World Health Organization
Global Vaccine Safety,
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INFORMATION SHEET
OBSERVED RATE OF VACCINE REACTIONS
HEPATITIS A VACCINE

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The Vaccines

Monovalent hepatitis A vaccine

Inactivated hepatitis A vaccines are whole-virion-based vaccines cultured on human fibroblasts or diploid cells, purified by ultrafiltration and chromatography and inactivated by formaldehyde. The final vaccine potency (per dose) is, depending on the vaccine, either expressed as ELISA units (EL.U.) or as units (U) or antigen units (AU) of hepatitis A antigen. The different hepatitis A vaccines contain different vaccine strains, excipients or final antigen content (table below). Nevertheless, all hepatitis A vaccines are considered immunogenic and all inactivated vaccines have similar safety profiles. New inactivated hepatitis A vaccines are being evaluated in clinical trials (Ren et al., 2002).

Live attenuated hepatitis A vaccines are currently under development. Two are licensed in China, but additional controlled trials are needed for final assessment of both safety and efficacy (Wang et al., 2000; GACVS, 2010). At this point the information sheet does not document known vaccine reactions because of this limitation.

Combination hepatitis A vaccine

Combined hepatitis A and B vaccines contain in each adult dose of 1 ml at least 720 EL.U. of inactivated hepatitis A virus, 20 µg of recombinant hepatitis B surface antigen protein, aluminium as adjuvant and 2-phenoxyethanol as a preservative. Trace amounts of thiomersal, neomycin, formalin and yeast protein are present from the manufacturing process (CDC, 2001). The children/adolescents formulation contains half the antigen content. These vaccines are given as two- or three-dose series.

Combined hepatitis A and S. typhi vaccines contain either 1,440 EL.U. or 160 AU of inactivated hepatitis A virus grown in human diploid cells and adsorbed onto aluminium hydroxide combined with 25µg Vi polysaccharide antigen of *S. typhi*.

Types of vaccines

	Vaccine antigens	Excipients
Monovalent	*GBM strain 160 EL. U/0.5ml dose* *M175 strain-720EL. U/0.5ml dose* *HM175 strain-1440 EL. U/1.0ml dose* *CR36F strain 25EL.U/0.5ml dose of viral antigen* *CR36F strain 50EL.U/1.0ml dose of viral anigen* *RG-SB strain*	Aluminium hydroxide adjuvant (0.3mg), 2-phenoxyethanol as preservative (2.5uL), formaldehyde 12.5ug, trace neomycin sulphate Adsorbed to biodegradable phospholipid vesicles (virosomes)
Combination	Combined hepatitis A and B vaccines contain in each adult dose of 1 ml at least 720 EL.U. of inactivated hepatitis A virus, 20 µg of recombinant hepatitis B surface antigen protein). Combined Hepatitis A and S. typhi vaccines contain either 1,440 EL.U. or 160 AU of inactivated hepatitis A virus grown in human diploid cells and 25µg Vi polysaccharide antigen of S. Typhi.	Aluminium as adjuvant and 2-phenoxyethanol as a preservative; Trace amounts of thimerosal, neomycin, formalin and yeast protein are present from the manufacturing process (CDC, 2001) Adsorbed onto aluminium hydroxide

Adverse events

Mild adverse events

Monovalent inactivated hepatitis A vaccine

Systemic adverse events: Mild injection site reactions have been reported with all inactivated hepatitis A vaccines. Symptoms are transient, more commonly reported in adults, and usually occur following the first dose (Braconier et al., 1999). The rate of injection site reactions varies depending on the specific study. The most frequently reported local adverse events have included injection site soreness (14-27% in children, up to 43-56% in adults) and induration at the injection site (4%) with lower rates of injection site erythema and pain noted after booster doses in 9% of children and up to 24% of adults. (CDC, 1999, Balcarek et al., 1995, Lee et al., 2000).

Systemic adverse events: Mild systemic adverse events have been reported after all inactivated hepatitis A vaccines and like local reactions may be less frequent after booster doses. Symptoms have included headache (4% in children, up to 16% in adults), malaise (7%), anorexia, feeding problems (8%) and fatigue, fever, diarrhoea and vomiting occurring in less than 5% of vaccine recipients (Van Damme et al., 1994; Feinstone, 1999; CDC, 1999). Symptoms usually resolved within 48 hours (Balcarek et al., 1995; Scheifele et al., 1993; Vimolket et al., 1998; Castillo de Febres et al., 1999; Dagan et al., 1999; Lopez et al., 2001).

Severe adverse events

Monovalent hepatitis A vaccine

No severe adverse events have been causally linked to hepatitis A vaccines (WHO, 2000; Niu et al., 1998; IOM, 2011).
In pre-licensure clinical studies involving more than 60,000 persons vaccinated, no serious adverse reactions were definitively attributed to hepatitis A vaccine. Post-licensure AEFI reports after vaccination of an estimated 1,3 million persons included anaphylaxis, Guillain-Barré syndrome, brachial plexus neuropathy, transverse myelitis, multiple sclerosis, and erythema multiforme (CDC, 1999) but none of those events could be conclusively linked to vaccine administration. Most of these events occurred among adults, and approximately one third have occurred among persons concurrently receiving other vaccines. For adverse events for which background incidence data are available (e.g. Guillain-Barré syndrome and brachial plexus neuropathy) the rates among vaccine recipients are not higher than would be expected for an unvaccinated population (CDC, 1999).

Combination hepatitis A vaccines

Hepatitis A and B vaccines - Adverse events following administration of combined hepatitis A and B vaccines were similar in type and frequency to those observed after vaccination with monovalent hepatitis A vaccines (Jarvis et al., 2003). The frequency of adverse events did not increase with subsequent doses.

Combined hepatitis A and S. typhi vaccines - Concurrent administration of inactivated Hepatitis A vaccine with a typhoid fever vaccine is considered safe (Dumas et al., 1997; Van Damme et al., 2001; CDC, 2001, Prado et al., 2002). As with monovalent hepatitis A vaccines, pain at the injection site was the most frequently reported local symptom and headache the most frequently reported systemic adverse event. All symptoms resolved without sequelae (Beran et al., 2000).

Other combinations - Simultaneous administration with pneumococcal conjugate vaccines in young children (Trofa et al., 2008), with DTaP and Hib in young children (Trofa et al., 2011), and with IC51 Japanese encephalitis vaccine in travellers (Kaltenböck et al., 2009) did not result in additional adverse reactions compared to control groups.

Other safety issues

Hepatitis A vaccine in individuals with chronic disease - Inactivated hepatitis A vaccines were well tolerated in patients with mild to moderate chronic liver disease (Keeffe et al., 1998), in liver and renal transplantation recipients (Arslan et al., 2001; Stark et al., 1999) and in dialysis patients (Fleischmann et al., 2002). The vaccine is actually recommended to reduce hepatitis A case fatality associated with some morbid conditions.

Vaccine interchangeability - Crossover immunisation between inactivated vaccines appears to be well tolerated for the product studied (Bryan et al., 2000; Zuckerman et al., 1998).

Pregnancy - The safety of hepatitis A vaccine during pregnancy has not been established but no evidence of risk has been documented either. Since the vaccine is prepared from inactivated virus the theoretical risk to the developing fetus is likely to be negligible.

Summary of mild and severe adverse events

Nature of Adverse event	Description	Rate/doses
Mild	Local reactions	
	Soreness	
	- children	14-27 per 100
	- adults	43-56 per 100
	Induration at the injection site	4 per 100
	Injection site erythema and pain noted after booster doses	
	- children	9 per 100
	- adults	24 per 100
	Generalized reactions	
	Headache	
	- children	4 per 100
	- adults	16 per 100
	malaise	7 per 100
	feeding problems	8 per 100
	fatigue, fever, diarrhoea and vomiting	<5 per 100
Severe	None proven to date	

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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