The Vaccines

There are three main types of rabies vaccine, the outdated nerve tissue vaccines, cell culture vaccines, and embryonated egg vaccines.

Cell culture vaccines and embryonated egg vaccines have replaced nerve tissue vaccines in industrialized countries and are the ones recommended for use by WHO. They are considered safe and well tolerated (Briggs et al., 2000, WHO, 2010 B). In comparison, nerve tissue vaccines can induce severe adverse reactions including a potential risk of rabies from incomplete virus inactivation (Plotkin, 2008) and are less immunogenic. They are still used in a limited and decreasing number of developing countries.

Nerve tissue vaccines
- Semple rabies vaccine contains a phenol or β-propiolactone-inactivated homogenate of rabies virus-infected goat or sheep brain tissue. The vaccine contains myelin basic protein and is used in an ever decreasing number of countries in Asia and Africa.
- Fuenzalida rabies vaccine is prepared from suckling mouse brain tissue and has decreased myelin content (Nogueira, 1988). This vaccine is used in a small number of Latin American countries.

Cell Culture Vaccines and Embryonated egg-based vaccines (CCEEV)

Cell Culture Vaccines (CCV)
- Human diploid cell vaccine (HDCV) contains the Pitman-Moore L503 or Flury strain of rabies virus grown on MRC-5 human diploid cell culture, concentrated by ultrafiltration and inactivated with β-propiolactone (Wiktor et al., 1980). This vaccine is licensed for intra-muscular use. It contains no preservative or stabilizer.
- Purified chick embryo cell vaccine (PCECV) is a sterile lyophilized vaccine obtained by growing the fixed rabies virus strain Flury LEP-25 in primary cultures of chick fibroblasts. The virus is inactivated with β-propiolactone, purified and concentrated by zonal centrifugation (CDC, 1998; Dreesen, 1997).
- Purified Vero cell rabies vaccine (PVRV) contains inactivated and lyophilized Wistar strain of rabies virus grown on Vero cell cultures in fermenters allowing mass cultivation. These are inactivated by β-propiolactone and purified by ultracentrifugation (Jaiiaroensup et al., 1998).
- Primary Hamster Kidney Cell vaccine (PHKCV) uses the Beijing strain and is inactivated with formalin and adsorbed to aluminum hydroxide. It also contains 0.01% thiomersal and 10 mg human albumin.

Embryonated egg-based vaccines (EEV)
- Purified duck embryo vaccine (PDEV) uses duck embryo cells as substrate. These are inactivated by β-propiolactone and purified by ultracentrifugation. PDEV contains thiomersal.

Adverse events

Mild adverse events

Local adverse events
Nerve Tissue Vaccines
Pain, swelling, tenderness, itching, erythematous patches may develop after the beginning of the anti-rabies treatment, fading in 6-8 hours and reappearing after the next dose.

Cell Culture Vaccines and Embryonated egg-based vaccines
- HDCV – Mild, transient local reactions (e.g., pain at the injection site, redness, swelling, and induration) occurred among 60 to 89.5 per 100 vaccinees. Most frequently reported was pain at the injection site occurring in 21—77 per 100 vaccinees (CDC 2008).
- PCECV – Similar, but less frequent local reactions than HDCV have been noted at a frequency of 4 per 100 vaccinees (Dutta JK, 1994; WHO, 2010 B)
- PVRV – Similar, but less frequent local reactions than HDCV have been noted among 7 per 100 vaccinees in an evaluation of safety of PVRV following post-exposure immunization (Wang, 2000; WHO, 2010 B).
Intradermal versus Intramuscular vaccination - Following post-exposure immunization adverse reactions were observed more frequent in patients receiving intradermal immunization of PCECV (48 per 100 vaccinees) or PVRV (51 per 100 vaccinees), as compared to patients who received intramuscular injections of this vaccine (33 per 100 vaccinees). All reactions were mild and resolved without treatment. In decreasing order of frequency, adverse reactions included erythema, pain and or swelling at the site of injection, and fever. (Briggs et al., 2000; Charanasri et al., 1992; Tanterdham et al., 1991, Suntharasamai et al., 1994; Quiambao et al., 2005).

Systemic adverse events

Systemic reactions occur less frequent compared to local reactions.

Nerve Tissue Vaccines

Systemic adverse events may include fever, headache, insomnia, palpitations and diarrhea (Wiktor, 1980).

Cell Culture Vaccines and Embryonated egg-based vaccines

- HDCV – Mild, transient systemic reactions include fever, headache, dizziness, and gastrointestinal symptoms that have been reported among 7-55.6 per 100 HDCV vaccinees (CDC 2008, Dreesen et al., 1997).
- PCECV – Fifteen per 100 vaccinees reported general symptoms.
- PVRV – Among PVRV vaccinees, mild and moderate reactions were infrequent, but similar after i.d. and i.m. vaccinations. Fever was seen in less than 6 per 100 vaccinees. Reactions after booster immunization were not different from those following immunization.

Severe adverse events

Severe adverse events are rare. They occur more common with nerve tissue vaccines than with CCEEV.

Nerve Tissue Vaccines

Neurological - Severe adverse events have been mainly neurological and resulted from an immune response to the myelin basic protein contained in the vaccine (Piyasirisilp et al., 1999). The incidence of these reactions varies widely from 0.0017 per 100 to 0.44 per 100 and is definitely lower in people receiving Cell Culture Vaccines and Embryonated egg-based vaccines and in people receiving properly manufactured vaccine of suckling mouse brain (Plotkin S et al., 2008). The reactions are neuro-paralytic and occur approximately 2 weeks after vaccination. They include:

- Meningo-encephalomyelitis
- Mono-neuritis multiplex – which may affect facial, oculomotor, glossopharyngeal, vagus or the optic nerve.
- Dorsolumbar transverse myelitis – which results in lower limb paralysis, decreased sensation and sphincter disturbance.
- Ascending paralysis of the Landry type (i.e. sudden onset of flaccid paralysis of the legs, followed by paralysis of the arms, usually developing between one to two weeks after the first injection).

Following administration of the Semple vaccine, the incidence of cases of neurological complications reported in the literature varies greatly, ranging from 0.14 per 1,000 to 7 per 1,000 cases per treatments. In the best surveys conducted among large numbers of patients in one institution in charge of post-exposure treatment, complications varied from 0.1 per 1,000 to 7 per 1,000 vaccinees with a case fatality rate of up to 10%. In case of Landry paralysis, the case fatality rate could reach 30% (Bahri et al., 1996). The Fuenzalida-type vaccine was associated with neurological complications in about 0.12 per 1,000 to 0.037 per 1000 courses including post-vaccination neuroparalytic syndromes resembling Guillain-Barré syndrome (Noguiera, 1996, Meslin et al., 1996) with a case fatality rate of 22% (Meslin et al., quoting Held et al., 1971).

Cell Culture Vaccines and Embryonated egg-based vaccines

Neurological – At least five cases of central nervous system disease, including transient neuroparalytic illness of Guillain–Barré type, have been reported among the millions of individuals given HDCV (Bernard et al., 1982; Boe & Nyland, 1980; Knittel et al., 1989; Tornatore & Richert, 1990; Moullignier et al., 1991). This rate may not be an increase above the background rate of about 1 per 100,000 per year (Plotkin et al., 2008). This low incidence after HDCV compares with a neurological complication rate of 0.625 per 1000 after nerve tissue vaccines, 0.125 per 1000 after suckling mouse brain vaccine and 0.031 per 1000 for PDEV (Plotkin et al., 2008).

Other adverse events - To corroborate the safety of Cell Culture Vaccines, the U.S. Food and Drug Administration (FDA) and CDC commented on rabies vaccine safety, reported through the Vaccine Adverse Event Reporting System (VAERS), to review 336 reports of adverse events following vaccination with PCECV in the U.S. (Dobardzic et al., 2007). Of the reported incidents 93% were non-serious and consistent with pre-licensure safety data. There were no reported deaths or serious events. Among the 7% of reports describing serious events were 20 hospitalizations and 13 neurological events. There was no pattern among the 13 neurological events beyond temporal relationship to vaccination. A total of 20 events, 3 serious, were classified as possible anaphylaxis.

Immunological - A rarer immune complex-like reaction (characterized by urticaria and sometimes including arthralgia, angioedema, nausea, vomiting, fever and malaise) has been noted in approximately 6 per 100 vaccinees receiving booster doses of HDCV. This reaction was less common in persons undergoing primary immunization (WHO 2002; Dreesen, 1986). In no case have these reactions been life-threatening. The reactions have been attributed to antigenicity conferred on the stabilizer – human albumin – by the beta-propiolactone used to inactivate the virus. The beta-propiolactone increases the capacity of albumin to form immune complexes (CDC, 1984; Anderson et al., 1987; Swanson et al., 1987).

Respiratory symptoms are mild. Epinephrine, antihistamines and occasionally steroids have been used in successful treatment of these reactions, which have resolved in 2 to 3 days (Plotkin et al., 2008). Allergic reactions have been noted after administration of PDEV (Dreesen, 1997).
## 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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<tbody>
<tr>
<td><strong>Mild</strong></td>
<td></td>
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<tr>
<td>Nerve tissue vaccines</td>
<td><strong>Local reactions</strong>&lt;br&gt;Pain, swelling, tenderness, itching and erythematous patches</td>
<td>21-74 per 100</td>
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<td></td>
<td><strong>Systemic reactions</strong>&lt;br&gt;fever, headache, insomnia, palpitations and diarrhoea</td>
<td></td>
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<tr>
<td>Cell Culture and Embryonated egg-based vaccines</td>
<td><strong>Local reactions</strong>&lt;br&gt;<em>HDCV</em> (e.g. fever, headache, dizziness, and gastrointestinal symptoms)&lt;br&gt;<em>PCECV</em>&lt;br&gt;<em>PVRV</em> (e.g. pruritus, erythematous rash, and pain)</td>
<td>4 per 100&lt;br&gt;7 per 100</td>
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<td></td>
<td><strong>Systemic</strong>&lt;br&gt;<em>HDCV</em>&lt;br&gt;- Transient fever, headache, dizziness, and gastrointestinal symptoms&lt;br&gt;- Immune complex-like reaction, 1st dose&lt;br&gt;- Immune complex-like reaction, booster dose</td>
<td>7 – 55.6 per 100&lt;br&gt;1.1 per 1000&lt;br&gt;6 per 100</td>
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<td><strong>Severe</strong></td>
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<tr>
<td>Nerve tissue vaccines</td>
<td>Meningo-encephalomyelitis, mono-neuritis multiplex, dorsolumbar transverse myelitis and ascending paralysis of the Landry type.</td>
<td>Neurological events reported but no evidence of a pattern of neurologic events plausibly related to vaccination</td>
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<tr>
<td>Cell Culture and Embryonated egg-based vaccines</td>
<td>Neurological disease</td>
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