

When evidence-based medicine (EBM) fuels confusion: multiple sclerosis after hepatitis B vaccine as a case in point

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Abstract

Background: Evidence-based medicine (EBM) may be used to discard valuable data under the pretext that it does *not* correspond to the “best” criteria of proof, even when no results complying with these “best” criteria are available. Since their infrequent occurrences make it impossible to assess most adverse effects using randomised clinical trials (RCTs), drug safety offers frequent examples of selective assessment of data based upon this poor understanding of the fundamental tenets of EBM. While the gold standard of pharmaco-epidemiology (case/control studies) is usually ranked amongst the lower levels of evidence and is unattainable in many instances, the majority of safety problems are simply assessed using subjective specifications (“acceptable”, “hard to interpret”, “not enough evidence”, “not causally demonstrated”). This vaccine-safety example illustrates that such specifications are almost always biased by prejudices and application inconsistencies.

Methodology: Taking it for granted that any review of evidence must be complete, it must also be emphasized that such reviews must be fair. This means that the significance of the results must be assessed according to: a) the reliability of their sources (sponsoring, methods used, transparency of results, vested interests) and b) the weight of evidence which, *in previous instances*, was deemed to be “sufficient” to justify regulatory measures or practical recommendations.

Principal Findings: Applied to the issue of demyelinating disorders after vaccination against hepatitis B, this conceptual framework makes it possible to show that: (1) the authors of most studies challenging the reality of a neurological risk have vested interests (which are not always of financial nature); (2) the criticism directed by national (French Agency, U.S. CDC) and international health agencies (WHO) towards investigations supporting a neurological risk after hepatitis B vaccination ranges from nonsense to documented forgery; and (3) even in the greatest journals, the process of publication has been tainted by the self-serving influence of the drug makers.

Conclusions/Significance: (1) The level of evidence demonstrating a significant risk of central demyelinating disorder after hepatitis B vaccine is far higher than that normally accepted to justify strong regulatory measures as exemplified by the historical precedents of thalidomide, aminorex, diethylstilbestrol, practolol, dexfenfluramine, tolcapone, and cerivastatin. (2) The dynamics of biased controversies over drug safety is based upon a worrying perversion of two key-points of scientific legitimacy: the publication process on the one hand, and the game of refutation on the other. However, the secular rules of Hippocratic prudence still offer valuable guidance to prescribers that, in practice, can be used to manage today’s money-driven controversies that focus on promoting the “benefits” of drugs while downplaying or ignoring the often all-to-real “risks associated with these same drugs.”

Keywords: drug hazards, evidence-based medicine (EBM), hepatitis B vaccines, medical controversies, multiple sclerosis

1. Introduction and rationale

In France, which was the country with proportionally the highest exposure to hepatitis B vaccination worldwide (approximately half of the population, corresponding to some 30 millions persons, with a scheme of boosters far more sustained than everywhere—3 injections at an interval of 1 month, one booster after 1 year and then every 5 years), I was requested as a medical expert witness to perform several dozen assessments concerning injuries ascribed by the plaintiffs to hepatitis B vaccines. In addition, I was commissioned to perform additional assessments by the French Court (Paris) in charge of the criminal inquiry into the national hepatitis-B vaccination campaign, which was launched in 1994. Overall, I spent probably some 5,000 hours studying hepatitis B vaccination issues, and had the opportunity of examining a number of confidential documents related to the vaccine’s registration and the post-marketing surveillance processes (since there is no *Freedom of Information Act* in France) as well as to the relations between health agencies, their experts and the manufacturers.

Regrettably, much of this documentation remains sealed by Court order according to French law. Thus, I am in the uncom-

fortable situation of being much more knowledgeable than the average physician on these issues. However, my right to speak about that which I know is severely restricted compared to the average physician’s. As a leading WHO expert told me during a TV program on hepatitis B toxicity: “I am not acquainted with the figures [of post-vaccine neurological hazards] but *I know* that they are not significant” (italics added for emphasis). How could it actually be that the assessment of vaccines (especially, the hepatitis B vaccines) is, *above all*, an area where those who are not acquainted with the evidence nevertheless feel themselves entitled to “know” the way it deserves to be interpreted?

In a number of instances, my extensive experience with confidential documentation has allowed me to indirectly cross-check the findings in the sealed documents with the published evidence. Moreover, it justifies a certain degree of assertiveness in my assessment of some related issues, e.g. those concerning potential *conflicts of interest* as well as *data distortions* (or even falsifications) in the medical literature or official communiqués. For current practices, the relevance of all these issues, needless to say, extends far beyond the sole topic of hepatitis B vaccines [3,4,20,62,69] and justifies the unusually extended methodological preliminaries that follow. This is the case because, con-

trary to Popper's contention, method is the way sciences can justify their epistemological status [42].

2. Methodological preliminaries

2.1 EBM as a new source of confusion in medicine

Although evidence-based medicine (EBM) was introduced 15-20 years ago as a new paradigm in order to root medical practice more deeply into scientific rationality, poor understanding of its principles often leads to a regrettable mistake: in the quest for "the best available evidence", the emphasis should be on the "available" evidence and not on "the best".

Having missed this crucial point, most health professionals now stand their ground with a naïve, but damaging, disdain for all data which is not derived from some prospective randomised controlled trial (RCT). This is the case because they have erroneously been taught to recognize RCT as a "gold-standard" for health-effect data.

However, their RCT orthodoxy is a problem because:

- ❖ A number of RCTs are simply not reliable in the way they were designed, executed, or analyzed. [Note: This reality is exemplified by the well-recognized fact that those RCTs supported by interested parties usually have more favorable outcomes than those supported by independent bodies]
- ❖ RCTs are not always feasible. [Note: This reality is quite clear with contraceptives (for ethical reasons), or with some safety issues (which would require unrealistic sample sizes).]
- ❖ Those who have the regulatory or financial responsibility for performing RCTs, (or, at least: investigations complying with the minimum standards for such) may be reluctant to conduct the requisite RCTs, because they may have good reasons to be anxious about the results. [Note: In one of the latest French official communiqués (Nov 29, 2005) on the safety of hepatitis B vaccines, one expert of the drug Agency criticized the manufacturers for "their lack of investigations regarding experimental research on the multiple sclerosis (MS) risk since the beginning of the national post-marketing surveillance investigation [June 1994]." It probably escaped this governmental expert that the implicit ramifications of such an acknowledgment of failure went beyond the sole manufacturers: If the shortage of appropriate investigations by the vaccine makers was serious enough to justify criticism from a governmental health agency, why did the latter not use its legal right to withdraw the drug from the market, or to suspend it until the requisite "best evidence" was available?]

In the real world, even *modest* evidence, when available, is more reliable than "the best" evidence, when such is not available (whatever causes may account for this unavailability). Therefore, when discussing "evidence of safety" in EBM, it is clear that the emphasis, in EBM, should be on the "available evidence" as opposed to the usually unavailable and, in some

cases, undoable but presumed "best"—well-designed RCT—"evidence."

On the other hand, whereas it has long been recognized that subjective specifications have no place in medicine as far as frequencies are concerned [64], EBM—in spite of its founders' devotion to improving the scientific status of medicine—has, in practice, often been used to justify the use of unscientific subjective evaluations to assess whether evidence is, or is not, "acceptable." This practice is justified using the pretext that EBM permits the use of subjective specifications to qualify the methodological reliability of available results. The following two illustrations underscore the inherent flaws in using this pseudoscientific approach.

1: Selective use of the occupation of the study group to invalidate adverse-effect findings

After the publication by Hernan *et al.* of a case/control study on the risk of MS after hepatitis B vaccination [50], the World Health Organization (WHO) [90] remarked that this study was performed in the UK, a country where the practice of vaccination was targeted towards high-risk individuals, and concluded accordingly that the study population *might* have included health care workers who "cannot be regarded as a representative sample of the general population."

However, the WHO experts did not explain why they did not raise the same objection regarding the Ascherio *et al.* study [5] whose population was exclusively made of nurses!

It is extremely difficult to understand why a *hypothetical* inclusion of *some* health care workers would be likely to spoil the "available evidence" of a study showing an impressive increase in the post-vaccine neurological risk, whereas the *definite* inclusion of a population *entirely* composed of nurses would make no difference in a study which failed to find such a risk.

2: Soundness of the database used (VAERS) depends on the outcomes reported by the study

Some time ago, authors whose devotion to systematic immunizations need no confirmation (Zhou W, Pool V, Iskander JK *et al.*) published a study devoted to vaccine safety which concluded that the U.S. Vaccine Adverse Event Reporting System (VAERS) was not only important for detecting vaccine-associated adverse events, but also for "reassuring the general public concerning the safety of a new vaccine, as in the safety assessments of varicella vaccine and hepatitis A." [92]

Likewise, when researchers from the FDA reaffirmed the safety of hepatitis A vaccine after a review of data from the VAERS, the database REACTIONS (accession number: 800686009) referred to this study under the headline: "VAERS data reaffirm safety of hepatitis A vaccine".

In spite of this robust optimism on the reliability of the VAERS in so far as it is likely to "reassure the general public" or to "reaffirm safety of vaccines", the methodological requirements of governmental experts or agencies concerning the quality of the evidence stemming from VAERS can

undergo dramatic change when the outcomes do not support the “safety” of vaccines.

For example, after an analysis of VAERS data suggesting that cerebellar ataxia, autism, mental retardation and permanent brain damage were significantly increased following MMR vaccination [33], the UK Medicines and Healthcare Products Authority immediately issued a strong statement dismissing the findings on the basis that “the authors failed to consider the limitations and biases inherent in VAERS data (...).”¹

When viewing clinical practice through an EBM filter, it is obvious that investigations corresponding to the alleged “best” methodological standards are lacking or *not* appropriate for most of our everyday needs—especially where safety issues are at stake. It is precisely in such situations that the fundamental requirement of EBM should be put into practice – what is the best *available* evidence **NOW**? – Instead researchers in vaccine studies continue to apply inappropriate subjective specifications and actually go no further than such lax practices until the “the best” evidence becomes available, which, in a number of instances, will probably *never* happen. This is why good reviews, open studies or retrospective investigations based upon observational evidence, when available, may be *better*—if not *the best*—compared with more rigorous contributions which have *not* been, or *cannot* be, undertaken for one reason or another [71], as the following striking example clearly illustrates.

In France, there exists a cohort of *paediatric* MS cases gathered since 1990, including now about 500 cases some of them with the disease developed as early as at *2 years of age* or even before. Since the blackout on relevant information is complete and the investigators have stubbornly refused to communicate relevant information publicly, it is difficult to guess the percentage of underreporting in this already substantial size cohort. However, in a private talk during winter 2004, I heard the General Director of the French Agency acknowledge that this situation was a very significant concern. Yet, it seems plain that, regarding a disease which is normally an extremely rare occurrence in children (and even more in young children), the blatant chronological coincidence of this frightening burst of paediatric MS with a peak of hepatitis B vaccinations² represents *in itself* a strong indicator of causation.

However, rather than recognizing this epidemiological evidence, public health officials now struggle to maintain that such a long delay (more than 13 years!) without proper regulatory action was indeed required so that they could perform the rigorous EBM-required case/control study, the

results of which are still *not* available but may, as a preliminary assessment, be anticipated as reassuring.

In terms of EBM, the level of proof derived from a case/control study is higher than that stemming from observational epidemiological evidence, isn't it? Thus, this is a perfect illustration of the way EBM principles may be perverted to falsify clear evidence from epidemiological observations.³ [Note: Since the vaccination campaign was performed in such confusion that in a number of instances, immunizations were not recorded in the children's medical dossier, it is easy to anticipate how a the results of a case/control study may be distorted as compared to the simple observation of an epidemic increase of paediatric MS cases following a mass campaign of vaccination in this age group.]

2.2 EBM as a measure of certainty about causation

In medical practice, the concern about “evidence” is implicitly related to a causal demonstration: even if everybody knows (or should know) the gap between statistical and causal inference, the former takes its place in clinical research by being used (rightly or wrongly) as a surrogate of the latter. What would be the point of performing a trial to show that use of drug *A* is associated with a statistically significant improvement if no one were inclined to consider that administration of *A* will *cause* a clinical benefit?

It is another epistemological paradox to hear manufacturers or health agencies so frequently contending that “statistical increase in the frequency of an adverse event *Y* in people receiving a drug *X* cannot be taken as establishing a causal relation between *X* and *Y*.” Yet, the wealth of the pharmaceutical industry is *exclusively* based upon the unchallenged assumption that any (even marginal) statistical increase in the frequency of such or such favourable clinical outcome in people receiving *X* justifies resounding marketing presenting the prescription of *X* as the obvious *cause* of this clinical improvement. For example, recent controversies about the benefits of antidepressants were solely related to the question of whether their use was associated with an improvement as compared to placebo, and never to the causal meaning of such an improvement inasmuch as it would be assessed as *statistically significant versus* placebo.

Contrary to a widespread belief, however, science is not focused on causal certitude—and excessive concern over this issue in medicine might be an indicator, among others, of its problematic status as a scientific practice [76]. As stated by the

¹ Statement from the Medicines and Healthcare Products Regulatory Agency (MHRA): study on safety of MMR vaccine by Geier and Geier - conclusions are not justified. Internet-Document, page (2 pages), 22 May 2003 (REACTIONS accession number 800888954).

² The official launch of the immunization campaign was in Sept. 1994; but as usual in similar situations, paediatric vaccinations started to increase at least from 1993 onwards, driven by the manufacturers' sales and marketing pressures.

³ Since, in post-marketing surveillance, underreporting generally conceals the real fluctuations of frequency in a given disease, it is easy to understand that the only situation where spontaneous/voluntary reporting may have a significance in terms of drug-induced causation is when the baseline incidence of the reported disease is extremely low (which was the case with phocomelias after thalidomide, or with vaginal adenocarcinomas in *young* females after diethylstilbestrol): this is precisely the situation with *paediatric* MS, especially in the youngest children. Amongst others, a worrying indicator of the non-reliability of the surveillance performed by the French Agency is that its experts focused the majority of their attention on reports in young adults (the age group where the background noise with MS is at its peak) [25] while ignoring neurological cases reported in young children—the exact opposite of what should have been done.

anthropologist Lévy-Strauss, who characterized magic as a “theory of causation”, obsession with causal certitude is a feature of the primitive mentality [57].⁴ On the other hand, the scientific mind appears far more relaxed in this regard, attempting to quantify uncertainty (e.g., using statistics) rather relying on misleading explanations (e.g., gods, demons, spirits, mi-asmias) to maintain the illusion of a known causation. Thus, in contrast to primitive mentality, one could say that scientific modernity is characterized by an ability to *tolerate* uncertainty.

As an eloquent precedent, it may be recalled that “uncertainty” was for a long time the defense of tobacco manufacturers, whereas the scientific demonstration of smoking hazards has been the victory of those able to deal with uncertainty (namely: the epidemiologists). Thus, as confirmed by a number of recent drug litigations, the argument on “causation and science” [87] is becoming one of the most dangerous forms of fundamentalism in modern society [36].

Whereas, convergent investigations from *post-mortem* studies show that society is still ready to pay a high price for a medicine which has a rate of significant errors in diagnosis higher than 20% [15], evidence from Courts suggests that the chief protagonists of this kind of medicine—drug manufacturers in particular—claim they should have no liability unless their mistakes are demonstrated with a 100% degree of certainty [21], that is with a zero-level of error.

Yet, although manufacturers, or their supporters, behave as if they were “causation” fundamentalists, when faced with the hazards of their drugs [36], they are clearly more tolerant with uncertainty where the efficacy of their drug products is concerned [54,61]. Thus, in forensic medicine and regulatory pharmaceutical practice, exaggerated concern about “certitude” in causation [87] undermines both patient protection certainty and any expectation or promise of reasonable compensation for the actual victims of toxic hazards, which was certainly not the aim of the legislator.

Faced by this serious societal issue, the medical expert witness should not deceive the judges or the public in mimicking manufacturers with their undue concern about causation, **but simply compare the level of certainty in the case at hand with the level usually considered as “sufficient” by drug specialists or health agencies.**

What does it mean, however, to say that evidence is “sufficient”?

A first criterion for assessing whether a causal relationship in respect of a drug is, or is not, “sufficiently” demonstrated is to assess available evidence for the case at hand as compared with that historically required in prior cases to justify significant regulatory or judicial measures.

- ❖ For example, whereas *hundreds* of case reports have been published in developed countries on the hazards of hepatitis B vaccine [40]—a drug normally administered to people in perfect health in the hope of preventing the extremely rare occurrence of *complicated* hepatitis B—, only *three* published cases (of dubious causality) of he-

patic reactions worldwide were deemed as sufficient by regulatory agencies to justify the withdrawal of tolcapone [19]—a quite useful anti-Parkinson drug prescribed where severely disable patients might have been willing to accept a high level of risk in the hope of even a modest benefit...

- ❖ After the publication of the previously mentioned case/control study by Hernan *et al.* [50], showing a 3.1-fold increase in the risk of multiple sclerosis (MS) related to hepatitis B vaccination, a number of medical experts—like most health agencies including the U.S. CDC [16], the French drug Agency² as well as the WHO [88]—pointed out that the results of this investigation depended on 11 cases only, such sample size being obviously “too small to draw definitive conclusions.”

Regardless of the underlying misconception about the cardinal issue of *statistical power* behind this statement (see section 3.3), let us recall the precedent of a study by Herbst *et al.* [46] which, *for the first time*, showed the risk of inducing adenocarcinoma of the vagina in young females previously exposed *in utero* to the drug known as diethylstilbestrol (DES). Published in 1971, before EBM was available to undermine epidemiological evidence of risk, this case/control study had dramatic consequences since, *within a few weeks*, the FDA once and for all withdrew the indication of DES in pregnant women and a drastic compensation scheme was soon introduced for the benefit of victims, the cost of which was to be paid by the involved manufacturers in proportions corresponding to their market shares.

Yet, the evidence from this investigation—henceforth referred to as a milestone in almost every textbook of epidemiology—rested on *eight* cases (seven of whom were exposed to DES) and 32 controls, as compared to the investigation of Hernan *et al.*, which included 163 cases (11 of whom were exposed to hepatitis B vaccine) and 1,604 controls.

In the same line of thought, it may be remarked that the only investigation on immune markers of a potential toxicity of hepatitis B vaccine which was co-sponsored by a manufacturer and the French regulatory authority [67]—the results of which were, coincidentally, totally reassuring—included a total of 12 subjects (*versus* 1767 in that of Hernan *et al.*) and no control. Yet, I am unaware of any official skepticism regarding this “vaccine supportive” study.

Another criterion that can be taken into consideration is based on the so-called “benefit/risk ratio.” Since, from a regulatory as well as a legal standpoint, the acceptability of a drug depends on its benefit/risk ratio, the level of certainty deemed by manufacturers or regulatory bodies as “sufficient” to guarantee the benefit may be used as an indicator of the level of certainty which should be normally required to justify significant concerns about the risk. Let us consider the following two illustrative cases.

As stated previously, the inclusion (although hypothetical) of health workers in the study by Hernan *et al.* [50] triggered

⁴ Translated in English as *The Savage Mind (Nature of Human Society)*, The University of Chicago Press, 1966

uncompromising skepticism from the WHO experts regarding the extrapolation of safety concerns to “the general population”. In contrast, however, it would be hard to find any expression of concern by the WHO with respect to the uncritical extrapolation of favorable efficacy results of vaccines which, notoriously, were mainly developed in high-endemic countries, with quite specific modes of contamination, risk factors as well as individual reactions to infectious aggressions.

- ❖ One need only read the U.S. *Physician Drug Reference* (PDR) to notice that the duration of the safety studies performed during the development of Engerix B[®] did not exceed *four days*—a classical duration in vaccine investigations. However, this 4-day safety-study duration seems fairly “optimistic,” however, for the assessment of potential long-term adverse reactions such as MS, auto-immune hazards, etc. Obviously, it is not only “optimistic but also illogical⁵, because it is very difficult to understand how—without investigations of a reasonable duration—one might give a vaccine credit for *beneficial* immune effects in the long term (i.e., a presumed durable immunity against hepatitis B virus) without any concern about *deleterious* immune effects (e.g., auto-immune reactions) in the same long term. Incidentally, if the post-marketing surveillance system of vaccines has such “inherent limitations” as those pointed out by the UK regulatory authority (see footnote 1), then it is completely *irresponsible* on the part of the same regulatory bodies to allow wide marketing of these products considering the striking lack of long-term safety data collected by the developing firm during their pre-marketing development. At a minimum, Hippocratic prudence should prevail and the requisite long-term safety data should be collected before allowing unlimited exposure to such drugs.

Thus, whereas regulatory agencies or legal courts should obviously not require a level of evidence regarding safety issues higher than that usually accepted from the manufacturers to register their vaccines, it is plain that this level of evidence is, *at best*, **extremely rare**.

2.3 EBM as a tool to overcome medical controversies

Since its very beginning, the world of sciences has been regulated by the “*publish or perish*” rule and by the Darwinian dynamics of citation by peers. This subtle equilibrium, which is certainly open to criticism but crucial for the epistemological perpetuation of the system, is obviously polluted by those who have the financial power of amplifying the importance of an individual by extensive duplication or selective quotation of his or her results [37].

⁵ Regrettably, scientific thinking does not seem a natural pre-requisite in the field of vaccine development. In a job advertisement issued by Sanofi-Pasteur on April 2007 for “clinical team leaders” in this field (“one of the most exciting sectors of the pharmaceutical industry”), it is clearly stated that although potentially “very useful” (indeed), “an understanding of the clinical aspects of infectious diseases—virology, immunology or microbiology—would be (...) not essential”, especially as compared to other more appropriate qualities such as “excellent presentation and communication skills.”

So, taking it for granted that, for *each* significant paper likely to cast doubt on the benefit/risk of a drug or a class of drugs, the manufacturers with an interest are certainly capable of triggering or influencing a vast number of published refutations (under the form of poorly designed studies, biased editorials, selective reviews, false meta-analyses or pseudo-“consensus conferences”), any serious reviewer must carefully avoid the trap of evidence “by weight”—as manufacturer-driven evidence is obviously far more weighty than that from independent researchers. As a case in point, let us consider once more the issue of neurotoxicity after hepatitis B vaccination.

Until now, no less than six case/control studies on the risk of multiple sclerosis have been performed worldwide, five of them published in peer-reviewed literature [5,23,50,82,83].⁶ Of these six studies, five failed to show a *statistically significant* increase in the relative risk of MS after hepatitis B vaccination, whereas that of Hernan *et al.* [50] found a 3.1-fold increase. As recalled above, this study by Hernan *et al.* was harshly criticized by most national or international health agencies, which used the discrepancy in available results to deny that any reliable evidence of a neurological risk had been proved. Besides the fact that this denial does not explain why the agencies of the same governments did agree, some years before, to include a neurological risk in the vaccines’ summary of product characteristics (SPCs), this mode of reasoning was inadmissible as demonstrated below.

If, during a criminal inquiry, a prosecutor was confronted with six witnesses, where, for the same facts, five of them supported a version A and one supported a version B of the crime, there would be an outcry or a roar of laughter if, without any assessment of the witnesses veracity or reliability, this prosecutor ruled either that: (1) version A is the true one (law of the majority), *or* (2) the inquiry must be terminated due to discrepancies between both versions (law of uncertainty).

Yet, however obviously inappropriate they may appear, both rulings are those of health agencies or most medical experts who, as far as the neurotoxicity of hepatitis B vaccines is concerned, contend either that: (1) overall, evidence is against any potential of neurotoxicity [88], *or* (2) discrepancies in available studies makes it impossible to assert anything reliable on the subject [47].

To return to our example, what would be expected of the prosecutor in such a situation? Simply to assess *in a critical manner* the respective values of these contradictory pieces of evidence: is this witness reliable, has he himself a criminal record, has he any kind of personal interest in version A or version B, did he testify while being under any kind of pressure, etc?

Exactly the same reasoning should be expected from a medical expert requested to assess the neurotoxic potential of hepatitis B vaccines, according to the methodological principles of EBM [72]. Incidentally, it is interesting that the intellectual framework which is now considered as an “epistemological revolution” in medical reasoning—evidence-based medicine—is based upon the word “evidence” which, in English (so far as

⁶ The sixth was only published as an abstract [78].

I know), has a marked judicial connotation. This is not a coincidence, as the frame of mind is exactly the same: To establish an inviolable requirement for a similar critical assessment of all available evidence.

Thus, when we *critically* consider the six available case/control studies with respect to their reliability, one obvious aspect dawns crucial to evaluating evidence. With respect to reliability, five of the six—by a coincidence, the five which failed to demonstrate a neurological risk!—have authors or sponsors with an obvious prejudicing interest in contending that there is no significant problem with the safety of hepatitis B vaccines:

- ❖ One was sponsored by a manufacturer [5],
- ❖ Three were organized and co-authored by members of the French health administration [78,82,83] and
- ❖ One, although regrettably silent on its sponsoring, was co-authored by CDC employees [23].

Thus, it is obvious that, when health agencies such as the French AFSSAPS or the U.S. CDC have spent much energy on the promotion of massive vaccination against hepatitis B, they may be biased against recognizing the devastating consequences of this promotion.⁷ In contrast, the remaining case/control publication, Hernan *et al.*'s study, [50] is the only one with independent financial support and no obvious conflicts of interest. Based on these facts, the reliability of the study by Hernan *et al.* [50] is obviously the less problematic, to say the least.

Although more trivial, another circumstance may be taken into consideration where an assessment of *differential* credibility is concerned. It was apparently missed by most reviewers who took part to the debate on hepatitis B vaccination that Miguel A. Hernan, the first author of the latest study, was also one of the co-authors in the study by Ascherio *et al.* [5] which had opposite conclusions. Considering my previous observation on conflicts of interest interfering with the performance and assessment of epidemiological research on hepatitis vaccines, it is likely that:

- ❖ Critical comments from a independent researcher [50] on one of *his* previous investigations [5] and
- ❖ The reasons he gave to contend that *his* more recent results (those showing an important increase in the relative risk) are more accurate than *his* previous ones (those failing to show an increase in the risk)

are clearly more reliable than those of agencies whose interest in distorting the available evidence is only too obvious.

3. Evidence supporting an association between hepatitis B vaccines and neurotoxicity

3.1 Case reports

Following an evocative time sequence, the first reports of neuropathies after hepatitis B vaccination were published in peer-reviewed literature soon after the introduction of the first of these vaccines, at the very beginning of the 1980s [66,70]. These reports then multiplied at an unusual rate for a preventive measure having a relatively modest population exposure [26,53,70,75,84,85]. Evidence that this vaccine neurotoxicity could include central demyelinating disorders also came fairly quickly. Moreover, the first reports came from authors with no known inclination to exaggerate the safety problems linked to drugs, namely the investigators of a post-marketing study *sponsored by one of the vaccine makers* [75] as well as the Australian regulatory authority [1]. Before long, additional case-reports were published [51,63]. Moreover, a number of more recent case-reports of central demyelinating diseases are available in medical literature [14,56,80,81].

Engerix B[®], the first of the recombinant hepatitis B vaccines, was introduced in Belgium in 1986. As previously discussed, the mention of a risk of vaccine-induced MS was added to this product's SPC in 1993. Considering the fairly long turn-around time to finalize such a regulatory measure, this means that sufficient evidence for this neurological risk was available at least one or two years before the MS risk was added to the product's SPC. Thus, these vaccine-associated MS cases occurred:

- within the short period of about 5 years after the first introduction on the market
- in the context of the relatively small exposure worldwide at this time.

In France, despite a modest overall exposure to the available hepatitis B vaccines at this time (probably no more than 5 million subjects), evidence of an unusual neurological toxicity with these vaccines was deemed sufficient by the French Agency to justify a national investigation of post-marketing surveillance beginning in June 1994 (that is although some 5 years after their effective introduction in the French market). The incidence of severe MS cases (according to the data from the national health insurance system) and the sales of hepatitis B vaccine doses are depicted in Figure 1, which shows a significant time-displaced correlation between the two factors.

Another observation of indisputable significance in post-marketing surveillance was a sharp increase in a disease whose spontaneous occurrence was minuscule before the introduction of the suspected vaccine. As noted previously (see footnote 3), this exactly corresponds to the burst of pediatric MS following the promotion of "universal" vaccination against hepatitis B. Although extremely crude because of the aforementioned information blackout by the investigators in charge of this cohort, it is possible to make a comparison of the incidence of MS in children before "universal" hepatitis B vaccination to the rate after the universal campaign was initiated. This is the case because of a review of MS in children published by the referral hospital [13].

⁷ For example, the last assessment of multiple sclerosis in France found less than 25,000 cases just prior to the start of the campaign of hepatitis B vaccination [22]; some ten years later (according to the same French CME journal), there were more than 60,000 cases [18].

Over a 20-year period (1966-1986), only 19 childhood cases were reported. In comparison, over the 14-year period (1990-2004) for the new cohort, there were 472 cases reported. Without considering the possible prejudice of potentially unsound procedures for case exclusion, this increase corresponds to a nominal 25-fold increase in cases over a period that is 30% shorter in duration. These figures speak for themselves. With the baseline the occurrence of MS in young children being extremely rare (about 1 case per year), this dramatic 25-fold increase during a period where mass vaccination against hepatitis B was the most drastic change in the health environment gives enormous credibility to the hypothesis of neurotoxicity linked to *this* vaccine – and to this vaccine only.

To my knowledge, Aventis-Pasteur, now Sanofi-Aventis, was the only manufacturer of a recombinant hepatitis B vaccine, to publish an assessment of its post-marketing safety data related to central demyelinating diseases [77]. Overall, the methodological credibility of this paper may be indirectly assessed by considering the authors' complete ignorance regarding both the data summarized in Figure 1 and the new epidemics of paediatric MS.

In spite of these suggestive biases, an essential point which the authors seem to have overlooked should be emphasized (see their Table 1): between 1993 and 1998 the annual rate of reporting related to the number of units sold showed a 1 to 200-fold variation (between 0.03 to 6.11 cases per 100,000 doses), which was to be expected and reflected the inherently fluctuating character of the voluntary notification process. However, over the same period of time the annual rate of central demyelinating diseases only showed a 1- to 2-fold variation (between 0.34 and 0.81 cases per 100,000 doses). Such stability is highly significant given how difficult it is to make the diagnosis of such polymorphous diseases. It is all the more remarkable that over the same period of time the number of doses distributed also varied from 1 to 5 (from 1.67 to 8.77 million doses). In other words, the number of demyelinating pathologies *remains remarkably in step* with the number of units sold (which, limited to the vaccine of Aventis-Pasteur, confirms the data summarized in Figure 1). Historically, in drug monitoring, such a clear link between the frequency of a disease and the exposure to a drug (that is, the number of units sold) is considered **as a strong argument in favour of the drug-induced mechanism of the disease under examination**.

Since then, a paper based upon the spontaneous reports received by the French Agency and co-authored by its main experts [25] admitted, *after years of denial*, that the number of *reported* cases of demyelinating disorders in the subjects exposed to hepatitis B vaccine alone was already higher than the number of *expected* disorders in this population. Considering the huge percentage of underreporting usually observed in a country like France (probably less than one report out of 100 drug-induced reactions), which was dramatically boosted in the case-in-point by the sustained efforts of officials to mock any health professional stupid enough to believe in any toxic potential of the hepatitis B vaccines, this official acknowledgment—although coded—strongly supports a pessimistic assessment of the increased incidence of MS after the vaccination

campaign (see footnote 7 and Fig. 1).⁸ Through 25 years of practice in drug safety, this is probably the first time I have seen a situation where the number of *spontaneous/voluntary* reports regarding a disease potentially induced by a drug is higher than the background noise of expected cases (when this background noise was not negligible; see footnote 3).

Likewise, based upon the spontaneous/voluntary reports collected in the U.S., a paper by Geier and Geier shows a clear excess of demyelinating disorders in the VAERS data [30]. Fairly recent, and indubitably more rigorous than the French analysis solely done by rough counting [25], the statistical method used by the U.S. authors was based upon case/control comparisons with another vaccine as control. In a clear response to undue criticism regarding their previous work on the same database (see the preceding discussion of one of their MMR papers [33]), the authors remarked that this method was “similar to that used by the CDC” in a previous investigation.

In its methodological simplicity, this body of observational evidence can be summarized, in what I have named *Epidemiology for Dummies* (in reference to the well-known series of books on computing), as: An elementary experiment in epidemiology can be carried out by anybody to get an idea of the scale of the health disaster caused by a campaign of hepatitis B vaccination.

In France, just prior to this campaign, it was estimated that less than 25,000 persons suffered from MS [22]; given a total of more than 100,000 general practitioners (according to the *Ordre National des Médecins*), this means that a number of doctors—and this was true for myself—had *never*, in their professional lives, met a patient with MS. Nowadays however, at all social or professional levels, anybody—health professional or not—knows of *several* cases of MS in people around him/her. I am less informed on the situation abroad, but U.S. and U.K. colleagues have consistently told me about an overall perception of increasing frequency of MS, especially in those occupations exposed to this vaccination (e.g., nurses or medical students).

Another epidemiological test “for the layman” is also quite evocative: Something you only observe under very specific conditions is not a “background noise” but a highly suggestive **signal**. Yet, from the very beginning the French health authorities have maintained that most cases of MS notified after vaccination were simply the «background noise» that could be expected in an exposed population including a large number of young women (including nurses, and nursing auxiliaries)⁹ given the natural distribution of the prevalence of this disease

⁸ An additional factor contributed to an unusually high rate of underreporting. Since, in many instances, the clinical manifestation of vaccine-induced MS may be quite late (some years after immunization), it is not a natural reflex for the attending physician to connect a delayed-onset disease, like MS, with a drug that was administered some years before.

⁹ Prior to the mass campaign, under the influence of the self-interested manufacturers, hepatitis B vaccination was made mandatory in health occupations. As it happens, this regulation was not only unevenly applied but also applied far more stringently to lower socio-economical groups (e.g., nurses, nursing auxiliaries, cleaning ladies) with a marked predominance of women.

(i.e., a peak in females around the age of 30). However, I obtained from one of my pharmaceutical clients a periodic safety update report on an oral contraceptive which covered a not insignificant sample of 70 million women-years. It was easy to verify that it contained *not one single notification* of MS. It is difficult to understand how a “background noise” should produce thousands of MS cases in a general population vaccinated against hepatitis B (including males, infants, children and elderly people) and *not even one report* after an exposure about 250 times greater¹⁰ (computed as person-day of treatment) in a population of young females where spontaneous MS reaches its peak. Obviously, in terms of “*Epidemiology for Dummies*,” these vaccine-related MS cases are not a “background noise” but a highly suggestive **signal**.

3.2 Additional evidence from observation

Although I have not yet had the opportunity to publish these observations, in a number of cases of post-vaccine MS I had to assess, I retrospectively found a significant worsening of initial symptoms when vaccine boosters were administered. Technically these outcomes are:

- ❖ Referred to as “positive rechallenge” and
- ❖ Usually considered as strongly evocative of a drug causal relationship

by those who specialize in the study of drug-induced diseases.

In a more systematic investigation, positive re-challenge, or significant exacerbation of symptoms following immunization, was also reported by Geier and Geier in another analysis from the VAERS [32].

3.3 Case/control studies

Contrary to what was wrongly echoed by casual reviewers and as rightly pointed out for the first time by Ascherio *et al.* [5], it is not true that the 3 case/control studies [78,82,83] performed at the request of the French Agency failed to demonstrate an increase in the post-vaccine risk of demyelinating disease. Factually, they failed to demonstrate a *statistically significant* increase, although *each of them* did find an increase in the relative risk. For example, the first one [83] had a 0.30 power to detect a 2-fold increase in the risk (this means that if the risk of demyelinating disorder was no less than *doubled* by hepatitis B vaccination, the study had more than 2 chances in 3 *to miss it*...) However, this lack of statistical significance, *far from demonstrating anything about the absence of a vaccine-induced risk*, was simply an *expected* consequence of a recurrent lack of statistical power in the investigations performed by the French Agency.

At the risk of appearing trivial, a few words on the basic notion of statistical power may be useful to clarify the issue, as the overwhelming silence on this striking recurrent weakness of the French case/control studies is staggering, and suggests, in most reviews, a veneer of statistical culture with poor grasp of its principles. Consider the following coin-toss example:

If, after tossing a coin 4 times, I obtain 75% of heads (3 heads/1 tails), nobody will conclude that the coin is dis-

torted. But if I obtain *the same* result (75% of heads) after tossing the same coin 400,000 times (300,000 H/100,000 T), everybody will agree that there is a problem with the coin. Yet, “statistical power” is precisely the difference between these two experiments, that is the means used to discriminate between the simple effects of *chance* on the one hand (3 H/1 T) and those of a real *defect* in the way the coin was manufactured (300,000 H/100,000 T) on the other hand.

Translated into terms of clinical or epidemiological research, the “statistical power” depends on the means the sponsor is willing to invest, especially as regards the number of included patients (which, by the way, is not the same parameter as the number of “cases” supposedly unacceptably small in the Hernan *et al.* study [50], discussed previously). Therefore, to remain with the same metaphor, the French Agency and its experts keep on claiming “nobody is stupid enough to contend that 3 heads/1 tail would mean that the coin is defective” (which is quite true); while ignoring the reality that they have *knowingly* not conducted the requisite studies required to determine the cause of the results obtained for the few cases examined, or, for the coin example, the reality that far more than four tosses are required to show whether or not the coin is actually “defective.” On the other hand, this situation gives additional support to my previous comments about the problematic reliability of the French Agency as far as the assessment of hepatitis B vaccines is concerned. Furthermore, the failure of one [78] of the three French studies to be fully published in a peer-reviewed medical journal is, again, another worrying indicator of its lack of methodological quality.

In the case of the study conducted under the sponsorship of a manufacturer (Ascherio *et al.* [5]), the major problems found in the published article were discussed in correspondence submitted by multiple authors [8,44,45,79]. Criticizing the procedures used for case exclusion, one of them asserted that the odds ratios should have been 1.9 (95-percent confidence interval: 1.1 to 3.3) rather than the published value of 0.7 and concluded that U.S. data were consistent with an “epidemiologically important increase in risk” [8].

In the same line of thought, M. Hernan (who was a co-author in the study by Ascherio *et al.* [5]) subsequently emphasized that the design used in the Ascherio *et al.* study might have downwardly biased odd ratios [50]. Likewise, Gout, a French neurologist who also took part in the abovementioned post-publication controversy in the NEJM columns [44], correctly remarked that Ascherio *et al.* only considered patients with a diagnosis of MS, “so they have excluded all possible central demyelinating events which can be either a first MS attack or a limited form of acute disseminated encephalomyelitis.” [43] In addition, previous work by Ascherio *et al.*’s team [48] suggested that the incidence of MS was quite heterogeneous in both the cohorts they included. This marked heterogeneity is likely to have masked a modest increase in relative risk, which may have been, nonetheless, large enough to account for a major health problem after exposure of 30 million people. But, although unnoticed up till now, the main objection may be that a cohort of nurses should have been the last one would have thought of in order to investigate the neurological risk

¹⁰ Under the credible hypothesis that the French vaccinee received, on average, between 3 and 4 doses of the hepatitis B vaccine.

from the HB vaccine. Indeed, as such immunization is more or less an occupational obligation, it was perfectly expectable that those with any neurological history or risk factor would be less likely to receive this vaccination; this was confirmed in the authors' Table 1, which showed that the percentage of hepatitis B vaccination history was only 43% in women with MS as compared to 60% in controls. In other words, there was a clear bias accounting for greater exposure to the investigated risk factor *in the controls* as compared to the cases. Finally, the overall percentage (40-60%) of HB vaccination in this population of U.S. nurses seemed rather low (and, in personal communications, experienced U.S. colleagues confirmed this point), raising doubts about the accuracy of the assessment of exposure.

The fifth study [23] was performed by the American CDC and co-signed by authors whose previous involvement in favour of hepatitis B vaccination is notorious. In contrast with the usual requirements in medical publishing, they remained silent on the financial sponsoring of their investigation. The final paper was succinct on the methodology used, as well as on the issues of statistical power. Although their final presentation is a superb model of how to go about depriving any reader the slightest opportunity for independent data cross-checking, it remains possible (Table 1) to see that the cases included *had a more frequent family history of demyelinating and autoimmune diseases*, an astounding bias likely in itself to ruin any further analysis (inasmuch as the cases were, *for these reasons*, less likely to be vaccinated than the controls). On the other hand, the time windows retained to analyze the occurrence of a neuropathy after vaccination (< 1 year, 1-5 years, > 5 years) were absurd: as they did not correspond to anything medically sound (e.g., < 1 year, < 5 years, < 10 years), the only explanation is that this unusual time division is probably an attempt to undermine the epidemiological evidence by inappropriate time-division. Finally, in spite of all these methodological weaknesses and as rightly pointed out by Hernan *et al.* [50], the risk of optic neuritis or MS still revealed a nonsignificant increase 1 to 5 years after vaccination against hepatitis B—i.e., within the less incongruous time window (inasmuch as the results from 0 to 5 years after vaccination were inexplicably missing, although this time window was obviously the most expected from a clinical standpoint.)

Finally, the sixth study [50]—coincidentally, the only one to show a clear increase in the post-vaccinal risk—is also the only one whose financing is above suspicion and/or whose authors are without previous involvement in hepatitis B vaccine promotion. It is also the only one not to display obvious methodological flaws or medical absurdities, e.g., concerning the time windows under consideration or the assessment of cases. This high quality is further corroborated, in contrast, by the mediocrity—to remain polite—of the critical comments directed against this investigation, examples of which were discussed previously. Moreover, I have been unable to find any critical comment that is likely to invalidate the conclusions, or undermine the significance, of this study. In addition, it is important to note that this investigation, *performed by an U.S. team on a database from the UK*, was a harsh blow to the continual, though unsubstantiated, comments by most health agencies, including the U.S.

CDC, the WHO and the French Agency, that the idea of a specific toxicity with hepatitis B vaccine occurred only in France and, thereby, corresponded to a new “French paradox.”

Beyond the preceding demonstration that the Hernan *et al.* study was by far the only one to offer consistent indicators of overall—methodological and medical—reliability, a crucial statistical issue appears to have been missed since the publication of this latest investigation. Actually, as discussed previously, *in one way or another*, each of these six case/control studies showed some *increase* in the relative risk of neuropathy after vaccination, five of them only failed to find a relative risk that was statistically significant (although, according to one reasonable recalculation [8], the increase from the Ascherio *et al.* study [5] did achieve statistical significance).

Yet, if the risk of inducing demyelinating neuropathy after vaccination were zero (i.e., the relative risk was 1.0), the theoretical probability of showing an increase in risk would have been 50%—exactly the same as the probability of showing a decrease in risk. To come back to the example of the coin, if the coin was not defective, the theoretical probability of getting more heads after six tosses would be exactly the same as the probability of getting more tails. However, if the coin were perfect, the probability of getting six heads after six tosses (i.e., of always observing an increase in risk) would only be 1/64, *which is highly significant from a statistical point of view*.

In terms of the six “risk” studies, if hepatitis B vaccines left unaltered the risk of developing a central demyelinating neuropathy after immunization, the theoretical probability of having studies suggesting an increase in risk would have been 3/6 studies, and certainly not 6/6.

3.4 Additional studies

Frequently quoted as evidencing a lack of MS risk, a study by Zipp *et al.* [93] has all the appearances of a “fake”: the successive data were inconsistent, the final publication carries no trace of a documented support by a manufacturer, and the figures given in Table 2 are obviously false. Moreover, including 65% of children in the population of a study aimed at studying a disease, MS, *which is almost never a paediatric disease*, looks more like a joke than an epidemiological investigation. In spite of its clear bias towards studies failing to show any increase in post-vaccine risk, the French Agency initially assessed this study as deserving to be “discarded” due to its to blatant inconsistencies (Feb 2000 communiqué).

In the same communiqué, the methodological weaknesses of Sadovnick and Scheifele's paper [73] were also correctly emphasised by the French Agency. However, the final assessment that, *in spite of this*, their conclusions were “acceptable” was more likely to correspond to a Freudian slip (any conclusion confirming the vaccines safety is “acceptable”) than to any sound evidence-based reasoning. Again, this telling admission adds to the evidence supporting my previous comments on the problematic reliability of the French Agency assessments as far as the safety of hepatitis B vaccines is concerned. In fact, my Figure 1, although related to different data, illustrates one of the main biases likely to distort Sadovnick and Scheifele's analysis, which was based upon a comparison between the situations before and after a vaccination program was implemented in a

region of Canada. In France, although launched in Sept 1994, the “universal” vaccination campaign was preceded by a clear increase in exposure. From the data given by Sadovnick and Scheifele, it is not possible to decide whether the implementation of a vaccination program was, or was not, associated with an actual increase in exposure since any such an implementation may initially simply correspond to an official acknowledgment of changing practices and not any significant increase in exposure. Additional weaknesses of this study were appropriately pointed out in a recent paper by Hernan and Jick [47].

3.5 Evidence supporting biological plausibility

In a recent paper [17], I summarized evidence supporting biological plausibility for hepatitis B vaccine inducing neurological disorders, including a impressive review by Faure [24] and a very interesting experiment by Poirriez about a case of myelitis [68] which, in parallel and independently, I was requested to assess.

Since then, additional papers have added to the evidence showing biological plausibility for a potential of hepatitis B vaccines to induce auto-immune reactions [12,58]: for example, one of them [12] suggested that as many as 60% of hepatitis B recipients may develop transient antibodies that are reactive to both the hepatitis B surface antigen and myelin oligodendrocyte glycoprotein.

It has to be emphasized that, quite early in some cases, warnings were issued by eminent scholars about a predictable potential of any hepatitis B vaccine to induce autoimmune hazards [52,94].

Although limited in scope as the regulatory authority always refused its financial support for such an investigation, a preliminary French investigation suggested an overrepresentation of HLA-DR 15 (46%) and HLA-DQ 6 (59%) in 26 and 22 patients, respectively, suffering from MS after hepatitis B vaccination, as compared to expected frequencies of about 20% and 40% respectively (Le Houezec, personal communication).

Finally, if confirmed by others, the personal observation of two American health professionals who worked in the same establishment and who also developed MS after being vaccinated at the same time (most probably from the same batch) could add credibility to Faure’s hypothesis regarding the risk of MS and batch contamination by minute amounts of hepatitis B virus polymerase [24]. This is the case because, however tiny this contamination might be, such contamination would be more, or less, marked depending on the level present in the batch under consideration.

3.6 Summary of the epidemiological evidence

Although distinct and performed in a completely independent manner, at least 3 investigations strongly support an unusual potential of hepatitis B vaccines to induce central demyelinating disorders. Ranked by decreasing level of evidence, these are:

- ❖ The case/control study performed by Hernan *et al.* [50] within the UK General Practice Research Database (GPRD), a well-known epidemiological source extensively used in the field of drug safety, the relevance of which was never seriously challenged by health authori-

ties so long it was used by the same team to give reassuring conclusions on vaccines hazards [10,11,55];

- ❖ The case/control study performed by Geier and Geier [30] within the U.S. VAERS database, the main tool normally used by the FDA to offer the U.S. citizen—children and newborns included—a long-term guarantee regarding the hazards of extensively administered vaccines for which evidence of safety from development does not extend beyond a few days of follow-up. As with the GPRD database, the relevance or reliability of the VAERS was never challenged by health authorities as long as the study findings could be used to “reassure the general public concerning the safety of a new vaccine;” [92]
- ❖ My own observational record of a significant surge in MS frequency [38,40], confirmed by leading French experts [18,22], whose association with exposure to hepatitis B vaccines cannot be denied (Figure 1).

It is of paramount importance to understand that, even considered *separately* from each other, each of these pieces of evidence would be, in itself, “sufficient” to draw definitive conclusions, based on the epistemological framework of *comparative* evidence which underlines the present review. For example:

- ❖ The methodological robustness of Hernan *et al.*’s investigation [50] is at least comparable to that of Herbst *et al.* [46] which, for more than 30 years now, has been viewed as a milestone in pharmaco-epidemiology and the regulatory or judicial correlates of which have been unambiguous; on the other hand, epidemiological evidence stemming from the former study is also far above that leading to brutal withdrawal of dexfenfluramine the valvular hazards of which, to the best of my knowledge, relied on no formal investigation at the time of withdrawal.
- ❖ The reach and significance of the analysis performed by Geier and Geier [30] based upon spontaneous reports related to hepatitis B hazards go far beyond that normally deemed as acceptable to withdraw the anti-Parkinson’s drug tolcapone [19] (see the preceding discussions); evidence from spontaneous reports in this regard is also much more consistent than that, say, which led to the withdrawal of cerivastatin in Aug, 2001.¹¹
- ❖ My own interpretation of the observed surge in MS following “universal” vaccination, combined with a sharp increase of pediatric MS in an age group where the expected frequency of this disease was negligible, is consistent with major steps in the history of post-marketing surveillance, exemplified by the thalidomide [59,86], the aminorex [74,89] and the practolol precedents [35,65].

¹¹ Since I was also commissioned as medical expert witness within the criminal inquiry opened into the hazards associated with cerivastatin, I can claim a minimal credibility in my respective assessment of the evidence corresponding to both stories.

Regarding frequencies, concern about the occurrence in the sole country of France of *hundreds* of reports about severe neurological complications occurring in people previously in perfect health is implicitly backed by the person chief responsible for the French epidemiological assessment of the potential hazards ascribable to hepatitis B vaccines who, just when the French universal campaign was launched, co-authored a paper contending that “receipt of more than *three* reports [worldwide, with any drug potentially targeted to sick people] is highly unlikely to be coincidental and constitutes an important signal requiring further investigations” [9].

The relevance of this assertion for drug monitoring, in general, and subsequent regulation is confirmed by the previous example of tolcapone, where ten spontaneous reports worldwide (three of them published) were deemed as sufficient to withdraw this drug although it was targeted to quite severely disabled patients.

Regarding causality, my concerns about the role of vaccines are also backed up by another paper co-authored (again: just prior to the vaccination campaign...) by the person responsible for the post-marketing surveillance of one of the hepatitis B vaccines available in France, the manufacturer of which subsequently published that paper which ignored the relevance of the dozens of MS reports it received after the administration of its vaccine [77]: “However, to reach causality certitude is the exception. When an adverse event shows itself in a repeatedly serious form, it is strongly advisable not to waste undue time in pointless or endless investigation. It may happen, therefore, that a drug is withdrawn more on a basis of high suspicion than of certainty” [6] (*italicization* added for emphasis). Once again, this resolute statement, the scope of which includes drugs administered to very ill patients, must certainly apply to teenagers in perfect health or to innocent newborns with a negligible risk of contracting a severe hepatitis B infection.

Then, though each of the 3 previous pieces of evidence would be, *in itself*, sufficient to draw a conclusion, their intrinsic demonstrative power is emphatically reinforced by:

- ❖ Their striking convergence;
- ❖ Their association with multiple additional observations (published case reports, positive rechallenges); and
- ❖ Consistent evidence of biological plausibility.

To sum up the epidemiological evidence, there is no room for doubt concerning an unusual potential of hepatitis B vaccines to induce central demyelinating disorders such as MS. The *objective* level of evidence in this regard is clearly far higher than the level of evidence that was:

- ❖ Previously accepted in situations requiring urgent regulatory measures or crucial decisions on compensation, as was the case for drugs such as thalidomide, aminorex, diethylstilbestrol, practolol, dexfenfluramine, and cerivastatin;
- ❖ Accepted by national and international authorities as “sufficient” to register hepatitis B vaccines as safe and beneficial (in spite of major doubts about the frequency,

and the duration, of immune response, the inventory of which is outside of the scope of this paper).

4. Towards a characterization of money-driven medical controversies?

As everybody knows, sustained though it was, the conjecture about Fermat’s last theorem stimulated the highest minds during centuries and contributed to major achievements in mathematics. But in medicine, the dynamics of controversies is the exact opposite, and, sadly, at odds with the fundamental principles of science.

A disturbing illustration of this situation is offered by the striking similarity in the situations of those who most contributed to demonstrate the hazards of hepatitis B vaccines, regarding two key points of the dynamics of sciences: *the way they were published*, on the one hand, and *the refutations* they triggered on the other.

As far as the publication process is concerned, it suffices to:

- Compare the unusual delay between the preliminary [49] and the final publication by Hernan *et al.* [50],
- Notice that the journal which accepted the latter was in no way in the forefront of the controversy; and
- Retrospectively reconstruct the difficulties met by the team in publishing the remarkable study they achieved.

But when, *on a given topic*, editors have taken responsibility for adding to scientific confusion by publishing investigations of deplorable credibility [93], of very poor design [73] as well as blatantly biased editorials [7,34] or reviews [91], one wonders on what rational basis valuable contributions on the same subject might be rejected. The same holds true for the publications by Geier and Geier. Apart from personal communication confirming the fact, it is plain that their major publications did not appear in those journals which most contributed to undermining the credibility of serious concerns about the safety of hepatitis B vaccines. Finally, although the majority of my observations concerned the French situation, I have encountered the sustained impossibility of publishing these observations in French medical journals. For example, the figures from the health insurance were only published in international journals [17,38,40], and never in a French one. I have also related [38] the way that, for a paper that was accepted up to the normally irreversible process of the corrections of proofs (and after attribution of a d.o.i. for my paper), I was informed by *Vaccine’s* editor that, based on “advice” he received, my contribution was to be rejected. Since that time, I have been awaiting additional comments concerning who was responsible for this “advice”, while noticing, as potentially relevant, that my name is exactly the same as another Marc Girard, who is a famous champion of vaccination and a regular contributor to the journal *Vaccine*.

As far as the process of refutation is concerned, I have already documented the excruciating mediocrity of the criticism directed toward the study by Hernan *et al.* [50]. To some extent, as noted previously, the failure of its detractors to come up with relevant criticism of this investigation is an indirect, but strong, indicator of this study’s scientific quality.

Regarding the work by Geier and Geier, their detractors' tragic-comic reversal of opinion about the reliability of the VAERS database speaks for itself. Moreover, it is even more depressing that unsupportable reversal of opinion was supported by some of the highest—and most renowned—experts from the federal health agencies.

Finally, the criticism related to my own observational work goes far beyond scientific inconsistencies to the point that the criticism proffered is a knowingly deliberate lie. As it happens, having ignored the trends displayed in Figure 1 and 2 for years, the French regulatory authority waited for me to mention them in my reports before challenging their significance on the grounds that, concerning a scheme of 100% reimbursement by the national health insurance, they only reflected the need for people suffering from MS to be registered in order to benefit from the new, but very expensive treatment by interferon beta. This knowingly false criticism was formally introduced in an expert report commended to the DGS (the French CDC) under the supervision of Prof. Dartigues (Feb. 2002), and then reiterated in the Public Hearing (Paris – Nov. 2004) triggered by the final publication of the Hernan *et al.* study [50]. This fabrication is now quoted by Courts to nonsuit plaintiffs filing claims for compensation after post-vaccine injury. However, this article is the first to establish that this denial was simply an obvious lie. As illustrated by Figure 3, which summarizes the French sales of interferon beta, it is plain that, for interferon products whose sales first began in 1996 and started to increase significantly within the period 1997-1998 and after, the increase in their usage certainly cannot account for an increasing trend in MS cases which is apparent even in the data prior to 1994 (see Fig. 1¹²), more than 2 years before the sales of interferon-beta began (see Fig. 3).

The involvement of the French health authority in such an indisputable manipulation is a stunning confirmation (if any is still needed) of the scale of the hepatitis B health catastrophe in France as well as of its determinism. Another convincing example was the “International Consensus Conference” (Paris, Sept. 10-11, 2003) which proved to become a pivotal element in the circular game of mutual reassurance being played by the French Agency, the U.S. CDC and the WHO (if nothing wrong was detected in France, there is no reason for concern in the U.S., and if these two countries of high exposure agree that the vaccine is safe, this may be extrapolated worldwide, hence to France—and to the U.S...) *None* of those investigators who documented safety concerns on the hepatitis B vaccines was ever informed about this conference, which was organized in the greatest secrecy and where, at length, the preliminary results from Hernan *et al.* [49] were presented by... R. Chen who co-authored the antagonistic study by DeStefano *et al.* [23]; whereas, the results of Geier and Geier [28,29,31], based upon spontaneous reporting, were presented by those governmental

French experts who, for years, had continually labored to deny evidence of a dramatic signal (Fig. 1). My own investigations were simply ignored, although the very idea of a “consensus conference” emerged as a direct response to a media scandal triggered by leaks from my reports commissioned by the criminal inquiry mentioned in the “Introduction.” Evidence of rigging was so blatant with this conference that, in an action unusual for a scientist, I sent a note to the Prosecutor of Paris to warn him about the criminal potential of too predictable conclusions in terms of public health.

In her recent book [4], M. Angell has convincingly showed that overall, pharmaceutical firms are not concerned with performing science. However, the hepatitis B story reveals that drug makers (and their traditional supporters in health agencies) go far beyond a simple disinterest for the scientific game, since, as this discussion has proven, they are knowingly *corrupting* medical science's most sacred rules. In the field of pharmacy, the *publication process* has been restricted by their censure while their *refutation* of adverse findings ranges from nonsense to fabricated studies and knowing lies.

5. Conclusion: Controversy versus evidence

Understood as a quest for the “best evidence”, EBM may be a dangerous threat for the scientific status of medicine, as it is currently being used to: (a) justify arbitrary assessments of available investigations as “not best enough” and (b) to stimulate endless expectations about new results supposed to be better than those already at hand. However, as demonstrated by the hepatitis B story:

- ❖ Newer is not necessarily better and
- ❖ Those who have unlimited means to produce new contributions also have the power to:
 - Drown evidence into false controversies and
 - Severely restrict the potential for any individual to master the essentials of a given set of problems.

With all due respect to their impressive achievements in the field of epidemiology and their indisputable intellectual integrity, it is a pity to read Hernan and his co-workers contending placidly that “any decision concerning hepatitis B vaccination needs to take into account the large benefits derived from the prevention of a common and potentially lethal infection” [50], or supporting the “conclusion that there is not enough evidence to establish the existence of an increased risk associated with hepatitis B in adults” [47]. This is the sad state of affairs for the hepatitis B vaccine because:

- ❖ Besides ample evidence casting serious doubts on the rates of responders, with respect to the relevance of the immune response in actually protecting against the disease as well as the duration of the response [60],
- ❖ *overall* statements of the supposed benefits of the hepatitis B vaccines are simply devoid of epidemiologic meaning. Although malnutrition is undoubtedly a major health problem worldwide, nobody thinks this is a reason to incite U.S. teenagers to become closer to their fridge. Where is the difference with the hepatitis B?

¹² The data in Figure 1 includes only “severe” MS cases recognised by the French national health insurance program. This means that, to interpret this data in terms of the date of first symptoms, the upper curve (that of MS) must be shifted to the left, which clearly underscores the reality that the beginning of the MS epidemic even predates the date when sale of interferon-beta was approved.

Supporting this lack of sound medical science, I have published the first translation of an interview where, with amazing ingenuousness, a salesman for the manufacturer of the Engerix B vaccine claimed: “*We started increasing the awareness of the European Experts of the World Health Organization about hepatitis B in 1988*” [39]. It is good news for nobody that “experts” of the WHO need drug makers’ salesmen to become “aware” of significant health problems all over the world...

- ❖ Even in the face of words of caution, the persistence in Hernan *et al.*’s references to the study by Zipp *et al.* [93] some six years after the French Agency (apparently the only agency to have had access to the inconsistent unpublished versions of this investigation), although not inclined to criticize studies favorable to the hepatitis vaccines, unambiguously acknowledged that the Zipp *et al.* study should be “discarded” is an eloquent confirmation of the dynamics of controversies on drugs. The picture is not likely to become clearer if “additional” data are still required and it proves impossible to discard those studies which do not meet elementary standards of scientific integrity (it was clear from the communiqué of the French Agency that this study was performed by the manufacturers, even though no acknowledgment of their support was made in the final publication).

As illustrated by the case in point, this power of drug makers to create undue controversies by their unlimited potential to stimulate the production of papers devoid of any value is a complete perversion of the cardinal process of publication in sciences [41]. As such, it represents a major threat for the scientific status of medicine and calls for an proportionate reaction from the medical community. In addition, tolerating—or even fuelling—controversy while going on to prescribe is a dangerous betrayal of our fundamental Hippocratic principle.

While our U.S. colleagues are observing an unprecedented drop in the frequency of breast cancer following a recent decrease in women’s exposure to hormone replacement therapy [27], the present paper has shown that, up until now, the French governmental agencies have been content to use simple lies or other dissimulations to account for more than a doubling of the MS cases in young adults or for an outrageous outbreak of MS epidemics among small children. It is time, therefore, to consider seriously the impact of “controversial” drugs in terms of morbidity or mortality—even in populations supposedly at risk.

As indicated in the “Introduction,” I have probably spent some 5,000 hours studying the pharmaco-epidemiology of hepatitis B vaccines. Moreover, though this acknowledged involvement in the vaccines sector attracts questions or requests from colleagues or patients all over the world almost every day, I must confess that I feel completely unable to give authorized advice even on very closed issues, such as the MMR or mercury controversy. This concerning admission is another indicator of the way drug makers, in spite of their documented disinterest for science [4], have become past masters at perverting the game of Science by drowning evidence in an unending flood of self-serving controversy.

The moral is quite simple: each time we acknowledge that “evidence is controversial”, we celebrate the victory of those whose advantage is to hide evidence behind artificial controversy fuelled by the power of money.

Finally, the moral of this moral is that, in any event where “controversy” is unavoidable, remember Hippocrates—and, in the meantime, avoid prescribing any of those drugs that are involved in any such “controversy.” This will cool the zeal of drug makers (and their experts) for the endless production of inadequate or confusing data.

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Competing interest

Dr. Girard works as an independent consultant for the pharmaceutical industry, including (at least until recently) vaccine manufacturers and a number of their competitors.

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Figure 1. Sales of hepatitis B vaccine in France as compared to the frequency of severe multiple sclerosis, 1982-2000 (Data from the French health-insurance system)

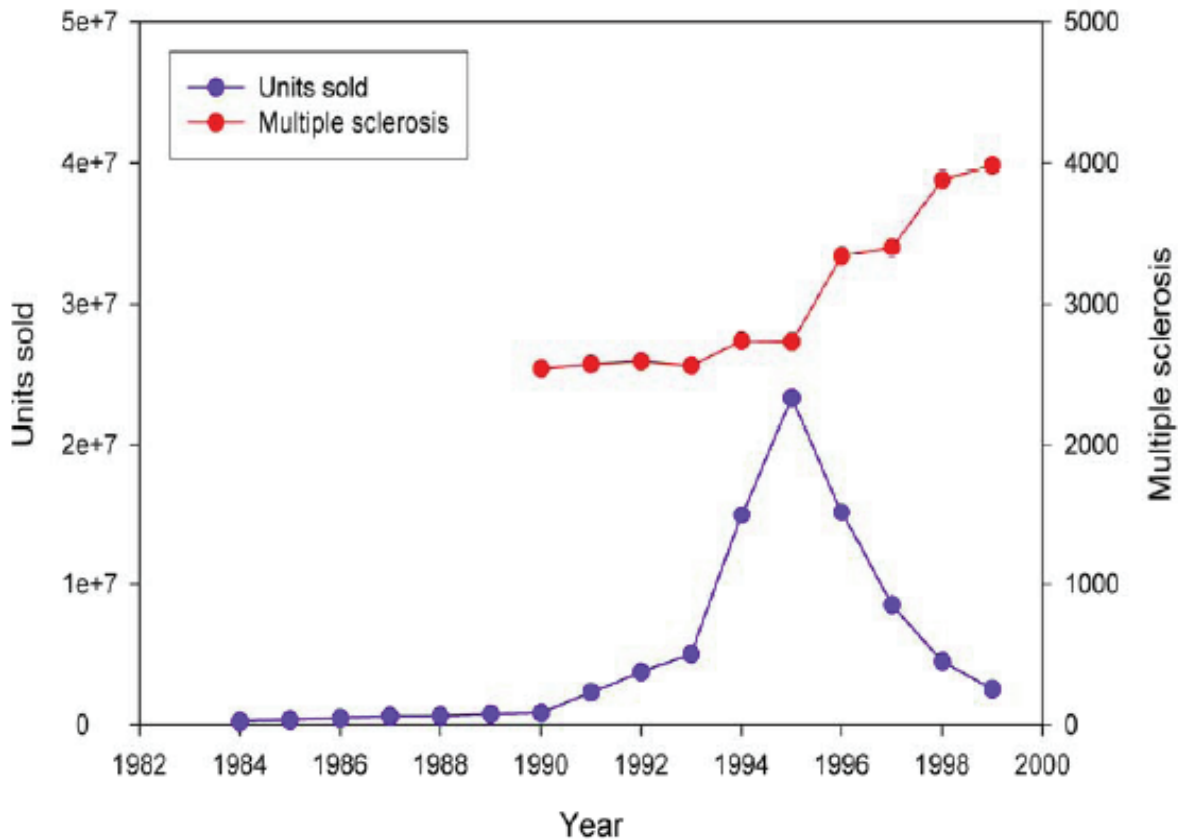


Figure 2. Number of cases of neuromuscular diseases and severe multiple sclerosis in France between 1990 and 2001. (Data from French health-insurance system.) The red arrow indicates the start of the “universal” vaccination campaign (Sept. 1994).

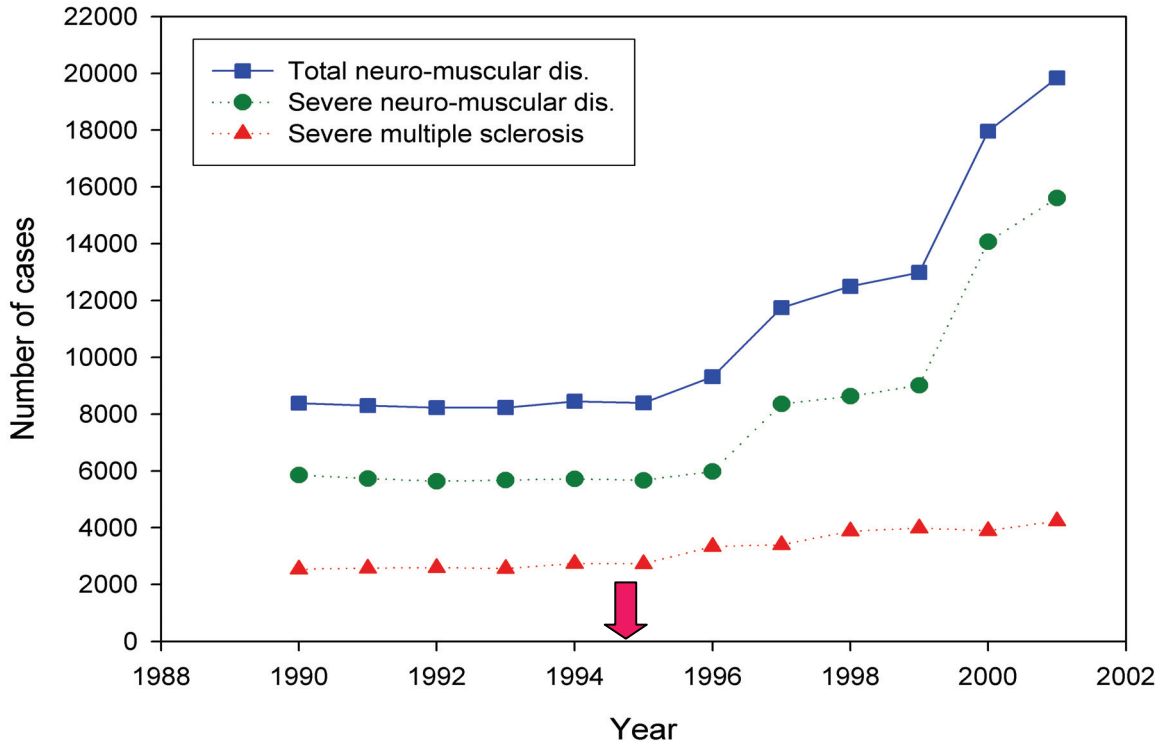


Figure 3. Sales of interferon-beta in France between 1995 and 2004. (Data from GERS)

