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Intradermal application of rabies vaccines

Report of a WHO consultation

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CONTENTS

1.	Opening Ceremony.....	1
2.	New developments in id application of rabies vaccines	1
2.1	Thailand.....	2
2.1.1	Reports from the Queen Saovabha Memorial Institute:.....	2
	Four-site intradermal (id) post-exposure treatment in previously rabies vaccinated subjects	2
	A modification of TRC-id: Attempt to eliminate the 90 day booster.....	3
2.1.2	Report from the Ministry of Public Health, Bangkok, Thailand.....	3
	Post-exposure rabies treatments modalities including vaccine types/regimens and failure.	3
2.1.3	Report from Siriraj Hospital, Mahidol University	4
	Safety and immunogenicity of PCECV given in 0,1 ml per id site.....	4
2.1.4	Report from Faculty of Tropical Medicine, Mahidol University	5
	Developments in id application of rabies vaccine.....	5
2.2	Sri Lanka: Intradermal administration of rabies tissue culture vaccine	6
2.3	Philippines: New developments of id application of rabies vaccines	8
2.4	India: Experience in intradermal immunization for rabies post-exposure prophylaxis.....	9
2.5	Laos: Current human rabies prevention activities.....	10
2.6	Viet Nam: Rabies situation and human rabies prevention	10
2.7	Pakistan: Human rabies prevention and control.....	11
3.	Selected technical items	12
3.1	Current intradermal post-exposure treatment regimens	12
3.2	Rabies vaccine potency requirements	13
3.2.1	Effects of rabies vaccine potency on the immune response and protection against disease	13
3.2.2	The NIH test.....	14

3.3 Evaluation of the safety and convenience of the proposed PCECV 0,1ml/id site regimen	16
3.3.1 Comments from: Dr Mary Warrell, Centre for Tropical Medicine, John Radcliffe Hospital, Oxford University, Oxford, United Kingdom	16
3.3.2 Comments from: Dr Chantapong Wasi, Siriraj Hospital of Mahidol University, Bangkok, Thailand, Dr Deborah J. Briggs, Kansas State University, College of Veterinary Medicine, Manhattan, Kansas, United States of America	17
3.4 When appearances deceive: Some considerations in improving access to rabies post-exposure treatment	18
4. Conclusions and recommendations	21
4.1 Vaccine Potency Requirement	21
4.2 Interchangeability of rabies vaccine type or regimen	21
4.3 Intradermal regimens.....	22
4.4 PET in immunosuppressed individuals.....	22
4.5 Future research themes.....	22
Annex 1	23
List of participants.....	23
Observers.....	25
Secretariat.....	26

1. OPENING CEREMONY

Dr Visith Sitprija, Director of the Queen Saovabha Memorial Institute (QSMI), Bangkok and Dr F.-X.Meslin, Department of Communicable Diseases – Surveillance and Response, World Health Organization, Geneva welcomed the participants on behalf of their respective organizations. They both wished international, local participants and observers very successful discussions and a very enjoyable stay in Bangkok.

Dr Meslin stressed QSMI's outstanding and early contribution to the subject and the fact that this led to its designation as a WHO Collaborating Center for Research on Rabies Pathogenesis and Treatment. He recalled that WHO as early as 1991 helped the development and promotion of reduced-treatment regimens using the intradermal (id) route. This was done as a way to decrease the cost of rabies post-exposure treatment (PET) and therefore increase access to id standard treatment using safe and efficacious cell-culture or highly purified embryonating rabies vaccines. Following the endorsement of the id route for PET made by the WHO Expert Committee on Rabies in 1992, three WHO Consultations on the subject held in Geneva in 1993, 1995 and 1996 endorsed one more id regimen and led to the issuing of detailed operating procedures for id application of four modern commercial rabies vaccine types¹ which had met WHO safety, potency and efficacy requirements when used for post-exposure id treatment of rabies.

The objective of the present joint WHO/QSMI Consultation was to further contribute to the cost-reduction of PET whilst ensuring that safety and efficacy are not compromised. The Consultation reviewed the current situation regarding the use of the id route particularly in those Asian countries which are pioneers in the field and the improvements as well as difficulties which its use may have evidenced. The Consultation addressed specific issues such as id dosage, minimum vaccine potency requirements and potency tests as well as other issues such as vaccine interchangeability and possible "hidden costs" of the id route.

2. NEW DEVELOPMENTS IN ID APPLICATION OF RABIES VACCINES

Id administration of second generation rabies vaccines was initiated in Thailand in the early eighties as a means to increase access to safe and efficacious treatment regimens and eventually to lead to the elimination of the use of nerve tissue rabies vaccines. Id regimens are an important part of the strategic plan to reduce the incidence of human rabies in Thailand. The successful experience in Thailand has encouraged other Asian countries to implement id rabies post exposure treatment. The following report on the status of id application of rabies vaccines is a summary of the data presented by medical professionals from Thailand and six other Asian countries.

¹ Document WHO/EMC/ZOO.96.6 - WHO recommendations on rabies post-exposure treatment and the correct technique of intradermal immunization against rabies

2.1 THAILAND

2.1.1 Reports from the Queen Saovabha Memorial Institute:

Four-site intradermal (id) post-exposure treatment in previously rabies vaccinated subjects

Presenter: Ms Pakamatz Khawplod, Queen Saovabha Memorial Institute, Bangkok, Thailand

The current WHO recommendations for a previously vaccinated patient who had a potential rabies exposure requires two injections given either intramuscular (im) or id on days 0 and 3. This regimen necessitates two clinic visits. To reduce the number of visits and the vaccine cost, we studied a post-exposure regimen requiring only one visit during which the patient receives 0.1 ml of vaccine at each of four id sites (called “4-site id booster” post exposure treatment). Two hundred patients were divided into ten groups. Results have been analyzed for eight groups so far. Vaccines used were commercial lots of human diploid cell rabies vaccine (HDCV) with a potency of 4,7 IU/dose, purified chick embryo cell rabies vaccine (PCECV) with a potency of 8,5 IU/dose and purified vero cell rabies vaccine (PVRV) with a potency 8,7 IU/dose.

Five of the eight groups were administered a dose im on each of days 0, 7 and 28 of either HDCV (2 groups), PCECV (2 groups) or PVRV (1 group). Patients received the same brand of vaccine for the post-exposure treatment as they had received for their primary vaccination series. Two groups of patients among the four groups having received HDCV or PCECV were then treated using the “4-sites id booster” and the other groups received two im shots on day 0 and 3. In both cases, post-exposure treatment had been given 365 days after the first preventive vaccine administration.

The three other groups (PCEC - two groups and PVRV- one group) received a preventive immunization regimen consisting of three id injections of 0,1ml per id site on days 0,7 and 28. One PCEC group received two im doses given on days 0 and 3 and the other two groups (one PCEC and one PVRV) received the “4-sites id booster”. Again, in both cases, post-exposure treatment had been given 365 days after the first preventive vaccine administration.

A comparison of the Geometric mean titers (GMT) and ranges of the rabies virus neutralizing antibody responses after pre-exposure and post-exposure vaccinations administered one year later was made. It was concluded that the “4-site id booster” post-exposure treatment administered one year after the pre-exposure series induced a significantly higher neutralizing antibody response than did the conventional two dose im regimen administered on day 0 and 3. When PCECV had been used for pre-exposure by the id route at 0,1 ml per site, the anamnestic response following the application of the “4-site id booster” regimen was equivalent to that conferred by two im post-exposure regimen which requires two clinic visits.

The “4-site id booster” post-exposure treatment requires only 1 clinic visit and only 40% of the im dose of PVRV or 20% of the im dose of PCEC. From these preliminary data the “4-site id booster” regimen appears to be a convenient, low cost and reliable post-exposure treatment in previously immunized (either im or id) patients.

A modification of TRC-id: Attempt to eliminate the 90 day booster

Presenter: Ms Pakamat Khawplod, Queen Saovabha Memorial Institute, Bangkok, Thailand

A retrospective review of our animal bite clinic patients revealed that 8 – 11 % of subjects did not return for the 90 day TRC-id booster. Nevertheless, there have been no rabies deaths in this population during the past 14 years. Therefore, a study was designed to determine if the 90 day booster could be eliminated by increasing the vaccine dose prior to day 90 using various schedules.

Eighty-one subjects were divided into four groups. Group 1: Control, was given the original TRC-id regimen 2-2-2-0-1-1 using PCEC with a potency of 7.0 IU/ml . Three other groups were given 0.1 ml as follows: Group 2: (2-2-2-0-2-0); Group 3: (4-2-2-0-2-0); and Group 4: (4-2-2-0-4-0). Geometric mean titers (GMT) in Group 2 were not significantly different from the GMT in the Control group on day 90 but they were lower on day 360. Group 3 had GMT that were significantly higher than the Control group on days 7 and 14, similar on day 90 and lower on day 360. GMT from Group 4 was significantly higher than the GMT of the Control group as well as Group 2 and Group 3 on day 90. Although all subjects in all groups had detectable neutralizing antibody titers on day 360, some titers were below 0.5 I.U./ml.

This study demonstrated the presence of adequate titers of at least 0.5 I.U./ml on day 90 when the vaccine dose is increased on day 28. When the day 90 booster dose is eliminated, lower titers were evident one year after primary vaccination. Since the day 90 booster has a significant risk of drop out, it might be prudent to increase the day 28 vaccine dose of the original TRC-id regimen from 0.1 ml at 1 site to 0.1 ml at 2 sites.

2.1.2 Report from the Ministry of Public Health, Bangkok, Thailand

Post-exposure rabies treatments modalities including vaccine types/regimens and failure

Presenter: Dr Praphasri Jongsuksuntigul, Director of the National Rabies Centre Ministry of Health, Nonthaburi, Thailand

Reported cases of human rabies in Thailand have continuously decreased from 185 to 56 during the period 1990 – 1998. A slight increase was reported in 1999 with 69 deaths. Cases are mainly reported from the central and northeastern regions of the country. These two regions together accounting for about 70% and 85% of all reported cases in 1990 and 1999 respectively. The number of persons that received post-exposure

treatment in Thailand almost tripled in 10 years from about 88 000 in 1990 to approximately 240 000 in 1999.

Many human rabies vaccines and rabies immunoglobulin are presently available in Thailand: Human diploid cell vaccine (HDCV), purified chick embryo cell vaccine (PCECV), purified vero cell rabies vaccine (PVRV), purified duck embryo cell rabies vaccine (PDEV), equine rabies immunoglobulin (ERIG) as well as human rabies immunoglobulin (HRIG). A vial of PCEC or PVRV costs approximately 250 bahts and ERIG 360 bahts per 5 ml (1000 IU) vial.

In Thailand all modern vaccines can be used according to the Essen 5 im doses regimen. For id application two regimens can be used: the 2-2-2-0-1-1 and 8-0-4-0-1-1 schedules. HDCV and PCECV used intradermally should contain at least 0.7 IU/0.1 ml. The volume is 0,1ml per id site for HDCV, PCECV and PVRV. If no RIG is available on day 0 the 8-0-4-0-1-1 schedule should be used. In case of severe bites the 8 sites regimen plus RIG is recommended.

A total of 382 human rabies deaths were investigated during the period 1994 - 31 May 2000. Twenty-three had received post-exposure treatment: 8 both vaccine and serum and 15 vaccine alone. All the 8 patients who died in spite of having received both vaccine and RIG had severe wounds on the face, neck, lip, shoulder and/or multiple wounds. Two of the 8 patients had received lower dosage of RIG than recommended. One of them had received a treatment combining the intramuscular and intradermal route. Two of the 8 cases were treated between 2 and 3 days after exposure. Considering the 15 patients who died and had received vaccine only, 3 had been treated by the intradermal route. All other received the vaccine intramuscularly.

2.1.3 Report from Siriraj Hospital, Mahidol University

Safety and immunogenicity of PCECV given in 0,1 ml per id site

Presenter: Dr Chantapong Wasi, Siriraj Hospital of Mahidol University, Bangkok, Thailand

Although the introduction of tissue culture vaccines for rabies has dramatically improved the immunogenicity and safety of rabies vaccines, they are often prohibitively expensive for developing countries. To examine whether smaller doses of these vaccines could be used, we tested the safety and immunogenicity of PCECV on 211 patients in Thailand with WHO category II and III exposures to rabies. The patients presented at two Thai hospitals and were randomized into three groups. Patients in Group 1 received 0.1 ml PCECV intradermally at two sites on day 0, 3, 7 and at one site on days 30 and 90 (2-2-2-0-1-1). Group 2 was treated similarly, except that PVRV was used instead of PCECV. Group 3 received 1.0 ml PCECV intramuscularly on days 0, 3, 7, 14, and 30. Serum was collected on days 0, 3, 7, 14, 30 and 90 and tested by RFFIT at Kansas State University. The geometric mean titers (GMT) of the rabies neutralizing antibody was determined. On day 14, the GMT of the per-protocol patients vaccinated with PCECV-id (n = 58) was equivalent to the GMT of the patients that received PVRV-id (n=59). The authors concluded that PCECV is a safe and highly immunogenic vaccine for post-

exposure rabies vaccination when administered id in 0.1 ml doses using the 2-2-2-0-1-1 schedule recommended by WHO.

2.1.4 Report from Faculty of Tropical Medicine, Mahidol University

Developments in id application of rabies vaccine

Presenter: Dr Arunee Sabcharoen, Faculty of Tropical Medicine of Mahidol University, Bangkok, Thailand

The need to find an economical method of using modern safe and effective second generation rabies vaccines prompted researchers from the Faculty of Tropical Medicine, Mahidol University to search for id regimens that induce satisfactory neutralizing antibody. In 1983 it was reported that rabies virus neutralizing antibodies (RVNA) were detected as early as day 7 in some subjects given 0.1 ml of human diploid cell vaccine (HDCV), at each of 8-sites on day 0 (8-0-0-4-1). The highest antibody titres from day 14 onward were reported in patients that received im administration of HDCV, but the multisite id regimen, which requires only one third of the volume of vaccine used in the im regimen, gave similar results, provided that a booster dose was given on day 90.

In a second report in 1984, RVNA were detectable within seven days of the first dose in all subjects in groups given 0.1 ml HDCV id at 8-sites (8-0-4-0-1/8-0-0-4-1) or four sites (4-0-4-0-1). The 8-sites groups geometric mean titres (GMT) were significantly higher on day 7 than the 4-sites id groups. From day 14 onward, all groups demonstrated excellent levels of RVNA. Suppression of the response to 8-site id vaccination by human rabies immune globulin (HRIG) was prevented by giving the second dose of vaccine on day 7 rather than day 14.

Based on the above mentioned two studies, the HDCV 8-0-4-0-1-1 regimen was selected for a new clinical trial. One hundred and fifty five patients (70 severe and 85 mild cases) bitten by proven rabid animals were randomly allocated to receive either the conventional course of Semple vaccine (SV) or HDCV (8-0-4-0-1-1). Equine anti-rabies serum (EARS) was administered on day 0 to the severely bitten patients. The results demonstrated that 88% of the patients given HDCV alone had detectable RVNA on day 7 in contrast to 2% in patients that received SV alone. Antibody persisted for at least one year post-vaccination in all HDCV patients tested in contrast to only 48% of patients that received SV. Suppression of the antibody response occurred in patients that received equine anti-rabies serum. There were no deaths attributed to human rabies in either group.

In 1987 the 8-0-4-0-1-1, and the 4-0-4-0-1-1 id regimens were investigated using PCECV and reported comparable RVNA response in both groups. In another comparative study with PCECV the same trend was observed. PCECV, 2-2-2-0-1-1 id with and without HRIG was evaluated for its immunogenicity. RVNA was detectable in all subjects in both groups from day 14 to day 365. No significant suppressive effects of HRIG on RVNA response were observed.

Clinical research demonstrated that RVNA response after id vaccination with HDCV and PVRV (with comparable potency) using the 2-2-2-0-1-1 regimen were similar and all subject had RVNA levels above 0.5 IU/ml by day 14. In addition, the initial antibody response of the subjects that received the 4-0-2-0-1-1 id regimen was higher than that of subjects that received the 2-2-2-0-1-1 id regimen.

In 1998 a clinical trial was conducted in children. The children received three doses of PVRV id (0.1 ml/dose), or PVRV im (0.5 ml/dose) on days 0, 7, and 28 and one booster dose (either id or im) one year later. Although children vaccinated id had significantly lower RVNA after primary immunization as well as after booster than children vaccinated im, there were no significant differences in the percentage of children with detectable titers (1:5 titer or ≥ 0.15 IU/ml) between the id and im groups after both primary and booster immunizations.

2.2 SRI LANKA

Intradermal administration of rabies tissue culture vaccine

Presenter: Dr Omala Wimalaratna, Department of Rabies Diagnosis Research and Vaccine Production, Medical Research Institute, Columbo, Sri Lanka

The local production of Semple vaccine was stopped in 1995. At present only imported cell culture rabies vaccines are available in Sri Lanka. A study was conducted in Thailand by an investigator from Sri Lanka to compare the im and id schedules. Forty medical students given preexposure rabies vaccination were included. Twenty-six received id and 14 received im. Blood was drawn on days 0 and 35. The GMT values were as follows: GMT on day 35 for the im group was 4.59 IU/mL; GMT on day 35 for the id group was 4.39 IU/ml. After her return to Sri Lanka in May 1997, her findings were presented to the Directorate General, Health Services, policy makers, senior officials in the Ministry of Health, and clinicians.

In August 1997, two major hospitals in Colombo were selected to initiate id vaccination: the National Hospital Sri Lanka and Lady Ridgeway Children's Hospital. These hospitals were selected because they had the highest consumption of anti-rabies vaccine in the country, have well trained staff, and have better and easy supervision. The 2 site id postexposure regimen was selected as the standard regimen. The medical staff and nurses in the out-patient department were educated as to the proper technique of id administration of rabies vaccine. There were two responsible officers identified in each institution. During the first week, daily visits were initiated to monitor progress. Later, visits were reduced to once or twice a week for two months. Rabies virus neutralizing antibody levels were determined in randomly selected patients to insure that the technique was being administered correctly and to determine patient compliance. A comparative study was conducted on the 2-site and 8-site id schedules. The results indicated that 60% of patients that received the 8-site had antibody level equal or superior to 0,5 IU/ml on day 7 and 30% of patients that received the 2-site regimen had antibody level equal or superior to 0,5 IU/ml on day 7. On March 8, 1998 other teaching hospitals were introduced to the technique. A massive education campaign was launched using

mass media to educate all categories of health staff, school children and the public. All major hospitals in the country were visited. Training programmes were conducted for nurses and medical officers. ERIG was introduced. By March 2000, all teaching, general and base hospitals were included in the new schedule. Altogether 27 hospitals excluding the north and the east were involved.

Every effort was made to visit each of the hospitals once in six to 12 months. In addition, contact by telephone for emergency consultation became available 24 hours a day. Medical officers trained in rabies PET are on duty in the Medical Research Institute, Colombo from 8 am to 5 pm on weekdays and from 8 am to 12 noon during weekends and public holidays to offer advice to patients referred from other medical institutions or who present on their own.

It is not intended to introduce the id schedule in district hospitals (bed capacity of 100) due to the lack of trained staff and poor supervision. Districts with a high incidence of rabies deaths were identified and health education programmes were conducted for all categories of health staff in collaboration with the Veterinary Public Health Service of the Ministry of Health.

The main challenges/difficulties which were encountered were:

- To convince the health professionals that the id schedule was safe and effective and recommended by WHO;
- The shortage of id syringes. It is suggested that the manufacturers could supply the syringes with the vaccine;
- The high turnover of medical officers in the out patient department responsible for most mismanagement of post-exposure treatment;
- The shortage of staff and resources. Supervision and lack of resources for determination of RVNA, specifically when ERIG is not available in high risk patients;
- Poor statistics;
- The temporary shortage of RIG.

Since the id schedule was introduced into Sri Lanka, no shortage of rabies vaccine and no adverse effect or untoward event following post-exposure treatment have been reported in the country.

2.3 PHILIPPINES

New developments of id application of rabies vaccines

Presenter: Drs Mary Elizabeth G. Miranda and Beatriz Quiambao, Rabies Research Programme, Veterinary Research Department, Research Institute for Tropical Medicine, Philippines.

The trend of rabies in the Philippines has remained stable at around 400 human cases per year for the past decade. In 1999, 53 373 patients received vaccine alone and 15 027 received vaccine and immune globulin for rabies post-exposure treatment (PET). The id regimen has been used at the Research Institute for Tropical Medicine (RITM), one of the two major rabies referral centers in Metro Manila, since 1993. In the RITM rabies registry data, the trend of id application has increased from 1 660 in 1994 to 12 973 in 1999. Ninety-one percent (50 549) of patients bitten by dogs received id treatment between 1994 – 1999. In addition, 1 029 patients bitten by cats were treated routinely with the id regimen.

The use of the id post-exposure regimen was officially adopted by the Department of Health in 1997. Since 1998, 140 Animal Bite Treatment Centers (ABTC) have been established nationwide. The ABTC are located in health facilities, preferably hospitals with at least one physician and one nurse trained in rabies PET including management of hypersensitivity reactions. ABTCs solely utilize the id regimen which is given free of charge. RIG is available in very few centers.

The main concerns with the id regimen were:

- Vaccine supply. At the ABTCs the vaccine supply is dependent upon a central supply from the Department of Health. When the supply is depleted, patients have to buy their own vaccine.
- Vaccine shortage. At ABTCs where only a few patients are seen, the staff are reluctant to open a vial for fear of wasting the rest of the vaccine if no other patients come.
- Technique: although it is easy to learn to administer the id technique (after given to ten patients), difficulty in injection of young children is often experienced. Vaccine either spills out or is given subcutaneously. When this happens, the id vaccination procedure is repeated. This occurs in approximately 5% of cases.
- Spillage. Despite the use of a hubless syringe, only four doses can be obtained from one vial containing 0.5 ml. On days 0, 3 and 7, only one syringe is used, aspirating enough vaccine for two doses.
- Reactions. Redness at the injection site is common (30 – 60% of cases). Puritus (112) and swelling (10%) are less common.

A cost comparison of rabies vaccine regimens has been made in the Philippines. A standard im regimen costs US\$ 216 (with biologicals –vaccine and ERIG accounting for more than 88% of the total cost), the 2-1-1 im regimen costs \$ 189 (a \$27 cost reduction or 12,5% decrease) and the TRC id regimen \$163 (a \$53 cost reduction or 24.5%). ERIG cost remain constant in all regimens whereas vaccine cost decreases from \$ 89 for the standard im to \$ 71 for the 2-1-1 and \$ 36 for the TRC id.

A study was conducted in RITM on the contamination rate of open vials of rabies vaccine with preservative (PDEV) and without preservative (PVRV). A total of 16 vials of vaccines (8 of each type) were opened. Eight vials (4 of each type) were inoculated with *Staphylococcus aureus* 4 of those (2 of each type) were kept at room temperature and the remaining 4 at refrigerator temperature - and 8 (4 of each type) were not inoculated. As before, 4 of those (2 of each type) were kept at room temperature and 4 at refrigerator temperature.

Small amounts (0,1ml) of vaccine were withdrawn from vials over a week's time as if the vials had been used for a post-exposure treatment schedule according to the 2-2-2-0-1-1 id regimen.

Samples from the vials were taken on day 0, 3,7,10 and 14 and cultured. No contamination of open (non-purposedly contaminated) vials of rabies vaccines, whether kept at room or refrigerator temperature, occurred up to 14 days after the vials opening. Vials of vaccine inoculated with *Staphylococcus aureus* and kept at room temperature had confluent growth regardless of vaccine type. Vials of vaccine with preservative intentionally inoculated with *S.aureus* and kept at refrigerator temperature grew less colonies than the vaccine without preservative.

2.4 INDIA

Experience in intradermal immunization for rabies post-exposure prophylaxis

Presenter: Dr S.N. Madhusudana, Associate Professor, Department of Neurovirology, National Institute of Mental Health and Neuroscience (NIMHANS), Bangalore, India

The use of id immunization in India, using both HDCV and PCECV, was initiated as early as 1986 at Central Research Institute, Kasauli. The vaccine regimen used was 0.1 ml of vaccine at 8 sites on day 0 and 4-sites on day 14 and at one site on day 90. This 8-site regimen (8-0-0-4-0-1) was used from 1986 to 1993 in Kasauli only. Adequate titers of rabies virus neutralizing antibodies (> 0.5 IU/ml) were detected in over 80% of vaccine recipients as early as day 7 and 100% of those on day 14. From 1986 to 1993, over 500 patients were vaccinated with the id technique and followed for three years. No treatment failures were reported in these patients. From 1994 onward, the id immunization with PCECV was continued at NIMHANS, Bangalore using the 8-site regimen recommended by WHO ((8-0-4-0-1-1).

A comparative study between the 2-site and the 8-site regimens revealed that the 8-site regimen produced significantly higher antibody titers on all days tested. The 8-site regimen was also tested in 35 people bitten by confirmed rabid dogs, with a three year follow-up. There were no treatment failures.

There were only minimal side effects to the id regimen. In conclusion, it is essential that the id regimen be approved by the National Authorities so that highly reactogenic sheep brain vaccine can be replaced in a phased manner.

2.5 LAOS

Current human rabies prevention activities

Presenter: Dr Somthana Douangmala, Director of National Center for Pediatric Infectious Diseases, National EPI Manager, Ministry of Health, Vientiane, PDR Laos

Both PVRV and PCECV are available in Vientiane, Laos. Three thousand patients are treated annually at the rabies vaccination section of the National Center for Infectious Disease Control and the provincial rabies vaccination units. Less than five deaths are reported annually, and this figure certainly reflects underreporting. The main causes of human rabies fatalities include: delay of treatment, negligence of rabies vaccination, and incomplete regimen of vaccination. The high cost of rabies vaccine and incomplete vaccination treatment are the main obstacles for the Lao people to receive adequate vaccination. In Laos the intra-muscular (im) route of administration is used for all categories of rabies vaccination and ERIG/HRIG are rarely used due to their high cost. However, no human fatalities have occurred after pre- and post-exposure treatments.

The id route of administration of rabies vaccines is not yet used in Laos. On May 18, 2000 the first introductory seminar on id application of rabies vaccines, held in collaboration with Chiron Vaccines, was conducted in Vientiane. One hundred and twenty medical officers and veterinarians from central institutions attended. Two more seminars will be conducted in the near future, one in northern Laos and the other in the southern part of Lao PDR.

2.6 VIET NAM

Rabies situation and human rabies prevention

Presenter: Dr Dinh Kim Xuyen, Chief of Rabies Control, NIHE, Ministry of Health, Hanoi, Viet Nam

From 1991 to 1995 rabies represented the first cause of mortality in Viet Nam among the first ten most prevalent communicable diseases with a rate of 0,43 death per 100,000 population. This rate was slightly above that of tetanus and twice that of Japanese encephalitis and 5 times higher than those related to measles, polio or diphtheria. In the following years the overall situation vis a vis communicable diseases has considerably improved and mortality rates have considerably decreased for all ten

diseases. Rabies was still ranking second behind tetanus in 1999 with a mortality rate of 0,10 death per 100 000.

From 1992 to 1999 the number of rabies post-exposure treatments per million inhabitants increased from 3629 to 7416. During the same period human rabies decreased from 0,56 to 0,10 fatalities per 100 000 population. Local vaccines produced on suckling mouse brains (SMB vaccines) were mostly used. Imported cell culture vaccines are available from chemists but very expensive. The intradermal route has been used with SMBV: from 6 to 8 daily injections according to the level of exposure and boosters. Viet-Nam is keen to discontinue its production of SMBV and use modern vaccines instead. These products should be preferably produced locally so that they are affordable for the segment of the population which most need it.

2.7 PAKISTAN

Human rabies prevention and control

Presenter: Dr Naseem Salahuddin, Department of Infectious Diseases, Liaquat National Hospital, Karachi, Pakistan

Although there are no known studies on the epidemiology of rabies in Pakistan, the incidence of dog bites from potentially rabid dogs is rising alarmingly. Newspaper reports indicate great public anxiety over this highly charged issue. In Karachi, with a population of 13 million, the major referral centers including government hospitals like Jinnah Postgraduate Medical Center, the Civil Hospital Karachi (CHK) and Edhi Cancer Centers report 55-60 cases of dog bite per day, including ten – 15 new cases. Private hospitals like the Aga Khan University Hospital and Liaquat National Postgraduate Medical Centre report three - five cases of dog bites per day. Cases occurring in rural areas probably go unreported. Periodic dog destruction campaigns in large cities have not significantly reduced the number of dog bite cases.

Data analyzed from a retrospective study from July 1992 to December 1994 in Karachi indicated that of the 40 cases of human rabies admitted to CHK, 85% were male and 55% were less than 15 years of age. Sixty-seven percent had received anti-rabies vaccine and none had received rabies immune globulin. The incidence of rabies in Karachi was estimated to be nine per million population.

The vaccine available for post-exposure prophylaxis is sheep brain vaccine (SBV), Semple type, produced by National Institute of Health Islamabad. It is purchased by provincial, federal and non-governmental hospitals. The administration of SBV includes 17 – 21 daily injections administered subcutaneously into the abdominal wall. Local reactions occur in nearly 65% cases, pain and erythema being the most common, and post vaccinal encephalitis is reported in 1 case per 120. Although the cost of SBV is low, (Rs. 180 per 50 ml vial), the indirect costs – transportation costs, lost wages, treatment of side effects, etc.- average Rs. 1414/ per treatment.

Imported cell culture vaccines available in Pakistan are HDCV, PVRV, PDEV and PCECV. They are, however, very expensive when administered in the standard Essen im technique: Rupees (Rs.) 9377 with HDCV. TRC-id regimen using PDECV would cost Rs. 1380, and TRC-id regimen using PVRV would cost Rs. 1442.

Despite the relatively low cost of the id regimens, these have not become popular due to several reasons: a) change on a large scale is always difficult to implement, b) confusing dosage schedules and hesitation among health staff to administer id injections, c) possible wastage of a single dosage vial when using a multidose which would offset the lowered cost of reduced dose.

In general, the emergency room physicians and general practitioners treating dog bite cases are inadequately trained to manage them. Interviews of these practitioners reveal that wounds are not adequately cleaned with soap and water and are often sutured, knowledge of vaccine administration is poor and RIG is almost never recommended because it is "too expensive." There is a great need to train care givers on management of animal bites.

3. SELECTED TECHNICAL ITEMS

3.1 CURRENT INTRADERMAL POST-EXPOSURE TREATMENT REGIMENS

Presenter: Dr F.-X.Meslin, Co-ordinator Animal and Food-related Public Health Risks, Department of Communicable Diseases- Surveillance and Response WHO, Geneva.

The WHO Consultations on the subject held in Geneva in 1995 and 1996 endorsed two regimens and these endorsements have led to the issuing of detailed operating procedures for id application of modern rabies vaccines². The two regimens endorsed by the experts are:

- the "2.2.2.0.1.1." regimen for use with purified vero cell vaccine (PVRV), purified primary chick embryo cell vaccine (PCECV) and purified duck embryo vaccine (PDEV). The vaccination consists of id injections of one fifth of the im dose (0.1 to 0,2 ml according to the volume after reconstitution of the id dose – this is 0,1 ml per site for PVRV and 0,2 ml for both PCEC and PDEV) at two locations on days 0, 3 and 7, and at one location on days 30 and 90.
- the "8.0.4.0.1.1." regimen for use with human diploid cell vaccine (HDCV) and purified primary chick embryo cell vaccine (PCECV). The vaccination consists of an injection of 0.1 ml id at 8 different id sites on day 0, four sites on day 7, and one site on days 28 and 90. This regimen is particularly recommended for severe exposure (single or multiple transdermal bites or

² Document WHO/EMC/ZOO/96.6 - WHO recommendations on rabies post-exposure treatment and the correct technique of intradermal immunization against rabies

scratches, contamination of mucous membranes with saliva) when no immunoglobulin is available.

Today these regimens can only be applied with a limited number of commercial vaccines i.e. those meeting WHO safety, potency and efficacy requirements when used for post-exposure treatment of rabies:

- human diploid cell vaccine (HDCV): Rabivac™
- purified vero cell vaccine (PVRV): Verorab™, Imovax™, Rabies vero™, TRC Verorab™
- purified chicken embryo cell vaccine (PCECV): Rabipur™
- purified duck embryo vaccine (PDEV): Lyssavac N™

3.2 RABIES VACCINE POTENCY REQUIREMENTS

3.2.1 Effects of rabies vaccine potency on the immune response and protection against disease

Presenter: Dr Mary Warrell, Centre for Tropical Medicine, John Radcliffe Hospital, Oxford University, Oxford, United Kingdom

Since the introduction of tissue culture vaccines, more than 25 years ago, the minimum potency of 2.5 IU/dose has been required. Why was this level chosen? The immunogenicity of a rabies vaccine increases with its antigenicity up to a certain level. When larger quantities of antigen are given no additional benefit can be seen. In the 1970's many experiments on animals and humans evaluated different doses and regimens of HDCV, the only TCV widely available at the time. Some of the data were presented in 1977 in Marburg, Germany, at a symposium on the standardization of rabies vaccines for human use produced in tissue culture.

Early studies in animals indicated no significant increase in antibody response between 2 and 6 IU/dose. In humans, vaccines with antigenic values of 1.1, 2.3 and 3.6 IU/dose gave proportional increases in antibody response, but increasing the antigenic value to 6.4 IU/dose showed no further benefit. Vaccines of potency ranging up to 13 IU/dose were tested in some studies. In one of these studies a vaccine containing 8 IU per dose was administered for pre-exposure immunization to 181 people. This vaccine was then diluted (or by giving ¼ of dose) so that each dose contained 2 IU and given according to the same vaccination scheme to 27 other people. The regimen using the diluted vaccine gave a slower and lower antibody response although still produced acceptable antibody levels by day 21. In conclusion, potency values greater than 2 IU per dose were of comparable immunogenicity.

After the meeting in Marburg, a working group evaluated the evidence and recommended 2.5 IU/dose for im treatment. In its report issued in 1981, the WHO Expert Committee of Rabies came to the same conclusions.

The three modern vaccines most used today were not included in the original studies, so any clinical data on immunogenicity are therefore valuable. A pre-exposure id vaccination regimen involving 3 shots given at 2, 3 and 4 months of age was provided to 117 Vietnamese children. The vaccine used was PVRV. It was given 0.1 ml per id site. Three batches of PVRV with different antigenic content were used, and the results of the immune response were as follow:

Potency Value (in IU/dose)	Antibody GMT on day 30 (in IU/ml)
3.5	11.8
6.4	13.5
12.0	10.4

The data demonstrate a lack of direct correlation between the potency of a cell culture vaccine and the immune response it induces in humans over this range of potency.

The early trials on id PET were performed with HDCV having an antigenic value of 2.55 to 3.39 IU per dose and PVRV containing 5.1 IU/dose. The HDC vaccine potency in the post-exposure trial of the 8-site method was 3.39 IU/dose. In the post-exposure trial of the 2-site method, the potency of PVRV was 3.17 IU/dose. The recommendation to encourage the use of these methods worldwide was made as a result of these findings.

The antigenic values of vaccines produced have varied greatly between batches, tending to increase in the last few years to more than 5 IU/dose for the 3 modern vaccines most used today. The need for higher potency rabies vaccines for use with economical intradermal (id) regimens has been suggested in papers published recently and been endorsed by some national health authorities. However no evidence has been given to support the increase of the potency of modern rabies vaccines for use with id regimens. The present minimum value of 2.5 IU per dose should be adequate for id regimens.

3.2.2 The NIH test

Presenter: Dr Michel Aubert, Laboratoire d'Etudes sur la Rage et la Pathologie des Animaux Sauvages, WHO Collaborating Centre for Zoonoses Control Programme Management, Malzeville, France

Many criticisms have been made regarding the NIH test in particular the high variability of the results, the fact that the test does not reproduce natural conditions of rabies vaccine use and that the choice of the challenge strain affects NIH values. These are reviewed in some detail in the following:

Results of the NIH test are highly variable:

The intra-laboratory variability (“repeatability”) is evaluated by performing several titrations of the same vaccine (different manipulations). For example in the WHO Collaborating Centre of Nancy, 28 independent tests on the same vaccine gave a mean $PD_{50} = 1.957$ (decimal logarithm of the inverse protective dilution 50 %), with a variance equal to 0.0302. Considering that the NIH titre is a difference of two PD_{50} 's, the variance of the NIH titre is evaluated as twice the observed variance of PD_{50} 's, i.e. = 0.0604. Practically, for a rabies vaccine with a titre precisely equal to 2.5 IU/ml (the minimal WHO potency requirement), 95 % of the NIH titrations performed on this vaccine would fall between 0.8 and 7.8 IU/ml.

This large variability explains why the correlation between NIH values obtained in different laboratories for the same vaccine is poor (low reproducibility). For example, the correlation between the NIH titres of 72 vaccines calculated in the WHO Collaborating Centre of Nancy on the one hand and vaccine producers on the other, was statistically significant ($p = 0.01$) but very dispersed ($R^2 = 0.13$). This correlation was significantly different from the relation $y=x$ that should be observed if both the control laboratory and the producers were able to obtain similar results for the same vaccines. Nevertheless, the poor reproducibility may also be explained by the narrow range of NIH values of tested vaccines: most vaccines were above the minimal threshold and producers tend to produce similar batches of vaccines.

In vitro methods for replacing the NIH tests have been proposed by several authors. In 1983 NIH titres given by six laboratories for three vaccines were compared to those given by 14 laboratories using a single radial immunodiffusion test (SRD). A lower variability of the SRD compared with the NIH test was noticed. Unfortunately it was realized that in vitro tests do not accurately reflect the protective activity of vaccines.

The NIH test does not reproduce natural conditions of rabies vaccine use:

The NIH test protocol does not mimic the use of rabies vaccine in the real world and conditions of the natural challenge (route of virus inoculation, virus strain). To analyze for the possible bias of the NIH test, a study was conducted using a single vaccine injection followed by a peripheral challenge with a wild rabies strain (the NIH test involves two vaccine injections and an intracerebral challenge with a fixed strain of rabies virus). The study demonstrated that PD_{50} 's obtained for various veterinary vaccines with both the NIH test and the "peripheral" test were significantly correlated.

Therefore the NIH test could be considered a good enough model for predicting results of the field application of veterinary (and probably human) vaccines in their respective target species. There no reason to replace the current NIH by a model better mimicking natural conditions. In addition the peripheral challenge with a field strain is difficult to carry out as it requires a huge amount of challenge virus : 160 000 times the number of LD50 required by intra cerebral route, and mice must be observed 42 days after challenge.

The choice of the challenge strain affects NIH titres:

Higher antigenic values are generally obtained when the virus strain used for challenge is homologous to that used in vaccine production. This was confirmed by an experiment comparing the protection given by various vaccines in mice challenged with CVS, SAD or LEP strains. All these laboratory strains represented a more severe challenge than the GS7 strain isolated from naturally infected foxes in Europe used in a peripheral test. Therefore the NIH test represents a more severe challenge test than what happens in vaccinated animals exposed to field virus strains under natural conditions.

Discussion:

A difference should be made between a) the minimal NIH titre compatible with an adequate level of protection, which must be verified by national control laboratories and, b) the safety margin established by vaccine manufacturers for batch release. In this latter case vaccine titres are largely above the minimal requirement to make sure the vaccine batch is not rejected by the national control authorities. A safety margin of 1 IU/dose was established for veterinary vaccines to ensure that most batches were above the WHO minimum requirement of 0.3 IU/dose. This safety margin with time became the minimal requirement. This minimal requirement of 1 IU/dose led to the production of batches with a potency of 2.5 IU/dose or more. This new safety margin may one day become the new minimum requirement for rabies vaccine for veterinary use. The same process has occurred in human vaccine production. This increasing trend may not be eventually beneficial to human health as vaccine potency alone is not reliable indicator of the protection a vaccine may confer.

3.3 EVALUATION OF THE SAFETY AND CONVENIENCE OF THE PROPOSED PCECV 0,1ML/ID SITE REGIMEN

3.3.1 Comments from Dr Mary Warrell, Centre for Tropical Medicine, John Radcliffe Hospital, Oxford University, Oxford, United Kingdom

Before any rabies vaccine licensed solely for im administration could be used according to an id regimen using a reduced amount of antigen, WHO previously suggested that trials be conducted to demonstrate that the vaccine and id regimen:

- induced similar immunogenicity to a vaccine & id or im regimen currently recommended by the WHO,
- demonstrated an absence of significant immunosuppression by concomitant RIG treatment,
- demonstrated protective efficacy in a trial in patients exposed to proven rabid animals.

Safety of the new 0.1 ml regimen:

The suggested id dose with PCECV is one tenth of an im dose, that is half of that currently recommended for the 2-site method with which there is clinical experience.

Another comparative trial of the same regimen and vaccine in Thailand showed a slow antibody response, and 3% and 5% of vaccinees had unacceptably low antibody levels (<0,5IU/ml) on days 14 & 90 respectively (Charanasri 1994).

In the study on PCECV 0,1 ml/id site presented in section 2.1.3 of this report, there was a wide variance of antibody results.

In a recent study of PCEC pre-exposure treatment (0.1 ml id at 2 sites on days 0, 7 & 28), low antibody levels (<0.5 IU/ml) occurred in a few of the vaccinees on days 28 and day 90 (Jaijaroensup 1999).

As per the WHO requirements for any new regimen and since there is a reduction by 50% in the amount of vaccine used, a post-exposure trial in patients bitten by proven rabid animals is indicated, but none has been performed. Only 3 patients in the study presented in section 2.1.3 were bitten by proven rabid animals and none of them received the new regimen.

Convenience and economical use:

One ampoule of PCECV contains 1 ml. According to current WHO recommendations all reconstituted vaccine without preservative should be used within a working day. To prevent wastage of vaccine, the new regimen would demand that 4 or 5 patients must be vaccinated on days 0, 3, and 7 of the treatment. Only a few large centers would be able to use it economically and the opportunity for bacterial or fungal contamination of the vial is greater than for current regimens.

3.3.2 Comments from: Dr Chantapong Wasi, Siriraj Hospital of Mahidol University, Bangkok, Thailand, Dr Deborah J. Briggs, Kansas State University, College of Veterinary Medicine, Manhattan, Kansas, United States of America

Safety of the new 0.1 ml regimen:

The data presented by Dr Wasi (see section 2.1.3) was from a good clinical practice monitored clinical trial comparing the serological response of subjects vaccinated i.d. with 0.1 ml of either PCECV or PVRV. In this study there was no statistically significant difference in the GMT between the subjects that received PCECV and the subjects that received PVRV. The study conducted by Charanasri, published in 1994, did not adhere to the same GCP standard as the Wasi study and did not include subjects vaccinated with PVRV for comparison.

A wide variance of rabies virus neutralizing antibody (RVNA) titers have been reported in many other published studies where the range of RVNA values are included.

The recent study by Jaijaroensup, published in 1999 used a 3-dose pre-exposure regimen, not a 5-dose post-exposure regimen as was reported in the study presented by Wasi and did not include PVRV or HDCV as a comparison rabies vaccine.

Convenience and economical use

All current rabies vaccines that are administered i.d. for post-exposure treatment should be limited to large centers where medical personnel experienced with i.d. administration techniques are available. WHO states that all rabies vaccines used i.d. should be used within 6 hours after reconstitution in order to prevent contamination.

3.4 WHEN APPEARANCES DECEIVE: SOME CONSIDERATIONS IN IMPROVING ACCESS TO RABIES POST-EXPOSURE TREATMENT

Presenter: Ms Y. Madrid, Procurement Services, World Health Organization, Geneva, Switzerland

A large scale switch to modern rabies vaccines from older, neural vaccines by many developing countries is desirable from a health standpoint, but difficult to implement given the relatively high price of the modern products. Interest in reducing the costs of treatment has been the primary driver in the development of reduced volume vaccine regimens. It is estimated that if such regimens are used with maximum efficiency the cost of vaccine for rabies post-exposure treatment can drop significantly (for example, from US \$35 to US \$11.2).

Is seeking cost reductions through lower vaccine volume regimens the answer (or at least a key component of such an answer) to improving access to modern rabies treatment?

Despite the great attraction of this option, the answer is not necessarily “yes.” Why is this?

- Despite the potentially large price reduction, the vaccine cost may still be considered too high for strained public health budgets facing many competing priorities.
- The overall direct cost of post-exposure treatment needs to include not just the vaccine, but also syringes and needles, and very importantly, the cost of a good quality immunoglobulin. Not all patients require immunoglobulin treatment, but because this component of treatment can be as much as three times more expensive than the vaccine cost it remains a key factor to consider. In fact, in terms of impact to public health budgets, it is possible that a 33% price reduction in immunoglobulin cost can yield equivalent or greater savings to those that can be realistically achieved through the adoption of certain reduced volume vaccine treatment regimens.
- It is unlikely that the maximum cost savings benefit can be achieved as there will almost inevitably be waste associated with using single dose vials in a multidose regimen. Although the cost savings may still be important, their magnitude in various “real-life” settings requires assessment.

- The reduced volume regimens tend to be more complicated to remember and administer correctly than the Essen regimen, and as a result, it is likely that more mistakes (and treatment failures) will result (particularly true where staff are not well trained and/or do not see patients with sufficient frequency). Also, the information available in the package insert accompanying the vial and the regimen advocated for use will not agree and this can further contribute to errors in administration.

The risks of unsafe injection and administration practices are higher with some of the reduced volume regimens. This is for several reasons:

- More injections may be required, thereby potentially multiplying risk.
- Unless proper sterile measures taken, there is greater contamination potential.
- Vial storage may be inappropriate because the vials are intended for single use and do not contain preservative. It is likely that some vials may be stored and used beyond 6-8 hours after first use.
- Although some of the regimens require less visits to a clinic by patients, this does not ensure that compliance with the full treatment will be higher. The pain associated with multiple intradermal injections during the first few visits is likely to be greater than that of a one dose intramuscular injection and may deter patients from returning. Further studies comparing of compliance rates for different regimens in “real-life” settings would be of value.
- Different reduced volume treatment regimens can only be used with a specific subset of vaccines available in the market, whereas the standard Essen regimen can be used with all the modern vaccines available. In effect, adoption of reduced volume treatment regimens differentiates (products can less easily be substituted for each other) an already oligopolistic market (that is, a market with few sellers and where there is a tendency towards stable pricing). This differentiation is unfortunate.
- It makes it more difficult for countries to switch among the available vaccines to obtain the lowest price. This is because switching to a lower cost vaccine may require changing therapeutic regimen and this brings with it several additional “hidden costs”, such as creating and distributing new treatment guidelines and re-training of staff.
- It makes it more difficult to consolidate purchases (because different buyers purchase different vaccines) to increase volume and negotiating power and thereby drive down prices.
- The two factors above give suppliers further control of price; that is, it gives them greater monopoly power in the market. In general, the greater the monopoly characteristics of the market the less incentive a supplier will have to embark into high volume, low price production (because this will lower total revenue). Hence, the more differentiated the market, the less the market adopts the characteristics that are deemed socially desirable and the more it adopts characteristics desired by producers.

Although low volume therapeutic regimens can be useful in lowering vaccine cost they do not necessarily yield optimal treatment cost savings to health benefit ratios. Furthermore, in some cases, the elaboration of yet more regimens may actually be counterproductive because these further differentiate the market. If this route to cost reduction is not the only answer to increased access to modern post-exposure rabies therapy, what actions can be recommended?

- To focus on developing regimens that can be used with the full range of available modern vaccines (or as many as possible).
- To focus on developing regimens that can reduce not just vaccine cost but immunoglobulin cost while not compromising effectiveness of treatment.
- To conduct studies examining the actual costs and practical implementation aspects of different regimens. For example, in some countries, it may make sense to use a reduced volume regimen in certain specialized centers and an Essen regimen elsewhere. Studies that can give more specific guidance as to the situations in which this would make sense would be useful.
- To increase supply of vaccine/immunoglobulin and number of suppliers.
- To invest in the development high-output production processes for modern vaccines and immunoglobulin.
- To provide technical support to assist in the expansion of production and exportation of high quality modern vaccines by producers in developing countries. (Note however, that a situation where a multitude of local manufacturers produce modern vaccines or immunoglobulin of questionable quality and low export potential is not desirable either from an access perspective or from an economic viability standpoint).
- To increase the purchasing power of buyers in the market.
- To use regimens that maximize the ability to select among the modern products available on the market based on price (i.e. avoid regimens that can be used with a very limited number of vaccines).
- To consolidate the purchase of vaccine and immunoglobulin among several buyers or negotiate jointly (or through a representative third party such as WHO) for price. This requires that as many countries as possible use the same regimen or compatible regimens (i.e. that do not require a different vaccine) and that they collaborate with each other in developing forecasts.
- To consider when purchasing vaccine overall costs, not just vaccine costs.
- There is no gain in purchasing vaccine at a lower price if producers are compensating with higher immunoglobulin prices. Examine the available alternatives offered by suppliers in view of the overall treatment costs.
- Invest in increasing public awareness and political will.
- Regardless of what cost reductions can be achieved, modern rabies post-exposure treatment will likely cost more than the treatment currently used in many countries. Additional financing is essential and this usually requires concerted

advocacy to highlight the issue and create political will to address it at all levels (country, region, global).

4. CONCLUSIONS AND RECOMMENDATIONS:

4.1 VACCINE POTENCY REQUIREMENT

- Because of the inter-laboratory variability of the NIH test, great caution is required when comparing results obtained in different immunogenicity studies. Assuming that there is no bias in the evaluation made by two laboratories, NIH titres expressed in IU/ml should only be considered significantly different when the evaluation given by one laboratory is more than 4 times than that of the other.
- The possibility of increasing the antigenic value required for vaccines for id use was discussed. The antigenic potency of all the WHO approved vaccines has proven similar and well above the minimum value of 2.5 IU/ampoule.
- Established minimum potency value of human and veterinary vaccines should not be increased by national authorities unless the need for a change is substantiated by clinical or field studies.
- To be approved for id use, any new candidate vaccine should be proven potent by the NIH test and its immunogenicity must be demonstrated with the volume intended for humans.
- Considering the difficulty and the cost of performing the NIH test regularly, countries importing vaccines may ask the collaboration of WHO collaborative center on rabies to confirm the potency of imported rabies vaccine batches.
- Any country willing to adopt an id regimen of proven efficacy with the recommended vaccines need not repeat immunogenicity studies in their own population.

4.2 INTERCHANGEABILITY OF RABIES VACCINE TYPE OR REGIMEN

- Interchangeability of modern rabies vaccine is not recommended. However, in countries such as the Philippines, Thailand and Sri Lanka as well as for example France and Germany (where usually only one rabies vaccine type - locally produced - is readily available) it has been practiced for many years, without reported untoward events, each time circumstances made it inevitable to interchange vaccine or route of administration.
- When completion of PET with the same modern rabies vaccine is not possible, the switch can be done provided that it is one of the WHO recommended cell

culture vaccine. As far as the change in route of administration is concerned, no immunogenicity study has been done yet. This practice should be the exception until such studies are conducted. Moreover, Ab monitoring is highly recommended in such patients.

4.3 INTRADERMAL REGIMENS

- No change should be made to the WHO recommendations concerning id post-exposure treatment methods (see section 3.1), but the following option is included:
- In Thailand, PCECV (Rabipur™) 0.1 ml per id site has been used for post-exposure treatment according to the 2-2-2-0-1-1 regimen. A recently published study (see section 2.1.3) showed good immunogenicity. The use of PCECV 0.1 mL per id site in a 2-2-2-0-1-1 regimen may be considered for use by national health authorities. This does not apply to any other vaccine.
- For all vaccines recommended by WHO to be used intra-dermally (see section 3.1), the vaccine insert should contain a statement saying: “This vaccine is of sufficient potency to allow its safe use in one of the WHO recommended intradermal post-exposure regimen in countries where relevant national authorities have approved the intra-dermal route for rabies PET”.

4.4 PET IN IMMUNOSUPPRESSED INDIVIDUALS

- The importance of wound treatment should be further stressed
- RIG should be administered deeply into the wound for all exposures belonging to categories 2 & 3
- Vaccine should always be administered and an infectious disease specialist with expert knowledge of rabies prevention should be consulted.

4.5 FUTURE RESEARCH THEMES

- The Consultation urges the scientific community to develop an alternative in-vitro test for potency testing.
- The development of a rabies vaccine with a preservative for use in ID regimens should continue.
- Studies should be conducted examining the actual costs and practical implementation aspects of different regimens. For example, in some countries, it may make sense to use a reduced volume regimen in certain specialized centers and an im regimen elsewhere. Studies that can give more specific guidance as to the situations in which this would make sense would be useful.

ANNEX 1

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