

# HEPATITIS B UNIVERSAL VACCINATION: LEARNING FROM FRENCH EXPERIENCE

Marc Girard  
1 bd de la République  
78000 Versailles (France)

**Purpose:** This update has been written for the numerous prescribers and health professionals who are logically disturbed by a growing discrepancy between the recommendation they are receiving of protecting public health by hepatitis B vaccination and an accumulation of alarming data on the hazards of this prophylaxis.

**Topics and key-points:** Focused on a recent case/controls investigation which showed a 3-fold increase in the relative risk of multiple sclerosis after hepatitis B vaccine, this review was made upon systematic referencing from published or public data. It was reminded that a benefit/risk assessment is a pre-requisite for any treatment: however, even French officials admit that the epidemiology of hepatitis B is still not known in our country; it is easy to demonstrate that no risks analysis was performed prior to the vaccine campaign, in spite of the huge increase in exposition (this situation being notoriously recognised as carrying important risks, qualitative as well as quantitative). Difficult to criticise on methodological grounds, the investigation by Hernan et al is the last piece of an impressive body of evidence which suggests that hepatitis B vaccines may be characterised by the *frequency*, the *variety* and the *seriousness* of their hazards.

**Perspective and projects:** Performed by an American team on a database from the UK, Hernan et al's study challenges those experts who claimed that the idea of a specific toxicity with hepatitis B vaccine would be a new "French paradox". In contrast, it reinforces those who complain that vaccinology is surprisingly far from the requirements of evidence-based medicine and suggests that it is urgent to re-assess in a rigorous way the benefit/risk of hepatitis B vaccine.

KEY-WORDS: risk/benefit; hepatitis B; prevention; prudence (Hippocratic principle of); multiple sclerosis; vaccination

In view of the seriousness of the situation, the title of the present article is deliberately indulgent. In fact when the vaccination campaign against hepatitis B was launched by M. Douste-Blazy in September 1994, any drug or any public health specialist could have presented the Minister with three objections based on common sense: what benefit, what risk (especially taking into account the change of scale, i.e. changing from a small, supposedly more exposed sub-population to the overall population, including children and babies) and what cost at a time when the finances of our Social Security system were already far from flourishing?

Experience has shown that the prophylactic hysteria that then seized our country did not leave any space for any professional amendment, even in the medical press. After the journal *Prescrire* had granted hepatitis B vaccine its "Golden Pill" award in 1981, it simply would have been sacrilege to question the risk/benefit ratio of this prophylaxis...

So what we mean by a "indulgent" title is that we have deliberately chosen to overlook the fact that in France we are still at the evaluation stage of the procedure. As we will demonstrate below, all the investigations which should normally have preceded a campaign on such a scale have purely and simply been omitted.

What we have today is a study [1] that documents a neurological risk compatible with tens of thousands of iatrogenous victims in our country. This study is no thunderbolt in a cloudless sky but only comes as confirmation of an unusual body of data which, although extremely alarming, has so far surprisingly been ignored. As the authors have admitted to us, publication of their results was postponed for months which, far from illustrating the liveliness of the scientific debate, points to the forces which can at the highest level influence the production and the circulation of medical and pharmaceutical information. Bearing all this in mind it was urgent therefore to produce a synthesis which could provide our colleagues with the basic information they need in their practice and which they often could not find up till now.

## 1. Methodological preliminaries: soft data and conflicts of interest

Contrary to "hard" data in physics, chemistry or, as is often the case in biology, it is generally recognised that the data in clinical research is "soft", that is it is not factual and its interpretation is not obvious. **As long as an expert has not intervened to interpret it, the data in clinical research cannot be exploited, one might almost say it has no reality.** Example.

The fact that the three case/control studies (only 2 of which have been published [3,4]) organised by the French health authorities to assess the neurological risk of hepatitis B vaccination have not lead to statistically significant results has been widely repeated and exploited. The fact as such is hardly questionable, *but how is it to be interpreted?* It is also well-known that the majority of the medical world (and the public) has come to equate this absence of statistical significance to an absence of risk. **However this interpretation is strange: the non-significance of the**

**studies is only to be *expected* from an astonishingly low statistical power.**

The only conclusion that can be drawn from this recurring lack of significance is that over a period of *ten years* since the first alert the French administration has not managed to carry out any investigation of sufficient statistical power.

So clinical research involves “soft” data and therefore the need for an expert to act as Great Master of Hermeneutics. As a consequence this also means **potential conflicts of interest**: in the field of pharmaceuticals where current regulation grants pharmaceutical companies monopoly in terms of development, manufacturing and distribution, it is difficult to claim any serious competence without declaring the degree of one’s professional connections to those firms.

Another example.

During the “Consensus Conference” held in Paris in September 2003 – we will come back to it later – it became increasingly difficult to ignore the fact that, unlike the national inquiry in pharmacovigilance initiated in France in June 1994, other investigations also based on spontaneous reports but of American origin have resulted in very worrying conclusions regarding the tolerance of hepatitis B vaccines. The defense came from the main investigator of the French investigation himself:

*This passive collection may favour the collection of reports stemming from accidental coincidences or from disorders whose diagnosis remains yet to be confirmed. Generally speaking, it is not sufficient to show a causal relationship.*

Bégaud, another responsible of the epidemiological surveillance carried out by the Agency, was even more assertive:

*The analysis of the incidence of notifications on the basis of pharmacovigilance data can only generate hypotheses (...) Due to the underreporting of side-effects which is probably not constant depending on the vaccines or from year to year, no etiological analysis can reasonably be made. Furthermore as is the case with spontaneous reports, no confounding factors have been taken into account. In no case therefore do the comparisons warrant any definitive conclusions.*

These considerations are common sense and confirm what every pharmacovigilance specialist knows, that an investigation based on spontaneous reports is not sufficient to “reveal a causal link”, to lead to “an etiological analysis” or indeed to warrant conclusions at all. The problem is that this obviously simplistic investigation represented *the entire extent* of the surveillance organised till 1997 by the French Agency. Meanwhile – even though the exact figures are not known – *at least 20 million French people* have been vaccinated and among them, a large number of babies and children.

This brief chronological reconstitution shows clearly that *if* the studies carried out – after considerable delay – by the French administration had demonstrated a causal relationship between, for instance, vaccination and MS, this would have caused an **unprecedented scandal**: indeed it would have been the confirmation that several months after an alert acute enough to justify a national inquiry (01/06/94) the

administration had incited millions of people in perfectly good health to get vaccinated, while neglecting to organise an *adequate* epidemiological surveillance.

One can therefore deduce – and that was the object of the demonstration – that in the epidemiological assessments which were within its responsibility as health authority and as leading promoter “universal” vaccination, the French health administration found itself faced with an acute **conflict of interest**. In admitting so late to iatrogenous causality, the administration would have de facto admitted its failure to carry out its *safety duties*, thus *endangering* almost half the French population.

## 2. Benefits from the vaccination against hepatitis B

In September 1994 at the time when the vaccination campaign was launched by the General Health Authority (DGS) under the aegis of M. Douste-Blazy, **the epidemiology of hepatitis B in France was not known**. The following excerpt from the Guide des vaccinations (1995, p.107) published by the DGS itself is very clear:

*The epidemiological surveillance of hepatitis B in France remains insufficient.*

This “insufficient epidemiological surveillance” means in particular that very little was known about: 1) the frequency and complications of this viral disease 2) what are the populations at risk and 3) what are the modes of contamination.

- ❖ Almost ten years later, while interviewed by the medical journal *Le Quotidien du Médecin* on 29/01/03, G. Bruckner, the General Director of the *Institut de Veille Sanitaire* (the French Center for disease control) justified the need for a new system of compulsory declaration of infectious diseases by admitting (underlined by the Expert) that:

*To become able of measuring hepatitis B incidence will help answer the questions raised by health insurance policies*

- ❖ Meanwhile the ignorance of the French authorities regarding the precise epidemiology of hepatitis B had been confirmed by other official sources:
  - After regretting “ the way the vaccination campaign got out of control” in a communiqué of July 1998, M.Kouchner, who was then the Secretary of State for Health, admitted at his press conference of 01/10/98:

*A reinforcement of epidemiological means is necessary in order to get an better idea of the situation [of hepatitis B] in France*

- An investigation in the year 2000 on the epidemiology of hepatitis B in two French departments concludes: “This is *the first* epidemiological study of hepatitis B in France” [5].

To the best of the author's knowledge this claim, although it clearly confirms the absence of previous studies (even on the limited scale of a couple of départements), has never been denied.

- The *Plan National hépatites virales C et B*, circulated by the health authorities in February 2002, once again admits that little epidemiological data on hepatitis B is available in France.

The risk situation among health professionals is no better documented. Despite extensive research we have not been able to discover any publication that would be *relevant to France* and which evaluates the risk/benefit ratio of the hepatitis B vaccination for the professional groups considered as being at risk. As late as 2003, i.e. 10 years *after* the modification of the article L.10 of the Public Health Code (making it mandatory to vaccinate health professionals), two representatives of the *Institut de Veille Sanitaire* admitted that "there is no centralised collection of cases in hospitals" and revealed that until 1997 the health insurance did not differentiate between the various types of viruses when collecting data on professional cases of hepatitis contamination. [6] In their Figure 7 the curve of evolution of cases of occupational hepatitis which have been recognised within the hospital near Paris area *shows a large decrease* after the early 1980s. This trend clearly diminishes the vaccination of health professionals was made mandatory, in 1991.

All this tends to suggest that the obligation to be vaccinated caused a slackening in the application of the non-specific prophylactic measures which had become the norm after the appearance of AIDS<sup>1</sup>.

Put together, this demonstrates that up till now the epidemiology of Hepatitis B has still not been investigated and that the French health administration has defined "medical care policies" *before* knowing the natural prerequisite, that is the incidence of the disease these policies are intended to fight. This applies both to health professionals (the target of article L.10 of the CSP) and to the population as a whole (the target of the September 1994 campaign).

### **3. Risks of the hepatitis B vaccine: the assessment by the French health authorities**

A number of documents clearly demonstrate that over the years the argumentation of the French Health administration on the safety of hepatitis B vaccines has focused on the following points:

1. There is a "background noise" related to the frequency of demyelinating diseases in a normal population and the number of cases observed after vaccination is no different from the number of cases that can be expected on the basis of this baseline frequency.

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<sup>1</sup> A recent multicentre study on hepatitis B virus prevalence in hemodialysis units from 3 continents is an indirect confirmation of the failure of universal vaccination since in countries (such as Italy or France) which adopted an extensive policy of vaccination, hepatitis B virus prevalence is higher as in the UK for example. (Burdick et coll, *Kidney Int* 2003 ; 63 : 2222-2229)

2. Overall the available data is reassuring and the latest published studies clear the vaccine of the suspicion of neurotoxicity.
3. If a risk exists, it can only be a low risk.
4. If a risk exists, it probably mainly concerns populations which present a particular susceptibility.
5. Whatever the iatrogenous risk of the vaccination may be, it is anyway smaller than its benefit: in other words the risk/benefit ratio of hepatitis B vaccines is undeniably favourable.
6. No causal relationship has been established with any degree of certainty.
7. An "International Consensus Conference" organised in September 2003 has conclusively cleared hepatitis B vaccines of most suspicions of iatrogenicity.

It is quite simple to refute these arguments one after another.

- ❖ In France there is no register of "expected cases" of MS. As to the evaluation of the number of cases that have really occurred, one would need to estimate the degree of **underreporting** which in this instance has been massive and even encouraged. Even the authorities have stopped denying that under-notification was never taken into consideration in the official statistics. The key argument which practitioners have used for years is like claiming " $a < b$ " when neither  $a$  nor  $b$  are known... Anyway the supporters of this "expected/observed" argument have recently – and several times – stated publicly that the number of cases notified *is larger than* the expected number. Their affirmations unfortunately only appeared in foreign publications [4, 7].
- ❖ The "overall reassuring" character of the data available is an artefact linked:
  - to the incapability (or maybe the unwillingness) of the French authorities to organise the methodologically adequate – in experimental as well as in statistical design – studies which the gravity of the health situation requires.
  - to the bias of selective quotation which consists in giving preference to any favourable studies whatever their weaknesses while ignoring or discrediting on principle any study demonstrating a strong link between the vaccine and neurological accidents. In this way after claiming that the study by Zipp et coll [8] should be "dismissed" (communiqué of Feb.2000) because of severe flaws, the administration discreetly reintegrated the same study in all its subsequent analyses. At the same time it now systematically ignores the case/control study it had itself organised and which proved a *statistically significant* thyroid risk (there are many more such examples).
  - to the perversion of the available data ("soft data") *via* inadequate interpretation. A perfect illustration is the unanimity displayed by the experts of the administration (including the ex-director of the DGS) in

interpreting the three French case/control studies as showing no causal relationship<sup>2</sup>.

- ❖ To say that the risk of MS after vaccination is “small” does not mean anything in general terms [9] and *even less so* when we are talking of a *preventive* campaign that affects tens of millions of people in perfect health. Bégaud, who was the Vice-President of the National Commission of Pharmacovigilance at the height of the campaign, publicly admitted that this risk was “at the very least” “epidemiologically significant” [10].

Here the lack of credibility of the argument comes from a fairly obvious contradiction: if it was true that the neurological risk was “low” and that regarding non-neurological risks “no pharmacovigilance signal [had been] strong enough to deserve consideration in a risk/benefit analysis” (report by Dartigues et al), then one may well wonder how the vaccination campaign managed to produce – in the very words of the same Dartigues et al – “one of the largest series of side-effects collected by pharmacovigilance since its beginning in 1974”. And this, despite undeniable efforts of misinformation in order to discourage doctors from reporting vaccine adverse effects.

- ❖ No documented argument supports the hypothesis that the neurological complications of the vaccination may be due to latent predisposition. Even the studies sponsored by vaccine manufacturers do not favour this hypothesis [11].
- ❖ As demonstrated above, the French administration has committed itself to a vaccination policy without the slightest preliminary assessment of the risk/benefit ratio of the vaccination, neither at the collective nor the individual level, and neither in the general population nor for those groups supposedly “at risk”.
- ❖ The authorities are hiding the fact that in their evaluation of a causal relationship at the individual level they have used their own method for causality assessment which attributes *on principle* a “doubtful” causality to **irreversible** complications[12]! It is therefore no use expecting to establish any degree of “certainty” when considering complications as little reversible as MS....

Furthermore, as in other instances outside France or not related to vaccination<sup>3</sup>, the pressure from the manufacturers has turned uncertainty into something specific to *the* issue whereas this is a inevitable issue in the causal assessment of *any* hazard of *any* drug (and the same holds true for efficacy!) Indeed the method for causality assessment which has been imposed for nearly 20 years by the French administration actually excludes – on principle too – “certainty” from the degrees of causality [13].

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<sup>2</sup> Interviewed by *Le Figaro* (18/12/02), the ex-director of the DGS goes as far as present lack of statistical power **or** absence of causality as an explanatory alternative... This suggests that this renowned epidemiologist deserved the accusation by the Parliamentary Commission of lacking “elementary common sense” (*Le Monde*, 27/02/04) even before the heat wave of 2003.

<sup>3</sup> De Laat W, Raff WK, Barton A. Epidemiology on trial. *Lancet* 2004; 360: 1611-2

- ❖ ANAES<sup>4</sup>, the French Agency for accreditation, itself has stipulated the principles of a consensus conference which are simple:
  - the need for transparency, which means for instance:
    - that the experts consulted have to explicitly state their potential conflicts of interest
    - a clear working agenda is normally circulated *one year* before the conference is held
      - the principle of contradiction, which means that experts effectively representing all points of view are invited.

Well documented (*Libération*, 10/09/03), the irregularities surrounding the organisation of this “consensus conference” have been so enormous that even non-professionals have protested. These protests cannot be accused of opportunism since they were made *prior to* the conference. A single example will suffice to illustrate the validity of the protests: whereas *not a single* expert – from France or from abroad – capable of documenting the toxicity of hepatitis B vaccine was invited or even *informed* of this conference, Chen, the co-author of a seriously flawed study [14], was invited to comment on Hernan et coll’s study, a work which had *not at that time been published*. In his “methodological” criticism Chen devoted a volume of objections five to ten times larger than the only abstract of the work available at the time [18]. On the other hand he ignored the above-mentioned weaknesses of the article by Zipp [8] or that of his own investigation [14]...

In fact all the people who have followed this affair, including the author, can confirm that starting in the Summer of 2003 the organisational machine of the conference suddenly got out of control. The time frame was totally incompatible with those principles of transparency already mentioned and which are intended to make it possible for anybody to position themselves vis-à-vis a working agenda specified well in advance. The reason for such a rush may be found in the financial press: under the title *Le marché de la prévention de l’hépatite B repart (The market for the prevention of Hepatitis B has picked up again)*, *La Tribune* of 29/09/03 salutes the perfect coordination between this Consensus conference – announced with much fanfare – in the second half of August 2003, i.e. *less than a month* before the actual conference – and the annulment expected on the 23/09/03 from the French Supreme Court of the two Versailles judgements that had condemned the manufacturers.

The rationale behind this farce is reflected in the words of a gastroenterologist who is one of the most virulent proponents of the vaccination campaign:

*It is undeniable that the recommendations of the jury [at the Consensus Conference] and the decision of the Supreme Court are a very strong argument in favour of the vaccination. [15]*

With all due respect to Justice, isn’t it a very sad state of affairs when the health specialists come to rely on the magistrates to justify public health measures?

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<sup>4</sup> Agence Nationale d’Accréditation et d’Evaluation en Santé. *Les conférences de consensus. Bases méthodologiques pour leur réalisation en France*, 1999 (disponible sur le site Internet de l’ANAES).



## 4. Risks of hepatitis B vaccine: a reassessment on the basis of available data

Based on rigorously conducted research, the newly published study by Hernan et coll [1] only confirms a body of qualitative and quantitative data which greatly exceeds the alert level normally required by the health authorities to apply extremely severe restrictive measures. For the experts of the Agency the occurrence of *three* cases - of very doubtful causality - in the world was enough to *remove* the anti-Parkinson drug Tasmar® *from the market*, although it concerned people severely ill and therefore ready to accept a higher level of iatrogenous risk... An even more striking example is the obligation to sell vasoconstrictors on prescription alone...

### 4.1. Qualitative Data

#### 4.1.1. Epidemiology for Dummies

In the style of this well-known series of books on computing, an elementary experiment in epidemiology can be carried out by anybody to get an idea of the scale of the health disaster caused by the generalisation of hepatitis B vaccination.

In France, ten to fifteen years ago, there were approximately 50.000 to 60.000 people suffering from MS. Given that we have in France around 100.000 general practitioners (according to the Ordre National des Médecins) this means that some doctors - and this is true for the author - had *never* met a patient with MS in their professional lives. Nowadays however, at all social or professional levels, people know of *several* cases of MS... Isn't it urgent that our colleagues stop and reflect upon the impact of such impressive epidemiological change?

Another epidemiological test « for the layman”: from the very beginning the French health authorities have maintained that most MS notified after vaccination were simply the « background noise » that can be expected in an exposed population that includes a large number of young women (nurses, nursing auxiliaries...) However, we have consulted a periodical report of tolerance of oral contraceptives which covered a not insignificant sample of 70 million women-years and we have been able to check that it contained *not one single notification* of MS. In the field of pharmacovigilance something you only hear under very specific conditions is not a “background noise” but a highly suggestive **signal** of the reality of an **alert**.

#### 4.1.2. A burst in paediatric cases of MS

The fact that until recently the occurrence of MS *in children* was something exceptional is common knowledge and easy to document from available medical data. At present one does not need to look further than the AFSSAPS communiqués to note that despite initial denials, numerous cases have been reported of MS in children as astonishingly young as *25 months*. At the same time one cannot help being struck by the multiplication of recent publications on the *a priori* exceptional category of paediatric MS, especially when the majority of articles come from

countries like Canada<sup>5</sup>, Italy<sup>6</sup> and, of course France<sup>7</sup>, that have adopted a policy of extensive vaccination.

The occurrence of MS in children being extremely rare, the *repeated* association of such exceptional events and the vaccination against hepatitis B gives enormous credibility to the hypothesis of neurotoxicity linked to *this* vaccine – and only to this vaccine.

This brings us to another epidemiological point: in order to test the hypotheses suggested by a tolerance alert severe enough to impose a national pharmacovigilance survey, the main point was to differentiate those cases that had actually been reported from the cases normally expected, i.e. from the “background noise”. The complementary analyses should have logically been carried out where the background noise was *minimal*, that is in children and even more so, in very young children where the rarity of spontaneously expected cases gives an enormous weight to cases actually observed after vaccination. Instead of that, the experts of the French agency have systematically used situations where the “background noise” was the loudest, that is in the population of young adults [5]. This regrettable long-lasting bias was diametrically opposed to what should have been dictated by commonsense. It was *more or less* like trying to tune a piano on the runway during take-off or next to one of the presses at Renault – instead of working in a sound-proofed room...

#### 4.1.3. A typical triptych

Practical experience as well as a simple inventory of all available literature on the subject confirm that, all things being equal – and particularly when compared with other vaccines – the vaccination against hepatitis B stands out because of 1) **the frequency**, 2) **the variety**, 3) **the gravity** of its complications<sup>8</sup>. This is not the place to document this point in detail, but we refer the reader to the literature available and point out that an AFSSAPS study revealed – among other forms of toxicity – a toxicity on the thyroid, though curiously, this study has not been published.

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<sup>5</sup> Boiko A, Vorobeychik G, Devonshire V *et al.* Early onset of multiple sclerosis. A longitudinal study. *Neurology* 2002; 59:1006-10

<sup>6</sup> Ghezzi A, Deplano V, Faroni J *et coll.* Multiple sclerosis in children: clinical features of 149 cases. *Multiple Sclerosis* 1997; 3:43-6.

Ruggieri M, Polizzi A, Pavone L *et coll.* Multiple sclerosis in children under 6 years of age. *Neurology* 1999; 53:478-84.

<sup>7</sup> Hamard H, Hamard P, Gohier P, Roussat B, Doummar D, Iba-Zizen MT. Infantile acute optic neuritis [French]. *Bulletin De l'Academie Nationale De Medecine* 2000; 184(7):1511-21.

Mikaeloff Y *et coll.* La sclérose en plaques de l'enfant. *La Lettre Du Neurologue* 2002; 6:201-4.

Roullet E. La sclérose en plaques de l'enfant. *Rev Neurol* 1998; 154:619-22.

Roullet E, Verdier-Taillefer M, Caillat S *et coll.* Multiple sclerosis with early onset: a case-control study. *Neurology* 1995; 45 (suppl 4):A333.

<sup>8</sup> As exemplified by Mark and David Geier's investigations based upon US data which have forced the experts of the Agency to face up to their disastrous lies about corresponding French vaccine reports. As recently as June 4, 2002 Geier and Geier wrote to me: “One we first started studying hepatitis B vaccine, we were suprised that a genetically engineered, highly purified, single antigen vaccine was associated with as many reactions as it was”

## 4.2. Quantitative data

### 4.2.1. Database REACTIONS

Despite obvious methodological limits, the analysis of the base REACTIONS leads to three interesting remarks:

- ❖ To an experienced specialist the number and the variety of the observations published on the safety of Hepatitis B vaccination are unusually high.
- ❖ This over-representation of the vaccine against hepatitis B is all the more striking that it is noticeable even *before* 1995 at a time when, contrary to other vaccines like polio or the MMR for instance, the exposure to this vaccine was quite confidential and there was no question of any “mediatisation” (Table 1).
- ❖ One only needs to look at the geographical origin of the articles to establish that the over-representation of the complications linked to hepatitis B vaccine is not limited to France: despite what has been claimed by many experts, the toxicity of hepatitis B vaccines is not a new “French paradox”, as conclusively confirmed by Hernan’s study [1].

Vaccine	Number of case reports	
	<i>prior to 1995</i>	<i>1983-2004</i>
Hepatitis B vaccine	42	102
Measle or MMR	20	40
Tetanus or DTP	13	27
Haemophilus influenzae type b	4	7
Polio or DTP	3	3

**Table 1 – Published case reports on various vaccine hazards in REACTIONS database**

### 4.2.2. The Manufacturers’ Data

To our knowledge, Pasteur Vaccins are the only manufacturers of hepatitis B vaccines commercialised in France who have published an assessment of the *French* pharmacovigilance data; their study focuses on central demyelinating diseases [16].

Without getting into a methodological criticism of this article<sup>9</sup>, 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 shows a 1 to 200-fold variation (between 0.03 to 6.11 per 100.000 doses), which is to be expected and reflects the eminently fluctuating character of the process of spontaneous notification. However over the same period of time the

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<sup>9</sup> The fact that this article has been published in a famous French medical journal and yet to-date no critical synthesis has been published is another illustration of the above-mentioned bias linked to a selective preference given to all data favourable to the vaccine. We are a long way from evidence-based medicine...

annual rate of central demyelinating diseases only shows a 1 to 2-fold variation (between 0.34 and 0.81 per 100.000 doses). Such *stability* is highly significant bearing in mind 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 has 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. It should be borne in mind that in pharmacovigilance such a clear link between the frequency of a pathology and the exposure to a drug (that is, the number of units sold) is generally considered **as a strong argument in favour of the iatrogenous origin of the pathology under examination.**

#### **4.2.3. The data from health insurance (CNAM)**

From the start of the vaccination campaign, the CNAM statistics (see Figure below) show *a two-fold increase* in the number of severe cases of MS and an even larger increase in "neuro-muscular diseases", which is highly significant in this context where the iatrogeny of the vaccine has multiplied the number of *atypical* forms of central demyelinating pathologies and where specialists are more and more reluctant to make formal diagnoses of MP in patients who have been vaccinated. The argument of the Dartigues report explaining this increase by the simple generalisation of treatments with interferon is not acceptable: a recent report by AFSSAPS<sup>10</sup> points out that the sales of immunomodulators (a category including interferon alpha) in hospitals have "known a period of relative stability between 1995 and 2000". As any first prescription of interferon must come from a hospital, such "stability" is not consistent with an increase of reimbursement by the French system of health insurance....

#### **4.2.4. The reports of French pharmacovigilance**

As far as central demyelinating pathologies are concerned, the heads of the French pharmacovigilance have recently [4, 7] admitted that the number of reports is now superior to the number of expected cases on the basis of 4.3 cases per 100.000 (which is the *maximum* evaluation of the number of cases of MS expected in the overall population). Since under-reporting is known to be common in our country and the administration's constant denials regarding the risk of the vaccine have made the situation even worse, the evolution of the number of cases *reported* only sets the scene for an unprecedented public health tragedy in our country: by definition, the thousands of cases *reported* to the health administration hide further thousands of cases of MS that have actually *occurred* after vaccination. Indeed the number is probably much higher bearing in mind how the measures of data management adopted in France allowed undue selection and elimination of a number of cases<sup>11</sup>

#### **4.2.5. The three French case/control studies**

It cannot be emphasized enough that the three case-control studies organised by the French health administration have *systematically* recognised an increase in risk,

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<sup>10</sup> Analyse des ventes de médicaments aux officines et aux hôpitaux en France 1992-2002. 4<sup>e</sup> édition, mai 2004.

<sup>11</sup> For example, requiring at least one relapse to make a definite diagnosis of MS should imply quite strict measures of patients follow-up, which was obviously not the case in the French pharmacovigilance inquiry.

despite the lack of statistical significance which is only to be expected from a consistent lack of statistical power. In this disturbing context the results of the meta-analysis initially promised by the Agency (communiqué of Feb. 2000) were not difficult to forecast. It is therefore difficult to understand why this project was finally abandoned under unconvincing pretexts. It then starts making sense that the expert in charge of this meta-analysis later publicly opposed the apparently reassuring conclusions of Ascherio et coll [17] to state that the American data were compatible with the French data that “at best” are consistent with “an epidemiologically important increase in risk” [10].

#### 4.2.6. The study by Hernan et coll [1]

Just the body of evidence briefly referred to above would have been enough to state **with certainty** that the hepatitis B vaccines present a disturbing neurotoxicity potential. The study by Hernan et coll which has just been published undeniably confirms it. As compared to the others investigations on the same topics, its financing suggests convincing investigators’ independence.

Available for over a year, the abstract [18] already suggested that the study was the first one so far not to display obvious flaws<sup>12</sup>. The complete text confirms this: its authors are among the most respected epidemiologists in the world and the methodology they use has allowed them to publish numerous uncontroversial studies, including various investigations showing the innocuousness of some other vaccines (BMJ 2004; 328: 364). The database they used is by far the best validated base in Europe and proved to be the most reliable in the field of iatrogenous toxicity. The time window (3 years) is – for once – realistic, both the validation process of the diagnosis and that of the vaccination history are credible, etc. In consideration of which, the relative risk of MS after vaccination against hepatitis B is 3.1, which is statistically significant (95% confidence interval: 1.5 to 6.3). This increased risk is characteristic of *this* particular vaccine: it is not observed after vaccination against tetanus and influenza. This also confirms the conclusions drawn from the base REACTIONS (see 4.2.1).

Based on a total number of people vaccinated of about 25 million<sup>13</sup>, the “background noise” of MS should have indicated a number of “expected” cases of about 12,500 to 25,000. According to the authors and contrary to what the experts from the Agency have without justification maintained all along, the risk *gets worse* when the time frame is extended. This *three-fold increase* of the relative risk is undoubtedly compatible with **tens of thousands of iatrogenous cases of MS**.

Not to mention other potential disorders [22].

## 5. Conclusion

A health catastrophe of probably unprecedented extent in our country, this “affair” of the vaccination against hepatitis B can be essentially explained by the exploitation of

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<sup>12</sup> Unlike Asherio et al’s or de Stefano et al’s studies, where even the *neurological* history was not evenly distributed between cases and controls...

<sup>13</sup> Estimations may vary between authors: by and large, from 20 to 30 millions of French people have been exposed to hepatitis B vaccination.

the sacrosanct concept of "public health", always a safe bet when dealing with French practitioners. Our colleagues have been deceived by the "WHO" stamp of approval even though it was not terribly difficult for people aware of the techniques of the pharmaceutical lobby<sup>14</sup> to see through it. They did not realize what considerable financial effects could be produced by the prophylactic zeal of the manufacturers (or their own experts who unfortunately happen to be the same as the experts of the administration). Meanwhile, the health authority deliberately ignored the known risks caused by a dramatic change of scale (an "universal" vaccination) in the prescription of products which had already provoked a serious safety alert.

It is interesting to note that our British colleagues, civil servants much better versed than us in statistics and epidemiology, have resolutely resisted the lure of the sirens of prevention, as one of the main manufacturers had to admit with undisguised vexation<sup>15</sup>

In just half a page the *British Medical Journal* repudiated once and for all the authority of "consensus conferences" and of international organisations that are not cautious enough in choosing their sponsors [20]. We might be well-advised to meditate on the irony of our British colleagues (where italics are mine):

*A week last Friday, Britain woke up and considered its risk of catching hepatitis B over breakfast. By 9 am, no fewer than 26 national and local broadcast bulletins had reported that "top medical experts" were advocating a strategy of universal vaccination in infancy against the virus. In maintaining its current policy of immunising only individual at higher risk of infection, it was implied, the Department of Health was failing in its important duty to protect children against the disease. The World Health Organisation has recommended a strategy of universal immunisation against hepatitis B (...)*

*There was two reasons why this topic was uppermost in the minds of the media that day. Firstly, SmithKline Beecham, the leading manufacturer of hepatitis B vaccine, convened a consensus panel to consider the issue last year; secondly, it paid the London public relations firm Shire Hall Communication to launch its report. The firm did a brilliant job*

*(...) Whether British taxpayers would be wise to play their part in the proposed universal immunisation programme is open to question*

*(...) Shire Hall certainly provided an object lesson in how to manipulate the media machine.*

That was as early as in 1996<sup>16</sup>.....

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<sup>14</sup> In this story, « WHO's voice » was that of the *Viral Prevention Hepatitis Board* created and sponsored by manufacturers [19].

<sup>15</sup> Sciences et Avenir, janvier 1997, n° 599, p. 27

<sup>16</sup> British Medical Journal 1996 ; 313 : 825

*Competing interest : Dr Girard works as an independent consultant for pharmaceutical industry, including vaccine manufacturers and a number of their competitors.*

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