The Vaccines

Japanese encephalitis (JE) vaccines are either inactivated or live attenuated.

**Inactivated vaccines**

Inactivated vaccines are either mouse brain-derived or cell culture-derived:

Mouse brain-derived vaccines - The only internationally approved vaccine is produced from infected adult mouse brain tissue in several Asian countries, where millions of doses have been administered since 1930s (Shlim et al., 2002; WHO, 1998). The countries using this vaccine include India, Japan, Malaysia, South Korea, Sri Lanka, Taiwan, Thailand, and Vietnam. The most widely used vaccine comes from the Research Institute of Osaka University (Biken) in Japan. Other manufacturers are found in South Korea, Taiwan, Thailand, and Vietnam. Major manufacturers have recently discontinued production of this vaccine (Cochrane review 2007 ref PATH). Increasing supply problems are expected in the coming years as manufacturers scale back production with the availability of new and improved JE vaccines;

Cell culture-derived vaccines - The cell culture-derived inactivated vaccine is manufactured exclusively in the People’s Republic of China and has been in use since the late 1960s where more than 70 million doses are administered annually. Due to its limited efficacy and the need for numerous doses, the vaccine is gradually being replaced by the SA 14-14-2 live attenuated vaccine. New, inactivated vaccines manufactured in Vero cells are currently in use in several countries.

**Live attenuated vaccine**

The only currently available live attenuated vaccine, the SA 14-14-2 vaccine 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 strain by serial passages in cell cultures (primary hamster kidney cells) and in animals (mice, hamsters) with successive plaque purifications in primary chick embryo cells. The vaccine was licensed in the PR China in 1988. The countries primarily using this vaccine include China (since 1988); Nepal (since 1999); South Korea (since 2001); India (since 2006) and Thailand (since 2007). A genetically engineered JE vaccine that combines the attenuated SA14-14-2 strain and yellow fever vaccine strain 17D (YF 17D) virus as a vector for genes encoding the protective antigenic determinants, has been tested in several clinical trials and is under continued assessment (Cochrane 2007).

### Type of vaccines

<table>
<thead>
<tr>
<th>Route</th>
<th>Vaccine antigens</th>
<th>Excipients</th>
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<tbody>
<tr>
<td>Inactivated</td>
<td><strong>Mouse brain-derived</strong>&lt;br&gt;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</td>
<td>Gelatin is used as a stabiliser and thiomersal as a preservative</td>
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<td><strong>Cell culture-derived</strong>&lt;br&gt;The P3 strain of the JE virus is grown in primary hamster kidney cells. The vaccine is formalin inactivated.&lt;br&gt;Vero cell-derived Inactivated SA14-14-2 is prepared using tissue culture</td>
<td>Serum albumin is used as a stabiliser.</td>
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<td></td>
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<td>Aluminium hydroxide as adjuvant.</td>
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<tr>
<td>Live attenuated</td>
<td>The SA 14-14-2 vaccine is based on a stable neuro-attenuated strain of the JE virus with a Yellow Fever vaccine acting as a viral vector.</td>
<td>Gelatin and sucrose used as a stabiliser</td>
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Adverse events

Mild adverse events

Local adverse events:

With inactivated vaccines local reactions at the injection site including erythema, oedema and tenderness have been seen in about 20% of vaccine recipients of the mouse brain-derived vaccine and 4% with the cell culture vaccine.

With the live attenuated SA-14-14-2 vaccine in a study in Korea, redness and swelling at the site of injection was reported in <1% of vaccinees.

Systemic adverse events:

Inactivated mouse brain-derived vaccine mild to moderate systemic reactions include headache, malaise, myalgia, low-grade fever, nausea, vomiting, abdominal pain, rash, chills and dizziness occurred in 5 to 30% of vaccinees (Monath 2002, Takahashi et al., 2000, DeFrates et al., 1999, Tsai et al., 1999, Poland 1990).

Inactivated cell culture vaccines mild systemic symptoms, such as headache and dizziness were reported in less than 1% of vaccinees. Fever reactions (temperature >38°C) were seen in 12% of vaccinees; their frequency was markedly reduced after a reduction in the bovine serum content of the vaccine (Monath, 2002; Tsai et al., 1999). Several clusters of adverse reactions after vaccine administration in Chinese schoolchildren were thought to be psychogenic in origin (Ahmad, 2002). The live attenuated vaccine SA-14-14-2 vaccine has been evaluated in several trials conducted in the PR China. Mild adverse events such as fever, irritability, skin rash, nausea and dizziness were very rarely reported (Yu et al., 1988). In an uncontrolled trial with almost 600,000 vaccinees, a very low incidence of adverse events including fever (5/10,000), skin-rash (1/10,000), nausea and dizziness (3 per million) was observed (Ma et al., 1993). In a subset of 266 vaccinated children from another trial, fever (5%) and irritability (4%) were the most frequently reported events in the first week after vaccination (Liu et al., 1997). In a small study involving Korean children, elevated temperature (7%), vomiting (1%), skin rash (1%), loss of appetite (1%) and irritability (1%) were observed during the first month after immunisation (Sohn et al., 1999).

Vero cell-derived Inactivated SA-14-14-2: The most frequent adverse events were skin and subcutaneous tissue disorders (24%, mainly rash), general disorders and administration site conditions (20%, mainly fever), nervous system disorders (20%, mainly headache) and gastrointestinonal disorders (16%).

Severe adverse events

Allergic adverse events:

Inactivated mouse brain-derived vaccine - hypersensitivity reactions, such as 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 and 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 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 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. Up to two cases of anaphylactic shock per 1 million doses of JE vaccine have been reported from passive surveillance in Japan. Two deaths from acute anaphylaxis in Korea have been attributed to the vaccine (Sohn, 2000; Tsai, 2000).

Risk factors for such serious 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.

Inactivated cell culture vaccine - following inactivated primary hamster kidney cell-derived JE vaccine, few serious adverse events have been reported. In a survey of vaccines, an urticaria has been observed in 6.6 per 100,000 (Tsai et al., 1999).

4 serious cases (neuritis, meningism, oropharyngeal spasm and iritis) from 10 phase III trials were reported from a study on the safety profile of the Vero cell-derived Japanese encephalitis virus vaccine prepared by propagating JEV strain SA 14-14-2 in Vero cells. This corresponds to a rate of 1.6 per 100,000 doses distributed in the first 12 months of post-marketing use. (Elisabeth Schueller et al 2011).

Live attenuated cell culture vaccine - an increased risk of allergic reactions has not been reported with this vaccine.
Neurological adverse events:

**Inactivated mouse brain-derived cell culture 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 temporarily 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), however, 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 reported in Japanese children with an incidence of 1 to 2.3 per million vaccinees (Ohtaki E et al., 1995).

**Inactivated cell culture vaccine** - an increased risk of neurological events has not been reported with this vaccine.

**Live attenuated cell culture 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. In the same study, adverse events observed in a convenience sample of 266 vaccinated subjects examined at days 1, 2, 3, and 7 after JE immunization included Fever >37.5°C (4.9%), Irritability (3.8%), Rash (2.2%) and vomiting (1.1%) (Zheng-Le Liu et al., 1997)

**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).

Other safety issues

Use of JE vaccine in Indian mass campaign - The safety of the live attenuated vaccine (SA 14-14-2) was reviewed following its use in a mass campaign in India when >9.3 million children aged 1 to 15 years were vaccinated. There were initial reports of serious adverse events, including fatal events, however reviews by experts including the Global Advisory Committee on Vaccine Safety (GACVS) concluded that these events, which included 2 clusters of cases of encephalopathy and encephalitis were unlikely to have been caused by the vaccine (WHO 2007).

### Summary of mild and severe adverse events

<table>
<thead>
<tr>
<th>Nature of adverse event</th>
<th>Description</th>
<th>Rate/doses</th>
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| **Inactivated Mouse brain** | Injection site reactions  
Headache, malaise, myalgia, low-grade fever,  
nausea, vomiting, abdominal pain, rash,  
chills and dizziness.  
Allergic reactions  
Anaphylaxis  
Neurological complications including encephalitis, encephalopathy, convulsions,  
peripheral neuropathy, transverse myelitis | 20 per 100  
5-30 per 100  
17 per 106  
1-2 per 106  
1-2.3 per 106 |
| **Inactivated Cell culture** | Injection site reaction  
Headache and dizziness  
High Fever >38°C  
Urticarial skin rash | 4 per 100  
< 1 per 100  
12 per 100  
6.6 per 105 |
| **Live attenuated SA-14-14-2** | High Fever  
Skin-rash | 5-7 per 100-104  
1 per 104 |
Observed Rate of Vaccine Reactions – JE Vaccine

References


