Introduction

In developing countries, where more than 99 percent of all human rabies deaths occur, nervous tissue antirabies vaccines are still the most widely used because of their relatively low cost and despite their variable potency and the risk of neurological complications. The supplies of modern and safe vaccines for many developing countries are grossly inadequate, whereas the demand for affordable and safe human post-exposure treatment (PET) is increasing in the developing world. Although the costs of modern vaccines are decreasing, the current price of a full intramuscular vaccine treatment is far beyond what an average family in Africa or Asia can afford.

Multi-site intradermal (ID) administration of small doses of cell culture rabies vaccine which have been shown to protect humans bitten by proven rabid animals and to reduce the costs of PET by 60 percent is an effective way of decreasing the cost of these much more potent, safe modern vaccines and of increasing the neutralising antibody response. In many developing countries, however, rabies vaccines are being given intradermally under inappropriate conditions and according to regimens whose efficacy is unproven.

A VMO Expert Committee in 1991 recommended intradermal application of modern rabies vaccines. This recommendation was re-assessed in January 1992. As new data had accrued since early 1993 it was time to re-evaluate the safety and efficacy of a method which should help to reduce the number of human rabies deaths. A VMO consultation was therefore held on 13-14 March 1995.

Recognised ID regimens:

An "ideal" vaccine regimen for PET should require a minimum quantity of vaccine, few visits to the clinic and rapid induction of immunity. These features need to be combined to produce an economical, efficient, safe regimen.

The Thai Red Cross (TRC) 222011 and the 804011 regimens have fulfilled these requirements. They have been used in restricted areas, mainly by experienced personnel.

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1 This paper is a summary of a paper presented at the Fifth Conference on Research Towards Rabies Prevention in the Americas, Mexico, 24-27 October 1995. It is reproduced here in response to the discussions held during the human rabies session.
From 1985 to 1994, however, approximately 70 000 TRC ID regimens were given in Thailand, with more than 29 000 in category 3 exposure.

- The Thai Red Cross 2-site intradermal method (222011), (for use with purified verocei rabies vaccine (PVRV), purified chick embryo cell vaccine (PCEC) and purified duck embryo vaccine (PDEV)) consists of injecting one ID dose at each of 2 sites on day 0, 3, 7 and a single site on day 28 and 90; the ID dose per site is one fifth of the volume after reconstitution of a single immunising intramuscular (IM) dose, i.e. if IM dose is 0.5 ml, ID dose = 0.1 ml/site; if IM dose is 1.0 ml, ID dose = 0.2 ml/Site.

- The 8-site 804011 regimen (for use with human diploid cell vaccine (HDCV) and PCEC vaccines where IM dose is 1ml) consists of injecting on day 0, 1 ml of vaccine divided between 8 ID sites (deltoids, anterior thighs, suprascapular and lower quadrant of the abdomen); on day 7, 4 x 0.1 ml ID injections (deltoids and thighs), and single 0. 1 ml ID boosters on days 28 and 90.

**Proposed WHO guidelines**

Knowledge of the correct methods of using modem tissue culture and embryonated egg vaccines intradermally is very poor in tropical areas with endemic dog rabies, where exposure to rabid animals is frequent vaccine is scarce, there is little money and no rabies immunoglobulin (RIG) available. For these reasons, a variety of untested, potentially dangerous ID regimens are being used in some places. The only regimens which have been demonstrated to be immunogenic today are the 222011 and the 804011 (see above).

The volume of the standard IM dose varies between different products, and some producers are in the process of changing from a 1 ml to a 0.5 ml ampoule. Attention should therefore be paid to the volume of the product after reconstitution.

It is therefore proposed to publish precise instructions on the currently recognised methods of y ED vaccination, to make optimum use of restricted resources, and on precautions to be taken to prevent vaccine contamination from multidose vials, as well as viral cross-infection.

These guidelines should be suitable for distribution to large and small clinics and rural health centres and to government organisations deciding on vaccine policies.

A draft outline of headings for the proposed Guidelines was presented during the consultation.

**Future research:**

There is a need for new ID vaccine regimens using products formulated in 0.5 ml vials. Immunogenicity studies in non-exposed volunteers must identify a satisfactory regimen before efficacy is tested in patients needing PET.
- The immunogenicity of a regimen beginning with 4-site ID injections (0.1 ml/site), e.g. 40202 (days 0-7-28) using the entire 0.5 ml vial on day 0 should be studied.
- The effect of smaller doses (0.05 ml/site) in 8 sites, still using one 0.5 ml vial on day 0, could be investigated. The 8-site ID PET regimen has only been tested with HDCV and PCEC in 1 ml vials.
- The value of giving a final injection on day 90 should be tested.
- Clinical trials of the efficacy of the optimum regimen emerging from prior immunogenicity studies, with and without RIG, in patients with proven exposure to rabies should be carried out. Studies without RIG could be conducted ethically only in countries where RIG is unavailable.

**Conclusions**

Implementing ID methods for PET would increase the use of PET globally. It was emphasised that these regimens are of comparable immunogenicity to the IM regimen and very much more effective and safer than vaccines of nervous tissue origin.

Although the original IM route of inoculation has been regarded as the optimum method of treatment, it may be considered that this is not the best way of using one dose of vaccine on day 0. The ID method has advantages especially in developing countries in the absence of RIG. There is no contraindication to the use of an ID regimen.

The decision to implement economical ID PET rests with government agencies which select policies for rabies prophylaxis in their own countries. Dissemination of information from such an authority by instruction of physicians, nurses and other health care workers is very important. Local or regional advisers, who could be contacted easily to give practical advice, would enhance the acceptance of the new methods.

**Further reading**


