Letter to the Editors

Hepatitis B vaccine and first episodes of central nervous system demyelinating disorders: a comparison between reported and expected number of cases

In 1994, in accordance with WHO recommendations, the French health authorities decided to extend hepatitis B (HB) vaccination to newborns and preteenagers. Vaccination for adults at increased risk of HB infection (especially health care professionals) has been mandatory since 1991. In July 1996, about 200 cases of central nervous system demyelinating disorders (CDD) following HB vaccine injection were reported to the French pharmacovigilance system, raising the question as to whether this association was fortuitous or not.

To explore this signal, the number of reported cases of CDD was compared with that expected under the hypothesis of no association, using Poisson cumulative probabilities [1]. The comparison considered spontaneous reports received by the French pharmacovigilance up to 31 December 1999. The analysis was restricted to subjects aged 20–44 years vaccinated in the period 1994–96. About 80% of CDD cases are expected to occur in this age group, and during the study period, HB vaccination was extensive in France. Between 1994 and 1996, 53 million doses of HB vaccine were distributed in France, 21.6 million to subjects aged 20–44 years. The most common immunization protocol used at the time of the study consisted of three injections of vaccine at 1 month intervals. On this basis, and assuming that all the doses were actually used, we estimated that 7.18 million subjects aged 20–44 years were vaccinated over the study period. As suggested by a panel of neurologists, we considered a time-window of excess risk of CDD of 2 months after a HB vaccine injection. A vaccinated subject is thus at increased risk for 4 months: one between the first and the second dose, one between the second and the third dose and two after the third and last dose. Background incidence rate was derived from data provided by several surveys of multiple sclerosis (MS) conducted in France before the start of vaccination [2]. Since about 80% of CDD episodes represent the onset of definite MS, we considered the highest incidence rate of MS available.

The annual incidence rate for subjects aged 20–44 years was estimated to be 42.9 per million. During the chosen time-window, 102.7 cases were expected to occur in vaccinated subjects (Table 1). Two senior neurologists validated all CDD cases reported to the French National Pharmacovigilance System. Among the validated cases, we retained those that filled the following criteria: (*i*) received an HB vaccine injection between 1 January 1994 and 31 December 1996, (*ii*) aged 20–44 years, (*iii*) presented a first CDD episode within 2 months after a HB vaccine injection. Among the cases reported up to the end of December 1999, 108 matched the case definition. This reported number was not significantly different from that expected at the 5% level. However, a mere 1.12-fold increase would result in a level significantly higher than that expected. A capture-recapture study conducted in France with three independent sources estimated an underreporting coefficient of 2 for the period 1994–96 (French Medicine Agency, internal report). Background incidence rates used are consistent with epidemiological data on MS in other European countries [3]. By considering that all HB vaccine doses sold have been used for complete vaccination, we do not take into account isolated injections (incomplete first immunization or booster) for which the at-risk time-window is 2 months, as against 4 months for the three-dose scheme. This could underestimate the expected number of cases. This underestimation remains moderate, e.g. a factor of 1.1 for a proportion of 20% single injections could be considered as a maximum for this extensive first immunization campaign.

Table 1 Comparison between reported and expected numbers of cases.

n vaccinated (10^6)⋆	7.18
Annual incidence rate (10^{-6})	42.86
n expected cases	102.7
n reported cases (1981–99)	623
n eligible reported cases†	108
Poisson probability	0.31
Critical number ($P<0.05$)	121
Critical under-reporting coefficient	1.12

⋆: 20–44-year-old between 1 January 1994 and 31 December 1996
†: 20–44-year-old subjects presenting with a first episode of CDD within 2 months after HB vaccine injection done between 1 January 1994 and 31 December 1996.

The results of this study do not provide strong arguments for ruling out the possibility of an association, causal or otherwise, between HB vaccine and first episode of central nervous system demyelinating disorders. Since the observed number of cases would exceed significantly that expected with a modest under-reporting coefficient strongly supposes a signal.

Annie Fourrier,[1] Bernard Bégaud,[2] Annick Alpérovitch,[3] Marie-Hélène Verdier-Taillefer,[3] Emmanuel Touzé,[3] Nicole Decker[4] & Jean-Louis Imbs[4]

[1]*Arme-Pharmacovigilance, Université Victor Segalen Bordeaux 2, Bordeaux,* [2]*Département de Pharmacologie, Université Victor Segalen Bordeaux 2, Bordeaux,* [3]*INSERM Unité 360, Hôpital Pitié-Salpétrière, Paris and* [4]*Centre Régional de Pharmacovigilance, Hospices Civils de Strasbourg, Strasbourg, France*

Received 8 May 2000, accepted 20 December 2000

Correspondence: Annie Fourrier, Pharm, MPH, Département de Pharmacologie, Université Victor Segalen Bordeaux 2, 33076–Bordeaux cedex, France. Téléphone: (+33) 5 57 57 15 61; Fax: (+33) 5 56 98 12 91; E-mail: annie.fourrier@pharmaco.u-bordeaux2.fr

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