



The Vaccines

Monovalent Hib vaccine

Several *Haemophilus influenzae* type b (Hib) conjugate vaccines have been developed and licensed. All vaccines contain the polyribosylribitol phosphate (PRP) isolated from the Hib capsule. The immunogenicity of PRP is limited in children under 2 years of age and requires conjugation to a protein carrier. Four different carrier types have been used – diphtheria toxoid (PRP-D), tetanus toxoid (PRP-T), CRM₁₉₇ (a non-toxic variant of diphtheria toxin HbOC), and the outer membrane protein complex of serogroup B *Neisseria meningitidis* (PRP-OMP). Thiomersal and adjuvants have been used in some preparations.

Although the vaccines differ in the protein carrier used, the size of the polysaccharide, the type of linkage, and immunogenicity there are no marked differences in the adverse event profile between Hib vaccines (Ward & Zangwill, 1999).

Combination Hib vaccines

Hib is combined with a number of antigens which include DTaP, DTwP, Hep B, IPV and meningococcal conjugate vaccines.

Adverse events with monovalent Hib vaccines

Mild adverse events

Local adverse events; Injection site reactions are common following administration of Hib vaccines. Within 24 hours of vaccination, 20-25% of recipients may experience pain and tenderness at the injection site (Institute of Medicine, 1994). These reactions are generally mild and transient. In most cases, they spontaneously resolve within two to three days and further medical attention is not required (Fritzell & Plotkin, 1992).

Systemic adverse events; Fever occurs in 2% of vaccinees (Valdheim et al., 1990).

Severe adverse events

Severe adverse events following administration of Hib vaccine are uncommon, making it one of the safest vaccines currently available. In a study of >4000 infants, there were no differences in the type and frequency of severe adverse events occurring among those receiving Hib conjugate vaccine and those receiving a placebo (CDC, 1991).

Adverse events with combination Hib vaccines

Hib–DTP: A combination of *Haemophilus influenzae* type b vaccine–diphtheria toxoid conjugate with diphtheria–tetanus–acellular pertussis (DTaP) vaccine did not result in significant differences in safety (Kovel et al., 1992) compared to DTaP alone. The rates of local and systemic adverse events did not differ according to the site of injection, arm versus thigh, or the concurrent or combined administration of DTwP (Scheifele et al., 1992).

The safety profile of combined HbOC–DTwP is comparable to that of the vaccines co-administered at separate injection sites. The incidence of local and systemic reactions is similar (Madore et al., 1990; Paradiso et al., 1993; Black et al., 1993; CDC, 1993). One exception is for swelling, not associated with increased tenderness or fever, after the first dose, which was more common (8.0% vs. 4.3%) with the combined product Hb–OC products in one study (Black et al., 1993).

The administration on the same day of either MMR vaccine or DTwP+OPV vaccine together with PRP-OMPC results in an increase in the rates of fever or irritability from 35% to 71% (Dashefsky et al., 1990). After PRP-T vaccine, no severe side-effects were observed and the rate of adverse reactions was consistent with the concurrent administration of diphtheria–tetanus–pertussis vaccine infants (Mulholland et al., 1994), children (Fritzell & Plotkin, 1994), and in an accelerated schedule (Booy et al., 1992; Begg et al., 1995).

Hib–DTwP–IPV: PRP-T vaccine mixed in the same syringe with diphtheria–tetanus–pertussis–enhanced inactivated poliovirus vaccine resulted in the same rate of local and systemic side-effects as for children receiving DTwP–IPV only, except for irritability and use of acetaminophen after the second dose. These were slightly but significantly more frequent in the DTP–IPV–PRP-T group (Dagan et al., 1994). PRP-T was given concurrently or combined with DtwP and IPV to healthy children at two, four and six months (Gold et al., 1994). Combination resulted more significantly in local redness (18% vs. 11%) but there were no differences in other local symptoms and systemic reactions occurred at similar rates in both groups.

Hib–MenCY–TT:

Haemophilus influenzae type b–*Neisseria meningitidis* serogroups C and Y–tetanus-toxoid conjugate vaccine (Hib–MenCY–TT) has been shown to have similar reactogenicity profile to separately administered Hib and Meningococcal C vaccines (Nolan et al 2007, Schmitt et al., 2007).

Other safety issues

Immunocompromised individuals including HIV: Hib vaccines are safe in HIV-infected individuals (Leroy et al., 1996; Dockrell et al., 1998) and studies show that vaccination of persons with human immunodeficiency virus infection was well tolerated except for mild soreness at the site of injection in some individuals (Kroon et al., 1997).

Anaphylaxis: Anaphylaxis was not reported during the pre-licensure clinical trials. Since then, post-marketing surveillance has identified very few cases of anaphylaxis (Milstien et al., 1987; Stratton et al., 1994). However, no reports of anaphylaxis following Hib vaccination have been published. After reviewing available data, the Institute of Medicine (IOM) concluded that there is not enough evidence to accept or reject a causal relationship between Hib vaccines and anaphylaxis (Stratton et al., 1994).

Guillain–Barré syndrome: No controlled studies have been conducted to explore the risk of GBS following Hib vaccination. GBS was not reported in any of the pre-licensure clinical trials. The Institute of Medicine identified seven cases of GBS that occurred following Hib vaccination, however, three of the individuals had received multiple vaccines and one had an implausible onset interval. Therefore, the IOM concluded there was inadequate evidence to accept or reject a causal relationship between Hib vaccines and GBS (Stratton et al., 1994).

Thrombocytopenia: During one Hib conjugate vaccine trial, a case of thrombocytopenia was reported; however, a subsequent study found the vaccine had no effect on platelet count (Lepow et al., 1984; Stratton et al., 1994). Since that time, post-marketing surveillance has identified several possible cases of thrombocytopenia following Hib vaccination (Milstien et al., 1987; Stratton et al., 1994). The Institute of Medicine reviewed available data and concluded that evidence was not adequate to accept or reject a causal relationship between Hib vaccines and thrombocytopenia (Stratton et al., 1994).

Transverse myelitis: The vaccine adverse event reporting system has identified, in the USA, three possible cases of transverse myelitis (TM) following Hib vaccination. However, there have been no reports of TM following Hib vaccination published in the literature and no cases of TM were reported in pre-licensure trials. Therefore, the Institute of Medicine concluded that the data was inadequate to accept or reject a causal relationship between Hib vaccines and TM (Stratton et al., 1994).

Diabetes: The association between Hib vaccination (HbOC) and Type 1 juvenile diabetes was investigated by examining existing data from participants and refusers from a large controlled prospective Phase III clinical efficacy trial conducted within the Northern California Kaiser Permanente between 1988 and 1990. Amongst >50,000 children who were assessed between 10 to 12 years of age there was no evidence that vaccination with Hib conjugate vaccine in infancy was associated with risk of diabetes later in life (Black et al., 2002).

Summary of mild and severe adverse events after Hib vaccine vaccine

Nature of Adverse event	Description	Rate/doses
Mild	<u>Local reactions</u>	
	Injection site reactions	1 per 10
	<u>Systemic</u>	
	Fever	1 per 50
Severe	None	

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 (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



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