World Health Organization
Global Vaccine Safety
Essential Medicines & Health Products
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INFORMATION SHEET
OBSERVED RATE OF VACCINE REACTIONS
JAPANESE ENCEPHALITIS VACCINE

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The Vaccines

The Japanese encephalitis (JE) vaccines currently available are either inactivated, live attenuated or live recombinant.

Inactivated vaccines

Inactivated vaccines include the newly developed cell culture-derived vaccines or traditional mouse brain-derived vaccines:

Vero cell-derived – In the last few years a number of cell culture-derived inactivated vaccines became available. The most widely used is the Vero cell-derived vaccine IC51 (also known as IXIARO in the US and Europe or JESPECT in Australia and New Zealand) and the related product JEEV manufactured by Biological E, which is prequalified by WHO. Other cell culture-derived products are nationally distributed in Japan, China and India.

Mouse brain-derived – Most inactivated mouse brain-derived products have been discontinued. In a few countries there is continued production for domestic supply, although in general these are being phased out.

Live attenuated vaccine

The only internationally available live attenuated vaccine, the SA 14-14-2 vaccine (also known as CD.JEVAX) is based on a stable neuro-attenuated strain of the JE virus . The SA 14-14-2 vaccine strain was obtained from its wild-type SA 14 parent by serial passages in animals and cell cultures and is produced in primary hamster kidney cells. The vaccine was first licensed in the PR China and has been prequalified by WHO. Many countries in Asia currently use this vaccine in their national immunization programme.

Live recombinant vaccine

Only one product in this class has been licensed. This vaccine is a genetically engineered JE vaccine that combines the protective antigenic determinants of the attenuated SA14-14-2 JE strain with the yellow fever vaccine strain 17D (YF 17D) virus as a vector backbone. The vaccine was first licensed in Australia in 2010 (trade name IMOJEV) and subsequently has been licensed in some Asian countries.

Table 1: JE vaccines and their composition

Type	Source of vaccine antigens	Relevant excipients
Inactivated	Vero cell-derived The attenuated SA14-14-2 strain of the JE virus is grown in Vero cells. The vaccine is formalaldehyde inactivated	Aluminium hydroxide (250 ug) as adjuvant
	Mouse brain-derived Most manufacturers produce vaccine from the prototype Nakayama strain of JE virus, whereas in Japan the vaccine for the domestic market is prepared from the Beijing-I strain	Gelatin (500 ug) is used as a stabiliser and thiomersal (0.007%) as a preservative.
Live attenuated	The SA 14-14-2 vaccine is based on a stable neuro-attenuated strain	Gelatin, used as a stabiliser
Live recombinant	The antigenic determinants of the SA 41-14-2 JE strain combined with the yellow fever vaccine virus strain 17D as a vector backbone	

Adverse events

Local adverse events:
Inactivated Vero cell-derived vaccines: Local reactions at the injection site including pain, redness, induration, swelling and tenderness have been seen in about 40% of adult vaccine recipients (Dubischar-Kastner et al., 2010) and in approximately 10 % of children aged 1-3 years when receiving their primary course of vaccination (Kaltenboeck et al., 2010). Severe local symptoms occurred in <1% of recipients (Dubischar-Kastner, 2010; Kaltenboeck, 2010).
Inactivated mouse brain-derived vaccines: Local reactions of any severity at the injection site (pain, itching, tenderness, hardening, swelling, and redness) have been seen in about 60% of adult vaccine recipients. Severe local reactions were reported in a significantly higher number of subjects after subsequent doses of mouse brain-derived vaccine (>4%) compared to inactivated Vero cell-derived vaccine (Dubischar-Kastner et al., 2010).
Live attenuated vaccine: Injection site reactions were reported in 40-44% of children aged 9 to 23 months (Feroldi et al., 2014; Kim and Houillon, 2014).
Live recombinant vaccine: Local reactions were reported in about 10% of adult recipients (Torresi et al., 2010) and in about 40% of children receiving their first dose (Chokephaibulkit et al., 2010; Feroldi et al., 2012).

Systemic adverse events:
Inactivated Vero cell-derived SA14-14-2: In clinical trials the most frequent systemic adverse events were headache, muscle pain, flu-like symptoms and fatigue, which were mostly mild to moderate in severity (Dubischar-Kastner et al., 2010). The most frequent adverse events reported from post-marketing use were skin and subcutaneous tissue (24%, mainly rash), general disorders (20%, mainly fever), nervous system disorders (20%, mainly headache) and gastrointestinal disorders (16%) (Schuller et al., 2011) and administration site conditions.
Inactivated mouse brain-derived vaccine: Mild to moderate systemic reactions included headache, malaise, myalgia, low-grade fever, nausea, vomiting, abdominal pain, rash, chills and dizziness have been observed in 5 to 30% of vaccinees (Monath 2002, Takahashi et al., 2000, DeFraites et al., 1999, Tsai et al., 1999, Poland et al., 1990).
Live attenuated vaccine vaccine: In recent randomized controlled clinical trials in children (Feroldi et al., 2014; Kim and Houillon 2014) around 50% of the children experienced mild to moderate systemic reactions including fever, vomiting, abnormal crying, drowsiness, appetite loss and irritability. Evaluation of the live recombinant vaccine in children in clinical trials indicate that 45% - 53% experienced systemic reactions of mostly mild to moderate severity (Chokephaibulkit et al., 2010; Feroldi et al., 2012; Feroldi et al., 2014; Kim and Houillon, 2013). These systemic reactions were fever, vomiting, abnormal crying, drowsiness, appetite loss and irritability.
Live recombinant vaccine: Solicited systemic reactions (fever, vomiting, abnormal crying, drowsiness, appetite loss and irritability) have been found to occur in around 45-52% of children, comparable to live attenuated JE vaccine and Hepatitis A vaccine (Chokephaibulkit et al., 2010; Feroldi et al., 2012; Feroldi et al., 2014; Kim and Houillon 2013).

Serious adverse events:

Inactivated Vero cell-derived vaccine: In clinical trials in adults and children, no serious adverse events related to vaccination have been reported. Four serious cases (neuritis, meningism, oropharyngeal spasm and iritis) from 10 phase III trials in adults were initially reported from 12-months postmarketing surveillance data of the Vero cell-derived Japanese encephalitis virus vaccine; however they were considered as unrelated to vaccination. The case of meningism was reclassified as non-serious upon further review and the cases of neuritis and oropharyngeal spasm recovered (Schuller et al., 2011).

Inactivated mouse brain-derived vaccine: Hypersensitivity reactions, including serious generalized urticaria, facial angio-oedema or respiratory distress, have been reported (18–64 per 10,000 vaccinees), principally in vaccine recipients from non-endemic areas: most have been described among adult travellers from Europe, Australia and North America. The events consisted of urticaria and/or pruritus (often generalised), angioedema (of the extremities, face, oropharynx and lips) and very rarely of respiratory distress (Monath, 2002; Shlim et al., 2002; Takahashi et al., 2000; Tsai et al., 1999, Plesner et al., 1997). A unique feature is that such reactions may occur as late as 12–72 hours following immunization (WHO, 2006). The median interval between immunization and onset was 18 to 24 hours after the first dose, with 74% of reactions occurring within 48 hours; however reactions may be delayed up to 10 days following vaccination (Berg SW et al 1997). In addition, 70% of these reactions developed after the second or a later dose with a median onset of 3 days. They have also been described as late type III allergic reactions (Monath 2002, Shlim et al., 2002; Leder et al., 2001; Tsai, 2000; CDC, 1993).

In Japanese children, systemic immediate-type reactions occurred with a frequency of 1 to 2 per million doses (Sakaguchi et al., 2001, Sakaguchi et al., 1998). These have been described as anaphylaxis with both cutaneous and respiratory symptoms, possibly related to the presence of IgE antibodies to the gelatin component of the vaccine, as well as cardio-vascular symptoms such as hypotension and cyanosis. Anaphylaxis is rare: two cases of anaphylactic shock per 1 million doses of JE vaccine have also been reported from passive surveillance in Japan.

Risk factors for serious allergic reactions included a history of allergies or asthma, young adult age and female gender. The pathogenesis of the hypersensitivity reactions is unclear but a gelatin allergy should be excluded.

Live attenuated vaccine: In recent clinical trials in children, two cases of pyrexia (1.5%) were reported as systemic adverse events (Kim and Houillon, 2013). No increased risk of allergic reactions were reported with this vaccine.

Live recombinant vaccine: No subject enrolled in clinical trials experienced allergic reactions.

Live attenuated cell culture vaccine – an increased risk of allergic reactions has not been reported with this vaccine.

Neurological adverse events:
Inactivated Vero cell-derived vaccine: An increased risk of neurological events has not been reported with this vaccine (Schuller et al., 2011).
Inactivated mouse brain-derived vaccine: The nerve tissue content of the vaccine raised concerns about possible neurological adverse reactions. Up to one case of acute disseminated encephalomyelitis (ADEM) per million vaccinees has been reported in Japan (Monath, 2002; Tsai et al., 1999). In Denmark, between 1983 and 1995, this rate reached 1 per 50,000 – 75,000 vaccinees for reasons not yet fully understood (Plesner et al., 1996). Only one fatal case (8-year old boy with a complex congenital heart condition), was noted during surveillance of more than 10 million doses administered in Japan and the US (Takahashi et al., 2000). Neurological complications including encephalitis, encephalopathy, convulsions, peripheral neuropathy, transverse myelitis and aseptic meningitis have been very rarely reported in Japanese children, with an incidence of 1 per million vaccinees (Ohtaki E et al., 1995).

Live attenuated vaccine: In a randomized trial of the safety of Japanese encephalitis vaccine (SA14-14-2) in 26,239 children prospectively followed for 30 days for severe adverse events such as encephalitis, meningitis and ‘‘all-cause’’ hospitalization, no cases of encephalitis or meningitis or severe reaction consistent with anaphylaxis occurred in either group (Zheng-Le Liu et al., 1997).

Live recombinant vaccine: Fever has been reported in about 15-20% of trial participants (Feroldi et al., 2014, Feroldi et al., 2012, Kim and Houillon, 2013, Chokephaibulkit et al., 2010). Currently no published post-marketing data are available to conclude on the risk of rare neurological adverse events

Vaccine-associated JE:
No cases of vaccine-associated disease were reported in a review of data covering a 20 year period that was presented to the GACVS in 2005 (WHO 2005).

Table 2: Summary of mild and severe adverse events after JE vaccine

	Description	Rate/doses
Inactivated Vero cell-derived	Pain, redness, induration, swelling and tenderness at injection site	10 to 40 per 100 doses
	Rash and other skin lesions	24 per 100 doses
	Fever, headache and other mild neurological conditions	20 per 100 doses
	Gastrointestinal disorders	16 per 100 doses
	Acute disseminated encephalomyelitis (ADEM)	1 per 50,000 to 1,000,000 doses
	Neurological events: Encephalitis, encephalopathy, convulsions, peripheral neuropathy, transverse myelitis and aseptic meningitis	1 per 1,000,000 doses
Inactivated Mouse brain-derived	Injection site reactions; Pain, redness, induration, swelling and tenderness	Upto 60 per 100 doses
	Headache, malaise, myalgia, low-grade fever, nausea, vomiting, abdominal pain, rash, chills and dizziness	5 to 30 per 100 doses
	Hypersensitivity reactions	18–64 per 10,000 doses
	Anaphylaxis	2 per 1,000,000 doses
Live attenuated SA-14-14-2	Injection site reactions	40-44 per 100 doses
	Fever, vomiting, abnormal crying, drowsiness, appetite loss and irritability	45 - 53per 100 doses
	Hypersensitivity reactions	No reports
Live recombinant	Injection site reactions	10 – 40 per 100 doses
	Fever, vomiting, abnormal crying, drowsiness, loss of appetite and irritability	45 to 52 per 100 doses
	Hypersensitivity reactions	No reports

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