Hepatitis B vaccination and first central nervous system demyelinating events: reanalysis of a case-control study using the self-controlled case series method

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Abstract

The hypothesis that hepatitis B vaccination is a risk factor for multiple sclerosis has been discussed at length. The data from an earlier case-control study were reanalysed using the self-controlled case series method. Using the matched cases from the case-control study, we found a relative incidence of 1.68, 95% CI (0.77 – 3.68) for the 0-60 day post vaccination risk period; this compares to an odds ratio of 1.8, 95% CI (0.7 – 4.6). When an additional 53 unmatched cases not used in the case-control study were included, the relative incidence was 1.35, 95% CI (0.66 – 2.79). Although slightly smaller in magnitude, the association between first central nervous system demyelinating event and hepatitis B vaccination obtained using the self-controlled case series method was similar to that found using the case-control method. Our results throw further light on the methodological aspects of the case series method. We recommend that, when case-control studies of vaccination and adverse events are planned, case series analyses based on the cases are also undertaken when appropriate.

Keywords: case series; hepatitis B vaccination; multiple sclerosis.
Running title: Hepatitis B vaccination and multiple sclerosis

1. Introduction

Multiple sclerosis (MS) is the most frequent demyelinating disease of the central nervous system (CNS) and is generally characterized by consecutive phases of exacerbation and remission. Several studies have assessed the relationship between MS and hepatitis B (HB) vaccination, but findings have not always been consistent [1-6]. In 2002, the WHO Global Advisory Committee on Vaccine Safety reviewed the available evidence and concluded that there was no reason to suggest a change in the recommendation for universal infant and adolescent immunization coverage with HB vaccine [7]. A range of methodological problems have been discussed in the literature, including low power, uncertain onset dates, incomplete risk factor information, and selection bias in the choice of controls [8-13].

Large scale HB immunization in adults was introduced in France the early 1990s. By 1995, about 25% of the adult population had been vaccinated. By mid 1996, 200 cases of demyelinating events had been reported as occurring after an injection of HB vaccine [1]. In 57% of the reported cases, the delay between HB vaccine injection and onset of neurological symptoms was 60 days or less. At the request of the French Medicines Agency, a multicentre hospital-based case-control study was performed in 1998 to assess whether HB vaccination was associated with an increase in risk of first CNS demyelinating event [1, 3]. The odds ratio of a first CNS demyelinating event within 2 months following an injection of HB vaccine was 1.8, 95% CI (0.7-4.6). The authors concluded that a strong association between HB vaccination and a first CNS demyelinating event in adults could be ruled out, but the possibility of a slight increase in risk could not be excluded.

The self-controlled case series method [14, 15] has been widely used to evaluate the associations between vaccinations and adverse events. This technique, when applicable, is powerful and allows for more complete control of confounders than other designs. When used along side cohort or case-control methods, it provided new insights into possible indication bias or other biases, and occasionally yielded contrasting results [16-18].

We reanalysed cases data from the case-control study published by Touzé et al [1], using the case series method. We used this opportunity to study a variety of modelling approaches in a concrete setting, thus shedding further light on the case series method and how it contrasts with the traditional case-control method.

2. Methods

2.1. The original data

The design of the original case-control study and the characteristics of the population have been published elsewhere [1]. Briefly, consecutive patients experiencing a first CNS demyelinating event who were referred to 18 departments of neurology between the 1st January 1994 and 31st December 1995 were included in the study and matched to controls (236 cases and 355 controls; 53 cases remained unmatched and were not included in the case-control analysis). This period pre-dated media attention and public concern about a possible association between MS and HB vaccination, which began in 1996. Cases were reviewed in 1998 by a panel of experts who were unaware of vaccination history. This panel classified cases according to whether they had multiple sclerosis (probable or definite).

In 1998, standardized telephone interviews were conducted in order to collect vaccination history, i.e. all vaccinations performed between July 1st 1993 and December 31st 1995. Patients were asked to refer to their vaccination certificates when responding.

The data from the original case-control study were obtained from the authors. Two sets of analyses are reported here. In the first set of analyses, reported in section 3, only data from the 236 cases used in the case-control study were included. These were the cases for whom matching controls could be found, and are referred to as matched cases. The purpose of this first set of analyses was to compare results obtained using the case-control and case series methods on the same data. We also explored some methodological aspects of the case series method, including methods for adjusting for age effects and for calculating confidence intervals. In the second set of analyses, reported in section 4, the case series method was applied to all cases, that is, the 236 matched cases included in the case-control study and the 53 unmatched cases that were not included.

2.2. The self-controlled case series method

The self-controlled case series method [14, 15] allows the strength of association between a time-varying exposure and a potentially recurrent adverse event, or a rare

non-recurrent event (such as the first CNS demyelinating event), to be investigated using cases only. The case series method is derived from an age-dependent Poisson model by conditioning on the number of events and on exposure histories. The conditioning leads to estimation of the relative incidence within individuals, and thus the case series method controls implicitly for fixed confounders over time. The case series analysis is particularly useful when information on such confounders is incomplete. A semiparametric version of the case series method, in which the underlying age effect is left unspecified, is also available [19].

A key assumption of the case series method is that events must not influence subsequent vaccinations. This would not have been appropriate had data been collected during a period of public concern about a possible link between HB vaccination and multiple sclerosis, which was not the case in this study. The validity of the assumption was checked by documenting numbers of vaccinations before and after the event. We also checked for a short-term post-event delay of HB vaccination by fitting a pre-vaccination risk period of 30 days [19].

We compared the results obtained through the self-controlled case series method to the published results obtained with the case-control method [1]. Note that it is valid to compare odds ratios and relative incidences, since first demyelinating events are rare. It is of interest to compare the precision of the estimates obtained using the case series and the case-control methods. This may be done by comparing the widths of the log-transformed confidence intervals (the log transformation is required as the estimates of the odds ratio and relative incidence are obtained by exponentiation). More directly, comparisons may be based on the ratio of the upper confidence limit to the lower confidence limit.

2.3. Implementation

The event dates were the index dates of the case-control study, namely the dates at which symptoms first appeared. These always preceded referrals, which spanned the period 1 January 1994 to 31 December 1995. To allow for this delay, we used observation periods beginning on 31 August 1993 and ending on 31 December 1995. This ensures that vaccination histories (collected from 1st July 1993) were complete when using a 0-60 day post-vaccination risk period. 234 of the 236 matched cases, and the 53 unmatched cases, had age at first symptoms within the observation period.

Thus the first set of analyses was based on 234 cases and the second set was based on 287 cases.

The main analyses included all cases with a first demyelinating event. Two subanalyses were performed using cases with probable or definite multiple sclerosis and using cases who referred to their vaccination certificates during the telephone interview.

The risk period of primary interest was 0-60 days inclusive after any HB vaccination. In the case-control study, the odds ratios for the two risk periods 0-60 days and 61-365 days were estimated jointly. Similarly, in the case series analyses we used two risk periods 0-60 days and 61-365 days after any HB vaccination. When there was overlap between risk periods at different doses, events were ascribed to the most recent dose. In addition, we performed an analysis using an indefinite post-vaccination risk period. This latter period was chosen in an attempt to test the hypothesis of Hernán et al [2] that the relative risk is raised during a 3 year period after vaccination. Note however that in the present study, an indefinite risk period corresponded to a theoretical maximum 2.33 years after vaccination, in view of the short observation period.

We used four methods of age adjustment: (1) no adjustment for age, (2) adjustment using 20 age classes of equal length spanning the event onset ages, (3) adjustment using 48 1-year age classes, and (4) semiparametric modelling in which the age categories are left unspecified. In view of the small numbers of events during the risk period, we calculated 95% confidence intervals for the relative incidence using the standard asymptotic (Wald) method and the profile likelihood.

The models were fitted with STATA version 8 [20], using the algorithms presented in [15].

3. Results for matched cases

Of the 234 matched cases included in the first set of case series analyses, 64 received at least one HB vaccination. Cases received up to 4 HB vaccinations, doses 1, 2 and 3 being the primary vaccination schedule and dose 4 a booster dose. Intervals between the first three doses were typically 1-2 months. Nineteen cases received a single dose, 10 received 2, 19 received 3 and 16 received 4 doses. 192 cases (82%) were classified as having definite or probable MS, and 150 (64%) referred to their

vaccination certificate during the telephone interview. A total of 13 events occurred within the 0-60 day post-vaccination risk period after the most recent dose received, 20 within the 61-365 day risk period after the most recent dose, and 7 occurred more than 365 days after the most recent dose. There were 24 events before the first dose received and 37 events before any one of the four doses.

Insert Figure 1 here

Insert Figure 2 here

3.1. Age effects

The earliest onset of symptoms of first CNS demyelinating event was at age 13 years and the latest was at age 60 years. The distribution of the age at first CNS demyelinating event is shown in Figure 1. The distribution of the age at HB vaccination in vaccinated cases (all doses combined) is shown in Figure 2.

Both events and vaccinations were age dependent, and hence there was a potential confounding effect of age if not fully allowed in the model.

Table 1 shows the relative incidence for the 0-60 day and 61-365 day risk periods using self-controlled case series models with no age effect, the parametric models with 20 and 48 age classes, and the semiparametric model, together with asymptotic (Wald) 95% confidence intervals. The estimates of the odds ratio obtained in the case-control study are also shown.

Insert Table 1 here.

Clearly, there is substantial confounding by age, particularly for the 0 – 60 day risk period. Unsurprisingly, 20 age groups were insufficient to remove the confounding effect of age, since these age groups remain wide (2.37 years) relative to the length of the observation periods (2.33 years). Confounding was slightly reduced but not eliminated by using 48 1-year age groups. The semiparametric model provided the most reliable estimates in this context, as no prior assumptions are made about the age effect. The case-control study matched controls to cases for age (± 5 years).

The widths (on the log scale) of the confidence intervals obtained using the case series method are smaller than those obtained using the case-control method. Using

the semiparametric model, the likelihood ratio test of the null hypothesis of no HB vaccine effect in either risk period gave the test statistic 1.72 on 2 degrees of freedom ($p = 0.42$).

3.2. Secondary analyses

From now on, all case series analyses were undertaken with the semi-parametric model. Table 2 shows the results of a dose-specific analysis using the semiparametric case series method. In this analysis the numbers of events for each dose were very small. The profile likelihood confidence intervals were more reliable, owing to the small numbers of events in each risk period. The likelihood ratio test of the null hypothesis that the effect was the same for all doses gives a chi square value of 1.99 on 6 degrees of freedom ($p = 0.92$). There was very little evidence for a dose-specific effect, though this could be due to the low power of the test.

Insert Table 2 here.

Table 3 shows the case series analyses using (a) the 0-60 days and 61-365 days after each dose, and (b) using indefinite post-vaccination risk periods. For (b), note that cases vaccinated prior to July 1st 1993 but recorded here as unvaccinated may validly be included in the analysis, since they contribute no information on the vaccination effect but do contribute information on the age effect. For the same reason, the 9 cases for whom only dose 4 was recorded, and who therefore received their primary vaccine course prior to 1st July 1993, are treated as unvaccinated as they provide no information on the vaccine effect (though this has little bearing on the results). Only asymptotic confidence intervals are presented (the confidence intervals obtained using profile likelihoods were very similar). The maximum post-vaccination time in the study was 2.29 years.

Insert Table 3 here.

Finally, including a 30 day pre-vaccination risk period was found to make little difference to the results. The relative incidence for the pre-vaccination period was

0.66, 95% CI (0.08 – 5.33). Including this pre-vaccination risk period in the model had little bearing on the results for the post-vaccination risk periods.

4. Results for matched and unmatched cases

Further analyses based on the 287 matched and unmatched cases were performed, using the semiparametric case series model and Wald confidence intervals. Of the 53 unmatched cases, 18 were vaccinated. Of these, 5 received a single dose, 4 received two doses, 4 received three and 5 received four. 6 of the 18 vaccinated cases had a first episode of CNS before the first dose was received, and 12 within the 61-365 days risk period after the most recent dose. No events occurred in the 0-60 day risk period, or more than 365 days after the most recent dose. A total of 44 unmatched cases were classified as having a definite or probable MS, and 27 referred to their vaccination certificate. There was no significant difference in the distribution of number of doses received (0 to 4) between the matched and the unmatched cases (χ^2=1.72 on 4 degrees of freedom, p = 0.79).

Table 4 shows results of the semiparametric case series analysis based on all the 287 cases, using (a) two risk periods: 0-60 days and 61-365 days after each vaccination, and (b) an indefinite risk period starting at the first dose. The likelihood ratio test of the null hypothesis of no association between HB vaccination and first demyelinating event in either the 0 – 60 or the 61 – 365 day risk period, based on all cases, yielded the test statistic 3.52 on 2 degrees of freedom (p = 0.17). The likelihood ratio test of the null hypothesis that the effect in both risk periods was the same for all doses gave a chi square value of 2.86 on 6 degrees of freedom (p = 0.83). Including a pre-vaccination risk period of 30 days in the model had little effect on the estimates; the relative incidence corresponding to this period was 1.06, 95% CI (0.23, 4.79).

Insert Table 4 here.

For the 0 – 60 day risk period, the relative incidences based on all cases, matched and unmatched, are closer to 1 than those based on the matched cases. This is because, among the unmatched cases, there was no event within a 0-60 day risk

period. In contrast, the relative incidences for the 61 – 365 day and indefinite risk periods are non-significant but larger than those obtained using matched cases only, owing to the relatively larger proportion of events within the 61 – 365 day risk period. The maximum post-vaccination time in the study was 2.29 years as before.

Insert Figure 3 here.

Figure 3 shows the estimated cumulative effect of age estimated using the semi-parametric model, relative to the age at the earliest event. The curve departs from a straight line, indicating age dependence of the underlying incidence of first demyelinating events. In particular, the incidence is lower before age 25 years and after age 40 years.

5. Discussion

The main finding of this analysis was that using a self-controlled case series method to reanalyse data from a case-control study led to similar results: that there was no strong association between HB vaccination and a first episode of CNS demyelinating disease, or between HB vaccination and definite or probable MS, within 2 months or 1 year of vaccination. However, as in the original case-control analysis, a weak association cannot be excluded. In our analysis based on all cases, matched and unmatched, we found that the relative incidence of first demyelinating events was 1.35, 95% CI (0.66 – 2.79) for the 0 – 60 day risk period following HB vaccination, and 1.78, 95% CI (0.97 – 3.27) for the 61 – 365 day risk period, with $p = 0.17$ for the test of no effect in either risk period.

We also investigated the hypothesis of an association between HB vaccination and a first demyelinating event (or MS) with indefinite post-vaccination risk period, which in the present context means up to 2.29 years after vaccination, owing to the short observation periods. We found little evidence of an effect: RI = 1.44, 95% CI (0.73-2.86) based on matched and unmatched cases. Thus we are unable to confirm the increased risk up to 3 years post-vaccination found by Hernán et al [2]. These findings support the conclusions of the WHO Global Advisory Committee on Vaccine Safety [7] that no changes to current recommendations for HB vaccination are warranted.

A detailed comparison between the case-control and the case series methods, undertaken on matched cases, provides some interesting insights into the two methods. The confidence intervals are narrower (on the log scale) using the case series method, indicating that greater precision, and hence better power of the case series method compared to the case-control method. For example, using the confidence intervals for the 0 – 60 day risk period presented in Table 1, the estimated relative efficiency of the case-control method, compared to the case series method using the matched cases, is 69%.

In the case-control study, 53 cases could not be used for lack of matched controls. Cases and controls were matched on age ±5 years; more stringent matching could have increased the number of unmatched cases. These cases could be used in the case series analysis, thus boosting the power further. The relative efficiency of the case control method compared to the case series method based on matched and unmatched cases is only 59% (for the 0 – 60 day risk period). Differences between the point estimates obtained using matched cases only, on the one hand, and matched and unmatched cases, on the other, are most likely attributable to chance effects.

The results of this study illustrate some of the advantages of the self-controlled case series method compared to case-control studies: complete control of time-invariant confounders, and use of cases only while retaining good power.

The main assumption behind the case series method is that exposures are independent of earlier events. This assumption would be invalid, for example, if the event were a contra-indication to vaccination. In the present study, there is no compelling evidence that this assumption was violated, since some HB vaccinations were given after the first demyelinating event. We found no evidence of delayed vaccination after an event, as evidenced by the non-significant relative incidence for the 30-day pre-vaccination risk period. In any case, if occurrence of a demyelinating event did subsequently reduce the chance of receiving HB vaccine, the effect would be to bias the relative incidence upwards. Note that the case-control method does not require exposures to be independent of earlier events, at least provided the event of interest is unique (or, as is the case here, is the first such event).

This study provides two further methodological insights into the case series method. First, we have shown that when there is potential for confounding by age, it is essential to control carefully for age effects, which is most effectively done using

the semiparametric model. Thus, as shown in Table 1 for the matched cases, the relative incidence for the 0 – 60 day risk period drops from a significant 2.11 without age adjustment to a far from significant 1.68, most of the drop occurring when more than 48 age groups are used. Second, the validity of asymptotic methods for calculating confidence intervals may be verified using the profile likelihood. These make some difference when the numbers of events within a risk period drops to below 4, as shown in the dose-specific analyses of Table 2.

We recommend that, when appropriate, if case-control studies of vaccination and adverse events are undertaken, parallel case series analyses should also conducted using the cases. These can be done at no further cost and, as shown by the present study, in some circumstances can produce an appreciable reduction in possible biases and a gain in power.

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