LEADING ARTICLE

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Demyelinating Disease and Hepatitis B Vaccination

Is There a Link?

Tom Jefferson[1] and *Harald Heijbel*[2]

1 Health Reviews Ltd and Cochrane Vaccines Field, UK Cochrane Centre, Oxford, England
2 Swedish Institute of Infectious Disease Control, Lund, Sweden

Abstract

The recent decision by the French government to compensate 3 recipients of hepatitis B vaccine preceding the onset of multiple sclerosis presumes a possible causal link and brings into question the use of current rules of causality assessment. Available evidence does not support a causal link or is equivocal but the accuracy of current methods of vaccine surveillance should be urgently improved. Larger and longer randomised trials, updated summaries of evidence, linked databases, prospective vaccination registers, bar-coding of vaccines and standardisation of adverse event definitions are possible measures to address current problems.

On 25th May 2000 the French broadsheet newspaper *Le Parisien* announced that the French Health Ministry (DGS) had decided to award damages to 8 people. Among whom were 3 people with multiple sclerosis, who had been previously immunised with a hepatitis B vaccine.[1]

The story was rapidly picked up by the French media and relayed by several outlets within hours of the story breaking.[2,3] The DGS swiftly moved to comment on the story, releasing a *communique de presse* pointing out that the decision, made for the benefit of the patients, was enabled by a 1978 vaccine accident compensation law aimed at the amicable resolving of disputes. The law allows for compensation of persons injured by compulsory vaccination.

The DGS also clarified that the decision was made notwithstanding the fact that the experts in charge of regular re-evaluation of the safety profile of hepatitis B vaccines had not found evidence of an association between hepatitis B vaccination and multiple sclerosis or autoimmune diseases. This sentence appears to flatly contradict the results of the meeting that the French National Commission of Pharmacovigilance held on 22nd March 2000. The conclusions of the Commission were released to the press on 23rd May 2000 and stated that there appeared to be 'a real number of cases [of demyelinating disorders] significantly higher than the number of expected cases.'[4]

The decision came hard on the heels of years of debate, heightened by the announcement by the DGS in October 1998 to suspend advisory hepatitis B vaccination for adolescent school children because of fears of its link with demyelinating disorders, especially multiple sclerosis and retrobulbar neuritis. The admission in writing by the French State of a cause and effect link between exposure to hepatitis B vaccine and a demyelinating disorder, immediately followed by a press release which in essence denied that admission, has added to the confusion

Table I. Studies assessing evidence of a causal association between hepatitis B vaccination and demyelinating disease

Study (country)	Design	Population	Odds ratio (95% confidence intervals)	Conclusions and remarks
Sadovnik and Scheifele[7] (Canada)	Before and after start of vaccination programme	578 308 adolescents in British Columbia	NA	Incidence pre- and postvaccination not significantly different
Touzè et al.[8] (France)	Case control	121 hospital patients with episode of demyelinating disease and 121 age and gender matched controls	1.4 (0.5 to 4.3) for 60 days' exposure; 2.1 (0.7 to 6.0) for up to 180 days' exposure	Cannot exclude causal association
Niu et al.[9] (US)	Case series review and retrospective cohort study	Children aged up to 10 whose adverse events were reported to VAERS and aged up to 6 who were immunised at a HMO	0.96 (0.91 to 1.01) for 30 days' exposure	No evidence of association of hepatitis B vaccination with 'all hospitalisation and/or emergency room visits'
Zipp et al.[10] (US)	Retrospective comparative cohort	134 698 individuals in US medical care database. 4 age and gender matched comparators for each case	1.3 (0.1 to 12.7) for 60 days' follow-up; 1.0 (0.5 to 2.5) for 3 years' follow-up	No evidence of association
Grotto et al.[11]	Descriptive review of cases from literature	3 cases after 7 to 42 days after exposure	Not calculated	Authors report cases linked to vaccine, without specifying on what basis
Monteyne and André[12] (Belgium)	Descriptive review of the facts		Not calculated	Coincidental association is the most plausible explanation
Confavreux et al.[13] (Europe)	Case crossover	643 individuals with relapsing multiple sclerosis included in disease database	Relative risk 0.71 (0.40 to 1.26) for up to 3 months exposure to any vaccination	Vaccination does not appear to increase the short term risk of a relapse in multiple sclerosis
Ascherio et al.[14] (US)	Case control	192 female nurses and 534 healthy control participants and 111 control participants with breast cancer	Relative risk 0.9 (0.5 to 1.6) for exposure at any time before onset of multiple sclerosis	There is no evidence of a causal association between hepatitis B vaccination and multiple sclerosis

HMO = Health Maintenance Organisation; **NA** = not available; **VAERS** = Vaccine Adverse Event Reporting System.

which continues to reign in France and around the world on the issue.

In the face of an increasing number of compensation claims, the French government's decision raises several methodological and ethical issues that need careful reflection.

1. What Evidence is Available of a Causal Link?

The first possible reports of an association between hepatitis B vaccination and neurological syndromes, are those of cases of Guillan-Barrè syndrome reported in 1988[5] and those of multiple sclerosis reported in 1991.[6] Despite the passing of a decade, studies assessing a possible causal link are few. The salient ones known to us are summarised in table I.[7-14]

The study designs are a mixture of analytical and descriptive, some including pharmacovigilance data. The weight of evidence either does not appear to favour a causal link or is equivocal. However, as all studies are observational in nature, the possibility of bias cannot be excluded. The best demonstration of the presence of bias is the reporting of cases of demyelinating diseases to the manufactures of one of the hepatitis B vaccines. During the period 1986 to 1998, of 364 cases of multiple sclerosis from 19 countries, 163 were from France. The publicity surrounding the alleged association between hepatitis B vaccine and multiple sclerosis clearly

acted as a beacon for the reporting of the cases of multiple sclerosis following immunisation at various time intervals.

There are other reasons for interpreting the results of any observational study, especially if small, with great care. Among these are the gradual onset of symptoms, the difficulty of defining the beginning and the clinical entity of demyelinating diseases and the sometimes hasty nature of the studies which are conducted rapidly in the hope of proving or disproving the alleged association. In addition there are the roles of interests of different lobbies, which although difficult to assess, are never far from the surface in emotionally charged arenas, such as vaccine-induced compensation. Lastly, bias is likely to lead to an overestimation of the strength of reported associations derived from observational studies by as much as a 5-fold factor, as shown in the field of antihypertensives.[15] There is no reason to doubt that the same be true for the field of vaccines. The alleged association certainly seems plausible. A case of abrupt onset of an multiple sclerosis-type clinical entity within minutes of the first hepatitis B vaccination has been observed (unpublished observation). While it seems plausible for hepatitis B vaccination to be a trigger for the onset of multiple sclerosis, is it likely that exposure to a hepatitis B vaccine would be a cause of the syndrome?

Theoretically the best study design to assess associations is the randomised controlled trial. Randomised controlled trials minimise the play of biases and are known to give the least exaggerated estimates of the strength of an association in the field of antihypertensives.[15]

Unfortunately as currently designed and powered, randomised controlled trials cannot help us in assessing any association between hepatitis B vaccination and multiple sclerosis, as the estimated all-age incidence of multiple sclerosis in France is too low (around 4 cases per 100 000) to be detected by past or current randomised controlled trials. The situation elsewhere in the world is much the same. Since the median size of trials of a hepatitis B vaccine is around 1000 participants,[16,17] even if the outcome 'demyelinating diseases' were included in the safety part of protocols, a meta-analysis of 100 trials with homogeneous outcomes, populations and appropriate duration would be eventually needed to begin giving a reliable answer to our study question.

2. How Can New Alleged Causal Associations be Evaluated and are Available Methods Sufficient for the Job?

Available evidence does not support a causal association between exposure to hepatitis B vacci-

Table II. Current methods of vaccine surveillance with methodological strengths and weaknesses[18]

Method	Strengths	Weaknesses
Individual case reports	Early warning value (if well reported)	Risk of confounding; further investigation always needed; differing case definitions
Passive surveillance	Early warning value	Further investigation always needed; under-reporting; differing case definitions
Active surveillance	Can detect rare adverse events (if denominator is large enough)	No control group; usually short follow-up; risk of confounding; differing case definitions
Pre- and postexposure studies[a]	Can detect common and rare adverse events if the denominator is large enough	Risk of confounding
Case control studies[a]	Can test hypotheses	Specific hypotheses testing only; inaccurate or biased exposure data; risk of confounding; differing case definitions
Randomised controlled trials[a]	Powerful, minimisation of all biases	May have insufficient follow-up and power; differing case definitions

a Comparative study designs.

Table III. Definitions of adverse events reported in 5 comparative studies of the effects of hepatitis B vaccines

Study (country)	Definition	Adverse events reported
Lakshmi et al.[19] (India)	Frequency of adverse effects following vaccination	Fever, local discomfort, headache, GI disorders
Usonis et al.[20] (Lithuania)	Incidence and severity of all solicited adverse reactions	**Local adverse reactions** Pain, severe redness >20mm, swelling >20mm **General adverse reactions** Diarrhoea, drowsiness, feeding problems, irritability, temperature >38°C (fever), vomiting
Poovorawan et al.[21] (Thailand)	Incidence of solicited local and general symptoms following the 3 dose primary vaccination course	**Local adverse reactions** Pain, redness, swelling **General adverse reactions** Fever, drowsiness, GI symptoms, irritability, unusual crying
Schiff et al.[22] (US)	Summary of related or possibly related adverse events following vaccination by treatment group	Application site oedema, asthenia, dizziness dyspepsia, fatigue, fever, GI disorders, headache, hypaesthesia, injection site pain, injection site reaction, malaise, myalgia, nausea, paraesthesia, rhinitis, somnolence, sweating, vomiting
Goldfarb et al.[23] (US)	Reported events	Crying, fever, redness, nonspecific adverse events

GI = gastrointestinal.

nation and demyelinating disease, but current methods of assessment could be improved to give a more definitive answer.

As vaccination campaigns are state-sponsored or compulsory programmes involving young and healthy cohorts, the importance of having robust methods of safety assessment that can give real-time answers to issues of associations cannot be overestimated. We have seen that in the case of the hepatitis B vaccine, several study designs have been used to assess the likelihood of causality (table II). Each design has strengths and weaknesses but some strengths complement some weaknesses. A major common problem in assessment of available data, regardless of study design, is the differing nature of definitions used to classify adverse events and of the lack of power to detect rare events. The former problem hinders the synthesis of evidence of safety.

Table III shows definitions of adverse effects used in the conduct of 5 studies.[19-23] In our small nonrandom sample no definition is alike, a problem common to most reports of vaccine safety studies.[18] All prospective studies, regardless of their design, will then be limited in their usefulness for the assessment of the safety profile of vaccines and the loss of potentially crucial information is considerable.

Given such limitations, how can we improve our methods to give real-time authoritative assessments of associations?

We have discussed the issue at length elsewhere,[18] but what follows is a summary of changes which we see as necessary to achieve better documentation of the safety of vaccinations:

- Bar-coding of vaccines: the use of bar-coded vaccines would decrease transcription errors and would make registration of lot numbers practical.
- Immunisation register: registers have been established to give information on vaccine coverage, but are a significant development also for vaccine safety since they provide denominators for vaccine safety work.
- Linked database vaccine studies: for the assessment of adverse events with an insidious onset a long time after immunisation, linked database studies could allow both better clinical trials and the relatively rapid assessment of exposure and effect. In some countries data on vaccinations can be linked to databases at national health registers. For example registers of cases of demyelinating diseases.

- Better information on outcomes: standardisation of case-definitions of possible adverse events for use in evaluation studies is long overdue. Equally, the powering of randomised controlled trials should be calculated with safety as well effectiveness of the vaccine in mind.
- Better trials: one possible future solution to current methodological problems with randomised controlled trials could be the conduct of large multicentre randomised controlled trials with enough power and length of follow-up (even after the breaking of allocation codes) to detect rare and hitherto unknown associations. This however would be a solution with an increased cost.
- Summaries of evidence: the systematic identification, collection, evaluation, summarisation and regular updating of available data on the safety of vaccines is an essential step on the road to answering questions about the safety of vaccines. Had a reliable and up-to-date summary of available evidence been available to the French Government, the decision whether to admit liability would have been taken in the context of the totality of available evidence.

3. What Other Issues Should We Examine?

Safety is a relative, not an absolute, term. When deciding to vaccinate, decision makers, as well as users such as parents, always make a trade-off between the unquantified risk of serious adverse effects and the possibility of contracting the disease. In the case of hepatitis B, this is a devastating chronic illness. A modelling study[24] from Italy, a country with a hepatitis B vaccination programme, elegantly demonstrates this point. Assuming a worst case odds ratio of 2.0 in a hypothetical cohort of 100 000 individuals vaccinated at the age of 12 years, 218 cases of multiple sclerosis would be 'caused' by hepatitis B vaccination exposure. 1099 cases of hepatitis B would be avoided in the same cohort. Much of the distrust which is sometimes engendered by government responses to concerns about vaccine safety could be prevented from arising if available information were to be made accessible, for example on the world wide web, in a format understandable to users. The cumbersome nature of the organisation of *post-hoc* studies also probably fuels the fear of government cover-ups (of which we have no knowledge in the field of vaccine safety). Fear and distrust add to the burden of the unfortunate persons with serious diseases such as multiple sclerosis. The partial relief of this burden is probably the reason for the French decision to compensate. This decision may be commendable from an individual point of view, but questionable from a public health one.

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Correspondence and offprints: Dr *Tom Jefferson*, Health Reviews Ltd, 35 Minehurst Road, Mytchett, Surrey, GU16 6JP, England.
E-mail: tjefferson@cochrane.co.uk