



## The Vaccines

### Monovalent hepatitis B vaccine

Hepatitis B vaccines (HBV) are composed of highly purified preparations of hepatitis B "s" antigen (HBsAg). This glycoprotein is a component of the outer envelope of the hepatitis B virus, and is also found as 22-nm spheres and tubular forms in the serum of people with acute and chronic infection. Early vaccines were prepared by harvesting HBsAg from the plasma of people with chronic infection (plasma derived vaccine) while more recent ones are obtained by expressing plasmids containing the corresponding gene in yeast or mammalian cells (recombinant DNA vaccine). An adjuvant, aluminium phosphate or aluminium hydroxide, is added to the vaccines that are also preserved with thiomersal when used in multi-dose vials. The concentration of HBsAg varies from 2.5 to 40 µg per dose, depending on the manufacturer (CDC, 1996; Mahoney et al., 1999). More than half a billion people have been immunized in the world since the beginning of the implementation of universal programmes, with very effective vaccine products, which are considered extremely safe.

### Combination hepatitis B vaccine

*Hepatitis A and B combinations* - This combines hepatitis B and A antigens in formulations that are suitable for paediatric or adult use.

*Hepatitis B combined with DTP, Hib and/or IPV* - Hepatitis B has been combined with acellular or whole cell pertussis antigens diphtheria, tetanus, Haemophilus influenzae type b (Hib) and/or inactivated poliomyelitis (IPV) in multiple vaccine preparations with four to six diseases being prevented from a single vaccine product.

## Adverse events

### Mild adverse events

In general, there are minimal reactions, such as local pain, myalgia and transient fever, mostly within 24 hours (see Table 1). Mild reactions tend to be less common in children than in adults (<10% vs. 30%). Several studies have compared reactions after different vaccines (Greenberg, 1996), different concentrations of the same vaccine (Pooverawan, 1993; Tan, 1990) and different schedules (Goldfarb, 1994; Giammanco, 1998). Some studies described reactions of a single vaccine (Soulie, 1991; McMahon, 1992; Leroux-Roels, 1997) or a novel adjuvant system (Thoelen, 1998). All report mild local and general reactions, lasting less than 48 hours.

### Severe adverse events

*Anaphylactic reactions* - The estimated incidence of anaphylaxis among vaccine recipients is 1.1 per million vaccine doses (95% CI 0.1-3.9) (Bohkle et al., 2003).

## Other safety issues

Despite numerous long-term studies, there is no evidence of serious adverse events that have been causally linked to hepatitis B vaccination. Several conditions that have been considered in the scientific literature are discussed below.

*Neurological disease* - There have been a number of severe neurological adverse events reported after hepatitis B vaccines and these primarily have included Guillain-Barré syndrome and multiple sclerosis (Shaw, 1988; Herroelen, 1991; Mahassin, 1993; Trevisani, 1993; Nadler, 1993; Tartaglino, 1995; Mahoney et al., 1999). Establishing a causal relationship between these diseases and hepatitis B vaccination is difficult because these conditions are rare, have a poorly understood pathogenesis, occur in the absence of hepatitis B vaccination and the onset of symptoms may be reported weeks to months after vaccination has occurred.

*Guillain-Barré Syndrome (GBS)* - The pathogenesis of GBS is poorly understood but it seems that GBS may be triggered by infection such as flu-like illness or with *Campylobacter jejuni*. Rarely, GBS has been reported to follow hepatitis B infection. Following the introduction of plasma-derived hepatitis B vaccine in the US, the possible association between GBS and a receipt of the first dose of vaccine was suggested (CDC, 1991). In 1991, GBS was reported at a very low rate (0.5 per 100 000 vaccine recipients). A review of case reports of adverse events and positive re-challenge of symptoms after hepatitis B vaccination has been interpreted as suggesting that vaccination could cause or trigger GBS in certain susceptible vaccine recipients (Geier et al., 2004). However, on the basis of a careful review of all available evidence and advice from the Global Advisory Committee on Vaccine Safety (GACVS), WHO considers that the complete data do not indicate a causal relationship between hepatitis B vaccine and GBS (WHO, 2009).

*Multiple sclerosis (MS)* - In France and the UK concern was raised in the communities that hepatitis B immunization might be linked with new cases or flare-ups of MS or other demyelinating diseases (Duclos, 2003). GACVS considers that data from spontaneous reports and epidemiological studies do not support a causal relationship between MS and hepatitis B vaccine. (Wkly Epidem Rec, 1997 and 2004). Compared to the background rate of MS in France, which is 1 to 3 cases per 100 000 persons, the notification rate of demyelinating diseases in temporal association with hepatitis B vaccination was 0.6 per 100 000 during the period from

December 1994 and December 1996. Observations in other countries show similar patterns to that observed in France; that is 0.1 to 0.8 cases of demyelinating disease per 100 000 vaccine recipients (Australia, Belgium, Canada, Germany, India, United Kingdom, United States) which corresponds to the usual background rate of disease occurrence. A number of studies have examined the association between MS and hepatitis B vaccination and the majority do not support an association (Zipp F et al., 1999, Sandovnick AD et al., 2000, Ascherio A et al., 2001, Touze et al., 2002, De Stefano et al., 2003) including a re-analysis using a new design that compares cases only (Hocine et al., 2007).

However, these findings have also been challenged. In a nested case-control study within the General Practice Research Database (GPRD) in the United Kingdom patients who had a first MS diagnosis recorded were compared with controls. The analyses include 163 cases of MS and 1,604 controls and the OR of MS for vaccination within 3 years before the index date compared to no vaccination was 3.1 (95% CI 1.5, 6.3). No increased risk of MS was associated with other vaccines which included tetanus and influenza vaccinations. The authors concluded that immunization with the recombinant hepatitis B vaccine is associated with an increased risk of MS (Hernan et al., 2004). The recent review by the U.S. Institute of Medicine included that study, three other epidemiological studies and one mechanistic study on the association of MS with hepatitis B. They concluded that the evidence is inadequate to accept or reject a causal relationship between hepatitis B vaccine and onset of MS in adults (IOM 2011). No similar neurological adverse events have been reported in infants (Levy-Bruhl et al., 1999, Mikaeloff Y et al., 2007).

The Global Advisory Committee on Vaccine Safety has concluded that analysis of data from spontaneous reports and epidemiological studies does not support a causal relationship between MS and hepatitis B vaccine. The most likely explanation is a coincidental association. The WHO recommendations, are that all countries should have universal infant and/or adolescent immunization programmes, and continue to immunize adults who may have an increased risk of hepatitis B (Hall et al., 1999; Halsey et al., 1999).

*Diabetes mellitus (DM)* - Claims have been made that administration of vaccines including hepatitis B vaccine can cause type I diabetes (juvenile or insulin-dependent diabetes mellitus – IDDM) in rats (Classen JB, 1996) and children (Classen JB et al., 1997). There is no evidence to support this claim (Karvonen M et al., 1999; Jefferson T et al., 1998). In Finland, elimination of mumps by immunization has coincided with a decrease in IDDM (Hyoty, 1993). Studies in Sweden failed to find a decrease in diabetes after stopping BCG (Dahlquist, 1995) or pertussis immunization (Heijbel, 1997). Similar studies and results have been documented in Sweden (Blom, 1991) and Canada (Parent, 1997). However, evidence from ecological studies of this type are very weak in determining the presence or absence of causality. A panel review of all the evidence to date was held in the United States and this found no association (Institute of Medicine, 1999; Institute of Medicine, 2011).

*Chronic fatigue syndrome (CFS)* - In Canada, during 1993–94, CFS was reported after hepatitis B vaccination (Delage et al., 1993). However, the Global Advisory Committee on Vaccine Safety Committee has concluded that, based on the evidence available, there are no grounds to support the association between CFS and Hepatitis B vaccination ([http://www.who.int/vaccine\\_safety/topics/hepatitisb/CFS/en/index.html](http://www.who.int/vaccine_safety/topics/hepatitisb/CFS/en/index.html)).

*Hair loss* - Hair loss has been reported after routine immunization, especially following hepatitis B vaccine (Wise B et al., 1997). Hair loss is a common event and it is extremely difficult to confirm a causal association with hepatitis B vaccine administration.

*Other auto-immune conditions* – A vaccine safety data linkage study has not demonstrated an increased risk of Graves disease or auto-immune thyroiditis following hepatitis B vaccination nor any association between the time interval since receipt of the vaccine and development of these conditions (Yu O et al., 2007).

*Hepatitis B in neonates and infants* - A recent review by the Food and Drug Administration (FDA) of case reports in the Vaccine Adverse Events Reporting System for the years 1991 to 1994 concluded that there were no unexpected adverse events in neonates and infants given hepatitis B vaccine. This was despite the use of at least 12 million doses of vaccine in these age groups (Mahoney FJ et al., 1999). Fever is reported to occur in 0.6 to 3.7% of neonates.

*Allergy to yeast* – An immune mediated allergy to yeast is considered a contraindication to immunisation with plasmid derived hepatitis B vaccine. One study suggested that *hepatitis B vaccination is associated with onset of wheezing episodes (Mullooly JP, et al.)*.

## Summary of mild and severe adverse events – Hepatitis B vaccine

Nature of Adverse event	Description	Rate/doses
Mild	<u>Local reactions</u>	
	Pain	3-29 per 100
	Erythema	3 per 100
	Swelling	3 per 100
	<u>Generalized reactions</u>	
	Temperature greater than 37.7°C	1-6 in 100
	Headache	3 in 100
Severe	Anaphylaxis	1.1 per 10 <sup>6</sup>

This information sheet has been developed in close collaboration with the Global Advisory Committee on Vaccine Safety (GACVS). GACVS experts are independent and have declared no interests related to the expertise displayed in this product. Information displayed has been developed using primary sources such as (Plotkin et al., 2008, Institute of Medicine of the National Academies, 2011) and from data derived from a literature search on Pubmed in 2008 using key words “vaccine antigen”, “Safety” and “adverse events”. An independent expert provided a first draft which was reviewed by nominated experts and the GACVS. Data of different vaccines that may be found in this product should only be compared if there is indication that a comparative randomised controlled trial has been undertaken. The information sheets will be updated as new information may become available at the following web link: [http://www.who.int/vaccine\\_safety/vaccrates/en/index.html](http://www.who.int/vaccine_safety/vaccrates/en/index.html)



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