

Hepatitis B and multiple sclerosis

Hepatitis B is a virus that causes inflammation of the liver and can lead to liver scarring and cancer. A vaccine to prevent hepatitis B has been very safe and effective. In the last decade there have been concerns that hepatitis B vaccine may be associated with development of the neurologic disorder multiple sclerosis. However, numerous scientific studies and expert panel reviews do not suggest a link between the hepatitis B vaccine and multiple sclerosis.

This fact sheet answers the following commonly asked questions. More general information on the hepatitis B vaccine is also available by following the links in 'Further reading'.

What is hepatitis B?

Hepatitis B is a viral infection that causes acute inflammation of the liver (hepatitis). It is transmitted from person to person by contact with blood and body fluids in activities such as sexual intercourse, intravenous drug use and blood transfusion. It can also be passed from an infected mother to her baby around the time of birth. There is evidence that children may transmit it to each other through contact that occurs while playing.

Some people with hepatitis B will develop chronic infection and are known as 'carriers'. Hepatitis B carriers may not know they are infected and may have no symptoms. However, chronic hepatitis B infection can lead to cirrhosis (scarring) of the liver or cancer of the liver. The chance of becoming a carrier is greatest when the infection is acquired at an early age. For example, an infected newborn baby has a 90% risk of becoming a carrier. This is why universal vaccination of all infants is recommended in Australia and many other countries. Each year approximately 600,000 hepatitis B related deaths occur worldwide and there are 350 million chronic carriers of the virus.

The vaccine against hepatitis B infection is made by recombinant DNA technology, which produces inactive (non-infectious) subunits of the virus. When injected into non-immune people, the vaccine gives a high level of protection against hepatitis B infection. The World Health Organization (WHO) has set a goal for all countries to have hepatitis B vaccination as part of their universal childhood vaccination programs.

What is multiple sclerosis?

Multiple sclerosis (MS) is a chronic illness resulting from inflammation and scarring of the myelin sheaths in the brain and spinal cord. Myelin forms a protective covering over nerves and helps conduction of electrical signals along nerves. MS is also known as a 'demyelinating disease'. People with MS can experience varying degrees of incapacity, such as loss of vision and impairment of physical activity, depending on the location and severity of the scarring. There is often a fluctuation in the disease symptoms over time, known as exacerbations and remissions. In Australia there are between 12,000 and 15,000 people with MS, and worldwide there are an estimated 2.5 million people with MS.

The cause of MS is unknown. It is suggested that in patients with a genetic predisposition, the disease may be triggered by environmental factors. Multiple sclerosis typically begins between the ages of 20 and 40, and is 2–3 times more common in women than in men. The incidence of MS varies geographically, with higher rates in temperate climates. Even within Australia there is a lower incidence of MS in Queensland compared with the cooler south-eastern states. Non-specific upper respiratory tract infections have been implicated in triggering or exacerbating MS, usually within a short time period after the infection. Triggers such as viruses are thought to cause viral mimicry of myelin antigens, and to activate immune responses that act against myelin proteins. However, the hepatitis B virus has not been implicated as a trigger.

Does hepatitis B vaccine cause multiple sclerosis?

No, the weight of all the currently available scientific evidence shows no association between hepatitis B vaccine and multiple sclerosis. Concern about hepatitis B vaccination arose from France in the mid 1990s. Following a mass hepatitis B vaccination program in France there were reports of MS developing in some patients a few weeks after receiving the vaccine. In 1998, the French government stopped the school-based hepatitis B component of the vaccination program while they investigated a possible relationship between hepatitis B vaccine and demyelinating disease. When studies of the French vaccine recipients were completed they showed that there was not a significant increase in the number of vaccinated people who developed MS as compared with

those who had never received hepatitis B vaccine. Since that time, there have been more than seven published studies that have consistently shown no association between receipt of hepatitis B vaccine and MS. Some of the other findings that support this include:

- A study in British Columbia, Canada, that investigated multiple sclerosis in 578,308 adolescents over an 8-year period before and after a hepatitis B vaccination program was begun showed no evidence of a link between hepatitis B vaccination and multiple sclerosis or other demyelinating disease.
- A study in 2001 of 192 women with MS and 645 control patients who did not have MS showed no increased risk of MS in those who received hepatitis B vaccine.
- Another study in 2001 looked at hepatitis B, tetanus, and influenza vaccines in patients with MS, and showed no evidence of these vaccines being associated with MS relapses (worsening of MS symptoms).
- A study in the United States of over 1,400 participants did not show any association between hepatitis B vaccination and MS or other types of demyelinating disease.
- Mass immunisation programs with hepatitis B vaccine in New Zealand, Taiwan and Alaska have not resulted in any serious adverse events or illnesses suggestive of MS.
- Extensive pre-licensure clinical trials of hepatitis B vaccine did not document MS as a side-effect.

Are there studies that suggest a link between hepatitis B vaccine and MS?

Despite many studies and expert reviews over the last decade that have found no association between hepatitis B vaccine and MS, the question of a link has been raised again by a study published in 2004 by Hernán and colleagues.

This study was performed by looking back at the medical records of adult patients in the UK who were immunised against hepatitis B by GPs. The authors based their results on a small number of MS patients (11) who had previously received the hepatitis vaccine, and suggest that there may be an increased risk of developing MS in the second and third years after receiving the vaccine. However, there are numerous misgivings that are important to understand regarding this study.

The following points are important to put the study in context:

1. The study relied on accurate recording of all immunisation records and disease symptoms by GPs. However, given the few patients involved, even a minimal difference in the way the information was recorded could alter the results.
2. In the UK, hepatitis B vaccine is only targeted toward adults at high risk of getting hepatitis B. Therefore, the persons who received the vaccine in this study are not representative of the general population and this may have skewed the results. Also, health workers in the study may have received their hepatitis B immunisation in the workplace, rendering information from the GPs incomplete and possibly affecting the study results.
3. Although there were 713 cases of MS in the database, only 11 were selected in the final analysis – this may have biased the results.
4. Information on the number of hepatitis B vaccine doses given, and the time over which they were given, is missing and means that interpretations regarding the effect of the timing and dosing of vaccine cannot be accurately made.
5. An association between receiving hepatitis B vaccine more than 1 year prior to the onset of MS seems unlikely given that viruses that may trigger the onset of MS are thought to have an affect within weeks.

An editorial accompanying this study stated that the “data presented do not provide proof of association sufficient to implement policy changes. The indisputable benefit that the HBV [hepatitis B vaccine] provides against infection must be weighed against any uncommon risks that remain disputed.” The World Health Organization has made a statement that “the findings do not provide convincing support for the hypothesis that immunisation with recombinant hepatitis B vaccine is associated with an increased risk of multiple sclerosis”. Because of the methodological problems of the Hernán study, and the fact that it is in contrast to many other studies, experts consider that the findings do not provide convincing evidence of an association between hepatitis B vaccine and MS.

Can hepatitis B vaccine make MS worse?

Worsening of MS can occur after non-specific viral illnesses. This is thought to be due to activation of the immune system caused by the infection. Although there have also been case reports in MS patients of worsening of their symptoms after vaccination, a well conducted study of influenza vaccine in people with MS did not show any worsening of MS after receiving vaccination. In addition, a study conducted in Europe involving 643 individuals with MS has shown no evidence of an association between recent receipt of hepatitis B vaccine (or tetanus or influenza vaccination) and MS relapses.

The National Multiple Sclerosis Society provides information on the importance of vaccinating people with MS with all appropriate vaccines, including the hepatitis B vaccine: <http://www.nationalmssociety.org/living-with-multiple-sclerosis/healthy-living/vaccinations/index.aspx>

What have expert reviews concluded?

The studies on hepatitis B vaccine and MS have been reviewed by the World Health Organization Global Advisory Committee on Vaccine Safety. They state that “multiple studies and review panels have concluded that there is no link between MS and hepatitis B vaccination”. The WHO also affirm that the recent study by Hernán and colleagues does not provide sufficient evidence to link hepatitis B vaccination to MS, and does not justify discontinuation or modification of programs with hepatitis B vaccine.

In addition, a review by the Institute of Medicine Immunization Safety Review Committee in 2003 found that there was no link between hepatitis B vaccine and certain neurological disorders such as MS. A systematic review from the Cochrane Vaccines Field in 2003 also found no evidence of an association between hepatitis B vaccine and MS. Statements by the US Centers for Disease Control and the National Network for Immunization Information support this position.

Further reading

More general information about hepatitis B vaccine is available from *Understanding Childhood Immunisation*, page 14, available from <http://immunise.health.gov.au/internet/immunise/publishing.nsf/Content/ucibooklet> (accessed Dec 2009)

Additional web-based information

1. US Centers for Disease Control and Prevention. FAQs about hepatitis B vaccine (Hep B) and multiple sclerosis. http://www.cdc.gov/vaccinesafety/Vaccines/multiplesclerosis_and_hep_b.html (accessed Dec 2009).
2. World Health Organization. Hepatitis B vaccination and multiple sclerosis (MS) http://www.who.int/vaccine_safety/topics/hepatitisb/multiple_sclerosis/en/ (accessed Dec 2009)
3. World Health Organization. The Global Advisory Committee on Vaccine Safety rejects association between hepatitis B vaccination and multiple sclerosis (MS) http://www.who.int/vaccine_safety/topics/hepatitisb/ms/en/ (accessed Dec 2009)
4. National Network for Immunization Information. Immunization issues: Hepatitis B vaccine and multiple sclerosis. http://www.immunizationinfo.org/immunization_issues_detail.cfv?id=74 (accessed Dec 2009)

Scientific papers

1. Institute of Medicine of the National Academies. Immunization safety review: hepatitis B vaccine and demyelinating neurological disorders. January, 2003. <http://www.iom.edu/en/Reports/2003/Immunization-Safety-Review-Hepatitis-B-Vaccine-and-Demyelinating-Neurological-Disorders.aspx> (accessed Dec 2009)
2. Sadovnick AD, Scheifele DW. School-based hepatitis B vaccination programme and adolescent multiple sclerosis. *Lancet* 2000;355:549-550.
3. Hall A, Kane M, Roure C, Meheus A. Multiple sclerosis and hepatitis B vaccine? *Vaccine* 1999;17:2473-2475.
4. Halsey NA, Duclos P, Van Damme P, Margolis H. Hepatitis B vaccine and central nervous system demyelinating diseases. *Pediatric Infectious Disease Journal* 1999;18:23-24.
5. MacIntyre CR. Hepatitis B vaccine: risks and benefits of universal neonatal vaccination. *Journal of Paediatrics & Child Health* 2001;37:215-217.
6. Ascherio A, Zhang SM, Hernan MA, et al. Hepatitis B vaccination and the risk of multiple sclerosis. *New England Journal of Medicine* 2001;344:327-332.

7. Confavreux C, Suissa S, Saddier P, et al. Vaccinations and the risk of relapse in multiple sclerosis. *New England Journal of Medicine* 2001;344:319-326.
8. Verstraeten T, DeStefano F, Jackson L, et al. Risk of demyelinating disease after hepatitis B vaccination - West Coast, United States, 1995-1999. Paper presented at the 50th Annual Epidemic Intelligence Service Conference, 2001, Atlanta GA.
9. Rutschmann OT, McCrory DC, Matchar DB, Immunization Panel of the Multiple Sclerosis Council for Clinical Practice Guidelines. Immunization and MS: a summary of published evidence and recommendations. *Neurology* 2002;59:1837-1843.
10. DeStefano F, Verstraeten T, Jackson LA. Vaccinations and risk of central nervous system demyelinating diseases in adults. *Archives of Neurology* 2003;60:504-509.
11. Hernán M, Jick SS, Olek MJ, Jick H. Recombinant hepatitis B vaccine and the risk of multiple sclerosis: a prospective study. *Neurology* 2004;63:838-842.
12. Naismith RT, Cross AH. Does the hepatitis B vaccine cause multiple sclerosis? [editorial]. *Neurology* 2004;63:772-773.
13. Touze E, Gout O, Verdier-Taillefer MH, et al. The first episode of central nervous system demyelination and hepatitis B virus vaccination [French]. *Revue Neurologique* 2000;156:242-246.
14. Zipp F, Weil JG, Einhaupl KM. No increase in demyelinating diseases after hepatitis B vaccination. *Nature Medicine* 1999;5:964-965.
15. Demicheli V, Rivetti A, Di Pietrantonj C, Clements CJ, Jefferson T. Hepatitis B vaccination and multiple sclerosis: evidence from a systematic review. *Journal of Viral Hepatitis* 2003;10:343-344.
16. Sturkenboom MC, Abenhaim L, Wolfson C, Roulet E, Heinzelf O, Gout O. Vaccinations, demyelination, and multiple sclerosis study (VDAMS): a population-based study in the UK [Abstract 238]. *Pharmacoepidemiology & Drug Safety* 1999;8(Suppl 2):S170-S171.
17. Fourrier A, Touze E, Alperovitch A, Begaud B. Association between hepatitis B vaccine and multiple sclerosis: a case-control study [Abstract 163]. *Pharmacoepidemiology & Drug Safety* 1999;8(Suppl 2):S140-S141.