Editorial

"Tell me who your friends are …"

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Abstract

When the Mikaeloff *et al.* study was announced, everybody (myself included) understood that the cases would be the 472 MS-diagnosed children in the "KIDMUS" cohort—an alarming number of children because pediatric MS is not a recognized medical condition. Therefore, it would be interesting to know why Mikaeloff *et al.* retained only 143 (less than one third) of these 472 children in their study.

There were a number of reasons to be highly suspicious of the validity of this study by Mikaeloff *et al.* besides *Archives of Pediatrics & Adolescent Medicine* publishing this problematic investigation and making it available without cost. Was it really necessary to publish an accompanying editorial touting this study under the fallacious pretext of "science"?

To conclude, Mikaeloff *et al.*'s investigation failed to answer the question which triggered its planning and execution, and was perfectly summarized by Tardieu—one of its co-authors—in 2004: Why, in a period where the main change in environment was vaccination against hepatitis B, did the 1990s show a burst of pediatric MS, a disease extremely rare in that age group and whose overall epidemiology, anyway, has normally been quite stable? To be more precise, why, following this vaccination campaign, did the KIDMUS cohort show a 25-fold increase in the frequency of pediatric MS as compared to previous records? A question strangely consistent with a more general one: "Why, as compared to the latest record prior to the vaccination campaign, did the widely accepted estimation of MS cases in the French population show an increase from about 25,000 at baseline in 1993 to the current 80,000-90,000?" To say nothing about this second interesting question: "Whatever its real cause, why did such an alarming situation not trigger from the French authority any investigation other than that of Mikaeloff *et al.*?"

Conflicts of interest: Dr. Girard works as an independent consultant for the pharmaceutical industry, including (at least until recently) the manufacturers of the hepatitis vaccine and some of their competitors.

Keywords: Hepatitis B vaccine, medical fraud, study methodology, Multiple Sclerosis (MS), KIDMUS cohort, Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSAPS)

Having extensive experience in detecting biased research which has been significantly augmented by thousands of hours spent in reviewing medical reports [1,2] as the court-appointed expert in the criminal inquiry which recently led the manufacturers of hepatitis B vaccines to face charges of manslaughter and aggravated fraud [3], I could not help reading the paper by Mikaeloff *et al.* (2007) [4] with a high degree of suspicion. Moreover, those in the media as well as the "experts," especially those who regularly neglected to declare their conflicts of interest with the vaccine manufacturers [5], who were most prone to hype this problematic study, were the same persons who were callously involved in promoting communications that French prosecutors are now calling "aggravated fraud". According to an old adage, *tell me who your friends are*, *and I will tell you who you are*.

In pharmacoepidemiology, a case/control design is normally used because it is a relatively inexpensive method to rapidly obtain reliable data required for a health impact alert when suspected adverse drug effects are observed. In Mikaeloff *et al.*, the first surprise is the alarming time lag from the time the unexpected apparently vaccine-related cases of childhood MS were identified until this study was completed. This study should have been completed at least 15 years ago—in the interval between the modification in the vaccine package insert for Engerix B that pointed out a risk of post-vaccinal multiple sclerosis (MS) in 1993 and the irresponsible launch of a pediatric campaign of vaccination in September of 1994. This is especially the case because, in 2004, during a private meeting, the Director of AFSSAPS (Agence Française de Sécurité Sanitaire des Produits de Santé—the French agency responsible for ensuring the effectiveness, quality and proper use of all healthcare products intended for human use) told me that the KIDMUS (Kids with Multiple Sclerosis) cohort was consistent with a frightening threat on public health and that carrying a formal case/control study was therefore a real emergency. In spite of this, an additional 3-plus years elapsed before the study was submitted. Moreover, during this period, these researchers refused to release any part of their information when asked about this health hazard by their French colleagues. Thus, their activities took place in an atmosphere more evocative of a secret plot than that of any sound pediatric research regarding a critical and urgent health issue in our country. In the meantime, the French authority did not take the elementary precaution to withhold any recommendation to vaccinate children against such a "terrible" disease as hepatitis B—which has a spontaneous resolution in 98-99% of all cases and about which I recently compelled one "expert" to confess that no more than about 60 cases occurred in this age group in France and most of these cases occurred in immigrants. [5]

doi: 10.1588/medver.2008.05.00179

Since statistically there is no benefit in using more than 3 to 4 controls per case in a case-control study, my suspicion about undue delays was heightened because the study was needlessly slowed down by a requirement for no less *than 10 controls* per case. This "controls" design number is not necessary even though the Hernan *et al.* study [6] (which seems to be the main paper that the study by Mikaeloff *et al.* was designed to rebut) also included a similarly large number of controls. This is the case because, unlike the French authors, the U.S. researchers used automated review of computerized records, so that there was no cost or time-delay penalty in selecting more than 4 controls per case. Thus, because there is no methodological justification for the subsequent waste of time and money for the additional controls in the Mikaeloff *et al.*'s study [4], one need only consider its media coverage [5] to understand the reason for the choice of the number of controls. This controls' choice allowed these authors to: (a) present this study as a definite refutation of Hernan *et al.*'s investigation [6], (b) claim it was "as big" as the previous study, and (c) play up this numerical equivalence even though it is devoid of any statistical significance.

This irresponsible inflation of the number of controls is all the more suspect because, at the same time, the number of childhood MS cases included in the study underwent a dramatic—and as yet unexplained—reduction. When the study was announced, everybody (myself included) understood that the cases would be the 472 MS-diagnosed children in the "KIDMUS" cohort—an alarming number of children in a country of 60-million inhabitants because pediatric MS is not a recognized medical condition. Therefore, it would be interesting to know why Mikaeloff *et al.* retained only 143 (less than one third) of these 472 children in their study. This reduction is even more suspect because, as recently as in 28 August 2007 (well after this paper had been accepted for publication), in response to a MP question about the benefit/risk ratio of hepatitis B vaccine in infants, the French Ministry of Health announced [7] Mikaeloff *et al.*'s impending publication, claimed that the cohort included "467 children" and, as it happens, emphasized that no less than… **twelve** controls would be matched to every case (a claim more likely to impress the average MP than anyone having even a minimum epidemiological or statistical background). Beyond the non-material inflation of the total number of children in the study, there is no scientifically sound justification for choosing a study design that intentionally uses less than one third of the available condition cohort and inflates the number of control children included by a factor of 2 to 4 beyond the number that sound science justifies.

Another significant cause for suspicion about the validity of the findings in this paper can be found in the companion paper by the same team [8], also duly mentioned by the French Ministry of Health. This suspicion arises because the companion paper clearly reveals the longstanding strategy of misdirection adopted by the French Agency, AFSSAPS, from the very beginning of the story, in 1994. This strategy involves shifting the real problem (is there any risk, for a *healthy* person, to develop MS after hepatitis B vaccination?), which is of concern to the about 60-million French citizens from the perspective of "universal" immunization,—to something without a genuine "universal" connection (is there a risk, for subjects *already* affected by MS, to experience relapse after vaccination?), which, in 1994, was only of concern to 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 children 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 [8]. How nice and reassuring!

As perverse as it was, this displacement also translates into a direct argument against the latest investigation by Mikaeloff *et al.* [4]. Actually, the main focus in the communication by the French AFSSAPS 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, based on Table 1 in Mikaeloff *et al.*, it appears that the risk of MS history was 2.6 times higher in the cases than in the controls. In other words, considering the "contra-indication" recommendations by the French Agency, this means that the probability of being vaccinated was significantly *lower* in the cases than it was for the controls – an interesting bias in a study such as 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. Factually, the vaccination campaign in French schools was poorly controlled and the vaccination records were a mess. Indeed, the records mess and the improvised nature of the program were precisely the pretexts used by the late Health Ministry B. Kouchner to suspend the pediatric campaign in Oct. 1998. Because of these vaccination program shortcomings, the vaccination certificate ("carnet de santé") was by far *the poorest document of relevance* to assess exposure regarding hepatitis B vaccine. Thus, given the problematic nature of the vaccination records, a valid comparison of vaccine exposure in the cases and the controls would have required appropriate serum antibodies testing for all candidates. This was not done. Lacking verification of vaccine exposure, it is obviously poor science to publish a study bypassing this fundamental check when the vaccination records are, as they were, known to be inaccurate. Thus, since the assessment of exposure in this study was obviously flawed, this flaw casts a high degree of suspicion on the conclusions of this study.

The publishers of the *Archives of Pediatrics & Adolescent Medicine* also deserve criticism. Although this is not politically correct to say, the medical journals share a huge responsibility in the oft lamented "publication bias" because of an increasingly flawed selection process. That process has led to the publication of incredibly poorly designed investigations [9], reviews intolerably prejudiced in their references [10-12], or even studies explicitly suspected of fraud [13] by regulatory agencies [14]. As previously stated, there were a number of reasons to be highly suspicious of the validity of this study by Mikaeloff *et al.* [4]. Besides publishing this problematic investigation and making it available without cost, was it necessary to publish an accompanying editorial [15] to celebrate it under the fallacious pretext of "science"? Completely unjustified in a

doi: 10.1588/medver.2008.05.00179

scientific journal, this hype reminds us that the same procedure [16] was used by the *New England Journal of Medicine*. The Ascherio *et al.* [17] and Confavreux *et al.* [18] investigations, both of which were favorable to the hepatitis B vaccination program, were published, in spite of their obvious weaknesses. However, the same journal failed to publish any similar celebration of the paper by Hernan *et al.* [6], by far *the best* study in the field to date, and, up till now, has regrettably remained 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 [19] as exemplified by comparing the promotion of the older vaccine against hepatitis B and the "new" vaccines against HPV. Even though separated by an interval of 15 to 20 years, it is clear that touting each of these vaccines as "the first" immunization against a cancer is closer to "aggravated fraud" than it is to "Science." Moreover, I am now reasonably confident that the HPV vaccines will be touted by the *Archives* with the same epistemological zeal as that used to celebrate the study by Mikaeloff *et al.* [4]

Since the time of the first revision of my paper addressing the problems with Mikaeloff *et al.*, another reason to criticize *Archives of Pediatrics & Adolescent Medicine* has emerged. In documenting an unexplained attrition of cases (by more than two thirds) and challenging the assessment of exposure, I did not express a personal opinion but rather addressed key points *of major scientific relevance* regarding any kind of epidemiological investigation. In addition, as far as I can ascertain, the official case figures documenting an unexplained surge in the MS frequency in France (as stated in the concluding paragraph) have, as of March 2008, *never* been published, even though their relevance in terms of public health cannot be overestimated. Finally, the whole of my commentary was based upon specific references, and objective crosschecking as well as my recognized expertise in the field of drug safety, in general, or hepatitis B vaccination, in particular. This makes it all the more edifying that it took *no more than 24 hours* for the editors of this journal to reject my correspondence as unable "to receive high enough priority rating for publication." This is but one interesting example (amongst others) of the impressive biases leading medical journals to accept or reject contributions of peers—especially in the field of vaccines. As I explained elsewhere, I regularly receive by mistake cheerful invitations from editors of major journals, which actually are intended to another *Marc Girard*, a perfect homonym and certainly a high-ranking scientist, but whose zeal in promoting vaccinations as well as his professional links with their manufacturers are notorious—even if his involvement in drug safety is less easily documentable, to say nothing on his medical qualification (to the best of my knowledge, his training—clearly excellent—was that of a veterinarian).

To conclude, Mikaeloff *et al.*'s investigation [4] failed to answer *the* question which triggered its planning and performance, and was perfectly summarized by Tardieu—one of its co-authors—in 2004 [20]: Why, in a period where the main change in environment was vaccination against hepatitis B, did the 1990s 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, did the KIDMUS cohort show a 25-fold increase in the frequency of pediatric MS as compared to previous records [2]? A question strangely consistent with a more general one: "Why, as compared to the latest record prior to the vaccination campaign, did the widely accepted estimation of MS cases in the French population show an increase from about 25,000 at baseline in 1993 to the current 80,000-90,000 [2]?" To say nothing about this second interesting question: "Whatever its real cause, why did such an alarming situation not trigger from the French authority any investigation other than that of Mikaeloff *et al.* [4]*?*" The French authority, despite 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") [21].

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doi: 10.1588/medver.2008.05.00179