

HEPATITIS B VACCINE

Heidi White

Review June, 2001

INTRODUCTION

As of the 1st of May, 2000, the hepatitis B vaccine for all newborns has been added to the Australian Standard Vaccination Schedule (ASVS) 2000-2002.¹ The Australian Government has endorsed this vaccination program which encourages all parents to allow their newborn babies to receive a shot of hepatitis B vaccine in the days shortly after birth. The new policy has come in response to World Health Organisation (WHO) recommendations for all governments to implement universal hepatitis B vaccination in an attempt to eradicate the hepatitis B virus (HBV) globally.² Nearly 100 countries, including most of Europe and North America have implemented a policy of universal hepatitis B vaccination.³

The United Kingdom (UK), however, is one of the few Western European countries that have chosen to NOT comply with WHO recommendations, preferring instead to control HBV by using a policy of selective vaccination of persons in high-risk groups.⁴ Expectably, the UK's position on this issue has not been retained without controversy.^{3,5,6}

In the UK (and Australia) the carriage rate of HBV is very low and the vast majority of new HBV infections occur in adults.^{4,7} Very few infections are acquired in childhood, the exception being for infants born to mothers who are "carriers" of HBV (ie "vertical transmission" from mother to baby). Universal infant hepatitis B vaccination in countries such as the UK can only prevent a very small number of childhood infections. Therefore policy makers have considered that universal infant hepatitis B vaccination would not be a cost-effective measure in the UK.³ Instead, they believe that a policy of universal antenatal screening, that tests all pregnant women for HBV, to be a better use of finite resources.⁶ This will effectively identify babies at risk of maternal transmission of HBV at birth, allowing for selective vaccination of those babies to occur. Dedicated follow up surveillance systems need to be in place in order to ensure that a high compliance with the hepatitis B vaccination regimen is achieved.³

In recent years the revelation that hepatitis B vaccine may be a cause of serious long-term adverse events has also led to continued debate in the USA as to whether a policy of universal infant hepatitis B vaccination should continue to be upheld.^{8,9}

THE AUSTRALIAN STANDARD VACCINATION SCHEDULE (ASVS)

All babies born after May 1st, 2000 will be offered 4 doses of hepatitis B vaccine, the first dose being given while the baby is still in hospital. For babies living in NSW, QLD, SA, ACT and NT, follow up doses will be given at 2, 4 and 6 months in combination with DTPa vaccine (Infanrix-HepBTM). Babies living in VIC, TAS and WA will be given follow up doses at 2, 4 and 12 months in combination with Haemophilus influenzae type b (Hib) vaccine (ComvaxTM).¹

Children born before May 1st, 2000 will not receive hepatitis B vaccine until they reach adolescence (10-13 years old), unless they come from a high risk group in which case they will receive the vaccine from birth. The adolescent hepatitis B vaccination schedule is different from the newborn schedule in that only 3 doses are given (as compared to 4 doses). The 2nd dose will be given 1 month after the initial dose and then the 3rd dose will follow on 5 months after the 2nd dose.¹

THE DISEASE

In infants and young children, infection with HBV may cause acute symptoms (usually mild) of hepatitis (inflammation of the liver) in only 5% of cases.⁷ The risk of HBV causing symptomatic infection increases with age with a reported rate of up to about 50% in adults.^{1,7} Symptoms of the acute illness can include loss of appetite, fever, nausea, abdominal pain, fatigue, myalgia (sore muscles), arthralgia (joint pain), skin rashes, pale faeces, dark urine and jaundice (yellowing of the eyes and skin).¹

Following acute infection with HBV, about 1 to 12% of adults can become chronic "carriers".¹ Carriers are also described as being "hepatitis B surface antigen" (HBsAg) positive. HBsAg is the outer protein coat of the HBV. Depending on the level of "infectivity" of the carrier mother, infants have a higher chance than adults of becoming carriers of the virus for many years. The level of infectivity (apart from the presence of HBsAg), is determined by the presence of hepatitis B e antigen (HBeAg) in the mother's blood. Women who are HBeAg-positive have a 50% to 90% risk of transmitting HBV to their baby, while HBeAg-negative women have a substantially lowered risk of from 5% to 10%.^{7,10} While carriers usually remain free of symptoms they can continue to spread the virus to other people. It is estimated that up to 25% of carriers are also at risk of developing liver failure (from cirrhosis) and hepatocellular carcinoma (liver cancer) in the future.¹ Therefore hepatitis B vaccine has also been strongly promoted as an "anti-cancer" vaccine.^{11,12}

Frequency of HBV infection and patterns of transmission vary markedly in various parts of the world. For example, in areas such as South-East Asia and Central Africa most people acquire infection at birth or during childhood and the carrier rate can exceed 10%. This is in contrast to countries such as Australia, UK, Northern Europe and the US where HBV infection occurs primarily in adulthood, with very low carrier rates of only 0.1 – 0.2% of the caucasian population.^{1,7,13}

RISK FACTORS FOR CONTRACTING HEPATITIS B

HBV is primarily found in blood and other bodily fluids such as vaginal secretions and semen. Its main routes of transmission are via sexual contact, sharing of contaminated needles, needle stick injuries and from infected mothers to their babies during birth.¹

The NHMRC (National Health and Medical Research Council) strongly recommends that hepatitis B vaccination be given to people in "high risk" groups such as:

- Infants born to carrier mothers. HBsAg is routinely tested for during pregnancy.
- Infants born to HBsAg negative mothers who belong to communities with a HBV carrier rate over 2%, such as Aboriginal or Asian populations.
- Sexual contacts of known HBsAg positive carriers.
- Sexually active male homosexuals, and clients of STD (sexually transmitted disease) clinics.
- Injecting drug users (IDU's).
- Haemodialysis patients.
- Recipients of certain blood products (eg clotting factors for haemophiliacs).
- Health-Care workers and embalmers.

The NHMRC HAVE NOT provided parents with full information about the risks of contracting hepatitis B. They have made the following statement in a parent information leaflet:

"Hepatitis B is a serious disease that can be contracted throughout life.....With the new infant vaccination program your baby will be protected from hepatitis B throughout infancy and early childhood when the risk of becoming a hepatitis B carrier is highest." ¹⁴

This is a misleading statement. It is true that the risk of "becoming a hepatitis B carrier" may be increased in early childhood, but only if they are actually exposed to the HBV. Considering the fact that babies and children do not normally engage in high risk practices (ie unsafe sex or injection of illicit drugs), they are therefore classed as being at a very low risk of acquiring HBV infection.

Therefore for the vast majority of infants who are not in a high-risk group, the REAL RISK of being exposed to the HBV is very near to zero. Hence the chance of an infant or child also becoming a HBV carrier is also extremely low.

Some would argue that all children should have this vaccine because there is a risk of "horizontal transmission" (eg from one child to another child) of HBV from contact with cuts or abrasions or by sharing toothbrushes. Saliva may carry levels of the virus, however it is unlikely to be infective unless it is injected directly into tissue. Contact sports also carry a very low risk of transmission.¹

There is also concern that HBV infection could occur from a needle stick injury, such as accidentally stepping onto a discarded syringe. This would have to be a very remote risk. And in the unfortunate, but very rare, instance of this occurring, then exposure to HBV infection will not be the only worry. Hepatitis B vaccine will not protect against HIV, thought to be up to 3% in the injecting drug user (IDU) population. Neither will it protect against the hepatitis C virus, which has a very high prevalence of about 65% in the Australian IDU population. This is in comparison to prevalence of HBV infection in IDU's of about 45%.^{15,16}

The best preventative measures to halt the spread of HBV (as well as hepatitis C and HIV) is to promote the practice of "safe sex" (by using condoms) and the use of clean needles by IDU's. If a person chooses not to follow these precautions, then even if they are "protected" against HBV, the hepatitis B vaccine will not be of much benefit if they eventually need a liver transplant from complications arising from hepatitis C infection, or develop AIDS from HIV.

If the Australian and USA governments think that our children should have hepatitis B vaccine, then no doubt we will also be told that it is in their best interests for them to also be injected with vaccines for hepatitis C and HIV as well. What is to stop the NHMRC from also added these vaccines to the ASVS and allowing them to be given to all newborns, once they have been put on the market? One wonders where it will all end. No one knows exactly how many vaccines an individual infant will be able to safely tolerate before they shows signs of acute and chronic damage to their developing neurological and immune systems. For some infants just a single dose of vaccine is enough to cause permanent brain damage. Other children may be able to tolerate many vaccines without any obvious adverse effects. There may be many reasons for why this occurs, but it would seem likely that some children will have a genetic pre-disposition for being unable to tolerate a particular vaccine. Unfortunately, at present there is no way of screening out which children are more likely to react badly.

So the practice of vaccination for all infants has become a game of Russian roulette. And it is inevitable that some will be losers.

LONG TERM IMMUNITY FROM THE VACCINE

Hepatitis B vaccination is regarded as being "seroprotective" if hepatitis B surface antibody levels (anti-HBs) exceed 10 mIU/mL.¹⁷ It is estimated that about 95% of healthy adults will achieve adequate anti-HBs levels after 3 doses of the hepatitis B vaccine. Around 5 % of fully vaccinated individuals will not produce detectable anti-HBs. These people are called "non-responders" and are at the same risk as non-vaccinated individuals of acquiring HBV infection. It has been shown that non-response to hepatitis B vaccination is associated with a genetic predisposition (inheritance of a recessive gene). A further 10% of fully vaccinated individuals who produce only low levels of anti-HBs (10 to 100 mIU/mL) are called "hyporesponders".^{18,19}

Clinical studies performed in only very limited numbers of children have shown that seroprotection occurs in about 99% of infants under 1 year of age, who receive 3 doses of the vaccine.²⁰ It was previously recommended in the last Australian Immunisation Handbook (6th Edition, 1997) that high risk babies need only receive 3 doses of the hepatitis B vaccine at 0,1 & 6 months. Yet the NHMRC is now recommending in the latest handbook (7th Edition, 2000) that all babies should receive 4 doses at 0, 2, 4 and 6 or 12 months of age.¹ Why is an extra 4th dose now indicated? Is this just another way for vaccine manufacturers to generate increased profits?

Premature infants less than 32 weeks gestation have a poorer immunological response to the hepatitis B vaccine than term babies. Therefore the NHMRC recommends that these babies receive a total of 5 doses at 0,2,4,6 & 12 months. This is to enable a greater percentage of premature babies to achieve protective levels of anti-HBs. Alternatively, hepatitis B vaccination in low risk premature babies can be delayed until when the baby is 2 months old, and be given as a 4 dose schedule at 2,4,6 & 12 months.¹

Between 30-50% of persons who develop adequate antibody after 3 doses of vaccine will lose detectable antibody within 7 years.¹³ So there is a concern that many children vaccinated as babies will not have a measurable level of anti-HBs by the time they are 7 years of age. Therefore hepatitis B vaccination of babies would seem to be of little benefit if immunity wears off while they are still in early childhood. So the question remains as to whether hepatitis B vaccine given in infancy, without the use of boosters, will still protect people if they engage in high-risk activities when they become adults. However, the NHMRC state that:

"Babies who have been fully vaccinated against hepatitis B will not require adolescent hepatitis B vaccination or boosters. There is good evidence to show that people who complete a course of hepatitis B vaccination have long lasting immunity."¹⁴

This is an assumption that is based on the theory of "immunological memory", which proposes that immunity continues to persist for long periods despite falls in anti-HBs levels to below 10 mIU/mL. The immune system is thought to be able to provide long term protection because there remains a pool of "memory B lymphocytes" (a type of white blood cell) circulating in the blood. On exposure to the HBV, the memory B cells "remember" from years ago any previous exposure to the HBsAg from the vaccine, and can then proliferate and produce anti-HBs within days.²¹

The theory of immunological memory originally arose from a study that examined the long-term immunity of hepatitis B vaccine in adult homosexual men who were followed up for 5 years.²² The results of this study showed that sub-clinical infection with HBV can occur after vaccination (about 7% of total vaccinated), as demonstrated by the appearance of "core antibody" (anti-HBc) to HBV in serum. (This would be in comparison to the appearance of "surface antibody" (anti-HBs) that occurs in response to vaccination.) Most of the infections occurred among those who were classed as being either a non-responder or a hypo-responder to the vaccine. The risk of infection with HBV was markedly increased in those individuals with an initially adequate response to the vaccine, but whose anti-HBs levels had fallen to below 10 mIU/mL. However sub-clinical infection with HBV was only rarely associated with acute hepatitis B disease (about 1% of total vaccinated). So while the vaccine was not able to prevent HBV "infection", it was theorized that the vaccine would provide long-term protection from clinically significant "disease".²³

It should also be noted that 2 out of the 55 men infected with HBV (3.6%) became carriers.²² Therefore fully vaccinated individuals with sub-acute infection may still become carriers of the HBV even if the incidence of the acute disease is reduced. And it is HBV carriers, not those who have symptoms of acute HBV disease, who are most at risk of death from cirrhosis or liver cancer.¹ There has also been a report of a child (born to a carrier mother) in whom vaccination had initially achieved "seroprotection" but who then became a carrier at 5 years of age, after the anti-HBs level had fallen to below 10 mIU/mL at 2 years of age.²⁴

It has been suggested that immunological memory from hepatitis B vaccine is evident from the large and rapid increases in anti-HBs that occur following booster vaccinations, even in people who have previously lost antibody.

Other in vitro (artificial test-tube environment) studies have shown that the number of memory B cells able to produce anti-HBs does not diminish as anti-HBs levels decline.²⁵ However, there is still a theoretical risk that the delay between infection with HBV, and the subsequent stimulation of memory B cells to produce anti-HBs, may allow for infection of hepatocytes (liver cells) to occur.²¹

Clinically significant breakthrough infections in immunocompromised individuals (eg HIV positive and renal transplant patients)²⁶ have demonstrated that this group can not rely on immunological memory to provide long term protection. Therefore boosters are recommended for immunocompromised individuals to maintain anti-HBs above 10 mIU/mL.²¹

The NHMRC expects the hepatitis B vaccine to provide protection from clinically significant hepatitis B disease and a carrier state for many decades, from birth to throughout adulthood, without the use of boosters. Studies to date have suggested that immunological memory in children vaccinated as infants would seem to last for at least 15 years.^{21,27} However, since the highest rate of HBV infection in Australia occurs in the 20-40 year old age group⁷, it is clear that much longer follow-up studies in high-risk populations will need to continue in order to determine how many years theoretical protection via the immunological memory mechanism could be expected to last.

In the light of the above statement to parents by the NHMRC, the approved Product Information for Engerix-B (March 1999) is more cautious about making claims of long term immunity:

"It is not known whether individuals who have responded to the vaccine will require boosters to ensure long term protection or whether natural boosting without symptoms and chronic infection will occur when vaccinees with anti-HBs titres below the protective level of 10 IU/L are exposed to the virus. Until such time as there is sufficient evidence to clarify the situation, it would seem wise to recommend a booster dose when the anti-HBs level falls below 10 IU/L."¹⁷

Of growing concern is the emergence of HBV mutants, most frequently the "G145R" variant. A study in Taiwan found that in the 10 years after the introduction of universal hepatitis B vaccination, the prevalence of mutant HBsAg varieties in children identified with HBV infection had more than tripled from 7.8% in 1984 to 28.1% in 1994. The prevalence of mutants in those diagnosed with HBV infection was higher among the fully vaccinated children (36%) than among the unvaccinated (10%).²⁸

Another study from Singapore found that the G145R mutant could be transmitted horizontally from family members to vaccinated infants even in the presence of high levels of anti-HBs. Liver damage was seen in one infant who was a carrier of G145R.²⁹

It is not clear whether the hepatitis B vaccine will be able to provide protection against the growing problem of mutant varieties of HBV. It has therefore been suggested that new vaccination strategies such as the inclusion of additional antigens into the hepatitis B vaccine, capable of generating production of antibodies to the most common HBV mutants, should be considered.^{28,30}

By the time vaccinated babies become young adults, and move into an age group whereby they are more likely to engage in high risk activities, there is a possibility that immunity from the vaccine will be very low. This could be due to either an initial non-response to the vaccine, loss of seroprotective levels of anti-HBs, waning immunological memory or the emergence of HBV mutants resistant to the current hepatitis B vaccine. At the present time, the use of hepatitis B vaccine in all infants is experimental. Only time will tell whether adults who have been fully vaccinated as babies will be protected from acute hepatitis B disease and from becoming carriers.

IS THERE A "NEED" FOR HEPATITIS B VACCINE IN LOW RISK INFANTS?

The government is pushing hepatitis B vaccine on little babies as part of the long-term "strategy" to eliminate HBV from the general population. The results of this programme will take many decades to evaluate. It has been suggested that the reason why selective vaccination programs targeting high risk groups (eg male homosexuals, sexually promiscuous heterosexuals, IDU's etc) have not been successful in eliminating HBV is not because of "vaccine failure", but because of "failure to vaccinate". In other words, they are saying that the reason for the failure is because uptake of the vaccine in high risk adult groups has been low.^{3,11} Hence they have decided that the only way to control the problem is to vaccinate the entire population. As if it was not enough that the vaccine was already offered to all high school students in year 8. Now, in an effort to expand the market of this vaccine, manufacturers have successfully convinced medical "experts" from organizations such as the NHMRC that the best way to control the problem is to universally vaccinate all newborns.

Newborn babies have been targeted for hepatitis B vaccination, NOT because they are at risk of contracting HBV, but because they are easily "accessible" while they are still in hospital. From a "compliance" point of view, it is simply easier to get all babies to take the vaccine, rather than trying to target high risk groups in whom full vaccination (with 3 doses) is much more difficult to achieve.³

In November 1991 the "Centers for Disease Control and Prevention" (CDC) recommended universal hepatitis B vaccination for all infants in the USA. In the months following the implementation of this new recommendation, surveys were sent to family doctors and paediatricians to assess the effect on clinical practice. The studies found that only 17% of family doctors and only 32% of paediatricians in the North Carolina area believed that universal hepatitis B vaccination was warranted in their practice.^{31,32}

Universal hepatitis B vaccination for all newborns is a policy that is based on convenience and opportunity, not need. This is quite evident from the fact that in Australia there are now two concurrent hepatitis B vaccination schedules. Babies born before May, 2000 are not required to have the vaccine until they are 10 –13 years old. If HBV infection was ever considered to be a real risk for children in Australia, then the NHMRC would be strongly recommending that the vaccine be given to all young children. Clearly this is not the case since it is currently recommended that the vaccine only be given to babies born after May 1st, 2000.¹ This double standard, with regards to the two concurrent hepatitis B vaccination schedules, clearly demonstrates that children in low risk groups do not need the vaccine from infancy.

CONTENTS OF THE HEPATITIS B VACCINES FOR YOUNG CHILDREN

Paediatric Engerix-BTM - SmithKline Beecham (SKB):
Hepatitis B surface antigen protein 10mcg
Aluminium hydroxide 0.25mg, *Thiomersal 0.005% = 25mcg, Sodium Chloride 0.9% to 0.5mL.
(*Note: Engerix-B is now also available as a thiomersal free formulation.)

Paediatric "preservative free" H-B-VAX IITM - Merck Sharp & Dohme (MSD):
Hepatitis B surface antigen protein 5mcg
Aluminium hydroxide 0.25mg, Formaldehyde solution 0.5 – 10mcg
Borax 35mcg, Potassium Thiocyanate 0.05 – 0.25mcg, Sodium Chloride 0.9% to 0.5mL

Infanrix-HepBTM - (SKB):
Hepatitis B surface antigen protein 10mcg
Diphtheria toxoid 25 Lf, tetanus toxoid 10 Lf, pertussis toxoid 25mcg, pertussis filamentous haemagglutinin 25mcg, pertactin 8mcg
Aluminium hydroxide 0.5mg and aluminium phosphate 0.2mg,
Formaldehyde <1mcg, Phenoxyethanol 2.5mcg (used as a preservative),
Sodium chloride 0.9% to 0.5mL

Preservative free Comvax™ - (MSD):

Hepatitis B surface antigen protein 5mcg

Purified capsular polysaccharide (PRP) of the Ross Haemophilus influenzae type b strain 7.5mcg conjugated to meningococcal protein 125mcg (OMPC)

Aluminium 0.225mg (as Aluminium hydroxide), Borax 35mcg (used as a pH stabiliser), Sodium Chloride 0.9% to 0.5mL

The hepatitis B vaccine in use today is a recombinant (genetically engineered) DNA vaccine. It contains a small portion of the HBV and does not contain the whole live virus (unlike MMR or oral polio vaccines). It is therefore classed as being a "non-infectious" type of vaccine. It is made by harvesting the surface antigen (HBsAg) of the HBV that is produced from cultures of yeast cells (*Saccharomyces cerevisiae*) which have been genetically engineered to contain the relevant HBsAg gene.¹⁷ Hypersensitivity to yeast is listed as a contraindication to the hepatitis B vaccine.²⁰

Engerix-B contains a preservative called thiomersal (also known as thimerosal) that has been used since the 1930's to prevent bacterial contamination in many common vaccines (eg DTPw, DT, tetanus, Hep B, Hib, Influenza). Thiomersal is a compound that is 50% by weight mercury.³³ Mercury is a heavy metal that is easily able to cross the placenta and the blood-brain barrier to reach brain tissue.³⁴ Mercury levels have been shown to significantly increase after vaccination with a hepatitis B vaccine containing thiomersal, especially in premature infants.³⁵ There have been reports of severe mental and neurological impairment occurring in children exposed to mercury in-utero (during pregnancy).^{36,37} It would appear that an infant is most sensitive to the neurotoxic effects of mercury during the pre and post-natal periods when processes of neuronal cell division and development are very active. Neurotoxic effects can range from cerebral palsy, hearing loss, visual impairment, ataxia (loss of muscle co-ordination) to mental retardation.^{34,38} Subtle developmental delays (with motor function, language and memory) have even been found to occur in children prenatally exposed to levels of mercury previously thought to be "safe".³⁹ Therefore common sense would suggest that the only "safe" level of mercury exposure in infants is nil. Research is also currently looking into the potential for neurotoxic chemicals, such as lead and methylmercury, to induce neurobehavioural problems such as attention deficit hyperactivity disorder (ADHD).⁴⁰

There is strong evidence that heavy metals such as mercury and gold can induce auto-immune disease in humans and experimental animals (rats and mice).⁴¹ Mercury compounds are thought to act as an environmental trigger, strongly stimulating auto-antibody production and the differentiation of auto-reactive T cells towards a pathogenic pathway that leads to the development of auto-immune disease in genetically susceptible individuals.^{42,43}

There is also evidence that low levels of exposure to mercury compounds can be toxic to the human immune system, causing death of T-cell lymphocytes (white blood cells).⁴⁴ Mercury has also been shown to affect the immune system by increasing levels of the IgE antibody.⁴⁵ IgE antibodies are known to be increased in people with asthma, allergies, hayfever and eczema.⁴⁶ Acute exacerbations of atopic dermatitis (eczema) in infants, ages ranging from 7 to 28 months, has been reported to occur 2-10 days after vaccination with thiomersal containing vaccines. These infants all tested positive to patch tests that demonstrated hypersensitivity to thiomersal.⁴⁷ Severe skin hypersensitivity reactions attributed to thiomersal allergy have also been reported specifically following hepatitis B vaccination.^{48,49}

In July 1999, the CDC in the USA announced that they have asked vaccine manufacturers to remove thiomersal from all vaccines as soon as possible, due to the theoretical risk that young babies may receive a level of mercury from vaccines that is above the "safe" limit.⁵⁰ So in response to this mandate the manufacturer SKB has formulated a "preservative free" hepatitis B vaccine (H-B-VAX II) for newborn babies. This all sounds very nice, but if parents read the list of ingredients they will notice that the vaccine contains far more than just HBsAg and could hardly be described as being non-toxic and "safe".

Aluminium has no clear biological role in the human body and may take many years to be eliminated.⁵¹ It is used in many vaccines as an adjuvant, allowing for high antibody levels to be obtained by using a minimal dose of the antigen and a reduced number of inoculations.⁵² The HBsAg particles are absorbed onto aluminium hydroxide gel which stimulates a stronger immune response than if free antigen was used alone. The aluminum adjuvant also has the effect of acting like a "depot" which allows the antigen stimulus to persist for longer in the body.

Aluminium, like mercury, is a heavy metal that may also be capable of triggering auto-immune disease.⁴³ Furthermore, many studies have shown that aluminum adjuvants strongly induce the production of the IgE antibody in mice,⁵³⁻⁵⁶ rats,^{57,58} guinea pigs,⁵⁹ as well as humans.⁶⁰⁻⁶³ It does this by stimulating the immune system to produce an exaggerated Th2 response (T helper cell type 2) that acts to promote the synthesis of IgE antibodies by B cells.⁶⁴⁻⁶⁷ As mentioned previously, IgE antibodies are increased in individuals with atopic diseases such as eczema, hayfever or asthma. It has therefore been proposed that vaccines, especially those containing aluminium adjuvants (such as tetanus,^{53,55,56,59,60,68} DT61,^{63,69-71}, DTPa or DTPw,^{58,62,72-75} Hib, Hib-HepB, Hep B or DTPa-HepB), may be an environmental factor that has contributed to the large increase in rates of atopic diseases over the last 30 years.^{59,76-78} Allergy or sensitization to aluminium has also been shown to occur after repeated exposure to DTP vaccines.^{79,80}

Aluminium is readily transported into brain tissue⁸¹ and is well known to be a neurotoxic substance in animals and humans.⁸²⁻⁸⁴ Aluminium may be retained in the brain for prolonged periods suggesting that accumulation may occur with repeated exposure.⁸⁴ Injection of aluminium into animals has been shown to produce behavioural, neuropathological and neurochemical changes partially similar to Alzheimer's disease.⁸⁴ Long-term impairment of neurological development in premature infants has been associated with exposure to aluminium contained in intravenous feeding solutions. The study showed that an increase in exposure to aluminium increased the risk of decreased mental development, with the potential to contribute to future educational problems.⁸⁵

Post vaccination granuloma is a vaccine reaction caused by aluminium adjuvants, in which chronically inflamed nodules develop under the skin surface at the site of the injection.^{86,87}

The use of aluminium adjuvants in vaccines is increasingly coming under question by scientists.⁸⁸ In recent years, aluminium from vaccines has been linked with "macrophagic myofasciitis" (MMF), an emerging clinical condition that was first reported in the medical literature in 1998.⁸⁹ The spate of recent cases of MMF in France might be explained by the governments decision to vaccinate nearly 40 million adults with the hepatitis B vaccine several years ago.

Patients with MMF complain of widely spread myalgia (sore muscles), arthralgia (sore joints), muscle weakness, fever and fatigue. Muscle biopsies from patients with MMF have showed unusual tightly packed aggregations of macrophages (large cells that cleanse the body by engulfing and killing foreign material).⁸⁹ Interestingly, the macrophages contained high amounts of aluminium, even though serum aluminium levels were normal, suggesting an impaired ability to clear aluminium from the deltoid muscle.⁹⁰ Measurable quantities of aluminium have been shown to remain at the vaccine injection site for periods of up to 8 years in some patients.⁸⁸

The site of the muscle biopsy is important for demonstrating the typical pathological features that will influence the correct diagnosis of MMF. There has been a report of a 45-year-old female patient who, having had a negative biopsy of the right deltoid (upper arm), then had a positive muscle biopsy in the left deltoid, the same side that was previously injected with the hepatitis B vaccine. Likewise, her 11-year-old son who was also diagnosed with MMF gave a positive muscle biopsy result from the same side (left deltoid) that had been injected with hepatitis B vaccine. Because MMF is a very rare condition the occurrence in 2 close family members strongly suggests that a genetic predisposition may exist in some individuals.⁹¹

Of even further controversy is the observation that a sizeable portion (9%) of the patients diagnosed with MMF also developed clinical symptoms and had MRI (Magnetic Resonance Imaging) findings that were definitive of multiple sclerosis (MS).⁹² Aluminium containing vaccines (hepatitis B and/or tetanus) had been administered from 15 days to 4 years before symptoms of myalgia had begun. CNS symptoms started from 3 months to 5 years after vaccination. Aluminium adjuvants in vaccines may be a common predisposing environmental factor leading to the development of MMF and MS in some individuals. MMF is also occasionally associated with other autoimmune disorders such as systemic lupus erythematosus (SLE), rheumatoid arthritis and Hashimoto's thyroiditis.⁸⁹ The authors believe that these findings should be taken into account with the recent and controversial debate that hepatitis B vaccine may be a cause of MS. They conclude by suggesting that deltoid muscle biopsy should be performed in MS patients with myalgias to look for myopathological changes suggestive of MMF.⁹²

The replacement of aluminium with less harmful adjuvants continues to be investigated by vaccine researchers.⁹³⁻⁹⁵

Formaldehyde is a widely used chemical in pressed wood products, disinfectants and as a fixative to preserve tissues (eg embalming of bodies). During the manufacture of the hepatitis B vaccine, antigen particles are treated with formaldehyde during the sterilization process before they are adsorbed onto aluminium hydroxide. Formaldehyde is a known carcinogen and is thought to be a cause of some types of cancer.^{96,97} Exposure to formaldehyde vapour can cause symptoms such as skin rash, headaches, nose bleeds, fatigue, cough, burning eyes and IgE-mediated sensitization.⁹⁸ Hypersensitivity to formaldehyde has also been associated with eczema in haemodialysis patients.⁹⁹

Phenoxyethanol is used as a preservative in Infanrix (DTPa) and Infanrix-HepB (DTPa-Hep B) vaccines. There has been a report of generalized eczema occurring in an 18-month-old boy attributable to phenoxyethanol contained in a DTP vaccine.¹⁰⁰

Once sensitisation to vaccine allergens such as thiomersal, aluminium, formaldehyde and phenoxyethanol has occurred, re-exposure to only minute quantities of the allergen is enough to be able to trigger an allergic reaction or cause exacerbations of IgE mediated diseases such as asthma or eczema. Sensitisation to vaccines is demonstrated by the observation that the rate and severity of local reactions (eg red, painful swelling of the entire injected limb with DTPa) increases with each successive dose.^{101,102}

Parents need to seriously consider whether they should consent for their baby to be injected with a vaccine containing toxic and potentially damaging ingredients. It is known that an infant's immune and neurological systems are not fully developed. There is concern that babies (especially premature) are vulnerable to damage to the nerves in the brain, since at birth relatively few nerve pathways have a "myelin sheath". Myelin is a fatty substance that coats the nerve fibers and acts as insulation and as a protective covering. The myelin helps to confine the electrical impulses along the nerve fiber and allows the impulses to travel much more quickly.

The process of "myelination" (laying down of myelin) in the human brain continues from before birth until adulthood. Vaccination exposes unprotected nerves (especially in young infants) to damage from toxic ingredients such as aluminium, mercury and foreign proteins. Vaccination may also cause "demyelination" (destruction of existing myelin) or prevent normal myelination of nerves. From one degree to another, this can have long lasting effects on neurological development and on patterns of learning and behaviour.

It is well known that vaccines (especially DTP) can cause seizures, acute encephalopathy (degenerative disease of the brain) and permanent brain damage. If this is the case, then it is also possible that vaccines may cause a mild or sub-acute form of encephalopathy that could manifest itself in various neurological conditions such as epilepsy, autism or ADHD.

So what evidence is there to suggest that the hepatitis B vaccine DOES NOT have the potential to contribute to the development of neurological and immune system diseases? Long-term studies assessing the adverse effects of hepatitis B vaccine in newborns is an area of vaccine research that is greatly lacking.

SIDE EFFECTS OF THE HEPATITIS B VACCINE

Parents can be expected to be told by vaccination providers (usually a midwife or doctor) that the hepatitis B vaccine may cause reactions such as low grade fever, soreness, redness and swelling, nausea, feeling unwell and joint pain.¹ But what parents are not told is that infants and young children have a much greater chance of experiencing a severe adverse reaction to hepatitis B vaccine than they ever will of contacting the HBV. Parents have the right to be informed that these reactions can include things such as:

- anaphylaxis (a life threatening allergic reaction)¹⁰³
- severe skin rashes or eruptions such as erythema multiforme¹⁷ or lichen planus¹⁰⁴ (bluish purple flat skin lesions lasting from 6 months to 2 years)

- transient liver dysfunction.105
- thrombocytopenia purpura, (an autoimmune disorder that leads to destruction of platelets and bleeding into the skin, characterized by small red spots called "petechia").106-108
- pancytopenia (insufficient production of red and white blood cells from bone marrow; also known as aplastic anaemia)109
- chronic fatigue syndrome (CFS) or myalgic encephalomyelitis (ME) (symptoms such as exhaustion, muscle fatigue, aches, co-ordination and balance problems or memory loss).110,111
- reactive arthritis (joint symptoms such as swelling, pain and stiffness lasting for many months)112
- vascular diseases such as vasculitis (inflammation of blood vessels)113 or Churg-Strauss vasculitis (where development of asthma and/or sinus problems often precedes evidence of vasculitis and eosinophilia)114
- glomerulonephritis (inflammation in the kidneys).103,115
- hair loss116,117

Auto-immune disorders118 Type 1 juvenile diabetes mellitus (insulin dependant diabetes mellitus – IDDM)119,120 Systemic lupus erythematosus (SLE)103 (a systemic disease in which many tissues and cells in the body are damaged by pathogenic auto-antibodies and immune complexes.) Sjögren's syndrome (destruction of exocrine glands causing dry eyes, dry mouth, dry cough; often associated with rheumatoid arthritis)121

rheumatoid arthritis.122,123 Research as shown that hepatitis B vaccination may be more likely to trigger the development of rheumatoid arthritis in individuals with a genetic susceptibility.124,125 Most recently, Fisher et al (2001) found that in children less than 6 years of age, arthritis was up to 6 times more likely to occur in those who had received hepatitis B vaccine (OR = 5.91).126.Otitis media (acute ear infection) and pharyngitis/nasopharyngitis126, loss of vision127,128 hearing loss129 and tinnitus (ringing in the ears).17,129

Peripheral nervous system (PNS) demyelinating diseases

- paralysis17
- Bell's palsy (involves the facial nerve causing droopy eyelid and muscle paralysis on one side of the face)17
- Guillain-Barre syndrome (GBS) (also known as "acute inflammatory demyelinating polyneuropathy", causing acute generalised weakness of muscles.)130-133

Central nervous system (CNS) demyelinating diseases

- Encephalopathy (degenerative disease of the brain)17
- Transverse myelitis (inflammation of the spinal cord causing paralysis)134

Multiple sclerosis (MS)¹³⁵⁻¹⁴³ is a condition characterised by chronic encephalitis (brain inflammation) and CNS demyelination (encephalopathy) visualised on MRI scans. MS may cause many symptoms ranging from: fatigue, weakness in limbs, ataxia (loss of muscle coordination), spasticity, visual blurring (from optic neuritis), diplopia (double vision), parasthesia (abnormal neurological sensations such as tingling, "pins and needles", burning), hypoaesthesia (numbness), dysarthria (difficulty speaking), vertigo (dizziness), cognitive dysfunction (eg memory loss, impaired attention), bladder or bowel dysfunction (eg incontinence, constipation). MS usually follows a "multiphasic" course where symptoms manifest as recurrent attacks (relapses) of neurological dysfunction followed by complete or partial remissions.

Acute disseminated encephalomyelitis (ADEM)^{139,144} is a rare condition of sudden onset that is clinically very similar to MS occurring most commonly following an acute viral infection (eg measles, chickenpox) or vaccination (eg rabies, smallpox, measles). Unlike MS, ADEM is an acute disease having a "monophasic" course that is generally of a self-limiting nature. But relapses may occur, making it very difficult to distinguish from MS. Severe cases may cause fever, headache, lethargy progressing to coma, seizures, hemiparesis (paralysis affecting one side of the body), quadriparesis (paralysis affecting all four limbs), meningismus (irritation to the meninges, the layers surrounding the brain and spinal cord) and may lead to permanent neurological disability or death.

- Optic neuritis (ON)^{130,139,145,146}, a demyelinating disease of the optic nerve causing visual blurring through to blindness. ON is frequently found in patients with ADEM and MS.

- Symptoms suggestive of neurological involvement such as prolonged screaming, an abnormal cry, agitation, apnoea (where breathing stops for prolonged periods), acute cerebellar ataxia¹⁴⁷ (loss of muscle coordination), visual disturbances, convulsions, tremors, twitches, hypotonia, hypertonia, abnormal sensations, stupor, drowsiness, dizziness, neck rigidity, confusion, headache and oculogyric crisis (circular movements of the eyeballs).¹⁴⁸

- Neonatal death (usually written off as "SIDS").¹⁴⁹

It should be noted that the ACTUAL number of serious adverse events and deaths due to hepatitis B vaccine is likely to be many times higher than the official numbers REPORTED. This is done in Australia through the "Adverse Drug Reactions Advisory Committee" (ADRAC) and in the USA through the "Vaccine Adverse Event Reporting System" (VAERS). ADRAC and VAERS are both "passive" systems of reporting adverse events to vaccines.¹⁵⁰ A passive system has a gross under-reporting of events compared to an "active" (mandatory) system of surveillance, as would be

used in controlled studies. It has been estimated that as little as 1% to 10% of adverse effects are ACTUALLY reported by doctors. Reasons for under-reporting can range from apathy, lack of time to file the report to the health authorities, to lack of awareness that the reaction could possibly be linked to the administration of the vaccine.

In October 1998 the French government suspended use of hepatitis B vaccine for school children after repeated reports of autoimmune and neurological reactions. 15,000 French citizens have filed a lawsuit against the French government accusing it of understating the vaccine's risks and exaggerating the benefits for the average person.¹⁵¹ The courts have found in favour of many of these vaccine injuries.¹⁵²

Yet any suggestion that hepatitis B vaccine is responsible for being a cause of serious disorders such as MS or SIDS is always greeted with a typical response from vaccine manufacturers and government policy makers: Deny any causal association between case reports of serious adverse events and the vaccine.^{149,153} Vaccine manufacturers have a huge financial interest in promoting the widespread use of vaccines. Any "vaccine scare" has the potential to pose a serious threat to their profits. So it is obvious that their opinions and "research" will always be heavily biased in favour of the "safety" of the vaccine. Biased researchers can easily manipulate statistics and use certain types of study methods that may mask any possible causal association between serious adverse events and the vaccine.

While the CDC and vaccine manufacturers such as Merck and SmithKline Beecham acknowledge that numerous case reports have demonstrated a "temporal association" (in relation to the timing of onset of disease following vaccination) between hepatitis B vaccination and MS, they will not accept that this also means that there is a "causal relationship".^{8,140,153} In other words, it has become very easy for them to write off the many case reports of serious adverse events as occurring simply by "chance alone" and are therefore only "coincidental". They therefore feel justified to constantly re-assure the public that vaccines are "safe" and that "the benefits outweigh the risks".

Groups such as the CDC who vigorously promote hepatitis B vaccination have claimed that there is "no scientific evidence" to suggest that hepatitis B vaccine is a cause of MS. Their blatant bias and the need to maintain public confidence in government sponsored vaccination programmes have led them to come to this conclusion based on three epidemiological studies.¹⁵⁴⁻¹⁵⁶ This opinion is held in spite of the fact that the results of another three case-control studies reported an increased risk of MS after hepatitis B vaccination.¹⁴¹⁻¹⁴³ Numerous case reports in the medical literature have also shown a strong temporal association.¹³⁵⁻¹⁴⁰

There are even case reports of similar symptoms of MS recurring within weeks of individuals receiving all three consecutive shots of the vaccine.^{137,139} How much "coincidence" does one need before health authorities acknowledge that such a strong temporal association does indeed also indicate a causal association?

And there are still more questions and issues that have not yet been addressed. For example; cases of acute disseminated encephalomyelitis (ADEM), a condition very similar to MS, have occurred following hepatitis B vaccination; the same cases that have been later reclassified as MS after further relapses occurred.^{139,144} There is a fine line when distinguishing ADEM from the first episode of MS.¹⁵⁷ Schwarz et al found that 35% of adult patients initially diagnosed with ADEM later developed clinically definite MS over an observed period of 3 years.¹⁵⁸ ADEM is well known to occur following vaccination, and is thought to be caused by an auto-immune reaction to myelin proteins in the brain triggered by exogenous antigen (from vaccines or virus).¹⁵⁷ In fact, ADEM and MS are considered to be clinical counterparts to "experimental allergic encephalomyelitis" (EAE), also known as "experimental autoimmune encephalomyelitis", a condition that is induced in laboratory rats and mice by vaccines.¹⁵⁸ EAE has most notably been induced with pertussis vaccine.¹⁵⁹

Optic Neuritis (ON), a CNS demyelinating disease of the optic nerve in the eye, has also occurred following hepatitis B vaccine.^{130,139,145,146} Acute bacterial or viral infections and/or vaccination often shortly precede the development of ON. It has been reported that from about 20% to 50% of children with ON will later developed MS.^{146,160,161}

Since cases of ADEM, MS and ON have been reported following the use of hepatitis B vaccine, research should now focus on seeing if this vaccine is also capable of inducing EAE in laboratory animals. As previously mentioned, the other anomaly that needs further investigation is the interesting association between the high proportion of macrophagic myofasciitis (MMF) cases (9%) that also develop MS.⁹² MMF has been linked by the WHO to vaccines that contain aluminium, most notably the hepatitis B vaccine.⁹⁰ Therefore these findings should also be taken into account in the debate surrounding hepatitis B vaccine and MS.⁹²

Biologically plausible mechanisms add weight to the many case reports of MS associated with hepatitis B vaccine, providing further evidence for a positive causal association. "Molecular mimicry" is one such hypothesis. Autoimmunity is induced when a person's own immune system makes a "mistake" and confuses one of the body's own proteins (auto-antigen) for a foreign protein (antigen).

According to the model of molecular mimicry, the immune system is stimulated to attack, via auto-reactive T cells and/or auto-antibodies, its own protein (self or auto-antigen) that has been copied or "mimicked" by the foreign protein through the sharing of similar immunological epitopes (sites on the surface of an antigen molecule to which a single antibody molecule binds).162,163

Viral antigens have been identified as foreign proteins capable of inducing autoimmunity, via the process of molecular mimicry. The hepatitis B vaccine contains an exact replica of a protein antigen found on the surface of the HBV, and has sequences of protein polypeptides that are also present in neurological tissues such as myelin.164,165 Therefore when the immune system is signaled to recognize and destroy protein sequences found in HBsAg, it can also recognize a similar sequence of peptides found in proteins contained in myelin tissue and will act to destroy it. Demyelination of the myelin sheath then occurs, breaking it down to expose the nerve axon resulting in neurological dysfunction. It would appear that sub-populations of people with a particular genetic makeup are going to be susceptible to developing autoimmune disorders from the hepatitis B vaccine.162

It has also been recognised that HBV infection can be associated with cases of demyelinating diseases including transverse myelitis166, optic neuritis167,168, chronic inflammatory demyelinating polyneuropathy (CIDP)169-171 and Guillain-Barre syndrome (GBS).171 It has been proposed that HBsAg-immune complexes that deposit in the neuronal tissue may play a role in causing conditions characterized by demyelinating neuropathy.169-171. If the HBV is able to cause autoimmunity, is it not feasible that the hepatitis B vaccine would also be capable of inducing autoimmune diseases?172

CONCLUSION

It would appear that the real risk of having a severe adverse reaction (in the short and long term) would have to greatly outweigh any possible benefit that the hepatitis B vaccine has to offer. The old cliché "the benefits outweigh the risks" can in no way be applied to the use of hepatitis B vaccine in the majority of neonates. The only party likely to benefit from a policy of universal hepatitis B vaccination is vaccine manufacturers with the annual generation of massive profits. However it is little babies and their parents who may end up paying a very high price with chronic health problems, permanent disability, and possibly even death.

Further information on hepatitis B vaccine can also be found at:

<http://www.avn.org.au>,
<http://www.ias.org.nz>,
<http://www.909shot.com> or
<http://www.vaccines.net>.

APPENDIX: VITAMINK

Most babies in Australia are given an injection of 1mg vitamin K (Konakion® MM Paediatric) shortly after birth to prevent "Vitamin K Deficiency Bleeding" (VKDB). So parents should also consider whether they will consent for their baby to be given two injections during the first few days of the baby's life. Hepatitis B vaccine and vitamin K are both given by intramuscular (IM) injection, which is an invasive and painful procedure. Therefore to reduce trauma to the baby's limbs, the injections should be given separately in opposite legs. Alternatively, vitamin K can be given as three oral doses of 2mg: The 1st dose at birth, the 2nd dose on day 3 to 5, and the 3rd dose on day 30.¹⁷³ A small number of parents have also chosen to not give any vitamin K prophylaxis to their infant. Parents should discuss the pro's and con's of these options with their health care provider before the birth of their baby.

ABBREVIATIONS:

ADHD = Attention deficit hyperactivity disorder
ADEM = Acute disseminated encephalomyelitis
ADRAC = Adverse Drug Reactions Advisory Committee
anti-HBs = hepatitis B virus surface antibodies
ASVS = Australian Standard Vaccination Schedule
CDC = Centers for Disease Control and Prevention (USA)
CNS = central nervous system
DT = diphtheria-tetanus vaccine
DTP = diphtheria-tetanus-pertussis vaccine
DTPw = diphtheria-tetanus-pertussis whole cell vaccine
DTPa = diphtheria-tetanus-pertussis acellular vaccine
EAE = experimental allergic encephalomyelitis
HBsAg = hepatitis B surface antigen
HBeAg = hepatitis B e antigen
HBV = hepatitis B virus
Hep B = hepatitis B
Hib = Haemophilus influenzae type b
IM = intra-muscular
MMF = macrophagic myofasciitis
MMR = measles, mumps & rubella vaccine
MRI = magnetic resonance imaging

MS = multiple sclerosis
MSD = Merck Sharp & Dohme
NHMRC = National Health and Medical Research Council
ON = optic neuritis
SIDS = sudden infant death syndrome
SKB = SmithKline Beecham
VAERS = Vaccine Adverse Event Reporting System (USA) WHO = World Health Organization

REFERENCES:

1. 7th Edition of the Australian Immunisation Handbook, 2000.
2. World Health Organisation. Expanded programme on immunization. Global Advisory Group- Part 1. Wkly Epidemiol Rec 1992 Jan 17;67(3):11-15.
3. Sloan D, Ramsay M, Goldberg D, Bramley C. Commentaries following article by Larcher VF, Bourne J, Aitkin C, Jeffries D, Hodes D. Overcoming barriers to hepatitis B immunisation by a dedicated hepatitis B immunisation service. Arch Dis Child 2001 Feb;84:114-119
4. Ramsay M, Gay N, Balogun K, Collins M. Control of hepatitis B in the United Kingdom. Vaccine 1998 Nov;16 Sup:S52-55.
5. Van Damme P, Kane M, Meheus A. Integration of hepatitis B vaccination into national immunisation programmes. BMJ 1997 April 5th;314:1033.
6. Mortimer PP, Miller E. Commentary: Antenatal screening and targeting should be sufficient in some countries. BMJ 1997 April 5th;314:1036.
7. Kaldor JM, Plant AJ, Thompson SC, Longbottom H, Rowbottom J. The incidence of hepatitis B infection in Australia: an epidemiological review. MJA 1996 Sep 16th;165:322-326.
8. Burton A, Douglas RG, Mahoney et al. Perspectives on hepatitis B vaccination. JAMA 1997 April 9;277:1124-1125.
9. Marwick C, Mitka M. Debate revived on hepatitis B vaccine value. JAMA 1999 July 7;282:15-17.
10. Gust ID. Control of hepatitis B in Australia. MJA 1992 June 15th;156:819-821.
11. Douglas R. The heritage of hepatitis B vaccine. JAMA 1996 Dec 11;276(22):1796-1798.
12. Jenkins CN, Buu C, Berger W, Son DT. Liver carcinoma prevention among Asian Pacific Islanders. Cancer 2001 Jan 1st ;91(S1):252-256.
13. Protection against viral hepatitis. Recommendations of the Immunization Practices Advisory Committee (ACIP). MMWR 1990 Feb 9;39(RR02):1-26.

14. Parent Information. Understanding infant hepatitis B immunisation. Immunise Australia program, NHMRC.
15. Crofts N et al. Incidence of bloodborne virus infection and risk behaviours in a cohort of injecting drug users in Victoria, 1990-1995. MJA 1997;167:17-20.
16. Crofts N et al. The force of numbers: why hepatitis C is spreading among Australian drug users while HIV is not. MJA 1999;170:220-221
17. Engerix-B. Product Information. March 1999.
18. Alper CA et al. Genetic prediction of non-response to hepatitis B vaccine. N Eng J Med 1989 Sep 14;321(11):708-712.
19. Alper CA. The human immune response to hepatitis B surface antigen. Exp Clin Immunogenet 1995;12(3):171-81.
20. H-B-VAX II. Product Information.
21. European Consensus Group on Hepatitis B Immunity. Are booster immunisations needed for lifelong hepatitis B immunity. Lancet 2000 Feb 12;355:561-565.
22. Hadler SC et al. Long-term immunogenicity and efficacy of hepatitis B vaccine in homosexual men. N Eng J Med 1986 July 24;315(4):209-214
23. Hall AJ. Hepatitis B vaccination: Protection for how long and against what? BMJ 1993 July 31;307(6899):276-277.
24. del Canho R et al. Ten-year neonatal hepatitis B vaccination program, The Netherlands, 1982-1992: protective efficacy and long-term immunogenicity. Vaccine 1997 Oct;15(15):1624-30.
25. West DJ et al. Vaccine induced immunologic memory for hepatitis B surface antigen: implications for policy on booster vaccinations. Vaccine 1996 Aug;14(11):1019-27.
26. Goffin E et al. Acute hepatitis B infection after vaccination.[letter] Lancet 1995 Jan 28;345:263.
27. Liao S et al. Long-term efficacy of plasma-derived hepatitis B vaccine: a 15-year follow-up study among Chinese children. Vaccine 1999;17:2661-66.
28. Hsu HY et al. Changes of hepatitis B surface antigen variants in carrier children before and after universal vaccination in Taiwan. Hepatology 1999 Nov;30(5):1312-1317.
29. Oon CJ, Chen WN, Goo KS, Goh KT. Intra-familial evidence of horizontal transmission of hepatitis B virus surface antigen mutant G145R. J Infect 2000 Nov;41(3):260-264.
30. Zuckerman AJ. Effect of hepatitis B virus mutants on efficacy of vaccination. Lancet 2000, April 22;355:1382-1384.
31. Freed GL et al. Family physician acceptance of universal hepatitis B immunization of infants. J Fam Pract 1993 Feb;36(2):153-157.
32. Freed GL et al. Reactions of pediatricians to a new Centers for Disease Control recommendation for universal immunization of infants with hepatitis B vaccine. Pediatrics 1993 April;91(4):699-702.
33. American Academy of Pediatrics: Thiomersal in vaccines - An interim report to clinicians. Pediatrics 1999 Sept;104:570-4.
34. Clarkson TW. Mercury: major issues in environmental health. Environ Health Perspect 1993 April;100:31-38.

35. Stajich GV et al. Iatrogenic exposure to mercury after hepatitis B vaccination in preterm infants. *J Pediatr* 2000 May;136(5):679-681.
36. Amin-Zaki L et al. Intra-uterine methylmercury poisoning in Iraq. *Pediatrics* 1974 Nov.;54(5):587-595.
37. Amin-Zaki L et al. Prenatal methylmercury poisoning. Clinical observations over 5 years. *Am J Dis Child* 1979 Feb;133(2):172-177.
38. Clarkson TW. The toxicology of mercury. *Crit Rev Clin Lab Sci* 1997 August;34(4):369-403.
39. Grandjean P et al. Cognitive performance of children prenatally exposed to "safe" levels of methylmercury. *Environ Res* 1998 May;77(2):165-72.
40. Schmidt CW. Poisoning young minds. *Environ Health Perspect* 1999 June;107(6):A302-307.
41. Bigazzi PE. Autoimmunity and heavy metals. *Lupus* 1994 Dec;3(6):449-453.
42. Bagenstose LM, Salgame P, Monestier M. Cytokine regulation of a rodent model of mercuric chloride-induced autoimmunity. *Environ Health Perspect* 1999 Oct;107 Suppl 5:807-810.
43. Fournie GJ, Mas M, Cautain B, Savignac M, Subra JF, Pelletier L, Saoudi A, Lagrange D, Calise M, Druet P. Induction of autoimmunity through bystander effects. Lessons from immunological disorders induced by heavy metals. *J Autoimmun* 2001 May;16(3):319-326.
44. Shenker BJ et al. Low-level methylmercury exposure causes human T-cells to undergo apoptosis: evidence of mitochondrial dysfunction. *Environ Res* 1998 May;77(2):149-59.
45. Murdoch RD et al. Enhancement of antibody production by mercury and platinum group metal halide salts. Kinetics of total and ovalbumin-specific IgE synthesis. *Int Arch Allergy Appl Immunol* 1986;80(4):405-11.
46. Howarth PH. ABC of allergies. Pathogenic mechanisms: a rational basis for treatment. *BMJ* 1998 March 7;316:758-61.
47. Patrizi A et al. Sensitization to thimerosal in atopic children. *Contact Dermatitis* 1999 Feb;40(2):94-97.
48. Noel I et al. Hypersensitivity to thiomersal in hepatitis B vaccine. *Lancet* 1991 Sept 14;338:705.
49. Rietschel RL et al. Reactions to thiomersal in hepatitis B vaccines. *Dermatol Clin* 1990;8:161-164.
50. Thiomersal in vaccines: A joint statement of the American Academy of Pediatrics and the Public Health Service. *MMWR* 1999 July 9;48(26):563-565.
51. Yokel RA, McNamara PJ. Aluminium toxicokinetics: an updated mini-review. *Pharmacol Toxicol* 2001 April;88(4):159-167.
52. Fiejka M et al. [Aluminium as an adjuvant in vaccines and post vaccine reactions]. *Rocz Panstw Zakl Hig* 1993;44:73-80.
53. Takenaka T et al. Regulation by cytokines of eosinophilopoiesis and immunoglobulin E production in mice. *Immunology* 1993 April;78(4):541-546
54. Fujimaki H et al. Induction of IgE antibody production to aero-

lized ovalbumin in mice treated intratracheally with aluminium silicate. *Int Arch Allergy Appl Immunol* 1986;79(2):206-210.

55. Gupta RK et al. Comparison of adjuvant activities of aluminium phosphate, calcium phosphate and stearyl tyrosine for tetanus toxoid. *Biologicals* 1994 March;22(1):53-63

56. Isaka M et al. Intranasal or subcutaneous co-administration of recombinant cholera toxin B subunit stimulates only a slight or no level of the specific IgE response in mice to tetanus toxoid. *Vaccine* 1999 Feb 26;17(7-8):944-948.

57. Bergstrand H. et al. The non-specific enhancement of allergy. II. Precipitation of anaphylactic in vitro response capacity and serum IgE and IgG2a antibody synthesis in primed but non-responding rats by injection of alum. *Allergy* 1983 May;38(4):247-60

58. Dahlback M et al. The non-specific enhancement of allergy. III. Precipitation of bronchial anaphylactic reactivity in primed rats by injection of alum or B. pertussis vaccine: relation of response capacity to IgE and IgG2a antibody levels. *Allergy* 1983 May;38(4):261-71

59. Vassilev TL. Aluminium phosphate but not calcium phosphate stimulates the specific IgE response in guinea pigs to tetanus toxoid. *Allergy* 1978 June;33(3):155-159.

60. Cogne M et al. Total and IgE antibody levels following booster immunization with aluminum absorbed and non-absorbed tetanus toxoid in humans. *Ann Allergy* 1985 Feb;54(2):148-51.

61. Mark A. et al. Immunoglobulin E responses to diphtheria and tetanus toxoids after booster with aluminium-adsorbed and fluid DT-vaccines. *Vaccine* 1995 May;13(7):669-73

62. Odelram H et al. Immunoglobulin E and G responses to pertussis toxin after booster immunization in relation to atopy, local reactions and aluminium content of the vaccines. *Pediatr Allergy Immunol* 1994 May;5(2):118-23

63. Aggerbeck H et al. Booster vaccination against diphtheria and tetanus in man. Comparison of calcium phosphate and aluminium hydroxide as adjuvants—II. *Vaccine* 1995 Oct;13(14):1366-74.

64. Grun JL et al. Different T helper cell subsets elicited in mice utilizing two different adjuvant vehicles: the role of endogenous interleukin 1 in proliferative responses. *Cell Immunol* 1989 June;121(1):134-145.

65. Brewer JM et al. In interleukin-4-deficient mice, alum not only generates T helper 1 responses equivalent to Freund's complete adjuvant, but continues to induce T helper 2 cytokine production. *Eur J Immunol* 1996 Sep;26(9):2062-6.

66. Brewer JM et al. Cytokines and the mechanisms of action of vaccine adjuvants. *Cytokines Cell Mol Ther* 1997 Dec;3:233-46

67. Brewer JM et al. Aluminium hydroxide adjuvant initiates strong antigen-specific Th2 responses in the absence of IL-4 or IL-13 mediated signaling. *J Immunology* 1999 Dec 15;163(12):6448-54.

68. Aalberse RC et al. IgE antibodies to tetanus toxoid in relation to atopy. *Int Arch Allergy Immunol* 1995 May-Jun;107(1-3):169-71

69. Dannemann A. et al. Specific IgE and IgG4 immune responses to tetanus and diphtheria toxoid in atopic and nonatopic children during the first two years of life. *Int Arch Allergy Immunol* 1996 Nov;111(3):262-7
70. Mark A. et al. Immunoglobulin E and G antibodies two years after a booster dose of an aluminium-adsorbed or a fluid DT vaccine in relation to atopy. *Pediatr Allergy Immunol* 1997 May;8(2):83-7
71. Nagel J. et al. IgE synthesis in man. I Development of specific IgE antibodies after immunization with tetanus-diphtheria (Td) toxoids. *J Immunol* 1977 Jan;118(1):334-41
72. Odent MR, Culpin EE, Kimmel T. Pertussis vaccination and asthma: Is there a link? *JAMA* 1994; 272(8): 592-593.
73. Kemp T et al. Is infant immunization a risk factor for childhood asthma or allergy? *Epidemiology* 1997 Nov; 8: 678-680.
74. Farooqi IS, Hopkin MH. Early childhood infection and atopic disorder. *Thorax* 1998 November; 53: 927-932
75. Hurwitz EL, Morgenstren H. Effects of Diphtheria-Tetanus-Pertussis or Tetanus vaccination on allergies and allergy-related respiratory symptoms among children and adolescents in the United States. *J. Manipulative & Physiological Therapeutics* 2000 Feb; 23(2):81-90
76. Björkstén B. Risk factors in early childhood for the development of atopic disease. *Allergy* 1994;49:400-407.
77. Taylor-Robinson AW. Multiple vaccination effects on atopy. *Allergy* 1999 April;54(4):398-399.
78. Brehler R, Luger TA. Atopy: Immunodeviation and environment. *J Allergy & Clin Immunol* 1999 Dec;104(6):1128-30
79. Nielson AO et al. [Aluminium allergy caused by DTP vaccine.] *Ugeskr Laeger* 1992 June 29;154(27):1900-1901.
80. Veien NK et al. Aluminium allergy. *Contact Dermatitis* 1986 Nov;15(5):295-297.
81. Redhead K et al. Aluminium-adjuvanted vaccines transiently increase aluminium levels in murine brain tissue. *Pharmacol Toxicol* 1992 April;70(4):278-80.
82. Committee on Nutrition. Aluminium toxicity in infants and children. *Pediatrics* 1986 Dec;78(6):1150-1154.
83. Erasmus RT et al. Aluminium neurotoxicity in experimental animals. *Ther Drug Monit* 1993 Dec;15(6):588-592.
84. Yokel RA. The toxicology of aluminium in the brain: a review. *Neurotoxicology* 2000 Oct;21(5):813-828.
85. Bishop NJ et al. Aluminium neurotoxicity in preterm infants receiving intravenous-feeding solutions. *N Eng J Med* 1997 May 29;336(22):1557-61.
86. Bordet AL, Michenet P, Cohen C, Arbion F, Ekindi N, Bonneau C, Kerdraon R, Coville M. Post-vaccination granuloma due to aluminium. *Ann Pathol* 2001 April;21(2):149-152.
87. Wolf F, Grezard P, Berard F, Clavel G, Perrot H. Generalized granuloma annulare and hepatitis B vaccination. *Eur J Dermatol* 1998 Sep;8(6):435-436.

88. Malakoff D. Public health. Aluminium is put on trial as a vaccine booster. *Science* 2000 May 26;288(5470):1323-1324.
89. Gherardi RK, Coquet M, Cherin P, Authier FJ, Laforet P, Belec L et al. Macrophagic myofasciitis: an emerging entity. *Lancet* 1998;353:347-352.
90. WHO Vaccine Safety Advisory Committee. Macrophagic myofasciitis and aluminium-containing vaccines. *WklyEpidemiol Rec* 1999;74:337-340.
91. Amoura Z, Costedoat N, Maisonobe T, Godeau P, Piette JC. Familial macrophagic myofasciitis. *Ann Rheum Dis* 2000 Nov;59:926.
92. Authier FJ, Cherin P, Creange A, Bonnotte B, Ferrer X, Abdelmoumni A, Ranoux D, Pelletier J, Figarella-Branger D, Granel B, Maisonobe T, Coquet M, Degos JD, Gherardi RK. Central nervous system disease in patients with macrophagic myofasciitis. *Brain* 2001 May;124(5):974-983.
93. Gupta RK, Rost BE, Relyveld E, Siber GR. Adjuvant properties of aluminium and calcium compounds. *Pharm Biotechnol* 1995;6:229-248.
94. Gupta RK, Siber GR. Adjuvants for human vaccines - current status, problems and future prospects. *Vaccine* 1995 Oct;13(14):1263-1276.
95. Davis HL. DNA vaccines for prophylactic or therapeutic immunization against hepatitis B virus. *Mt Sinai J Med* 1999 March;66(2):84-90.
96. Formaldehyde. Council on Scientific Affairs. *JAMA* 1989 Feb 24;261(8):1183-1187.
97. Blair A et al. Epidemiological evidence on the relationship between formaldehyde exposure and cancer. *Scand J Work Environ Health* 1990 Dec;16(6):381-393.
98. Wantke F et al. Exposure to gaseous formaldehyde induces IgE-mediated sensitization to formaldehyde in school-children. *Clin Exp Allergy* 1996 Mar;26(3):276-280.
99. Kessler M et al. [Allergic risks of hemodialysis. Results of an allergologic investigation in 138 patients.] *Nephrologie* 1990;11(4):249-254.
100. Vogt T et al. Generalized eczema in an 18-month-old boy due to phenoxyethanol in DTP vaccine. *Contact Dermatitis* 1998 Jan;38(1):50-51.
101. Rennels MB et al. Extensive swelling after booster doses of acellular pertussis-tetanus-diphtheria vaccines. *Pediatrics* 2000 Jan;105(1):e12.
102. Deloria MA et al. Association of reactions after consecutive acellular or whole-cell pertussis vaccine immunizations. *Pediatrics* 1995;96:592-594.
103. Grotto I et al. Major adverse reactions to yeast-derived hepatitis B vaccines - a review. *Vaccine* 1998 Feb;16(4):329-34.
104. Usman A, Kimyai-Asadi A, Stiller MJ, Alam M. Lichenoid eruption following hepatitis B vaccination: First North American case report. *Pediatr Dermatol* 2001 March-April;18(2):123-126.
105. Lilic D et al. Liver Dysfunction and DNA antibodies after hepatitis B vaccination. *Lancet* 1994 Nov 5;344(8932):1292-1293.
106. Poullin P et al. Thrombocytopenic purpura after recombinant hepatitis B vaccine. *Lancet* 1994 Nov 5;344(8932):1293.

107. Neau D et al. Immune thrombocytopenic purpura after recombinant hepatitis B vaccine: retrospective study of seven cases. *Scand J Infect Dis* 1998;30(2):115-118.
108. Ronchi F et al. Thrombocytopenic purpura as adverse reaction to recombinant hepatitis B vaccine. *Arch Dis Child* 1998 March;78(3):273-274.
109. Viallard JF, Boiron JM, Parrens M, Moreau JF, Ranchin V, Reiffers J, Leng B, Pellegrin JL. Severe pancytopenia triggered by recombinant hepatitis B vaccine. *Br J Haematol* 2000 July;110(1):230-233.
110. Report of the Working Group on the Possible Relationship between Hepatitis B Vaccination and the Chronic Fatigue Syndrome. *Can Med Assoc J* 1993 August 1;149(3):314-316.
111. Fleming C. The glass cage. *BMJ* 1994 March 19; 308:797.
112. Hassan W et al. Reiter's syndrome and reactive arthritis in health care workers after vaccination. *BMJ* 1994 July 9;309:94
113. Le Hello C et al. Suspected hepatitis B vaccination related vasculitis. *J Rheumatol* 1999 Jan;26(1):191-194.
114. Vanoli M, Gambini D, Scorza R. A case of Churg-Strauss vasculitis after hepatitis B vaccination. *Ann Rheum Dis* 1998 April;57:256-257.
115. Carmeli Y et al. Hepatitis B vaccine side-effect. *Lancet* 1993 Jan 23;341(8839):250-251.
116. Wise RP et al. Hair loss after routine immunizations. *JAMA* 1997 October 8;278(14):1176-8.
117. Sepkowitz S. Hair loss after immunization [letter]. *JAMA* 1998 January 14;279(2):117-118.
118. Cohen AD et al. Vaccine-induced autoimmunity. *J Autoimmun* 1996 Dec;9(6):699-703.
119. Classen JB. Childhood immunisation and diabetes mellitus. *N Z Med J* 1996 May 24;109(1022):195
120. Classen JB. The diabetes epidemic and the hepatitis B vaccines. *N Z Med J* 1996 Sep 27;109(1030):366
121. Toussirot E, Lohse A, Wendling D, Mougin C. Sjögren's syndrome occurring after hepatitis B vaccination. *Arthritis Rheum* 2000 Sep;43(9):2139-2140.
122. Biasi D et al. [Rheumatological manifestations following hepatitis B vaccination. A report of 2 clinical cases]. *Recenti Prog Med* 1994 Sep;85(9):438-40.
123. Maillefert JF et al. Rheumatic disorders developed after hepatitis B vaccination. *Rheumatology (Oxford)* 1999 Oct;38(10):978-83.
124. Pope JE et al. The development of rheumatoid arthritis after recombinant hepatitis B vaccination. *J Rheumatol* 1998 Sep;25(9):1687-93.
125. Gross K et al. Arthritis after hepatitis B vaccination. Report of 3 cases. *Scand J Rheumatol* 1995;24(1):50-52.
126. Fisher MA, Eklund SA, James SA, Lin X. Adverse events associated with hepatitis B vaccine in U.S. children less than six years of age, 1993 and 1994. *Ann Epidemiol* 2001 Jan;11(1):12-21.
127. Baglivo E et al. Multiple evanescent white dot syndrome after

hepatitis B vaccine. *Am J Ophthalmol* 1996 Sep;122:431-2.

128. Brezin AP et al. Visual loss and eosinophilia after recombinant hepatitis B vaccine. *Lancet* 1993 Aug 28;342(8870):563-4.

129. Bonfils P et al. [Fluctuant perception hearing loss after hepatitis B vaccine.] *Ann Otolaryngol Chir Cervicofac* 1996;113(6):359-361.

130. Reactions to hepatitis B vaccines. *Australian Adverse Drug Reactions Bulletin* 1990 August.

131. Creange A et al. Lumbosacral acute demyelinating polyneuropathy following hepatitis B vaccination. *Autoimmunity* 1999;30(3):143-146.

132. Sinsawaiwong S, Thampanitchawong P. Guillain - Barre syndrome following recombinant hepatitis B vaccine and literature review. *J Med Assoc Thai* 2000 Sep;83(9):1124-1126.

133. Shaw FE et al. Postmarketing surveillance for neurologic adverse events reported after hepatitis B vaccination. Experience of the first three years. *Am J Epidemiol* 1988 Feb;127(2):337-52.

134. Renard JL et al. Acute transverse cervical myelitis following hepatitis B vaccination. Evolution of anti-HBs antibodies. *Presse Med* 1999 July 3-10;28(24):1290-2.

135. Herroelen L, de Keyser J, Ebinger G. Central-nervous system demyelination after immunisation with recombinant hepatitis B vaccine. *Lancet* 1991 Nov 9th;338(8776):1174-1175.

136. Nadler JP. Multiple sclerosis and hepatitis B vaccination. *Clin Infect Dis* 1993 Nov;17(5):928-929.

137. Kaplanski G, Retornaz F, Durand J, Soubeyrand J. Central nervous system demyelination after vaccination against hepatitis B and HLA haplotype. *J Neurol Neurosurg Psychiatry* 1995 June;58(6):758-759.

138. Gout O, Theodorou I, Liblau R, Lyon-Caen O. Central nervous system demyelination after recombinant hepatitis B vaccination. Report of 25 cases. *Neurology* 1997;48:Suppl:A424. Abstract.

139. Tourbah A, Gout O, Liblau R, Lyon-Caen O, Bougniot C, Iba-Zizen MT, Cabanis EA. Encephalitis after hepatitis B vaccination: recurrent disseminated encephalitis or MS? *Neurology* 1999 July 22nd;53(2):396-401.

140. Soubeyrand B et al. [Central nervous system demyelinating disease following hepatitis B vaccination with GenHevac B. Review of ten years of spontaneous notifications (1989-1998)]. *Presse Med* 2000 April 15th;29(14):775-80

141. Touze E, Gout O, Verdier-Taillefer MH, Lyon-Caen O, Alperovitch A. [The first episode of central nervous system demyelination and hepatitis B virus vaccination.] *Rev Neurol (Paris)* 2000 Mar;156(3):242-246.

142. Fourrier A, Touze E, Alperovitch A, Begaud B. Association between hepatitis B vaccine and multiple sclerosis. *Pharmacoepidemiol Drug Safety* 1999;8:Suppl:S140-S141. Abstract.

143. Sturkenboom MCJM, Abenheim L, Wolfson C, Roulet E, Heinzelf O, Gout O. Vaccinations, Demyelination and Multiple Sclerosis Study (VDAMS), a population-based study in the UK. *Pharmacoepidemiol Drug Safety* 1999;8:Suppl:S170-S171. Abstract.

144. Hynson JL, Kornberg AJ, Coleman LT, Shield L, Harvey AS, Kean MJ.

Clinical and neuroradiologic features of acute disseminated encephalomyelitis in children. *Neurology* 2001 May 22;56(10):1308-1312.

145. Stewart O et al. Simultaneous administration of hepatitis B and polio vaccines associated with bilateral optic neuritis. *Br J Ophthalmol* 1999 Oct;83(10):1200-1201.

146. Roussat B, Gohier P, Doummar D, Iba-Zizen MT, Barbat V, Jarry D, Cabanis EA, Hamard H, Nordmann JP. [Acute optic neuritis in children: clinical features and treatment. A study of 28 eyes in 20 children.] *J Fr Ophtalmol* 2001 Jan;24(1):36-44.

147. Deisenhammer F et al. Acute cerebellar ataxia after immunisation with recombinant hepatitis B vaccine. *Acta Neurol Scand* 1994 June;89(6):462-463.

148. Jane Orient, M.D., Statement of the ASSOCIATION OF AMERICAN PHYSICIANS & SURGEONS (APPS) to the US House subcommittee on Criminal Justice, Drug Policy and Human Resources of the Committee on Government Reform U.S. House of Representatives. Hearing into the safety of hepatitis B vaccine. June 14th 1999. <http://www.avn.org.au/hepb2.htm>

149. Nui MT et al. Neonatal death after hepatitis B vaccine: the vaccine adverse event reporting system, 1991-1998. *Arch Pediatr Adolesc Med* 1999 Dec;153(12):1279-82.

150. Rosenthal S et al. The reporting sensitivities of two passive surveillance systems for vaccine adverse events. *Am J Public Health* 1995 Dec;85(12):1706-9.

151. Suspension of hepatitis B vaccination condemned. *BMJ* 1998 Oct 17th;317:1074.

152. Durand de Bousingen D. Drug firm compensates patients for suspected hepatitis B vaccine failure. *Lancet* 2001 May 19th;357:1598.

153. Monteyne P, Andre FE (Smith Kline Beecham Biologicals). Is there a causal link between hepatitis B vaccination and multiple sclerosis? *Vaccine* 2000 April 3;18(19):1994-2001.

154. Zipp F, Weil JG, Einhaupl KM. No increase in demyelinating diseases after hepatitis B vaccination. *Nat Med* 1999;5:964-65.

155. Sadovnick AD, Scheifele DW. School-based hepatitis B vaccination programme and adolescent multiple sclerosis. *Lancet* 2000 Feb 12th;355:549-550.

156. Ascherio A, Zhang SM, Hernan MA, Olek MJ, Coplan PM, Brodovicz K, Walker AM. Hepatitis B vaccination and the risk of multiple sclerosis. *N Engl J Med* 2001 Feb 1st;344(5):327-332.

157. Hartung HP, Grossman RI. ADEM. Distinct disease or part of the MS spectrum. *Neurology* 2001 May;56:1257-1260.

158. Schwarz S, Mohr A, Knauth M, Wildemann B, Storch-Hagenlocher B. Acute disseminated encephalomyelitis. A follow-up study of 40 adult patients. *Neurology* 2001 May;56:1313-1318.

159. Lublin FD. Delayed, relapsing experimental allergic encephalomyelitis in mice. Role of adjuvants and pertussis vaccine. *J Neurol Sci* 1982 Nov-Dec;57(1):105-110.

160. Riikonen R et al. Optic neuritis in children and its relationship

to multiple sclerosis: a clinical study of 21 children. *Dev Med Child Neurol* 1998 June;30(3):349-359.

161. Riikonen R. The role of infection and vaccination in the genesis of optic neuritis and multiple sclerosis in children. *Acta Neurol Scand* 1989 Nov;80(5):425-431.

162. Ewing C et al. Insights into the aetiology and pathogenesis of multiple sclerosis. *Immunol Cell Biol* 1998 Feb;76(1):47-54.

163. Gran B et al. Molecular mimicry and multiple sclerosis – a possible role for degenerate T cell recognition in the induction of autoimmune responses. *J Neural Trans Suppl* 1999;55:19-31.

164. Fujinami RS, Oldstone MB. Amino acid homology between the encephalitogenic site of myelin basic protein and virus: mechanism for autoimmunity. *Science* 1985 Nov 29;230(4729):1043-1045.

165. Shaw Sy et al. Analogous amino acid sequences in myelin proteolipid and viral proteins. *FEBS Lett* 1986 Oct 27; 207(2):266-270.

166. Matsui M et al. Recurrent demyelinating transverse myelitis in a high titre HBs-antigen carrier. *J Neurol Sci* 1996 Aug;139(2):235-237.

167. Galli M, Morelli R, Casellato A, Perna MC. Retrobulbar optic neuritis in a patient with acute type B hepatitis. *J Neurol Sci* 1986 Feb;72(2-3):195-200.

168. Achiron LR. Postinfectious hepatitis B optic neuritis. *Optom Vis Sci* 1994 Jan;71(1):53-56.

169. Tsukada N et al. Chronic neuropathy associated with immune complexes of hepatitis B virus. *J Neurol Sci* 1983 Oct;61(2):193-210.

170. Inoue A et al. Chronic relapsing demyelinating polyneuropathy associated with hepatitis B infection. *Neurology* 1987 Oct;37(10):1663-1666.

171. Tsukada N et al. Demyelinating neuropathy associated with hepatitis B virus infection. Detection of immune complexes composed of hepatitis B virus surface antigen. *J Neurol Sci* 1987 Feb;77(2-3):203-216.

172. Shoenfeld Y et al. Vaccination and autoimmunity-‘vaccinosis’: a dangerous liaison? *J Autoimmun* 2000 Feb;14(1):1-10.

173. Konakion MM Paediatric. Product Information.