REPORT OF A WHO CONSULTATION ON INTRADERMAL APPLICATION OF HUMAN RABIES VACCINES

Geneva, 13-14 March 1995

Photos were furnished by © Dr. H. Wilde, Queen Saovabha Memorial Institute, Bangkok, Thailand & © Dr. D. Warrell, University of Oxford, UK.
REPORT OF
A WHO
CONSULTATION ON
INTRADERMAL
APPLICATION OF
HUMAN RABIES
VACCINES

Geneva, 13-14 March 1995

WORLD HEALTH ORGANIZATION
VETERINARY PUBLIC HEALTH UNIT
Contents

1. INTRODUCTION .................................................................................................................. 5

2. RECENT DEVELOPMENTS IN INTRADERMAL POST-EXPOSURE TREATMENT (ID/PET) .... 5
   2.1 PET with the purified duck embryo rabies vaccine (PDEV) in the Philippines ......... 5
   2.2 The id 222011 regimen of purified vero cell rabies vaccine (PVRV) and human diploid cell rabies vaccine (HDCV) in Thai children .................................................... 6
   2.3 Experience with German purified chick embryo cell (PCEC) in Thailand .................. 6
   2.4 PDEV and Japanese PCEC in Thailand ........................................................................ 7

3. RECENT PET FAILURES IN THAILAND ........................................................................... 8

4. GENERAL CONSIDERATIONS ON ECONOMICAL INTRADERMAL RABIES VACCINE PET REGIMENS ......................................................................................... 9

5. TECHNICAL AND REGULATORY ASPECTS .................................................................... 9
   5.1 ID use of rabies vaccines for PET in Thailand ............................................................... 9
   5.2 Views of vaccine manufacturers ................................................................................ 10

6. EVALUATION OF THE CURRENT WHO EXPERT COMMITTEE RECOMMENDATION ON ID/PET .......................................................... 10

7. PROPOSED WHO GUIDELINES FOR INTRADERMAL ADMINISTRATION OF RABIES VACCINES IN POST-EXPOSURE SITUATIONS ............................................. 11

8. FUTURE RESEARCH ......................................................................................................... 11
   8.1 On id regimens ........................................................................................................... 11
   8.2 On related subjects .................................................................................................. 12

9. DISCUSSION AND CONCLUSIONS ............................................................................ 12
   9.1 The role of id regimens in post-exposure treatment .................................................. 12
   9.2 The cost of vaccine .................................................................................................. 13
   9.3 The use of RIG ........................................................................................................ 13

REFERENCES ......................................................................................................................... 15

ANNEX I List of participants .................................................................................................. 16

ANNEX II DRAFT OUTLINE OF WHO GUIDELINES FOR INTRADERMAL APPLICATION OF RABIES VACCINE .......................................................... 18
1. INTRODUCTION

Dr F-X Meslin, Chief, Veterinary Public Health, welcomed the participants (Annex I) on behalf of the Director-General of the World Health Organization.

In developing countries, where more than 99% 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 Asia or Africa can afford. Multi-site intradermal administration of small doses of cell culture rabies vaccines which have been shown to protect humans bitten by proven rabid animals and to reduce the costs of PET by 60%, is an effective way of decreasing the cost of these much more potent, safe modern vaccines, and of increasing the neutralizing antibody response. In many developing countries, however, rabies vaccines are being given intradermally under inappropriate conditions and according to regimens whose efficacy is unproven.

The WHO Expert Committee in 1991 recommended intradermal application of modern rabies vaccines for PET according to the 222011 Thai Red Cross schedule. In addition, this Committee identified the pre-requisites and conditions appropriate for this route of vaccine administration. This recommendation was re-assessed in January 1993 and it was concluded that no revision was necessary at that time. As new data have 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.

Dr A. Sabchareon was elected chairperson and Dr M.J. Warrell, rapporteur.

2. RECENT DEVELOPMENTS IN INTRADERMAL POST-EXPOSURE TREATMENT (ID/PET)

2.1 PET with the purified duck embryo rabies vaccine (PDEV) in the Philippines

Rabies post-exposure treatment with PDEV (5.8 IU/ml) using a multisite intradermal (id) regimen was studied prospectively, and compared with PDEV given according to the standard 5-dose intramuscular (im) regimen.

Eighty-four patients with a low risk of rabies exposure were allocated to the id, and 72 to the im regimen. The patients in the id group received 0.2 ml of the reconstituted vaccine over both deltoids on days 0, 3 and 7, and one 0.2 ml injection each on days 30 and 90. Purified equine or human rabies immunoglobulin (RIG) was also given on day 0. Serum was obtained from each patient on days 0, 7, 14, 30, 90, 180 and 365, and titrated for rabies virus neutralizing antibody (VNA) by the rapid focus fluorescent test (RFFIT).

The results of 108 patients, with complete series of antibody determinations up to day 90, are summarized in the following two tables.

Nine (6%) of the 156 patients (4 im, 5 id) showed signs of adverse reactions. All these were resolved with antihistamine treatment and none were severe enough to warrant admission to hospital.
Table 1. Philippine comparative study of 0.2 ml id and standard im regimens with PDEV vaccine. Geometric mean titres (GMT)(IU/ml).

<table>
<thead>
<tr>
<th>Route of injection</th>
<th>Day 7</th>
<th>Day 14</th>
<th>Day 30</th>
<th>Day 90</th>
</tr>
</thead>
<tbody>
<tr>
<td>id</td>
<td>0.69</td>
<td>6.51</td>
<td>2.8</td>
<td>2.72</td>
</tr>
<tr>
<td>im</td>
<td>0.29</td>
<td>3.27</td>
<td>5.24</td>
<td>3.38</td>
</tr>
</tbody>
</table>

Table 2. Percentage seroconversion rate above 0.5 IU/ml.

<table>
<thead>
<tr>
<th>Route of injection</th>
<th>Day 7</th>
<th>Day 14</th>
<th>Day 30</th>
<th>Day 90</th>
</tr>
</thead>
<tbody>
<tr>
<td>id</td>
<td>61</td>
<td>96</td>
<td>93</td>
<td>94</td>
</tr>
<tr>
<td>im</td>
<td>43</td>
<td>94</td>
<td>93</td>
<td>98</td>
</tr>
</tbody>
</table>

2.2 The id 222011 regimen of purified vero cell rabies vaccine (PVRV) and human diploid cell rabies vaccine (HDCV) in Thai children

VNA responses were measured by the RFFIT following the 222011 id regimen of PVRV (0.5 ml/ampoule, AV 6.53 IU/dose) and HDCV (1 ml/ampoule, AV 6.52 IU/1 ml dose). Healthy boys were randomly allocated to receive either PVRV (n=24) or HDCV (n=22). The ‘Thai Red Cross’ (TRC) schedule, 222011, consists of an injection of 0.1 ml id at two different sites on days 0, 3, 7, and one injection at one site on days 30 and 90.

All the recipients were sero-negative on day 0. Only one HDCV recipient (4%) seroconverted (>0.5 IU/ml) by day 7, the others in both PVRV- and HDCV-vaccinated groups seroconverted by day 14. After day 14, the VNA levels declined progressively. The GMTs of the PVRV recipients were not significantly different from those of the HDCV recipients: 5%, 5% and 36% of the PVRV recipients had VNA levels <0.5 IU/ml on day 90, day 180 and day 365 respectively, while 4% and 9% of HDCV recipients had NA <0.5 IU/ml on day 90 and day 365 respectively.

No serious side-effects of id PVRV were observed.

2.3 Experience with German purified chick embryo cell (PCEC) in Thailand

PCEC was given id according to the TRC schedule (minus the last injection) to seven members of one family (age range 4-49 years) who were exposed to rabid puppies in their house. Two vaccinees (aged 9 and 15 years) showed VNA levels of 0.10 IU/ml on day 7. All of them had high antibody level on days 14, 28, 56, 180 and 365, despite having received their final injection on day 30.
PCEC was also given id according to the 222011 regimen to young healthy veterinary and medical students. PCEC given with and without human RIG elicited VNA on days 14, 28, 90, 180 and 365. No suppressive effect of human RIG was demonstrated.

PCEC vaccine has been used by a variety of id regimens in four Thai district hospitals, and the results of serological tests have been encouraging.

In a recent study from Songkla Hospital in 1994-1995, five batches of PCEC bought on the local market were given id according to the 222011 regimen to 40 post-exposure vaccinees followed-up. Serum samples from 18 vaccinees were examined. Two of them had had previous vaccination. All showed high VNA levels (GMT 4.95, 95% confidence level, 3.64-6.73 IU/ml, range 2.89-10.53 IU/ml) on day 14.

Batches of PCEC vaccine available in Thailand had antigenic values above 5 IU/dose.

2.4 PDEV and Japanese PCEC in Thailand

The immunogenicity of PDEV was studied when administered id according to the TRC schedule at two different dosages (ie 0.1 ml and 0.2 ml id per site). The VNA levels showed wide variation following the 0.1 ml dose. Satisfactory VNA levels were obtained, however, using the 0.2 ml id dose, with and without RIG treatment.

The immunogenicity of a primary chick embryo fibroblast (PCEC) vaccine registered and produced in Japan for human post-exposure treatment was tested at the Queen Saovabha Memorial Institute (QSMI), by the im and id routes, and compared with the TRC regimen using PVRV. GMTs on day 7 and 14 were very similar and close to 5 IU/ml on day 14. After im treatment, the titre of VNA remained at this level on days 30 and 90, but the GMTs decreased following id injections, although they remained above 1 IU/ml on day 90 (see Table 3).

Table 3. Neutralizing antibody response to PVRV & Japanese PCEC given by the id TRC regimen. (GMT & range)

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>n</th>
<th>Day 7</th>
<th>Day 14</th>
<th>Day 30</th>
<th>Day 90</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCEC</td>
<td>18</td>
<td>0.12</td>
<td>5.67</td>
<td>4.12</td>
<td>1.72</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(&lt;0.04-0.85)</td>
<td>(1.33-14.33)</td>
<td>(1.93-11.89)</td>
<td></td>
</tr>
<tr>
<td>PVRV</td>
<td>25</td>
<td>0.11</td>
<td>12.82</td>
<td>5.79</td>
<td>2.94</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(&lt;0.04-0.60)</td>
<td>(2.49-40.29)</td>
<td>(1.78-16.21)</td>
<td>(0.75-8.41)</td>
</tr>
</tbody>
</table>
3. RECENT PET FAILURES IN THAILAND

Human rabies in Thailand has been steadily declining from 370 deaths (0.78 per 100 000 population) in 1980 to 93 deaths (0.16 per 100 000 population) in 1993. One of the preventive measures implemented in Thailand is increasing the availability of proper post-exposure treatment. According to existing surveillance of PET and human rabies (which is notifiable), there has been approximately one failure for every 26 000 PET.

During the period 1980-1986, there were 12 human rabies deaths despite PET with tissue culture rabies vaccines. Examination of the cases revealed the most likely causes to be: delayed treatment, inappropriate wound care, and severe bites but no rabies immunoglobulin treatment.

Bamrasnaradura Infectious Hospital, Department of Communicable Disease Control for 1988-1994 reported six human rabies deaths after PET (see Table 4). All had severe exposure (bites on face, head and fingers). Four cases were children aged 3 to 9 years old and two cases were adults aged 44 and 45 years old.

Nationwide surveillance of human rabies in 1993 revealed four human cases (out of 93 total deaths) despite PET. All had severe exposure (bites on head, cheek, ear, nose and hand). Three patients were children aged 3 to 12 years old and one was 41 years old. The incubation period was 13 days for all except one which was 11 months. None of the patients had been given RIG, but all had received 3 to 5 doses of PVRV or PVEC.

In 1994, a girl died of rabies following multiple facial dog bites. The wounds had been cleaned six hours after the injury, using soap and povidone iodine, and then sutured. PVEC vaccine was given (0.1 ml id at 2 sites), but ERIG (40 IU/kg, half into the wounds and half into the gluteal area) was delayed until 25 hours after the bites. Similar doses of PVEC were given on days 3 and 7. Her symptoms of rabies encephalitis began on day 10, and she died 7 days later.

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Year of report</th>
<th>Sex</th>
<th>Age in yrs</th>
<th>Residence</th>
<th>Animal</th>
<th>Location of bite</th>
<th>IP* in days</th>
<th>Vaccine &amp; route used</th>
<th>RIG</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1988</td>
<td>M</td>
<td>6</td>
<td>BKK</td>
<td>Dog</td>
<td>Face 1 site</td>
<td>12</td>
<td>PVRV 800 IU</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1989</td>
<td>M</td>
<td>9</td>
<td>Cha-Cheng-Sao</td>
<td>Dog</td>
<td>Face, head, arm, 12 sites</td>
<td>25</td>
<td>TCV x4 im Yes</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1989</td>
<td>M</td>
<td>8</td>
<td>Petcha-boon</td>
<td>Dog</td>
<td>Mouth 2 sites</td>
<td>14</td>
<td>PVEC x3 No im</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1990</td>
<td>F</td>
<td>3</td>
<td>Samutsa-korn</td>
<td>Dog</td>
<td>Face 5 sites</td>
<td>20</td>
<td>PVRV id 2 x2</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>1991</td>
<td>M</td>
<td>45</td>
<td>Pathum-thani</td>
<td>Dog</td>
<td>Rt finger 3 sites</td>
<td>30</td>
<td>TCV x4 im No</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>1994</td>
<td>M</td>
<td>44</td>
<td>Nakorn-Ratsima</td>
<td>Dog</td>
<td>Rt Thumb</td>
<td>30</td>
<td>PVRV x4 No im</td>
<td></td>
</tr>
</tbody>
</table>

* Incubation Period  → Source of infection  ← Tissue culture vaccine, origin unknown  *Number of injections
4. GENERAL CONSIDERATIONS ON ECONOMICAL INTRADERMAL RABIES VACCINE PET REGIMENS

In many rabies endemic countries (e.g. Africa, Indian subcontinent and parts of South-east Asia) rabies vaccine of any kind is in short supply, patients may not complete post-exposure vaccination courses and RIG is unobtainable. These constraints must be taken into account in designing an «ideal» vaccine regimen, which should therefore 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 and yet simple regimen.

The TRC 22201 and the 804011 regimens have fulfilled these requirements but they have only been used in restricted areas, mainly by experienced personnel. 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 an 0.5 ml ampoule. There is now a need to modify the id regimens to produce a new schedule which will be applicable for use with all the recommended vaccines (see Annex 2) in areas with limited vaccine supplies and where no RIG is available.

The 8-site 804011 regimen consists of: on day 0, 1 ml of HDCV 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.

This regimen produces a rapid neutralizing antibody response not suppressed by human RIG and proved protective in a post-exposure trial of patients with bites by proved rabid dogs. RIG was not given unless patients had multiple bites or bites on the head, neck or hands. VNA levels were monitored frequently. By day 7, antibody was detected in 88% of 42 patients who did not have RIG, and at 1 year all 72 patients tested had VNA, in 71 the level was >0.5 IU/ml. This method has a wide margin of safety since an adequate antibody response is produced if only 4 of the 8 injections are id.

5. TECHNICAL AND REGULATORY ASPECTS

5.1 ID use of rabies vaccines for PET in Thailand

Sheep brain tissue-derived rabies vaccine (i.e. Semple-type vaccine) and the suckling mouse brain (SMB) vaccine, are no longer produced or available in Thailand. Production of Semple vaccine was stopped in 1983, and of SMB vaccine in 1993. Four imported cell culture or embryonating egg rabies vaccines (HDCV, PVRV, PCEC and PDEV) are now available in the country. During the past few years, the demand for these vaccines has increased by 10-15% each year and this has resulted in a high rate of PET (228 per 100 000 population in 1993). During the same period there has been a reduction in reported human rabies cases.

A new recommendation was issued by the Thai Ministry of Public Health on the basis of a technical review made by the National Immunization Advisory Committee in 1992. Two regimens (the standard Essen im and the TRC id) are now recommended for rabies prophylactic immunization. The Thai Ministry of Public Health suggests, in addition, that id PET be used in hospitals with well trained staff.

From preliminary data, 15 000 (13% of total) and 30 000 (22% of total) id PET were administered in 1992 and 1993 respectively. Most of them (approximately 12 000 persons a year),
were treated at the Thai Red Cross (QSMI). Most reported failures (see section 3) were observed in people given PET im. The use of the id regimen has proved to be both economical and helpful in preventing vaccine shortage.

5.2 Views of vaccine manufacturers

5.2.1 Pasteur-Mérieux. The intradermal administration of modern tissue culture vaccines (TCVs) offers an attractive alternative to im administration, especially in countries where cost is a major issue, and nervous tissue vaccines (NTVs) are still used.

The TRC 222011 id regimen using PVRV has been widely documented in clinical trials and in practice. From 1985 to 1994 approximately 70 000 TRC id treatments were given, with more than 29 000 in category III exposures.

However, the available data are still considered insufficient to determine (1) whether this experience can be extrapolated to all modern TCVs and (2) whether the id route offers the same guarantee of efficacy as the im route in the most critical situations, e.g. patients with multiple severe bites, young patients, absence of RIG, lack of patient compliance for the day 90 injection, vaccines of borderline potency, and inadvertent subcutaneous instead of id administration of vaccine.

Because the id route should not be a «second best», its recommended use should be restricted to vaccines, settings and indications in which it has been well tested.

5.2.2 Berna - Swiss Serum & Vaccines Institute. As shown in Table 2, PDEV id induces seroconversion at least as efficiently as PDEV im by day 7. Since 1994, the instructions accompanying Lyssavac N Berna (PDEV) has recommended all three vaccine schedules suggested in the WHO Expert Committee Report, 1992. The high degree of stability and the addition of a preservative make PDEV suited to multiple id use. It has been decided to reduce the volume of reconstitution of one dose from 1 ml to 0.5 ml, and therefore to double the antigen content per unit volume.

5.2.3 Behringwerke AG. PCEC rabies vaccine was licensed in 1985 in Germany, Thailand and India. Since then it has been used im on a large scale in these and in several other countries. PCEC vaccine was satisfactorily tested by the id route in simulated post-exposure trials in about 250 volunteers before being used in post-exposure antirabies vaccination in bitten patients from January 1994 to February 1995 in the Songkla Hospital, Thailand (see section 2.3).

6. EVALUATION OF THE CURRENT WHO EXPERT COMMITTEE RECOMMENDATION ON ID/PET

In September 1991 the WHO Expert Committee on Rabies' recommended the use of the id route for post-exposure treatment. Only one vaccination regimen was retained in the report of the WHO experts, the TRC 222011 schedule. According to this report, all modern cell culture and embryonating egg vaccines with a potency of at least 2.5 IU per dose could be used according to the TRC regimen. The experts listed a number of special precautions which had to be adhered to when the id technique was used (staff training, conditions and duration of vaccine storage after reconstitution, use of disposable syringes and needles).

This recommendation was re-assessed in 1993. The informal group which met in 1993
concluded that there were indications that the immunogenicity of the three vaccines under review (PVRV, PDEV and PCEC) compared favourably and so did the average potency per full im single immunizing dose at the time of release. It was considered at that time that no revision was necessary.

Further studies of the TRC id schedule, with and without RIG, were encouraged by the participants in the above discussions using vaccines other than PVRV. As variations in vaccine potency between batches are inevitable, it was recommended that clinical studies should use batches of relatively low potency. Dose response studies, giving varying amounts of antigen, were suggested to define safety margins. It was also mentioned that in all of these trials a second vaccine (e.g. HDCV) and a well tested schedule, should be included for comparison. The group also strongly recommended that the use of new vaccines with existing schedules or new schedules should only be considered after careful review of data obtained in trials with the specific vaccine and/or schedule under consideration.

7. PROPOSED WHO GUIDELINES FOR INTRADERMAL ADMINISTRATION OF RABIES VACCINES IN POST-EXPOSURE SITUATIONS

Knowledge of the correct methods of using TCVs 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 RIG available. For these reasons, a variety of untested, potentially dangerous id regimens are being used in some places. The id regimens which have been demonstrated to be immunogenic to date are:

- 8-site intradermal method (804011), *0.1 ml at 8 sites day 0, 4 sites day 7, single site days 28 and 91 (for use with HDC and PCEC vaccines where im dose is 1 ml)

- Thai Red Cross 2-site intradermal method (222011), * one id dose at each of 2 sites on days 0, 3, 7 and single site on days 28 and 90 (for use with PVRV, PCEC and PDEV), id dose per id site is one fifth of the volume after reconstitution of a single immunizing 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.

It is therefore proposed to publish precise instructions on the currently recognized methods of id 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 organizations deciding on vaccine policies.

A draft outline of headings for the proposed Guidelines is presented in Annex 2.

8. FUTURE RESEARCH

8.1 On id regimens

There is a need for (a) new id vaccine regimen(s) using products formulated in 0.5 ml vials (see section 4). 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.

For all these studies, randomized comparison should be made with current effective regimens using 8-site or 2-site injections on day 0 (i.e. TRC 222011 and 804011), with and without RIG. An im regimen might be used as a standard control, and each study should preferably include vaccines from more than one manufacturer.

- Clinical trials of the efficacy of the optimum regimen emerging from the 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.

8.2 On related subjects

- The role of other types of immune response induced by antirabies vaccines, for example cell-mediated immunity, NK cell function, cytokines and N protein non-neutralizing antibody should be studied further.

- The effect of HIV seropositivity and chloroquine on the immune response to post-exposure rabies vaccination should be further investigated.

- Vaccine interchangeability should be studied. The immunogenicity following the use of different cell culture or embryonating vaccines given consecutively during the same post-exposure course should be examined.

- An attempt should be made to standardize the RFFIT results between several laboratories, and continue to search for a better alternative test.

- The pharmacokinetics of equine RIG following im injection, could be studied using a sensitive enzyme immunoassay to detect the predictably low blood levels. Different sites of im injection might be tested, e.g. gluteal, anterolateral thigh and deltoid.

- Research should continue towards finding an alternative to RIG, which is in increasingly short supply. A combination of several monoclonal antibodies might be suitable.

- Investigation of new adjuvants and modelling of an ideal single-dose post-exposure vaccination course using slow-release preparations should be conducted.

9. DISCUSSION AND CONCLUSIONS

9.1 The role of id regimens in post-exposure treatment

Implementing id methods would increase the use of PET globally. It was emphasized 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 third world countries in the absence of RIG. There is no contraindication to the use of an id regimen.
The decision to implement economical id PET tests 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 advisors, who could be contacted easily to give practical advice, would enhance the acceptance of the new methods.

9.2 The cost of vaccine

The cost paid by the patient for vaccine may be ten times the manufacturers' price in some areas. There was unanimous agreement that governments should be asked not to levy taxes on imported essential life-saving pharmaceutical products, such as rabies vaccines, and that the consumer price of these essential biologicals should be regulated.

9.3 The use of RIG

In Asia, 99% of PET consists of vaccine alone. Worldwide, RIG is used with only 9% of courses of PET. Despite this, whenever it is available, RIG is an essential part of PET, especially for patients with severe bites (on the head, neck and hands). The following problems with RIG administration were identified and recommendations made:

a) RIG treatment of children. For small children, the calculated dosage of RIG may be insufficient to infiltrate all wounds. Sterile saline can be used to dilute the volume 2- or 3-fold to permit thorough infiltration. The total dose of RIG should not be increased for fear of reducing the vaccine-induced VNA response.

b) Site of injection. Wound infiltration is the most important part of RIG administration. If any of the dose remains after infiltration, it can be given im into the anterior thigh, and if necessary divided between the two thighs. Injections should not be given into the gluteal region as they may not be into muscle.

c) Method of wound infiltration. Caution is needed if injecting into a tissue compartment, e.g. finger pulp. Excess fluid can result in increased compartmental pressure and lead to necrosis.

Care is needed to avoid RIG seeping out of wounds during infiltration. If such a loss does occur, the volume should be estimated and replaced.

d) The use of intradermal skin tests before ERIG treatment. The id skin test detects IgE mediated Type I hypersensitivity, a reaginic response to previous exposure to the antigen. Anaphylaxis following an injection of serum results from complement activation by Fc fragments, or aggregated IgG molecules, which the skin test would not detect. This is confirmed in practice:

- At the QSMI in Bangkok, skin tests on 150 patients gave false positive results in 23%, while anaphylaxis followed a negative skin test in one patient.

- Data from patients with reactions following intravenous antivenom treatment showed that the skin test had a positive predictive value of only 32%, and a sensitivity of 55%. The skin test failed to predict all 12 anaphylactic reactions in 25 patients given intravenous antivenom.

It was concluded that there is no evidence that conjunctival or id skin testing predicts anaphylaxis or serum sickness reactions; on the contrary, they might induce sensitivity. These tests should therefore no longer be used.
Patients with a history of atopy or previous antivenom treatment may be pre-treated with antihistamines and adrenaline. Corticosteroids are best avoided as they might interfere with the immune response to the PET. Physicians should be aware that reactions can occur several hours after injection.
References


ANNEX 1

LIST OF PARTICIPANTS

Mr Pierre-Etienne Cambillard, Marketing and Sales, Prevention/Immunoregulation, Behringwerke AG, P.O. Box 11 40, D-35501 Marburg/L, Germany (Fax: +49 6421 394224)

Dr M. Donnier, Département Marketing International, Pasteur Mérieux Séums & Vaccins, 58 Avenue Leclerc, F-69342 Lyon Cédex 07, France (Fax: +33 - 72 73 7997)

Dr R. Glück, Head, Virology Department, Swiss Serum and Vaccines Institute, P.O. Box, 3001 Bern, Switzerland (Fax: +41 31 908 6775)

Dr M. von Hedenström, Behringwerke AG, Postfach 1140, D-35001 Marburg/L, Germany (Fax: +49 6421 3946)

Dr Ch. Herzog, Chef du Département Medicinal, Swiss Serum and Vaccines Institute, P.O. Box, 3001 Bern, Switzerland (Fax: +41 31 908 6775)

Dr Darika Kingnate, Zoonoses Section, Communicable Diseases Control Department, Division of General Communicable Diseases, Tiwanon Road, Nonthaburi 11000, Thailande (Fax: 66 2 281 0869 or 591 8432)

Dr Jean Lang, Chef de Projet Rage, Medical Direction, Pasteur Mérieux Séums & Vaccins, 58 Avenue Leclerc, BP 7046, F-69348 Lyon Cédex 07, France (Fax: +33 - 72 73 77 37)

Dr Vara Meesomboon, Chief, Zoonoses Section, Communicable Diseases Control Department, Division of General Communicable Diseases, Tiwanon Road, Nonthaburi 11000, Thailande (Fax: 66 2 281 0869 or 591 8432)

Dr Mary Elizabeth G. Miranda, Rabies Research Program, Research Institute for Tropical Medicine, Department of Health, Alabang, Muntinlupa, Metro Manila, Philippines (Fax: +63 2 - 842 2245)

Dr W. Pohl, Dept of Clinical Research and Immunology, Behringwerke AG, P.O. Box 1140, D-35501 Marburg/L, Germany (Fax: +49 6421 394 667)

Dr O. Raynaud, Département Médical et Marketing International, Pasteur Mérieux Séums & Vaccins, 58 Avenue Leclerc, F-69342 Lyon Cédex 07, France (Fax: +33 - 72 73 7997)

Dr Yolande Rotivel, Laboratoire de la Rage, Institut Pasteur, 28 rue du Docteur Roux, F-75724 Paris Cédex 15, France (Fax: +33 40 61 30 15)
*Dr C.E. Rupprecht, Chief, Rabies Laboratory, VRZB, Division of Viral & Rickettsial Diseases, National Center for Infectious Diseases, Centers for Disease Control, 1600 Clifton Road, N.E., Atlanta, GA 30333, USA  (Fax: +1 404 - 639 1058)

Dr A. Sabchareon, Head, Department of Tropical Paediatrics, Faculty of Tropical Medicine, Mahidol University, 420/6 Rajvithi Road, Bangkok 10400, Thailand  (Fax: +66 2 246 8340)  (Chairperson)

Dr Siriwan Sirikawin, Infectious Disease Physician, Bamrasnaradura Hospital, Nonthaburi 11000, Thailand  (Tel: 66 2 588 3116; Fax: 66 2 588 3729)

Dr C. Wasi, Department of Microbiology, Faculty of Medicine, Siri Raj Hospital, Bangkok, Thailand  (Tel: 411 31 11; Fax: 66 2 418 16 36)

Dr Henry Wilde, Head, WHO Collaborating Centre for Research on Rabies Pathogenesis and Prevention, Queen Saovabha Memorial Institute, Thai Red Cross Society, Bangkok 10330, Thailand  (Fax: +66 1 254 0212)

**Secretariat**

Dr Mary J. Warrell, Nuffield Dept of Clinical Medicine, University of Oxford, John Radcliffe Hospital, Headington, GB-Oxford 0X3 9DU, UK  (Fax: +44 865 - 750 506)  (Rapporteur)  (Temporary Advisers)

Dr David A. Warrell, Nuffield Dept of Clinical Medicine, University of Oxford, John Radcliffe Hospital, Headington, GB-Oxford 0X3 9DU, UK  (Fax: +44 865 - 750 506)  (Temporary Advisers)

Dr V. Pervikov, Vaccine Research and Development, Global Programme for Vaccines, WHO, Geneva, Switzerland

Dr F.-X. Meslin, Chief, Veterinary Public Health, Division of Communicable Diseases, WHO, Geneva, Switzerland  (Secretary)

Dr K. Stöhr, Veterinary Public Health, Scientist, Division of Communicable Diseases, WHO, Geneva, Switzerland.

* Unable to attend
ANNEX 2

DRAFT OUTLINE OF WHO GUIDELINES FOR INTRADERMAL ADMINISTRATION OF RABIES VACCINE IN POST-EXPOSURE SITUATIONS

Introduction

The continuing problem of rabies is most acute in poorer countries of Africa, Asia and South America, where more than 99% of all human rabies deaths occur. Rabies vaccines of nervous tissue origin are still widely used, but these are outdated and should be replaced by safer modern tissue culture and embryonating egg vaccines. These are prohibitively expensive if given by the conventional im method, but less than half the amount of vaccine can be used effectively and safely by using economical id multi-site regimens. These id schedules are of equivalent efficacy to the standard im regimen, and are considerably safer than nervous tissue vaccines.

Vaccines proven to be efficacious to date:

- Human diploid cell vaccine (HDCV)
- Purified vero cell vaccine (PVRV)
- Purified chick embryo cell vaccine (PCEC), Behring only
- Purified duck embryo cell vaccine (PDEV)

Requirements of an id vaccine regimen:

- Economy. It uses a small volume of vaccine. It requires only a few visits to the clinic.
- Safety. It induces a rapid rise of detectable VNA (> 0.5 IU/ml in 100% of vaccinees at day 14). There is a strong antigenic stimulus at the first visit. Immune response is unaffected by RIG treatment.
- Efficacy. It should be strictly tested in patients bitten by rabid animals, and followed for 1 or 2 years to ensure no rabies deaths

Intradermal regimens demonstrated to be immunogenic to date:

- 8-site intradermal method (804011), 0.1 ml at 8 sites day 0, 4 sites day 7, single site days 28 and 91 (for use with HDC and PCEC vaccines where im dose is 1 ml)
- Thai Red Cross 2-site intradermal method (222011), one id dose at each of 2 sites on days 0, 3, 7 and single site on days 28 and 90 (for use with PVRV, PCEC and PDEV), id dose is one fifth of im dose per site, 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.
Correct technique of intradermal immunization (includes practical details and photographs)

Storage of reconstituted vaccines. If great care is taken with aseptic technique, a dose of vaccine may be withdrawn from an ampoule and the remainder used for another patient, provided that the vial is immediately stored at 4°C. A sterile needle and syringe must be used to draw up vaccine for each patient. Although the vaccine antigen is very stable at 4°C, there is a high risk of contamination by microorganisms, especially of rabies vaccines which do not contain a preservative. Ideally, all vials of reconstituted vaccine should therefore be used within 24 hours.

Criteria for use - no contraindication

Site effects of vaccine treatment

Management of patients bitten by rabid animals:

- Assess risk of infection
- Wound cleaning
- Vaccine treatment
- Passive immunization
  - Products and dosage
  - Infiltration of wound (dilute RIG if necessary for children)
  - Hypersensitivity testing not recommended
  - Signs and treatment of reactions
  - Record treatment details

Deaths from rabies despite vaccine treatment

No defects in vaccine quality have been observed, but the success of treatment depends on close adherence to recommended methods.

Post-exposure treatment of previously vaccinated patients

Urgent booster doses of a modern potent vaccine are needed on days 0 and 3, and no RIG treatment is necessary providing that the patient has previously had a complete pre- or post-exposure course of a potent vaccine, or that rabies neutralizing antibody (≥0.5 IU/ml) has been demonstrated at any time in the past.

Pre-exposure vaccination

 Annex

References to support recommendations.

Vaccine Potency. Vaccine should contain ≥2.5 IU/im dose. It should be noted that modern cell culture and embryonating egg vaccines used successfully with the TRC id post-exposure regimen had a potency of 0.5 IU/id dose.