

WHO Position Paper on Rabies Vaccine - 6 August 2010

Grading of scientific evidence

Table I: Efficacy of cell-culture-based rabies vaccines^{*}

Settings: Global

Question: What is the scientific evidence that cell-culture-based rabies vaccines, used according to WHO's recommendations, are efficacious against rabies and/or induce antibodies against rabies virus following intramuscular (i.m.) or intradermal (i.d.) immunization?

Conclusion:

High scientific evidence that cell culture-derived rabies vaccines when used according to WHO's recommendations are efficacious against rabies and/or induce antibodies against rabies virus following intramuscular or 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
21	Observational ¹	No serious	No serious	Most studies present serological evidence ²	No serious	High ³

¹ All studies on vaccine efficacy are based on observational studies as obviously, placebo-controlled studies on this fatal disease are unacceptable. Normally, observational studies achieve only low quality of evidence in this grading system.

² The majority of the 21 studies present indirect evidence of efficacy based on assessments of the concentration of neutralizing antibody following vaccination.

³ The quality of scientific evidence is upgraded from low to high based on the large number of publications consistently showing excellent vaccine efficacy achieved by different types of cell-culture-based vaccines, and with intramuscular (i.m.) as well as intradermal (i.d.) routes of administration.

Direct evidence of the efficacy of cell-culture derived rabies vaccines (administered in conjunction with rabies immunoglobulin, when available) is provided by several authors. Thus, *Bahmanyar M et al (1976)* reported no rabies among 47 persons who received HDCV following severe bites by rabid dogs and wolves. *Quiambao BP et al (2005)* observed no rabies cases during one year of follow-up after i.d. PCEC administration to 113 category III exposed individuals in Thailand. *Chutivongse S et al (1988)* reported no cases of rabies following i.m. or i.d. PVRV administration to 566 Thai children with proven exposure to rabid animals. Similarly, in China 171 severely rabies-exposed patients were still alive 6 months after post-exposure administration of PVRV (*Wang 2000*). Several other field studies have been performed to evaluate clinical results of PVRV in post-exposure prophylaxis of proven rabies cases using i.m. or i.d. routes of administration (*Suntharasamai 1986, Chutivongse 1990, Sehgal 1994, Jaijaroensup 1998, Quiambao 2008*). No rabies cases occurred during the respective follow-up periods.

Indirect evidence of the efficacy of cell-culture-based rabies vaccines is provided by a large number of serological studies. So far, no cases of rabies have been reported in individuals with neutralizing antibodies

at or above the concentration of 0.5 IU/mL. In healthy individuals, titres above this minimum are achieved in practically 100% of vaccinees following completion of the WHO recommended immunization schedule (*WHO Expert Consultation on Rabies First Report, 2004*). *Morris J et al (2006)* reviewing 10 prospective cohort studies of such vaccines found that one year after primary immunization (3 i.m. doses) 87.9-100 % of the vaccinees had rabies antibody levels of ≥ 0.5 IU/mL. *Ranney M et al (2006)* showed that of 38 travelers who had received pre-exposure prophylaxis (HDCV or PVRV) within the last 1-5 years, 37 demonstrated neutralizing antibody titers of ≥ 0.5 IU/mL. Type of vaccine, method of administration, number of vaccinations, and time since vaccination did not influence rabies antibody titer. Similarly, *Ajjan N et al (1989)* found excellent immunogenicity of both HDCV and PVRV in 144 volunteers following pre-exposure prophylaxis with either HDCV or PVRV vaccine.

Anderson LJ et al (1980) using HDCV (and on day 0, human immunoglobulin) for i.m. post-exposure prophylaxis found that by day 42, all of 87 vaccinees had developed neutralizing antibodies at concentrations >0.5 IU/mL. *Nicholson KG et al (1978)* followed i.m and i.d. antibody responses to HDCV in 77 vaccinees. An antibody response was detected in all participants already after a single dose of the vaccine. At 2, 3, and 12 months the geometric mean titers were twofold higher for i.m. than for i.d. immunization, but the antibody response to a booster dose was similar irrespective of the route of primary immunization.

Sehgal S et al (1995) reviewed the immune responses obtained with i.m. PCEC over a 10-year period covering controlled trial as well as trials under field conditions, and including pre- as well as post-exposure prophylaxis. All the 1375 vaccinees developed satisfactory antibody responses. *Vodopija I et al (1999)* studied 47 individuals who received post-exposure PCEC vaccine intramuscularly. All developed neutralizing antibodies 2 weeks following immunization, also when human rabies immunoglobulin was administered concomitantly with the first vaccine dose. *Charanasri U et al (1992)* comparing i.d. and i.m. application of PCECV in 100 volunteers found antibody concentrations in all vaccinees by day 14 and for the duration of the one year observation period. Similarly, *Briggs DJ et al (2000)* compared the immune response of PCECV and PVRV administered i.d. or i.m. to 211 individuals following category II or III exposures. The vaccinees developed antibody concentrations regardless of route of administration. After 14 days, the mean titre of 59 patients vaccinated intradermally with PCECV was equivalent to that of patients who received PVRV.

Tanterdtham S et al (1991) found neutralizing antibodies 2 weeks after vaccination with PCECV and throughout the 16 months of observation in all 29 vaccinees who had received i.d. post-exposure immunization. *Suntharasamai P et al (1994)* found excellent immunogenicity of i.d. PCECV, with or without concomitant human rabies immunoglobulin, in 133 individuals who received post-exposure prophylaxis, and noted that human rabies immunoglobulin did not significantly suppress the immune response. On the other hand, *Pappaioanou M et al (1986)* showed that concomitant administration of chloroquine can reduce the antibody response to primary i.d. immunization with HDCV.

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