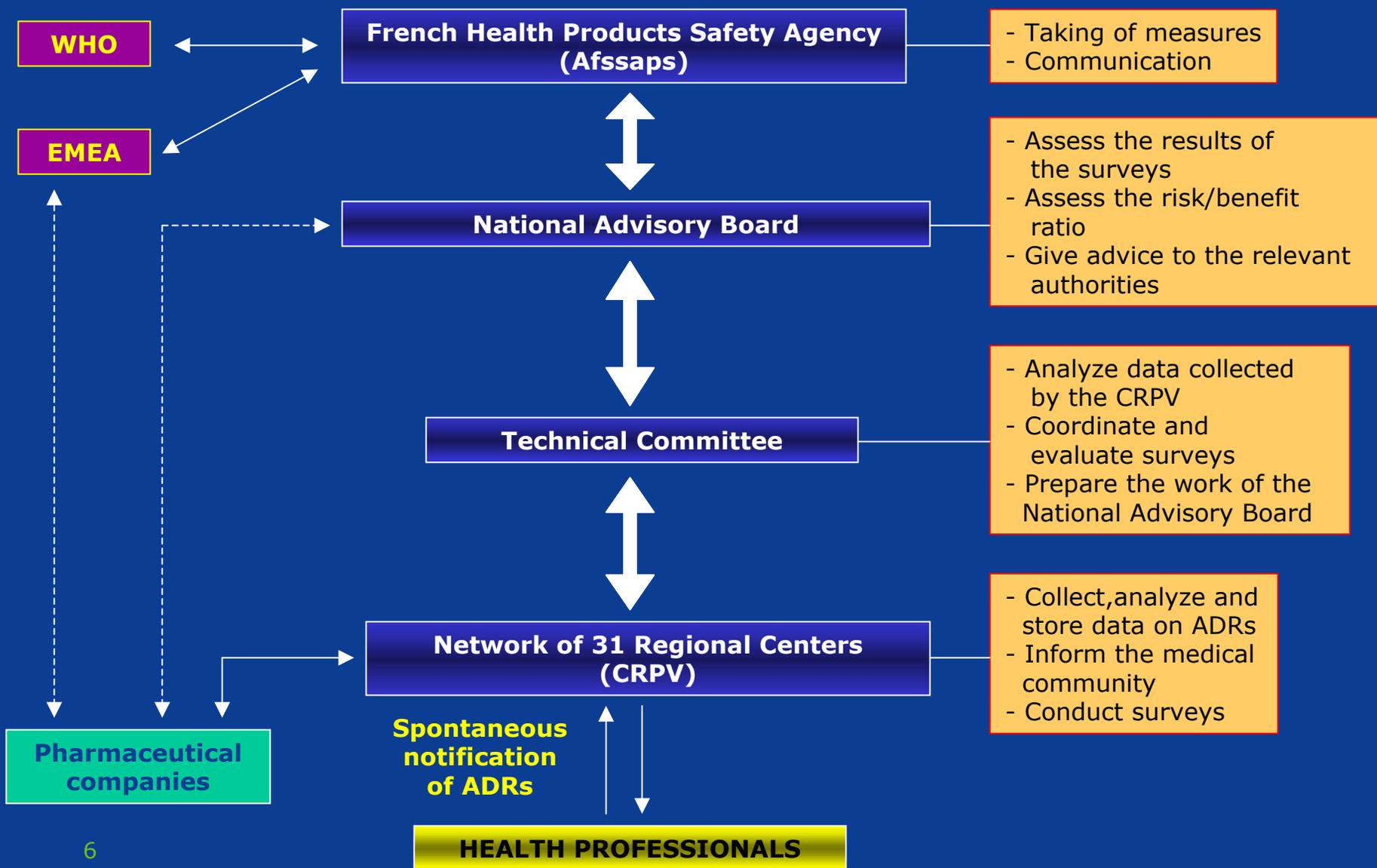
How does the French pharmacovigilance system collect ADRs?



- As in other countries, the French system is based on « **Spontaneous reporting** » by healthcare professionals who voluntarily report any effect they believe to be attributable to a drug taken by a patient
=> UNDER-REPORTING of ADRs unavoidable.
- No Consumer reports **unless medically confirmed.**

- All prescribers (GPs, dentists, mid-wives) and pharmacists must use an official report form called **CERFA form** :
 - ➔ - All **serious** or **unexpected** suspected ADRs
- Pharmaceuticals companies must use an official report form called **CIOMS form** and periodic safety update reports (**PSURs**)
 - ➔ - All **serious** suspected ADRs occurred in France
 - All **serious** ADRs reported in EU when France is Rapporteur or Reference Member State
 - All **serious** and **unexpected** ADRs reported outside EU

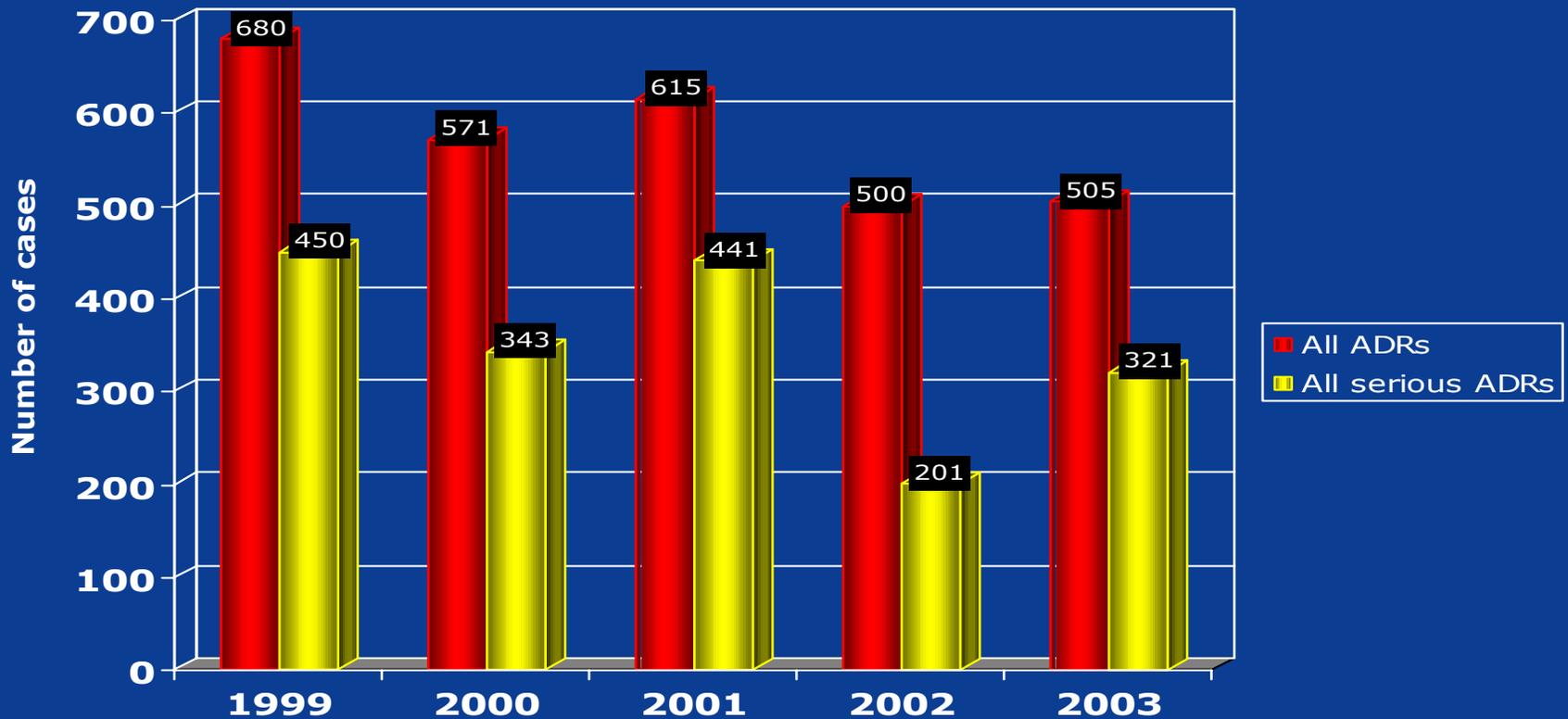
How is the current french pharmacovigilance system organized?



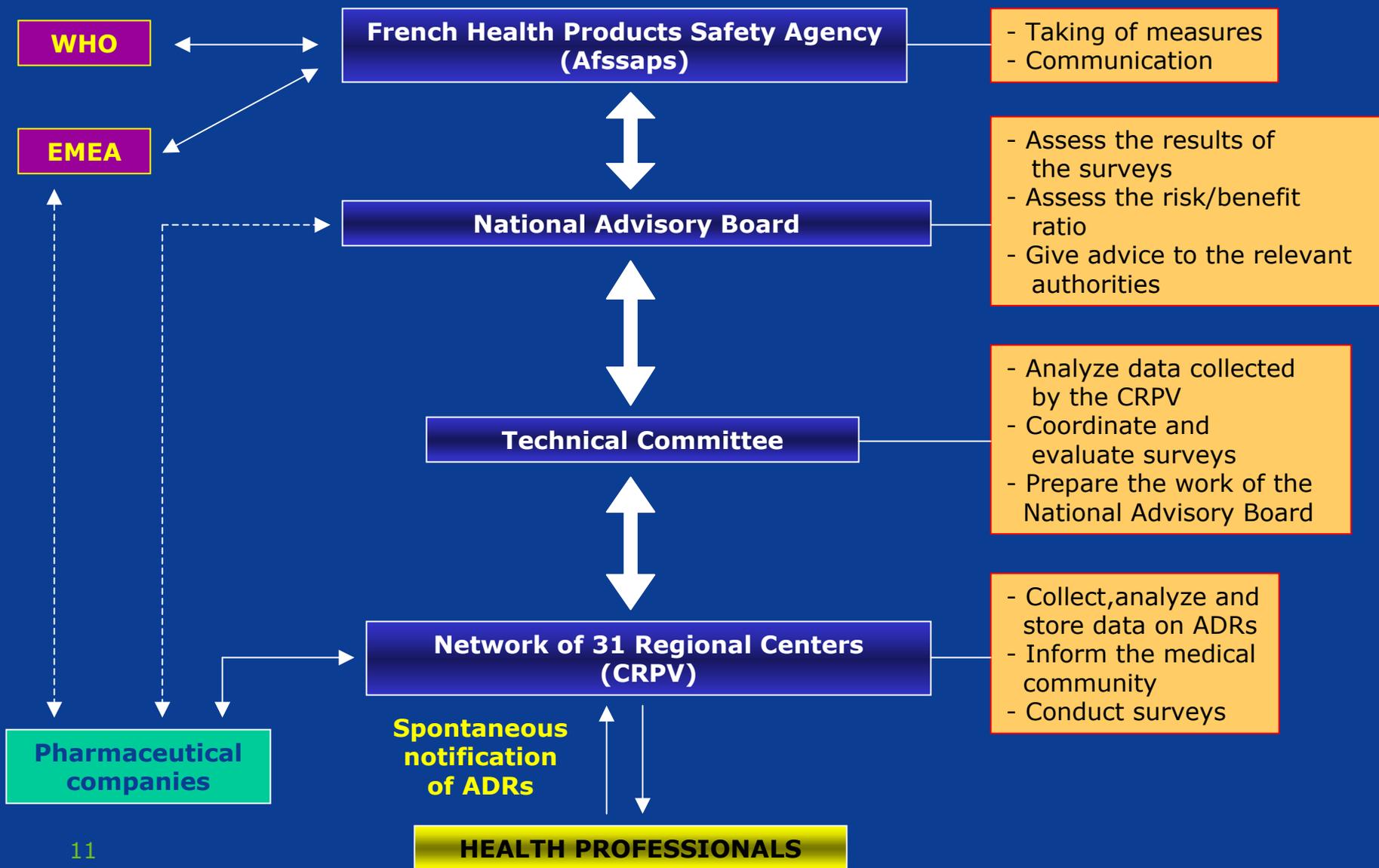
- All CRPV and pharmacovigilance department of pharmaceutical companies use **the same method of imputability** based on the evaluation of chronological and semiological criteria derived from observation called *intrinsic imputability* and/or, relevant literature called *extrinsic imputability*.

- Case reports **medically confirmed** entered into a **common computerized database** with :
 - **Causality score**
 - **Large amounts of data used for pharmaco-epidemiological studies (age, time to onset, outcome,..) and to explore drug utilization**
- **Since 1985 : > 250,000 case reports entered.**

Distribution of all ADRs cases reported to the CRPV after administration of vaccines used in the French routine immunization schedule between 1999 and 2003



How is the current french pharmacovigilance system organized?



What are the different missions of the pharmacovigilance unit of the Afssaps ?



MISSIONS

- **Coordinates CRPV activities**
- **Organizes all meetings held by the Technical Committee and National Advisory Board**
- **Analyzes safety data sent by pharmaceutical companies and EU Members states**
- **Exchanges informations with the interested parties (EMA, others Members states, WHO, MAHs,...)**
=> close cooperation ensuring a common evaluation and management of safety concerns

What are the original features of the current French pharmacovigilance system ?



- System based on a **decentralized** collection and validation of safety data through regional centers and a **centralized** evaluation and decision making process at the Afssaps
 - => **rapid response time in detecting new and serious ADRs as well as in taking decisions if a problem endangers public health**
- Reporting of ADRs **mandatory** for the prescribers and the pharmacists
- Its methodology based mainly on case reports **medically confirmed**
- Its decision to appoint the **same person** as the President of the Technical Committee and of the National Advisory Board which facilitates the **coherence** and the **rapidity** of the system
- Its involvement in **epidemiological studies** and in informing the **medical community** on drug toxicities.

HB immunization and risk of central demyelinating events

Official pharmacovigilance survey



- **WHO's recommendations about HB immunization**
 - **In 80's** : only high-risk groups (haemodialysis, blood transfusion, healthcare workers and neonates [mother=chronic carrier of HBs Ag]).
 - **In 1991** : immunization policy showed a relative failure => In order to stop circulation of HBV, WHO recommended broadening of vaccination programmes in all countries.
- **December 1993** : HB immunization recommended for **infants** and **adolescents** by the French Vaccinations Technical Committee.
- **1994-1995 schoolyear** : HB immunization mass campaign in schoolchildren was **initiated by the French Ministry of Health**.

- **Beginning 1994** : Some cases of central demyelinating events after HB immunization were notified to the network of the CRPV.
=> A potential link between central demyelinating disorders and Hb immunization was hypothesized.
- **Technical Committee on May 1994** : Analysis of these neurological case reports.
- **June 1994** : The CRPV of Strasbourg was asked to conduct an official **survey** for central and peripheral demyelinating disorders after HB immunization.
=> Since June 1994, yearly updated safety review of this area since the marketing date of the HB vaccine was presented at the National Advisory Board by the CRPV of Strasbourg.

- **Analysis of updated safety review on central and peripheral demyelinating events reported since the marketing date of the HB vaccine (1981) until the end of August 1994**
 - n = 20 cases of which some suggested flare-up of **multiple sclerosis**
 - **No causal link really established**
 - **Mentions in the SPC of HB vaccines about exceptional occurrence of neurological adverse effects and specific precautions for patients with personal history of multiple sclerosis were proposed.**

- **Under the heading « Undesirable effects » (section 4.8) :**

*« Peripheral neuropathies (polyradiculonevritis, facial paralysis, neuritis including Guillain Barre syndrome, optical neuritis, myelitis including transverse myelitis), encephalitis, demyelinating disease of the CNS (exacerbation of **multiple sclerosis** symptoms) occurring within a few weeks after vaccination. A definite causal relationship between these conditions and the vaccine has not **been established** ».*

- **Under the heading « Warning and precautions » (section 4.4) :**

*« It is reminded that any stimulation of the immune system may induce an exacerbation **in patients with multiple sclerosis**. In hepatitis B seronegative patients suffering of multiple sclerosis, **the risk-benefit ratio** of anti hepatitis B vaccination must be assessed, considering the possibility of exposure to the virus ».*

Did the EU Member States agree with the French proposals ?



- **March 1995** : Member states were informed about the French proposals because two out of three HB vaccines used for immunization in schoolchildren, were registered through **European procedure**.
- **June 1996** : EU member states agree to include the neurological disorders under the heading « Adverse effects »

BUT, did not consider the arguments sufficiently convincing to justify Europe-wide acceptance about the precaution in patients with a personal history of multiple sclerosis.



Nonetheless, the French medical community was informed about this precaution with a *Dear Doctor Letter* sent by the Afssaps on **November 2, 1995.**

Is spontaneous reporting sufficient to investigate the relationship considered ?



- **No firm conclusion could be drawn from the successive updated safety reviews issued from spontaneous reporting to enhance understanding of the potential link between HB immunization and the risk of central demyelinating disorders**
=> On August 7, 1997, the Afssaps was asked by the Ministry of Health to set up without delay epidemiological studies.

Why did the French Ministry of Health discontinue the mass HB immunization in schoolchildren ?



- **September 21, 1998** - International Experts Meeting organized by the Afssaps :
 - reviewed updated data of demyelinating cases reported until **March 31, 1998**
 - analyzed the results of three case-control studies, of them two were conducted in France. (Touzé and al. 1998 and 2000)
- => **In conclusion, the results of these studies failed to establish the causality between central demyelinating effects and HB immunization. Nonetheless, as HB immunization could trigger factors in susceptible individuals as people with a family or personal history of multiple sclerosis, experts didn't totally exclude a low risk between HB immunization and multiple sclerosis.**
- **October 1, 1998** : according to the **principle of caution**, HB immunization in school was discontinued. But, it **remains recommended** in infants, adolescents and high-risk adults.

International consensus meeting on September 10/11, 2003



- **After the decision of the Ministry of Health in October 1998, the use of HB vaccines declined sharply although HB immunization remains recommended in infants, adolescents and high-risk adults.**
 - => The French healthcare authorities were asked by the Ministry of Health to organize the international consensus meeting in order to provide updated recommendations of HB immunization.**
- **September 10/11, 2003 – International consensus meeting : analysis of an updated review of all pharmaco-epidemiological data concerning HB disease and prevention worldwide, particularly in France, including :**
 - an updated review of central demyelinating case reports**
 - a presentation of the Hernan's case-control study by the author via a telephone call**
- => HB immunization recommended in infants, and unvaccinated children and adolescents.**

- **Analysis of the Hernan's case-control study published on September 2004**
 - => **National Advisory Board concludes that recommendations provide by the experts during the International Consensus Meeting held in September 2003 remain unchanged.**
- **Vaccinations Technical Committee** : Similar conclusions with those of the National Commission on September 21, 2004.
- **WHO** confirms these recommendations in September 2004.
- Nonetheless, in view of the results of the published Hernan's study, the French regulatory authorities are asked by the Ministry of Health to organize an **Experts Public Hearing** in order to statuate on the recommendations provide by the Experts of the International Consensus Meeting held in September 2003.
 - => **November 9, 2004 – Experts Public Hearing : Conclusions ongoing.**

Why is this vaccine safety concern confined to France ?



3 possible explanations

- 30 million inhabitants, almost **half of the french population**, vaccinated against HB between 1984 and 2003 (of which approximately **20 million adults**) mainly between 1994 and 1998 (HB immunization in schoolchildren).
- French popular **press** and **television** programmes raised concerns among the French public that HB immunization may be linked to new cases or flare-ups of MS or other demyelinating diseases.
=> Overall use of HB vaccine dropped in France since 1998.
- Several French **anti-vaccination consumer organization** and, a number of **patients** with MS **claim** that their disease was caused or exacerbated by HB immunization.

- To date, no risk of central demyelinating events after HB immunization in **infants** demonstrated :
 - **No case reported in children under the age 24 months since initiation of mass immunization in infants in 1994.**
- Hernan's study showed that HB immunization, in **adults**, is associated with an **increase risk of MS.**
- **Ongoing** debate about **children and adolescents**
 - **To date, 33 MS case-reports (of which 6 patients with family history of MS) for approximately 10 million children vaccinated.**
- The question about HB immunization in patients with a **family history** of MS remains open.