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## Hepatitis B vaccination and the risk of multiple sclerosis in children

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**"Tell me who are your friends..."**

With an extensive training against biased research gained through thousands of hours spent in medical reports<sup>1,2</sup> ordered in the setting of the criminal inquiry which recently led the manufacturers of hepatitis B vaccines to face charges of manslaughter and aggravated fraud<sup>3</sup>, I could not help reading the paper by Mikaeloff et al (2007)<sup>4</sup> with a high degree of suspicion. And it is fair to note that in the medias as well as the "experts" – esp. those regularly neglecting to declare their conflicts of interest with the vaccine manufacturers<sup>5</sup> –, those most prone to hype this problematic study were the same as those which used to be harshly involved in promoting communication that French prosecutors tend now to charge as "aggravated fraud": *tell me who are your friends, says an old French proverb, and I will tell you who you are...*

Whereas in pharmacoepidemiology, the case/control design is normally used as a cheap recourse to rapidly get reliable data in case of a health alert, the first surprise here lies in the formidable time lag required to have these results: they should have been available some 15 years before, in the interval between the modification in the international sheet of Engerix B pointing out a risk of post-vaccinal multiple sclerosis (MS) in 1993 and the irresponsible launch of a pediatric campaign of vaccination in Sept. 1994. Still in 2004, during a private meeting, the Director of AFSSAPS told me that the KIDMUS cohort was consistent with a frightening threat on public health and that carrying a formal case/control study was therefore a sheer emergency: in spite of this, 3 additional years have been needed, while in the meantime the investigators stubbornly refused to release any piece of information when asked by French colleagues, in an atmosphere more evocative of a plot than of any sound pediatric research regarding a critical and urgent health issue in our country...

Needless to say: in the meantime, the French authority did not take the elementary precaution to withhold any incitation to vaccine pediatric subjects against such a "terrible" disease as hepatitis B – with a spontaneous resolution in 98-99% of cases and about which I recently compelled one "expert" to confess that no more than some 60 cases did occur in this age group in France, most of them in migrants.<sup>5</sup>

Suspicion about undue delays grows even more acutely as the design of the study was needlessly hampered by the selection of no less *than 10 controls* per case, when the accepted wisdom is that there is no clear advantage in using a maximum of 3-4 controls per case. Yet, the Hernan et al study<sup>6</sup> (which, quite suggestively, appears as the main foil of the authors) also included the same number of controls: but as

they confirmed once asked on this point (personal communication), unlike the French authors the US researchers used automated data, so that there was no penalty in cost nor in delay in selecting more than 4 controls per case. Thus, as there can be no methodological justification to the subsequent waste of time and money in Mikaeloff et al's study<sup>4</sup>, it suffices to consider its media coverage<sup>5</sup> to retrospectively grasp the trick: presenting this study as a definite refutation of Hernan et al's investigation<sup>6</sup> while substantiating that the former was "as big" as the latter and making a terrible racket on this numerical equivalence devoid of any statistical significance...

This childish inflation of the number of controls is all the more suspect as, in the same time, the number of included cases underwent a dramatic – and yet unexplained – reduction. When the study was announced, everybody (I included) understood that the cases would be the 472 children of the KIDMUS cohort – a frightening sample size, incidentally, regarding a disease such as MS which is in no way a pediatric condition in a country of 60 million of inhabitants. Yet, it would be interesting to know why of these 472 children, Mikaeloff et al retained only one third: as recently as in 28 Aug. 2007 (whereas the paper was already accepted for publication), in her response to a MP question about the benefit/risk ratio of hepatitis B vaccine in infants, the French Ministry of Health announced<sup>7</sup> Mikaeloff et al's publication claiming that the cohort included "467 children" and, as it happens, insisting over the fact that no less than... **twelve** controls would be matched to every case (an argument more likely to impress the average MP than any professional equipped with a minimum of epidemiological or statistical culture)... Beyond the obvious promotional trick, it is still as difficult to see any scientific rationality in the methodological choice of decimating the sample of cases while inflating that of controls.

Another high index of suspicion is related to the companion paper by the same team,<sup>8</sup> also duly mentioned by the French Ministry of health, and which pertains to the longstanding strategy of mystification adopted by the French Agency from the very beginning of the story, in 1994: shifting the real problem (is there any risk, for a *healthy* person, to develop a MS after hepatitis B vaccination?) – which concerned some 60 million of French citizen in a perspective of an "universal" immunization – to something without genuine connection (is there a risk, for subjects *already* affected by MS, to experience relapse after vaccination?) – which concerned about 25 000 persons at that time. Likewise, whereas any reasonable physician in this country was concerned by the risk of triggering MS in exposing some 10 million of pediatric subjects to hepatitis B vaccination, Mikaeloff et al – with the obvious support of their Ministry – were apparently very happy to claim that out of the... *33 children* with pre-existing MS and then exposed to this vaccine, there was no evidence of any risk of relapse:<sup>8</sup> how nice and reassuring!...

For perverse as it was, this displacement translates also in a direct argument against the latest investigation by Mikaeloff et al.<sup>4</sup> Actually, the main focus in the communication by the French Agency since 1994 was about the potential contra-

indications of the vaccine in the tiny subpopulation of people with a familial or personal history of MS. Yet, if one considers Table 1, it appears that the risk of MS history was 2.6 times higher in the cases than in the controls: in other terms and according to the abovementioned recommendations by the French Agency, this means that the probability of being vaccinated was significantly *lower* in the cases as compared with the controls – an interesting bias in a study such this one...

Although my previous remarks should be sufficient to crack the credibility of this study, there is another methodological objection regarding the exposure ascertainment. In fact, the vaccination campaign in French schools occurred in an atrocious mess and improvisation: indeed, mess and improvisation were precisely the pretexts taken by the late Health Ministry B. Kouchner to suspend the pediatric campaign in Oct. 1998. Therefore, the vaccination certificate ("carnet de santé") was by far be *the poorest document of relevance* to assess exposure regarding hepatitis B vaccine: although doubts exist regarding the long-term efficacy of the vaccine, the only way of comparing exposure between the cases and the controls should have been serum antibodies, and this is a sheer scandal to publish a study bypassing such an elementary checking. Therefore, the assessment of exposure in this study was severely flawed and this justifies considering its conclusions with the highest degree of suspicion.

The *Archives of Pediatrics & Adolescent Medicine* deserve a final criticism. Although this is not politically correct to say, the medical journals share a huge responsibility in the too lamented "publication bias" due to their severely flawed process of selection leading to the publication of incredibly poorly designed investigations,<sup>9</sup> reviews intolerably prejudiced in their references,<sup>10-12</sup> or even studies explicitly suspected of fraud<sup>13</sup> by regulatory agencies<sup>14</sup>. As documented above, there were a number of reasons to develop a high degree of suspicion against the current study by Mikaeloff et al<sup>4</sup>: besides of publishing this problematic investigation – and *in free access* –, was it necessary to publish an accompanying editorial<sup>15</sup> to celebrate it under the fallacious pretext of "Science"? Completely unjustified in a scientific journal, this hype reminds us the same procedure<sup>16</sup> used by the *New England Journal of Medicine* once the Ascherio et al<sup>17</sup> and Confavreux et al<sup>18</sup> investigations – both of them favorable to the hepatitis B vaccination – were published, in spite of their obvious weaknesses: in the meantime, the same journal failed to publish any similar celebration of the paper by Hernan et al<sup>6</sup> – by far *the best* study in the field – and, up till now, remained regrettably silent on the reasons for its refusal to publish this remarkable investigation... This is a worrying bias to consider that data favorable to vaccines are "scientific" by essence<sup>19</sup> as exemplified by comparing the promotion of vaccine against hepatitis B on the one hand, against HPV on the other: at some 15-20 years of interval, that both vaccines could be, each, "the first" immunization against a cancer is closest of "aggravated fraud" than of "Science" and I am now reasonably confident that this will be published by the *Archives* with the same epistemological zeal as that used to celebrate the study by Mikaeloff et al<sup>4</sup>...

To conclude, Mikaeloff et al's investigation<sup>4</sup> failed to answer to *the* question which triggered its planning and performance, and was perfectly summarized by Tardieu – one of its co-authors – in 2004<sup>20</sup>: why, in a period where the main change in environment was vaccination against hepatitis B, did the 90ties show a burst of pediatric MS, a disease extremely rare in that age group and whose overall epidemiology, anyway, is normally quite stable. To be more precise, why, further to this vaccination campaign, the KIDMUS cohort showed a 25-fold increase in the frequency of pediatric MS as compared to previous records?<sup>22</sup> A question strangely consistent with a more general one: why, as compared to the latest record prior to the vaccination campaign, the widely accepted estimations of MS frequency in the French population showed an increase from about 25,000 at baseline to 80,000-90,000 today?<sup>22</sup> To say nothing about this second interesting question: whatever its real cause, why such alarming situation did not trigger, from the French authority, any investigation more appropriate than that of Mikaeloff et al<sup>4</sup> who, in spite of these dramatic – and yet unexplained – figures concerning our children, keep holding that *tout va très bien, Madame La Marquise* (“All is well, Madam the Marquise”).<sup>21</sup>

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Conflicts of 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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