

WHO Position Paper on Rabies Vaccine - 6 August 2010

Grading of scientific evidence

Table III: Safety of cell-culture-based rabies vaccines*

Settings: Global

Question: What is the scientific evidence that cell-culture-based rabies vaccines are safe?

Conclusion: Moderate level of scientific evidence that cell-culture-based rabies vaccines are safe. (However, transient local reactions may occur, in particular following intradermal administration).

*Include cell-culture-derived rabies vaccines based on human diploid cells (HDCV), Vero cells (PVRV), chick embryo cells (PCECV - or PCEC), hamster kidney cells (PHKCV) and duck embryo cells (PDEV)

Quality assessment						Summary of findings
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Quality
14	Observational	No serious	No serious	No serious	No serious	Moderate ¹

¹Upgraded from low to moderate quality of evidence based on the consistent finding that no serious adverse events have been causally linked to any cell-culture-based vaccine, regardless of route of injection.

All cell-culture-based rabies vaccines can be administered intramuscularly (i.m.), but some are approved also for intradermal (i.d.) use. In recent years, trials assessing safety are commonly comparing i.m. with i.d. administration.

I.m. administration: Andersen LJ et al (1980) reported that following HDCV immunization, no serious reactions occurred, but mild local or systemic reactions were observed in 19.0% and 21.4%, respectively, of the 90 vaccinees. Ajjan N et al (1989) found no serious adverse reactions among 144 volunteers who received either HDCV or PVRV.

Wang et al (2000) evaluated the safety of PVRV following post-exposure immunization of 171 Chinese patients. No serious adverse events were observed, but 12 patients (7.0%) had at least one local reaction, mostly pruritus, erythematous rash, and pain.

Following administration of PCECV, Dutta JK (1994) found that only 4% of 1375 vaccinees had experienced reactions. The safety of this vaccine was confirmed by Sehgal S et al (1995) in preclinical, controlled trials of 116 volunteers. Vodopija I et al (1999) found none or only mild and transient local reactions following PCECV immunization of 47 individuals.

I.d./i.m. or i.d. administration: Sabchareon A et al (1998) comparing i.m. and i.d. administration of PVRV found that mild or moderate systemic reactions were infrequent, but similar after i.d. and i.m. vaccinations. Fever and headache were reported by $\leq 6\%$. The reactions after booster immunizations were not different from those following primary immunization. Chutivongse S et al (1995) showed that 202 pregnant Thai

women who received post-exposure rabies prophylaxis using PVRV experienced an adverse reaction rate similar to that of similarly vaccinated non-pregnant women.

Following post-exposure immunization of 211 individuals, *Briggs DJ et al (2000)* reported that adverse reactions were more frequent in patients receiving i.d. immunization of PCECV (48%) or PVRV (51%), as compared to patients who received i.m. injections of this vaccine (33%). In decreasing order of frequency, adverse reactions included erythema, pain and or swelling at the site of injection, and fever. All reactions were mild and resolved without treatment. *Charanasri U et al (1992)* arrived at similar conclusions concerning the safety of PCECV based on analyses of i.d. post-exposure vaccination of 65 individuals. Also, PCECV was found to be well accepted and safe by *Tanterdtham S et al (1991)* who assessed post-exposure vaccination of 29 individuals, by *Suntharasamai P et al (1994)* following post-exposure prophylaxis of 133 volunteers, and by *Quiambao BP et al (2005)* who vaccinated 113 individuals.

During the period 1997-2005 the US Vaccine Adverse Event Reporting System (VAERS) received 336 reports of AEFIs potentially associated with PCECV. Of these, 93% were non-serious. The serious events were mainly of neurologic and allergic nature. No common pattern was identified among the 13 reported neurological reactions. The allergic reactions were mostly urticaria, rash and angioedema. Suspected anaphylaxis was reported in 3 cases. There were no deaths (*Dobardzic A et al 2007*)

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