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Analyse des données disponibles sur le lien éventuel entre vaccination contre le VHB et pathologies démyélinisantes du système nerveux central et périphérique

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Results of epidemiological and clinical studies

Table 9.I : Atteintes démyélinisantes du système nerveux central (ADSNC) type sclérose en plaques (SEP) ou épisode aigu de démyélinisation (EAD)

Etudes publiées

Références bibliographiques	Pays	Type d'étude	Résultats
Zipp et coll., 1999	Etats-Unis	Cohorte	ADSNC OR (6 mois) = 1,3 IC ₉₅ = [0,4 - 4,8] OR (12 mois) = 1,0 IC ₉₅ = [0,3 - 3,0]
Soubeyrand et coll., 2000	France	Etude écologique	ADSNC 0,54 pour 100 000 doses distribuées
Touzé et coll., 2000	France	Cas-témoins monocentrique	EAD OR (2 mois) = 1,7 IC ₉₅ = [0,5 - 6,3] OR (2 mois-6 mois) = 1,5 IC ₉₅ = [0,5 - 5,3]
Sadovnick et Scheifele, 2000	Canada	Cohorte rétrospective (11-17 ans)	SEP Avant la campagne vaccinale (11-12 ans) : 9 SEP/ 288 657 vaccinés Durant la campagne vaccinale : 5 SEP/ 289 651 vaccinés
Confavreux et coll., 2001*	France	Cas-crossover	Rechute de SEP OR = 0,67 IC ₉₅ = [0,2 - 2,17]
Ascherio et coll., 2001	Etats-Unis	Cas-témoins (NHS)	SEP OR = 0,7 IC ₉₅ = [0,3 - 1,8]
Fourrier et coll., 2001	France	Approche	ADSNC Facteur de 1,1 pour atteindre un nombre

		attendus- observés	de cas notifiés significativement > au nombre de cas attendus
Touzé et coll., 2002	France	Cas-témoins multicentrique	<p>EAD Tous les sujets : OR (2 mois) = 1,8 IC₉₅ = [0,7 - 4,6] OR (2 mois-12 mois) = 0,9 IC₉₅ = [0,4 - 2,0] Sujets avec certificat de vaccination : OR (2 mois) = 1,4 IC₉₅ = [0,4 - 4,5] OR (2 mois-12 mois) = 1,0 IC₉₅ = [0,6 - 1,9]</p> <p>SEP Tous les sujets : OR (2 mois) = 2,0 IC₉₅ = [0,8 - 5,4] Sujets avec certificat de vaccination : OR (2 mois) = 1,6 IC₉₅ = [0,4 - 5,6]</p>
DeStefano et coll. Arch Neurol 2003, 60 : 504-509	Etats-Unis	Cas-témoins (HMO)	<p>SEP et névrite optique OR (< 12 mois) = 0,9 IC₉₅ = [0,6 - 1,5] OR (entre 1 et 5 ans) = 1,6</p> <p>SEP OR = 0,8 IC₉₅ = [0,5 - 1,4]</p> <p>Névrite optique OR = 1,2 IC₉₅ = [0,5 - 3,1]</p>
Hernan et coll., 2003	Royaume- Uni	Cas-témoins nichée dans une cohorte (GPRD)	<p>SEP OR (1 à 3 ans) = 2,4 IC₉₅ = [1,2 - 4,9]</p>

*Etude portant sur le risque de rechute de SEP, et non le risque de survenue de SEP

Etudes non publiées

Auteurs	Pays	Type d'étude	Résultats
Weil et coll., 1998	Etats-Unis	Cohorte rétrospective	<p>ADSNC OR (2 mois) = 0,6 IC₉₅ = [0,1 - 4,6] OR (6 mois) = 0,6 IC₉₅ = [0,2 - 2,0] OR (12 mois) = 0,7 IC₉₅ = [0,3 - 1,7] OR (24 mois) = 0,6 IC₉₅ = [0,3 - 1,5] OR (36 mois) = 1,0 IC₉₅ = [0,5 - 2,5]</p>
Costagliola et coll., 1999	France	Approche capture- recapture	<p>ADSNC Facteur de sous-notification compris entre 2 et 2,5</p>
Abenhaim et coll., 1998	Royaume- Uni	Cas-témoins (VDAMS / GPRD)	<p>SEP et démyélinisation OR (2 mois) = 1,4 IC₉₅ = [0,8 - 2,4] OR (12 mois) = 1,6 IC₉₅ = [0,6 - 3,9]</p>

Critical evaluation of the results

With the critical evaluation of the studies on any controversial topic [e.g., hepatitis B vaccination (HBV) and demyelinating disease (DD)], it is important to first describe the key assumptions and framework underlying such an evaluation before applying them to the specific studies.

A clear distinction should be drawn between the tasks of risk assessment (i.e., issues related to understanding just the risk of HBV alone) from that of the risk management (i.e., issues related to balancing the risks and benefits of HBV). As long as the upper bounds of the magnitude of the risk for DD after HBV (if real) is known, complete knowledge² about this potential risk (while ideal) is not a prerequisite for making a) risk management decisions on whether HBV should be given or not (under what kind of “informed consent”), and b) risk assessment decisions on what further research on this potential association is needed. In fact, b) is feasible only if a) results in a decision that allows sufficient HBV exposures to continue. Historically in the US, for example, this was how the uncertainty about the risk of Guillain-Barre syndrome (GBS) after each season’s influenza vaccination was handled. Since the etiology of the attributable link between GBS and the 1976-1977 (“Swine flu”) vaccine of slightly less than 1/100,000 doses was never established (Schonberger et al., 1979), the risk of the recurrence of GBS after another influenza season’s vaccine was always present. At the time of their annual influenza vaccinations, the public in the U.S. was informed of this low but as of yet incompletely understood risk, as well as the benefits. Tens of cases of GBS after influenza vaccination are reported annually; ongoing research has permitted better elucidation of the attributable risk (Lasky et al., 1998), and hopefully the etiology.

In general, vaccine X can be said to cause adverse event Y, if a) there is a relatively unusual/pathognomonic adverse event (e.g., smallpox vaccine – associated myopericarditis) (Centers for Disease Control and Prevention, 2003); b) a highly specific laboratory finding (e.g., mumps vaccine viral strain isolated from spinal fluid of patient with meningitis) (Miller et al., 1993); and/or c) an elevated risk is found among vaccinated compared to unvaccinated via a clinical trial or epidemiologic study (Miller et al., 1993; Kramarz et al., 2001; Murphy et al., 2001). With HBV and DD, neither conditions a) or b) are met (currently) and c) is our only option.

a) With any epidemiologic study on vaccine safety, the ease of its conduct and our confidence in the validity of the results are proportional to our confidence in the constituent data that goes into the analysis (e.g., the vaccine exposure, the adverse event outcome, and whether bias or confounding might be present). Unfortunately for the issue of HBV and DD, there are considerable challenges in each of these realms that jointly conspire to muddy our ability to discern the truth (table 9.II). It is not surprising, therefore, that the “Truth” has been elusive given we are trying to study the association between a poorly documented exposure and an outcome with a poorly defined onset (especially in retrospect), in which confounding, bias, and effect modification may also be present!

Table 9.II: Challenges in conducting or interpreting epidemiologic studies of hepatitis B vaccination (HBV) and demyelinating disease (DD)

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1. General
 - 1.1. Only observational data available, no randomized trials
 - 1.2. Studies conducted in different countries with very different health care systems
 - 1.3. 8/13 (62%) studies in table 9.I are unpublished or published in very brief formats that do not allow intensive evaluation (e.g., abstract, letter).
 - 1.4. In vaccine safety studies, the combination of a significantly elevated RR and a nonrandom clustering of onset intervals (time between HBV and onset of DD) among vaccine exposed cases is highly suggestive of a causal relationship. Unfortunately, this onset interval plot is presented for very few studies (Ascherio, Hernan).

2. HBV Exposure

² Examples of such knowledge about DD after HBV include whether a specific risk exists, and if so, the exact level of risk, the risk factors, the biologic mechanisms.

- 2.1. Coverage in adults generally low except in health care workers and France 1996-98
 - 2.2. With routine pediatric HBV policy; unlikely to have repeat massive dosing of HBV in adults over short time again
 - 2.3. Generally poorly documented, not computerized
 - 2.4. Multiple dose schedule complicates ascertainment and analysis
3. Adverse Event Outcome
 - 3.1. Range of outcomes of interest; only some formally studied; conclusions possible only on specific outcome studied
 - 3.1.1. Incident multiple sclerosis (MS)
 - 3.1.2. Relapse MS
 - 3.1.3. First episode central nervous system (CNS) demyelinating disease (CDD)
 - 3.1.4. First episode of peripheral nerve demyelinating disease
 - 3.1.5. Etc.
 - 3.2. Current understanding of the pathophysiology and cause of DD still limited; though studies suggest role of genetic susceptibility + environmental factors
 - 3.3. Evolving diagnostic tests in neurology (e.g., CAT, MRI scans), may affect longitudinal studies (e.g., Ascherio study goes back to 1976).
 - 3.4. Insidious onset of DD, first symptom precedes medical diagnosis by months-years. Since study design and analysis depend critically on this "index date", how was this date ascertained (prospectively vs. retrospectively, medical records vs. patient recall) is very important. Which date was used to "anchor" the ascertainment? (e.g., first occurrence of symptom, symptoms recalled at first medical visit, symptoms recalled at first medical diagnosis). How consistently was this ascertainment performed? What is the best method to ascertain this date? (e.g., medical record review alone, phone interview, both?)
 - 3.5. What risk window for a causal association is the most biologically plausible? This should be determined a priori to avoid "fishing expedition".
 4. Confounding
 - 4.1. Confounding by contraindication (mirror image of confounding by indication in pharmacoepidemiology) = healthy vaccinee effect; immediately pre-DD or post-DD diagnosis patients are less likely to be vaccinated than healthy persons. If index date in cases are inaccurately ascertained, this would result in an erroneous "protective" effect of HBV.
 - 4.2. Confounding by occupation: compared to the general population, health care workers are more likely to receive HBV and if have DD, may be more likely to be diagnosed earlier.
 5. Bias
 - 5.1. Any time a retrospective study is conducted after media publicity of a vaccine safety concern, the risk of differential ascertainment of vaccination exposure history and/or features of the adverse event outcome between the cases and the noncases is high.
 6. Effect modification
 - 6.1. Age is an important effect modifier for risks after many infections (e.g., morbidity and mortality of measles, varicella) and by analogy, probably to any risk of DD after HBV. 12/13 studies examined this issue only in adults 18+ years old. Only one (of 13) study (Sadovnick) examined this risk in adolescents and none of the studies examined risk of DD after HBV in children; both populations where HBV is highly recommended or targeted.
 7. Power
 - 7.1. In most vaccine safety studies, defining several potential "risk window" are needed. For rare associations/outcomes, this significantly increases the study power requirements.
 - 7.2. Even if an elevated risk was observed, some may argue that this is only a temporary "triggering" phenomenon (vs. "causing" permanent increase). To evaluate this hypothesis requires:
 - 7.2.1. Longer study period (where elevated relative risk (RR) during one study period is followed by a "compensatory" decrease in RR during the next study period; such that the net RR over both study periods is 1.0).
 - 7.2.2. Larger sample size since need to examine multiple risk windows
 - 7.2.3. Such large, longitudinal cohort studies with minimal loss to followup difficult to organize
 - 7.3. "Fragile" data, very few exposed cases in most studies, error in a few cases could change results.
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- b) Nevertheless, epidemiology is the art of making sense of imperfect data (George Comstock). In doing so, it is also useful to keep in mind the following maxims: i) Mass vaccination campaigns can elicit false [e.g., Guillain-Barre syndrome (GBS) after oral polio vaccine (OPV) (Rantala et al., 1994)], as well as real vaccine safety signals [e.g., GBS with swine influenza vaccine (Schonberger et al., 1979)], or show multiple causes (Lasky et al., 1998). ii) Epidemiology is a relatively “crude” research tool for studying small risks. Inferences about causality are reasonable for large RR values (e.g., ≥ 4). But for RR values between 1 and 2, it is extremely difficult if not impossible to distinguish between a real effect and an artifact due to inadequate control for bias or confounding. iii) When no statistically significant association is found, it is consistent with either: (1) the null hypothesis (i.e., there is truly no association) or (2) a Type II (false negative) error occurred due to inadequate statistical power to examine a very small association. iv) For interpreting studies of rare associations, the 95% confidence intervals are of equal or perhaps even greater importance than the point estimate. Two studies with different point estimates but overlapping confidence intervals may both be glimpses of the same “truth”. v) Fortunately in vaccine safety studies, if enough exposed cases occur to generate a nonrandom distribution (i.e., clustering consistent with a biologic pattern) of onset intervals, this provides a powerful independent complementary source of evidence on causality. vi) Some unexpected findings are real (i.e., need to keep an open mind). vii) Options for explaining discrepancies between study findings: (1) one set of studies is “right” and the other is “wrong”; (2) both are right and there is actually no discrepancy as each study examined a different specific research question; (3) Earlier studies more flawed, but contribute to improving later studies; tincture of time and experience helpful in Science.

The methodologic challenges of studying HBV and DD, while formidable, are not unique to the field of vaccine safety. Several “solutions” have been developed to minimize methodologic problems in vaccine safety studies. These in turn provide a useful checklist to evaluate each study on this topic:

- a) Awareness of the study participants re: the study hypothesis
- b) HBV exposure status ascertainment recorded electronically, prospectively and independently of outcome ascertainment (e.g., via immunization registry)
- c) Case ascertainment based on medical record review to ensure case definition met
- d) Ascertainment for date of first symptom of DD based on medical record documentation that occurred prior to current study
- e) Ascertainment of HBV status and date of first symptom of DD from medical record supplemented by other data sources (e.g., patient interview)
- f) Controls representative of the general population
- g) Control exposures (e.g., other vaccines) also studied
- h) Presentation of the onset interval of the exposed cases

Table 9.III arrays the published controlled studies (i.e., excluding ecologic studies, capture-recapture studies) by these desired study characteristics. In general, the relative validity of a study is proportional to the number of desired characteristics fulfilled. While there has been improvement in desired study methodology over time, there are relatively few studies with actually all or almost all of these desired characteristics.

How then shall we interpret these findings cumulatively? The US Institute of Medicine (IOM) Immunization Safety Review Committee reviewed this topic in 2002 (Immunization Safety Review Committee, 2002). Similar to this Committee, it consisted of independent

scientists without prior involvement in this issue. The IOM Committee had the experience of reviewing three other controversial vaccine safety topics (+ 2 large books, IOM staff) prior to this review. This Committee has the advantage of seeing some of the studies in published form (e.g., Destefano) as well as new unpublished studies (e.g., Hernan).

We can therefore avoid reinventing some of the wheels by using the conclusions of the US IOM report as a starting point:

- a) Evidence favors rejection of a causal relationship between HBV in adults and MS.
- b) Evidence was inadequate to accept or reject a causal relationship between HBV and all other DD.

Subsequent to the US IOM review, two unpublished studies presented to the US Committee have since appeared in print (Touzé et al., 2002; Destefano et al., 2003) and one new study (Hernan et al., 2003) has appeared in abstract form only. This Committee must decide on whether it will include the Hernan study in its current evaluation or not; and if so, at what weight. The US IOM Committee noted that “published reports that have been subject to a rigorous peer review process carry the most weight in the committee’s assessment... In general, the committee cannot rely solely on unpublished data in making its scientific assessments (regarding causality or biological mechanisms) because they have not undergone a formal review and must, therefore, be interpreted with caution.”

In arriving at its decision on the proper weight for the Hernan study, this Committee will want to consider the following factors, positive and negative/cautionary:

Positive considerations:

- a) The authors, especially Hershel and Susan Jick, are world renowned pharmacoepidemiologists, with extensive experience using the General Practitioners Research Database (GPRD), including over one hundred publications on drug safety.
- b) The first author, Miguel Hernan at Harvard University Department of Epidemiology, was also an author on the earlier Ascherio study; he reports that the current study is methodologically superior as the date of first DD symptom was collected based on extensive medical chart review rather than relying on nurse recall from retrospective survey in the Ascherio study.
- c) Significantly elevated RR ~ 4 was found in two time intervals post-HBV, but not two “control” vaccines (tetanus and influenza).

Negative/cautionary considerations:

- a) It is published in abstract form only and has not undergone formal rigorous peer review yet; the work of even the best epidemiologists can be improved by such peer review, especially in an arena (vaccine safety) that they’ve had relatively little experience.
- b) The possible role of confounding by occupation needs to be ruled out: HBV is indicated for health care workers and such persons may be more likely to seek care of DD sooner than the general population. This information was specifically ascertained for and controlled for in the Destefano study. It has not been sought and therefore not adjusted for in the Hernan study. Note that tetanus and influenza vaccines are not specifically indicated for health care workers like HBV and therefore this confounding is not an issue for these vaccines. This possible confounder turned out not to have been one in the Destefano study; nevertheless, it may or may not be a confounder in a different study population in a different country (i.e., UK GPRD).

- c) The inclusion of cases with onset through December 31, 2000 (after onset of publicity in France) may be problematic. Need to examine the distribution of the 11 exposed cases by calendar time to make sure that the publicity did not somehow result in an ascertainment bias in GPRD. This may occur because HBV history external to the GPRD can be added retrospectively.
- d) The completeness and quality of the GPRD vaccination data are unclear, especially for occupationally indicated (and administered?) vaccinations like HBV. In the Destefano study, ~50% of HBV exposure information in both cases and controls was not in the administrative dataset and was supplemented via patient interview. There is no guarantee that this nondifferential underascertainment also occurred in the GPRD.
- e) In the Destefano study, the average age of first symptoms from the patient interview was 3 to 5 years earlier than the corresponding date from medical records. If this were also true for the GPRD data, it would suggest that many of the exposed cases in the current study may actually have been vaccinated after onset of symptoms. Empirical evidence is needed to show that the medical record assignment of first symptom date alone in Hernan study is more reliable than combination of patient interview plus medical record review recall as was used in the Ascherio and Destefano studies.
- f) The study is based on only 11 exposed cases. Errors on a small number of cases could alter the findings.
- g) The biological mechanism for a >1 year delayed onset of DD after HBV is unclear, especially since there is no such association between DD and wild hepatitis B virus infection. The “signals” from pharmacovigilance and early controlled studies were for a much shorter time interval.

The Hernan study is probably too “new” to allow this Committee or anyone else to fully sort out why its findings are so different from other studies or to adequately peer review it. Fortunately, because it is a case-control study nested within a longitudinal cohort, it is possible to calculate an attributable risk to guide policymakers. A few additional comments relevant to interpreting the Hernan study follows:

- 1) While the Destefano paper showed an overall RR for HBV and either multiple sclerosis (MS) or optic neuritis (ON) of 0.9 (0.6-1.5), the distribution of RR across risk windows differed more markedly for HBV than any other vaccine studied: 0.8 (0.4-1.8) for <1 year, 1.6 (0.8-3.0) for 1-5 years, and 0.6 (0.2-1.4) for >5 years. An important question is whether the Destefano analysis for 1-5 years, when reanalyzed by one year intervals, show a pattern similar to the Hernan study for years 2 and 3 post-HBV. When this is done, however, the data do not corroborate the Hernan study (table 9.IV + figure 9.1).

Table 9.IV: Reanalysis of table 4 in Destefano et al. : Odds ratios of association between timing of hepatitis B vaccination and the risk of demyelinating disease

Time of vaccination before index date (years)	Odds ratio	95% confidence limits	
5+	0.637	0.232	1.750
4- <5	1.240	0.249	6.182
3- <4	1.659	0.341	8.075
2- <3	0.812	0.187	3.531
1- <2	1.581	0.499	5.007
<1	0.512	0.173	1.516

- 2) In comparing these two studies, despite the many similarities highlighted in table 9.III, it is important to keep in mind the key methodologic differences summarized below:

	Destefano	Hernan
Published in peer review journal	Yes	No
Country	US	UK
HBV exposure information	Administrative + phone interview	Administrative only
Date of first DD symptom	Medical record + phone interview	Administrative only
Control for confounding by occupation	Yes	No

- 3) These important methodologic differences aside, the 95% confidence intervals for both studies overlap. Statistically speaking, the two studies may in fact be representing the same “truth”. The a priori power calculations in the Destefano study of 80% power to detect an OR <2 were more than met (332 cases enrolled vs. 262 required). The confidence intervals in the Hernan study are especially wide.
- 4) The US and UK may differ in population susceptibility to MS.
- 5) Separately, figure 1 in the Ascherio paper is intriguing. While the overall RR was <1.0, the plot of onset intervals among the 9 exposed cases was surprisingly consistent with a nonrandom clustering.

Is it possible and useful to conduct a meta-analysis of the available studies? What are their limits? Which results could one expect?

Because of the heterogeneity in study designs (table 9.III), conducting a meta-analysis of all the studies on this issue would be inappropriate. On the other hand, assuming methodologic differences between the Destefano and Hernan studies can be reconciled or bridged (e.g., add patient interview for DD onset and HBV history and include longer followup >5 years to the Hernan study), a meta-analysis of the Destefano and Hernan studies may be worthwhile. Meta-analysis usually require N>2 however.

In conclusion, future studies/actions can be suggested :

- Plot the onset interval of the exposed cases from all the studies to see if the pattern is nonrandom or not
- Followup CDD cases in Touzé studies to assess % evolve to MS vs. just initial monophasic illness
- Ecologic study of MS case in France: has it changed overall given sharp increase then drop in HBV coverage?
- Conduct pharmacogenetic study of MS, prevalence of MS genetic susceptibility, differences between HBV exposed and nonexposed MS patients?
- National Vaccine Injury Compensation Program funded by excise tax as part of solution in France
- Better pharmacoepidemiologic capability via large-linked databases (e.g., VSD, GPRD) to complement excellent pharmacovigilance in France, also funded by excise tax.

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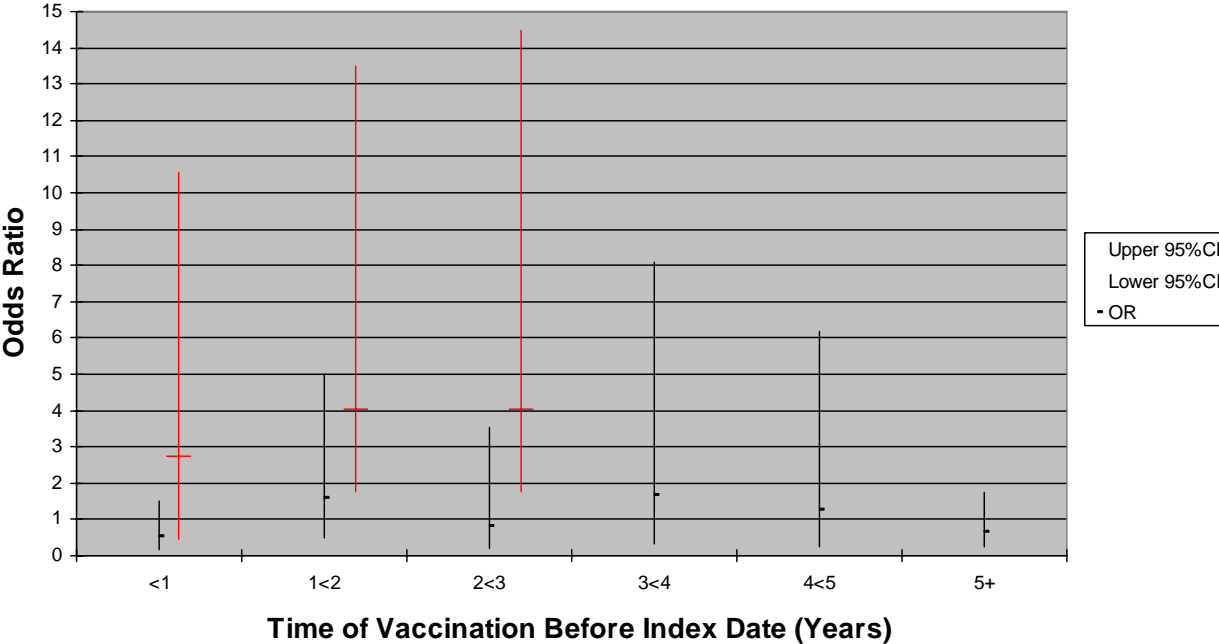
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Table 9.III: Analysis of Published Controlled Studies of Hepatitis B Vaccination and Demyelinating Diseases (DD) by Presence or Absence of Desirable Study Methods

Study	Awareness of the study participants re: HBV + DD hypothesis	HBV status recorded electronically, prospectively + independently of outcome ascertainment	Case ascertainment based on medical record review to ensure case definition was met	Ascertainment for date of first symptom of DD based on prior medical record documentation	Ascertainment of HBV status and date of first symptom of DD supplemented by other sources	Controls representative of the general population	Control exposures (e.g., other vaccines) also studied	Presentation of the onset interval of the exposed cases
	(No)	(Yes)	(Yes)	(Yes)	(Yes)	(Yes)	(Yes)	(Yes)
Zipp 1999	No	Yes	No	No	No	Yes	No	No
Touzé 2000	Yes	No	Yes	Yes	Yes (HBV)	No	Yes	No
Touzé 2002	Yes	No	Yes	Yes	Yes (HBV)	No	Yes	Yes
Confavreux 2001	No	No	Yes	No (looked at relapses)	Yes (HBV)	No	Yes	No
Ascherio 2001	No	No	Yes	No	Yes	No	No	Yes
DeStefano 2003	No	Yes*	Yes	Yes*	Yes	Yes	Yes	No
Hernan 2003	No	Yes	Yes	Yes	No	Yes	Yes	Yes

*Two methods used: medical records supplemented by phone interviews

Odds Ratio of Association Between Timing of HBV and Risk of DD, Destefano vs. Hernan*



- Destefano et al. Arch Neurol 2003
- Hernan et al. (abstract) Pharmacoepi and Drug Safety 2003

Figure 9.I