



Analysis of vaccinations as a possible cause of Multiple Sclerosis

Draft: June 6, 2008
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Introduction

Vaccines are administered to prevent certain infectious diseases but may also themselves carry a risk for the same or other diseases. Because of their composition, vaccines can be potentially considered as both toxic agents and infectious agents. They contain pathogens, pathogenic toxoids, or subunits suspended in a medium that may also contain other factors such as adjuvants or preservatives. Their purpose is to provoke an immune response in the recipient that will defend the body in the event of natural exposure to the infectious agent.

Because vaccinations prime the immune system, and because immune factors are considered to play a major role in MS, it is conceivable that vaccination may therefore play a role in MS. For instance, molecular mimicry, or immunologic similarity between an antigen in a vaccine and an autoantigen such as a myelin peptide, could trigger an immune response against the autoantigen. Vaccines could also contain superantigens that might set off a widespread immune response that somehow leads to or exacerbates disease processes in the central nervous system.

Several studies have examined whether vaccinations are associated with an increased risk of MS or an initial demyelinating symptom. Others have investigated whether vaccinations can increase the risk of exacerbations, disability progression, or new MRI changes in people already diagnosed with MS. While studies in this latter category do not address vaccinations' effect on the risk of MS onset directly, any association between vaccination and events in established MS may suggest a role for that vaccine in the initial stages of MS as well.

Published papers on the topic of vaccinations and MS range widely in terms of methodology. Case reports or small observational studies cannot establish causality but sometimes draw attention to the need for further study on the topic. More conclusive evidence may be provided by case/control and cohort studies, as well as analyses of large medical databases.

To date, the vaccine most intensively studied in connection with MS onset is the hepatitis B vaccine. The focus on this vaccine followed case reports of post-vaccination demyelinating disease in Belgium and France, which eventually led France to halt a large-scale vaccination program in schools. Other vaccines that have been studied in conjunction with MS include tetanus, influenza, and measles vaccines.

This document discusses the research performed to date on the role vaccinations may play in MS. For each type of vaccine studied, we present the published evidence concerning its effect on risk of MS onset or MS disease activity. Details of each of the studies mentioned here can be found in the associated file <http://www.acceleratedcure.org/downloads/phase2-vaccination-studies.xls>.

Hepatitis B:

Note: Because we identified numerous studies focusing on the hepatitis B vaccine, and because these studies have not all reached similar conclusions, we have provided brief summaries of the relevant investigations in a table below.

Effect on MS risk: As mentioned in the introduction, case reports of individuals experiencing demyelinating symptoms within a few weeks after vaccination sparked interest in this vaccine as a possible trigger of MS¹⁻³. It should be noted that many of the individuals described in these case reports had had neurological events in the past or a family history of MS.

A number of case-control studies, cohort study analyses, and medical records-based investigations of hepatitis B vaccine and MS have followed these case reports. Most of these found no increased risk of experiencing a demyelinating episode^{4,5} or being diagnosed with MS⁶⁻⁹ for vaccinated vs. unvaccinated individuals. Populations analyzed in these studies included adults as well as children and adolescents. However, three studies from France could not exclude a modest influence of the vaccine in triggering a demyelinating episode¹⁰⁻¹², and a UK-based medical records study found that hepatitis B vaccination was associated with risk of MS within three years with an odds ratio of 3.1¹³. The authors of the UK study noted that although they did find an effect on MS risk for hepatitis B vaccine, only 7% of the MS cases in the study had been vaccinated, and therefore this vaccine does not represent a widespread risk factor for the disease.

Effect on established MS: Two studies have examined the potential effect of hepatitis B vaccination on relapses in people with established MS^{14,15}. Neither could demonstrate an increased risk of relapse. Similarly, the second study did not find any effect of hepatitis B vaccine on EDSS or MRI characteristics.

Table: Studies investigating the potential role of hepatitis B vaccination in MS

Lead author, year	Type of investigation	Conclusions	Type of study	Cases/controls	Country/region
Herroelen, 1991 ¹	CNS demyelination following vaccination	Two cases described of exacerbation or onset of MS 6 weeks after vaccination.	Case reports	2 patients: 1 with known MS, 1 with no previous neurological disease	Belgium
Gout, 1997 (abstract) ²	Primary demyelinating events in less than 8 weeks following vaccination	Clinical symptoms of demyelination in these cases occurred after first or subsequent vaccinations. Many of these patients had additional (usually previous) conditions, such as abnormal CSF or transient neurological manifestations.	Case reports	25 cases	France

Tourbah, 1999 ³	CNS inflammation following vaccination	Individuals described with clinical and MRI features of a CNS inflammatory disease within 10 weeks after hepatitis B vaccination. Many of the subjects had family history of MS or personal history of MS-like symptoms.	Case reports	8 cases	France
Zipp, 1999 ⁴	Effect of vaccinations on risk of CNS demyelinating episode	No significant difference in demyelinating episodes was found between vaccinated and non-vaccinated individuals at any of the analyzed time points.	Review of medical and claims records from six HMO plans	134,698 individuals in a US healthcare database	USA
Sadovnick, 2000 ⁶	Development of MS following a vaccination program in schools	There were 9 cases of adolescent MS in the prevaccination period group and 5 in the vaccination period group, indicating no relation between vaccination (at age 11-12) and MS onset.	Examination of population data obtained from the BC Centre for Disease Control, the BC Children's Hospital, and pediatric neurologists	289,651 people in 6 th grade during the vaccination period (267,412 were vaccinated); 288,657 who were in 6 th grade before the vaccination period	British Columbia, Canada
Confavreux, 2001 ¹⁴	Effect of vaccinations on risk of MS relapse	Vaccinations were not found to increase the risk of relapse	Comparison of vaccinations received in periods preceding relapses and relapse-free periods	643 MS subjects	France, Spain, Switzerland
Ascherio, 2001 ⁷	Effect of vaccinations on MS risk	No increased risk of MS was found among women given the hepatitis B vaccinations. Also, there was no correlation between the number of vaccine doses and MS development.	Nested case-control study	192 female nurses with MS and 645 matched controls: 534 healthy, 111 with breast cancer	USA
Fourrier, 2001 ¹⁰	Effect of vaccinations on risk of CNS demyelinating episode	Number of cases with an initial demyelinating episode within two months of a HepB vaccination was greater than expected but not significantly so	Epidemiological analysis	Millions of vaccinated individuals	France
Touze, 2002 ¹¹	Effect of vaccinations on risk of CNS demyelinating episode	No strong relationship was seen between hepatitis B vaccination and development of a demyelinating event within two months, but a slight increase of risk could not be excluded.	Multicenter, hospital-based case-control study	236 MS cases and 355 matched controls (117 pairs and 119 triplets)	France
DeStefano, 2003 ⁸	Effect of vaccinations on MS risk	None of the analyzed vaccines (including hepatitis B) were associated with increased risk of MS.	Analysis of medical records and phone interviews	332 MS and 108 ON cases; 950 matched	USA

				controls	
Hernan, 2004 ¹³	Effect of vaccinations on MS risk	Hepatitis B vaccination was associated with MS with an odds ratio of 3.1.	Prospective nested case-control study	163 MS and 1,604 matched controls	United Kingdom
Ozakbas, 2006 ¹⁵	Effect of hepatitis B vaccination on MS relapse rate, EDSS, or MRI characteristics	No differences were seen between the vaccinated and unvaccinated cases in terms of relapse rate, EDSS, or MRI characteristics.	Case-control analysis of medical records and MRIs	11 MS cases with first clinical symptoms after vaccination, 71 unvaccinated MS cases, and 20 healthy controls	Turkey
Mikaeloff, 2007 ⁹	Effect of vaccination on risk of conversion to MS in children with a clinically isolated syndrome	Neither hepatitis B vaccine nor tetanus vaccine were associated with a significant increase in the risk of MS conversion, regardless of the exposure duration.	Analysis of cohort database and vaccination records	356 children in the KIDSEP cohort	France
Hocine, 2007 ¹² (reanalysis of data from Touze, 2002)	Effect of vaccinations on risk of CNS demyelinating episode	No evidence was found for a strong association between HB vaccination and first MS episode, but a weak association could not be excluded	Case series analysis	289 MS cases	France
Mikaeloff, 2007 ⁵	Effect of vaccinations on MS risk	Neither exposure to HB vaccine nor number of immunizations was associated with a significant increase in the risk of a first MS symptom	Case-control	143 children from the KIDSEP cohort; 1122 matched controls	France

Influenza:

Effect on MS risk: Two studies of medical records included influenza vaccine as one of several vaccines analyzed^{8, 13}. Neither of these studies found that influenza vaccine increased the risk of MS.

Effect on established MS: At least 13 studies have analyzed whether influenza vaccination affects the risk of MS relapse or disability progression. None of them demonstrated an association between flu vaccination and subsequent relapse. In fact, one research team found relapse rates to be increased in subjects who contracted an influenza-like illness during the course of the study, suggesting that influenza vaccine may prevent relapses in people with MS¹⁶.

Measles:

Effect on MS risk: One questionnaire-based study with a small number of subjects associated measles vaccine with an increased risk of MS¹⁷; another, slightly larger, case-control study found no increased risk of MS for this vaccine⁸. A few publications have discussed the failure of measles vaccine to *prevent* MS, demonstrating that measles infection does not cause MS as once previously conjectured.

Tetanus:

Effect on MS risk: The UK study that detected an increased risk of MS for hepatitis B vaccine found no such effect for tetanus vaccination¹³. In addition, one vaccination-focused case-control study and one systematic review of nine case-control studies concluded that tetanus vaccines appear to reduce the risk of MS^{8, 18}. Another found no increased risk in children with a clinically isolated syndrome of converting to MS after tetanus vaccination⁹.

Effect on established MS: Confavreux, et al. (2001) found that neither tetanus vaccine nor other vaccinations increased the risk of relapse in people with diagnosed MS¹⁴.

Others:

No other individual vaccination (such as typhoid, yellow fever, rubella, hepatitis A, pneumococcal), nor total number of vaccinations received, has been associated with increased MS risk or any features of MS such as relapse.

Conclusion:

Most vaccines have not been analyzed extensively for a potential role in triggering MS or promoting MS disease activity. There are a few exceptions:

- Hepatitis B vaccine has received more scrutiny than any other vaccine in terms of its potential effect on the development of MS. While most studies have concluded that it does not increase the risk of MS, a few have detected a positive effect or the possibility of an effect. The fact that many different study designs have been used complicates a straightforward comparison of these divergent results. Because the study that found a significant increase in MS risk for hepatitis B vaccination was based on a small number of vaccinated MS cases, and because of the benefits conferred by this vaccine and its safe administration in millions of people, health organizations such as the CDC and the WHO have recommended that hepatitis B vaccination programs not be altered because of potential MS concerns.
- Tetanus vaccination may actually reduce the risk of MS. One recent case-control study conducted in the US found that tetanus vaccination was associated with a decreased risk of MS⁸. This finding is supported by the results of a systematic review of nine case-control

studies which examined the effect of tetanus vaccination on MS, generally along with several other types of potential risk factors. The results of this review indicated that tetanus vaccination reduces the risk of MS by one-third.

- At least thirteen studies have analyzed whether influenza vaccination increases the risk of relapse or other signs of disease activity in people with MS. None of these associated influenza vaccination with adverse MS-related effects.

In conclusion, while it is biologically plausible for vaccinations to increase the risk of MS onset or disease activity, there is as yet no compelling evidence that any particular vaccination, or total number of vaccinations, strongly increases the risk of MS. It is possible that certain vaccinations may slightly increase the risk of MS. However, the percentage of people who receive any given vaccination and go on to develop MS is small in comparison with the total number vaccinated. Therefore, any vaccinations that increase the risk of MS can presumably trigger MS only when combined with other genetic and/or environmental factors.

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