

Anti-hepatitis B vaccine and central demyelinating disorders (CDD)

The French data

A Fourrier ¹, A Alperovitch ², E Touzé ², JL Imbs ³, B Bégaud ¹

1: Département de Pharmacologie, Bordeaux

2: Unité Inserm 360, Paris

3: Centre régional de pharmacovigilance, Strasbourg

Background

HB Vaccine policy

1981: launch of the first anti-hepatitis B vaccine in France

1991: mandatory immunization of high risk groups (e.g. health professionals)

1994: immunization campaign targeting newborns and adolescents (10-11 years)

France (60 millions inhabitants)

1994-1996: 53 millions doses (60% in > 20 years old)

1994-2000: 85 millions doses (45% of the French population)

Pharmacovigilance data

**1993-1996: 199 reports of central demyelinating disorders (0 in newborns),
772 reports in 2001**

67%: 20-44 years old

57%: within two months after HB vaccine injection

Studies conducted

Observed versus expected comparison (fall 1998, spring 2000)

Br J Clin Pharmacol 200; 51: 489

Pilot case control study (summer 97) *Rev Neurol 2000; 156: 242-6*

Field multicentre case control study (France, spring 1998) (*in press*)

GPRD case control study (1998)

Observed versus expected comparison

(summer 98) - 1994-1996, 20-44 years

Expected cases

Annual incidence rate of demyelinating disorders: 42.9 per 1 000 000

Number exposed subjects: sales data, primo-vaccination (3 doses separated with 1 month)

At-risk time-window: 2 months after each injection, 4 months in case of complete-vaccination (3 doses)

Observed cases

CDD cases reported to pharmacovigilance: first episode of CDD, validated by 2 independent neurologists, 20-44 years old subjects, vaccinated between 1994-1996, occurred within 2 months after HB vaccine injection

Statistical comparison

Poisson cumulative probabilities

Observed versus expected comparison

	1998
n vaccinated (94-96)*	7.18 10⁶
n expected	102.6
n reported	280
n eligible**	83
Poisson Probability	0.97
Critical number (p < 0.05)	121
Under-reporting coefficient	1.5

*** 20-44 years old**

**** first episode, no previous neurological diseases, 20-44 years old, HB vaccine injection between 01/01/94 and 12/31/96, within two months after HB vaccine injection**

Pilot case control study

(Touzé E. et al, Rev Neurol 2000; 156: 242-6)

1997: Cases and controls recruited in a single center (Pitié-Salpêtrière hospital, Fédération Française de Neurologie, Paris)

121 matched (age, gender) pairs were studied

Cases were more more frequently exposed to HB vaccine within the 60 days preceding the neurological event, as compared to controls (adjusted odds ratio = 1.7, 95 % CI : 0.5-6.3)

This case-control study did not allow to conclude to, nor to rule out confidently a possible slight association between HB vaccine and a CDD or a first episode of MS

Further studies were requested by the Agence du médicament

Multicenter case-control study

Study conducted in 1998 on request of and funded by the French Medicine Agency

Département de Pharmacologie Clinique de l'Université Bordeaux II

(B. Bégaud, A. Fourrier, C. Rue-Fenouche, V. Rondé-Oustau, I. Jeantaud) (coordinating centre)

Unité 360 INSERM “Recherche Epidémiologique en Neurologie et Psychopathologie”, Paris

(A. Alperovitch, E. Touzé, M.H. Verdier-Taillefer)

Study design

Spring 1998, 17 French departments of neurology agreed to participate

In each participating center, trained neurologists reviewed the medical records of all in or outpatients referred between January 1st, 1994 and December 31, 1995 in order to select eligible cases and controls

Independent experts reviewed medical data of selected cases and controls

Cases and controls eligible for the study were asked by mail to participate and return their written consent in case of agreement

Eligibility criteria for cases

- To have been examined in one of the participating centres between January 1, 1994 and December 31, 1995**
- To have presented a first ever episode of CNS demyelinating disease within the 6 months preceding the examination**

The definition of a first episode of CNS demyelinating disease was similar to that used to define an episode of multiple sclerosis (onset or relapse), neurological symptoms compatible with CNS white matter lesions, lasting at least 24 hours, leading to a medical consultation

Patients with a prior neurological or visual event suggestive of possible CNS demyelination lasting more than 48 hours were excluded

Eligibility criteria for controls (2 for 1 case)

Matched to the case on

- sex, age (\pm 5 years),**
- center**
- date of referral : \pm 2 months**

Controls were patients referred for pathologies not known or suspected to modify the probability of vaccination (migraine or headache (except trigeminal neuralgia), non-inflammatory rheumatological diseases, vascular or other neurological diseases

Patients with auto-immune diseases or chronic severe neurological diseases were excluded

Sampling

Cases		Controls
453	Eligible	820
51	Not validated	98
56 (13.9%)	Lost	190 (26.3%)
21 (5.2%)	Refusal	55 (7.6%)
10 (2.5%)	No answer to phone call	31 (4.5%)
4 (1%)	Death	1 (< 1%)
311	Sample for interview	445
16 (5.14%)	Subjects with	26 (5.84%)
6 (0.19%)	CI for immuzation	7 (1.57%)
53	Unable to answer	
	Cases without controls	
	Controls without cases	57
236	Sample For Matched	355
	Analysis	

Data collection

Clinical data were collected by neurologists from medical records

Standardised phone interview

Education, occupation, marital status, number of children, place of residence, place of birth

Data on socio-demographics characteristics and vaccination were collected by the coordinating centre (phone interviews blinded to status)

The following vaccinations were considered : hepatitis A, hepatitis B, tetanos, poliomyelitis, diphteria, yellow fever, influenza, meningitis, tuberculosis, cholera

Referral to vaccination certificate was required during the phone interview

Statistical analysis

Conditional logistic regression analysis : odds ratio with 95% confidence interval

Adjustment for potential confounders : socio-demographic characteristics, any other immunization during the exposure period, injection of HB vaccine within 61-180 days preceeding the reference date

General characteristics of cases and controls

	Cases (n = 236)	Controls (n = 355)
Mean age \pm SD (years)	33.6 \pm 9.6	34.2 \pm 9.8
Female gender (%)	76.7	77.5
Born in France (%)	92.0	88.7
Living in urban area (%)	75.4	80.0
Living alone (%)	22.5	21.7
No children (%)	40.7	36.3
Education level (%)		
Low	31.4	34.9
Medium	31.4	29.3
High	37.2	35.8
Occupation (%)		
Blue collar	46.2	45.1
White collar	26.7	29.6
No occupation	27.1	25.3
Health professional (%)	10.6	14.9
Family history of MS (%)	2.1	
Date of first consultation		
1st half-1994 (%)	28.4	24.9
2nd half-1994 (%)	23.3	23.4
1st half-1995 (%)	27.1	29.7
2nd half-1995 (%)	21.2	22.0

Other characteristics of cases and controls

- **193 (81.8%) cases were classified as definite or probable multiple sclerosis at the time of the study (*i.e.* 4 years after date of first referral)**
- **Dates of vaccination were documented from vaccination certificate in 83.1% of cases and 92.7% of controls claiming to have been immunized**

Occurrence of a first ever CNS demyelinating episode within the 2 months following HB vaccination

	Number exposed		OR* (95% CI)
	Cases	Controls	
Total study population			
All	13/236 (5.5)	12/355 (3.4)	1.8 (0.7 - 4.6)
Subjects with definite or probable MS**	11/193 (5.7)	10/297 (3.4)	2.0 (0.8 - 5.4)
Subjects without any other vaccination	9/219 (4.1)	6/319 (1.9)	2.5 (0.8 - 7.9)
Subjects reporting having a vaccination certificate			
All	9/152 (5.9)	12/253 (4.7)	1.4 (0.4 - 4.5)
Subjects with definite or probable MS**	9/127 (7.1)	10/217 (4.6)	1.6 (0.4 - 5.6) t
Subjects without any other vaccination	6/138 (4.3)	6/241(2.5)	1.5 (0.4 - 6.2)

* adjusted for age, exposure outside the time-window, marital status, number of children, education level, other vaccinations, health occupation, place of residence, country of birth

** diagnosis established from follow-up data

Occurrence of a first ever CNS demyelinating episode and HB vaccination according to the time-window

Time window	Number of exposed		OR * (95% CI)
	Cases	Controls	
Total study population			
0-2 months	13/236 (5.5)	12/355 (3.4)	1.8 (0.7 - 4.6)
2-12 months	26/236 (11.0)	42/355 (11.9)	0.9 (0.4 - 2.0)
Subjects reporting having a vaccination certificate			
0-2 months	9/152 (6.0)	12/253 (4.7)	1.4 (0.4 - 4.5)
2-12 months	20/152 (13.2)	36/253 (14.2)	1.0 (0.6 - 1.9)

*adjusted for age, exposure outside the time-window, marital status, number of children, education level, other vaccinations, health occupation, place of residence, country of birth

Discussion

Higher lost to follow-up in controls (unknown address)

Hospital controls (vaccination coverage 19% versus 21.5% in the same population in a national survey ; same age distribution)

Interviews in 1998, high media coverage, possible differential recall between cases and controls

Power: for 50% increase of risk, 2000 cases and 2000 controls required

Conclusions

This study ruled out the existence of a strong association (OR " 3) between HB vaccine and occurrence of a first demyelinating event in adults

A slight increase of risk within the two months following HB immunization cannot be excluded