Special Report

WHO Consultation on Human and Dog Rabies Prevention and control, held at Annecy, France 7-9 October 2009

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The WHO Consultation meeting on Human and Dog Rabies Prevention and Control was held at Annecy, in France from October 7th to 9th, 2009. **A Draft Report of this meeting dated 10th November, 2009** is available with me and is being circulated through the APCRI Journal, for the benefit of those readers, who did not have access to it. This activity is being done with the objective of circulation of information of high academic and scientific value.

Opening Session:

The meeting was opened by Anastasia Pantaliss representative of the Gates Foundation and François Meslin representing the World Health Organization welcomed the participants on behalf of their respective organizations. This Consultation was organized back to back to the first annual meeting of the International Coordinating Group of the Gates Foundation funded project for rabies control in developing countries held in WHO Headquarters Geneva from 5-7 October to benefit from the participation in the scientific consultation of the national coordinators and advisers of the Gates Foundation funded projects in Kwa Zulu Natal, Tanzania and the Philippines. François Meslin thanked the Gates Foundation for having accepted to sponsor this meeting as part of the above project. Raffy Dersy kindly accepted to chair of the first session on human rabies prevention and Alexander Wandeler the session dealing with dog rabies control and elimination.

Session 1 on human rabies prevention

Chaired by Dr Raffy Dersy Coordinator of national rabies control in the Philippines

National Centre for Disease Prevention and Control, Department of Health, Manila.

Agenda item 2.1.1:

Shorten Essen 4 doses instead of 5:

Presented by Dr Charles Rupprecht, head rabies laboratory, CDC Atlanta on behalf of the US ACIP working group on rabies.

On the basis of the peer-reviewed literature, unpublished data, epidemiological reviews and expert opinion, the evidence in support of a reduced, 4-dose vaccine schedule for consideration in healthy patients during rabies post-exposure prophylaxis. No increase in adverse events was identified or suggestive from the deletion of the last dose of rabies vaccine during prophylaxis. Recommendations for immunization in persons with altered immunocompetence have been presented previously (CDC, 1993; CDC, 2008). Various immunosuppressive agents, drugs and illnesses can interfere with active immunity after vaccination. Seroconversion may be less than ideal among immunosuppressed persons as attributable to infection (Tantawichien et al, 2001; Panichamen et al., 2001). **Until such time that additional evidence is forthcoming, prophylaxis should be administered using 5 doses of vaccine in persons with broadly defined immunosuppression. Serum samples can be tested for rabies virus neutralizing antibody by the RFFIT to ensure that an acceptable antibody response has developed.**

Taken together, previous studies indicate that prophylaxis combining wound treatment, local infiltration of RIG, and vaccination is uniformly effective when appropriately administered, regardless of the fifth and last dose of rabies vaccine administration. **Clearly, human rabies may still develop whenever other key elements of rabies post-exposure prophylaxis regimens are omitted, delayed or incorrectly administered.**

Agenda item 2.1.2:

The one-week PEP regimen ("4-4-4")

Presented by Prasimporn Shantavasinkul, Queen Saovabha Memorial Institute, the Thai Red Cross Society (WHO Collaborating Center for Research on Rabies Pathogenesis and Prevention), Bangkok, Thailand.

Patients exposed to a rabid animal often travel long distances to receive post-exposure prophylaxis

(PEP) which requires 4 or 5 visits. Reducing the number of clinic visits would not only reduce costs for the patient but may also help increase compliance by the patient to receive complete PEP. We made an effort to develop PEP completed in one week. We administered the four-site intradermal injections of 0.1 ml of purified Vero cell rabies vaccine (PVRV) at deltoids and thighs on days 0, 3 and 7 with and without equine rabies immunoglobulin (ERIG) 40 IU/ Kg. A control group received the WHO approved and widely used Thai Red Cross (TRC) regimen (two-site intradermal injections on days 0, 3, 7 and one injection on days 28 and 90) with ERIG. We then determined rabies neutralizing antibody (Nab) up to day 360. Geometric mean titers (GMTs) of subjects receiving four-site ID regimen, with or without RIG, had significantly higher Nab than the control group on day 14 and 28 ($p<0.001$). All subjects in all groups had Nab at least 0.5IU/mL on days 14 and 28. The Percentages of subjects who had Nab of at least 0.5IU/mL from day 0 through day 360 were not significantly different among the three groups. After any PEP regimen, WHO requires Nab of at least 0.5 IU/ml on days 14 and 28.

The one week PEP therefore appears promising. It increased immunogenicity over the two-site ID schedule and it is convenient and can be used in small clinics as it consumes almost the entire supplied vaccine ampoule volume.

Agenda item 2.1.3:

Providing PEP booster in one day using 4 site ID:

Presented by: Prapimporn Shantavasinkul, (see above)

According to WHO recommendations individuals previously immunized against rabies need only 2 IM or ID booster injections (one on day 0 and one on day 3) when re-exposure occurs. Rabies immune globulin (RIG) administration is not required in those patients. An earlier study had demonstrated that patients receiving during one clinic visit only, four intradermal (ID) injections (2 on deltoids and 2 on thighs) of 0.1mL of tissue culture rabies vaccine had satisfactory antibody titres. These titres of rabies neutralizing antibody (RVNA) were significantly higher than the standard two-booster dose on days 0 and 3. The four-site ID booster vaccination is being routinely used in the Queen Saovabha Memorial Institute since 1998. We carried out a retrospective study of all patients who received the four-site ID boosters at QSMI. The out-patient records were reviewed from 1998 to 2008. A total of 5,116 patients received the four-site ID regimen and 3,335 of this group (65.2%) incurred severe potential rabies exposures (WHO category III) and 253 patients (4.9%) were bitten by laboratory confirmed rabid animals. The youngest was 2 year-old and the oldest was 83 year-old. There were 2,453 male patients (48.1%). The longest period since primary rabies vaccination was 25 years. None had serious adverse reactions and there were no reports of human rabies deaths among this group.

The four site ID booster schedule is effective, saves transportation expenses as well as loss of working time and may reduce non-compliance. This can be an advantage for patients living in rural regions and for international travellers.

Agenda item 2.1.4:

The 4 site intradermal PEP regimen

Presented by: Dr. Mary Warrell, Oxford Vaccine Group, University of Oxford, Oxford UK.

According to Dr Warrell WHO advice supporting the use of the intradermal route for PEP has not been popular mainly because (a) in comparison with the IM regimen, ID treatment may be considered inconvenient by medical staff, due to the time taken for immunization and exposing the injection sites may be considered unacceptable by the patient (b) the use of single dose intramuscular rabies vaccine vials as multidose is an off-label use of the product in most countries (c) sharing of vaccine ampoules is necessary, so they are only economical when used in clinics with enough daily bite victims.

To reduce these problems a 4-site regimen was chosen with the following features:

- The principle of the 8-site regimen was used: giving a large vaccine dose on day 0 might be especially beneficial to patients who miss later doses.
- Vaccine was given in 4 instead of 8 sites on the first day to make it more acceptable and applicable with vaccine of any ampoule size.
- The same total amount of vaccine is needed as for the other ID regimens.

A four-site regimen "4-0-2-0-2" was studied (Warrell 2008) consisting of four ID injections using a whole vial divided between the deltoid and thigh areas on day 0, two 0.1 ml doses ID over the deltoids on day 7 and one 0.1 ml dose ID over the deltoid on days 28 and 90. This 4-site regimen was compared with the 8-site ID, the 2-site ID and the standard IM regimen in a non-inferiority immunogenicity study using with PVRV (0.5 ml / vial).

The outcome of the study revealed that (a) all three ID regimens proved equally immunogenic, and are not inferior to the IM 'gold standard' method (b) there was no detectable advantage of giving injections in 8-sites rather than 4-sites on day 0 (c) because the 4-site regimen has the same vaccine dose and timing as the 8-site regimen, which is not suppressed by concomitant RIG; and has been tested after proven exposure to rabies it is assumed likewise this 4 site regimen will not be suppressed by RIG.

Agenda item 2.2

Duration of immunity after vaccination:

Presented by Dr Deborah Briggs, College of Veterinary Medicine, Kansas StateUniversity, USA.

The development of immunological memory after vaccination with cell culture rabies vaccines is a critical component in the establishment of long lasting immunity against rabies in humans (Dietzschold, 2008). Since their development over three decades ago, modern cell culture rabies vaccines (CCV) have proven to be highly effective in preventing human rabies, both when administered as pre-exposure vaccination (PrnP) or when used in association with immunoglobulins for post-exposure prophylaxis (PEP) (WHO, 2007; Briggs, 2007). Of the millions of persons that have received CCV, less than a handful of vaccination failures have been reported, all of which have occurred in developing countries and most of which involved deviations from the WHO recommended PEP protocol (Rupprecht, in press; Wilde, 2007). Although one human death has been reported in a person that was previously vaccinated with a CCV and subsequently exposed to a rabid puppy (Bernard, 1985), this patient did not seek nor was given the WHO recommended two dose PEP booster series after the exposure occurred.

Several clinical trials recently published have proven that individuals that have received an initial three to five dose series of modern cell culture rabies vaccine will have long term immunity even lasting for decades (Nirnpoon et al., 1999; Cherradin et al., 2001; Suwansrinon et al., 2006; Brown et al., 2008). These published data also indicate that individuals that received their primary series up to 21 years previously will elicit a good anamnestic response after booster vaccination. Individuals that have been vaccinated with a modern cell culture vaccine will respond to a booster vaccination regardless as to whether the vaccinated individual had measurable antibody present or not at the time that the booster was administered (Hornen et al., 1982; Cherradin et al., 2001). It is clear from the published information that routine booster doses of vaccine after primary series vaccination are not required for most of the general public living in areas of risk.

For laboratory technicians, researchers, and others working in environments where they may be frequently subjected to high doses of virulent rabies virus as part of their routine activities routine serological evaluation should continue to be conducted. This group of potentially frequently exposed individuals should receive one routine booster dose of CCV should their titer falls below the level of 0.5 IU/mL. Finally, all individuals that have been previously vaccinated with a CCV manufactured according to WHO recommenda-tions, and are subsequently exposed to rabies (as per the WHO definition of exposure), should receive two booster doses of CCV, one dose to be administered on day 0 and the second dose on day 3 (WHO, 2004).

Agenda item 2.3:

Do we need to state a vaccine potency by intradermal dose:

Presented by Beatriz Quiambao, Research Institute for Tropical Medicine, Alabang, Philippines

The relationship between antigen dose and antibody response was investigated in a limited number of studies (Tauber 1986, Lang 1999, Sudarshan 2005 and Beran 2006). These results indicate that the immunogenicity of rabies vaccine increases with the dose up to a certain level, above which larger doses give no additional benefit. Unfortunately the low dose studies did not reach this plateau level, so the optimum immunogenicity is not known.

Certain countries such as Thailand, the Philippines and Sri Lanka have requested a higher potency rabies vaccine for use with ID PEP immunization mostly because (a) many if not all, the trials on ID regimen were done using vaccines with potency much higher than the 2.5 IU/ml (b) concern about low antibody levels using 0.1 ml of WHO accredited vaccines with 1.0 ml/ vial vaccines (c) concern over newer rabies vaccines from emerging markets some being recommend for ID use, but no immunogenicity data are available.

Reviewing the potency values of vaccines used in major ID clinical trials it should be underscored that in early dose-finding and first post exposure PEP trials used vaccines with potency ranging from 2.55 (HDCV) to 7.5 (PCECV) IU per vial and that in later studies PCECV potency tended to get higher (6 to 9.16 IU per vial). There was no difference in the antibody levels induced by three ID PEP regimens using two PVRV batches of potency 5.3 IU/dose in 165 subjects, and 8.4 IU/dose in 64 subjects (Warrell 2008).

It should be noted that the decision to request made by some National Regulatory Authorities to require a higher potency for ID use was made at the time of the introduction of the universal 0.1 ml ID dose. There were unpublished Thai data showing low antibody level with PCECV 0.1 ml/ site 2-site. (The antigenic value was 6.75 or 9.0 IU/ml). One possible explanation is that the challenge virus used in the RFFIT was not closely related to the vaccine strain, reducing the antibody levels for PCECV compared with other vaccines (Moore 2006, WHO 2007a). The unpublished Thai results are no longer considered relevant.

The minimum acceptable potency of a rabies vaccine has not changed since 1978. The WHO still endorses an antigenic value of at least 2.5 IU/IM dose. If only the WHO accredited vaccines are considered evidence should be made available to support the need to request higher potency. If other than WHO currently accredited id vaccines are used in a volume of 0.1 ml per ID site they can be recommended for global use with current ID regimens provided producers comply with WHO manufacturing control and potency recommendations and these vaccines are demonstrated to fulfil additional WHO recommendations for vaccines to be used by the id route.

The overall conclusion of this review is that the presence of insufficiently tested vaccines on the market should have no effect on the potency requirements of the WHO accredited vaccines. The problem arises when a regulatory authority registers a vaccine even if not all the requirements have been met. There are no international controls over which vaccine a country or agency may import. If the minimum potency requirement were to increase as an intended safety measure, there is no guarantee that the producers would comply.

Agenda item 2.4

Prevention of human rabies in vulnerable populations :

Presented by Dr Charles Rupprecht, Head WHO Collaborating Centre for Reference and Research on Rabies, CDC Atlanta on behalf of the PAHO/ AMRO Centre for zoonoses, Rio de Janeiro, Brazil.

Amazonia has unique characteristics. Risks for rabies are increasing due to environmental disturbances and migration. Vampire attacks to humans are frequent. Access to health care services is extremely difficult and expensive. Many countries in this part of the world have not stopped the production and/or use of suckling mouse brain vaccines (SMBV).

Many PEP are initiated and discontinued by the exposed patients.

Direct consultations by Member States' ministries of health with PAHO/AMRO and their Collaborating Centres focused on PEP schedules better adapted to limited Amazonian populations health care access and vaccine cold chain maintenance. For example a country consulted about the possibility of using a PEP schedule 0, 3, 21, and 28 because it was impossible for the intervention teams to maintain the cold chain after day 3, or to come back with more vaccine on day 7 after first injection. This schedule was not used, but they vaccine and vaccinatipes were flown by helicopter in an operation that would be very difficult to repeat as often as needed. In addition there is resistance from the medical community to use any IM schedule not recommended by WHO and to use intradermal schedules (even those recommended by WHO). PAHO/AMRO would like to suggest that this WHO Consultation discuss PrEP and PEP for areas with very limited health care access. PAHO/AMRO request the consultation to take note of the situation

of special areas as the Amazon and elaborate a recommendation aiming at increasing administration of PEP and PreEP using modern rabies biologicals in high risk areas. PAHO/AMRO also consider imperative to conduct studies for the generation of evidence on the efficacy and safety of schedules using current vaccines with reduced number of doses and longer intervals between visits that would take into consideration limitations of access to areas with high risk of vampire bat attacks, as well for the development of new vaccines.

Agenda Item 2.5

Optimal usage of RIG

Presented by Dr David Anderson on the basis of his paper entitled WHO Guidelines dealing with immunoglobulin use in rabies prevention (Asian Biomedicine vol.1 No 1 June 2007, p 103-107).

D. Anderson argued that calculating the dose of RIG according to the weight of the patient, is without rational basis. Considering that it is the RIG injected into and around the wound that is important he suggested a modification of the WHO Guidelines for post-exposure prophylaxis in particular that no RIG residue is injected anymore at sites other than bite wounds.

Conclusions and Recommendations presented by D. Anderson

- Numerous experimental studies point to the efficacy of locally as well as systemically injected preparations of RIG of either equine or human origin. For obvious reasons, the only controlled studies of RIG for the prevention of rabies have been done in animals, although the Tehran wolf bite experience strongly supports its use in man. The remaining conclusions in man have inevitably been surrogate studies, looking at circulating levels of antibody.
- Despite its undoubted importance, rabies immunoglobulin is almost never given to victims of rabid dog bites in poor parts of the world where rabies is still a major public health problem.
- Where resources are scarce, it makes sense for the minimum effective dose to be given in the optimal way to the maximum number of victims at risk. This is the basis for the local administration of RIG into wounds. If the required dose can be safely reduced, this will also reduce cost, which is a major factor in why it is so rarely being used.
- Studies to determine the dosage of RIG were carried out nearly 35 years ago. They resulted in the recommendation for systemic administration intramuscularly into a site distal to the wound. They aimed to achieve circulating antibody levels. The dosage was crudely calculated based on the body weight of the patient. **It has since been recognized that RIG should be given locally into and around the wound where it is needed to neutralize virus prior to it entering nerve endings. Furthermore, later studies cast doubt on the method of the earlier dose calculations..**
- **HRIG has a longer half-life than ERIG and this was the basis for doubling the dose of the latter. This may not be relevant when injections are given into the wound.**
- **It is well documented that vaccine alone will save the majority of animal bite patients. It is not possible, however, to reliably predict which patient will succumb to rabies if wounds are not injected rapidly with virus neutralizing RIG. Subjects with severe facial, head and hand bites, areas with a large supply of superficial nerves, are particularly prone to a short incubation period and treatment failures when no RIG is used. This is the very patient who will die if RIG is not instilled locally.**

D. Anderson's proposed amendments of the current recommendations set out in section A 3(2) page 69, annex 1 Guidelines for post-exposure prophylaxis of the first Report of the WHO Expert Consultation on Rabies (TRS 931, WHO 2005) were the following:

For passive immunization, the whole dose of rabies immunoglobulin is given into the wound(s). The maximum total amount of ERIG administered for all individuals regardless of body weight should be 1000 IU, with the total amount now determined by the size of the wound(s) and the volume of RIG that can be safely infiltrated. It is not necessary or useful to inject any residual RIG into a distal site.

Agenda Item 2.6

Recommendation for PrEP for Children

Presented by Thiravat Hemachudha on the basis of a paper by Chirapol Sinthunawa *et al*. (Faculty of

environmental science, Mahidol University and WHO collaborating centre for research and training on viral zoonoses, Chulalongkorn University, Bangkok, Thailand

2.6.1 Pros and cons of PrEP introduction:

Despite a success in reducing rabies deaths from almost 200 to less than 20 annually, this can not be considered a success in Thailand. More than 400,000 persons required rabies post-exposure prophylaxis (PEP) in 2003. This is more than previously (93,641 cases in 1991; 183,815 in 1996 and 350,535 in 2001). The number of PEP in 2008 had risen to 500,000 but samples submitted for testing in rabies diagnostic laboratories have been declining. However, the percent of samples that were confirmed infected with rabies remained unchanged during the last decade within a range of 23-30% (MOPH report). We are apparently not controlling the disease in its vector, the dog. Efforts in other canine rabies endemic Asian countries will very likely yield similar unsatisfactory results. Promotion of public concern for voluntary vaccination and sterilization of dogs has had only limited success and focused mostly on owned dogs. Community dogs remain inaccessible due to lack of motivation and sustained cooperation from the public sector. Children under 14 years represent the most likely victims of rabies exposure and deaths. Lack of education, access to PEP and shortage or poor distribution of biologicals for PEP remain a major worldwide problem and add to the number of deaths. There was also a considerable delay for PEP in this age group.

Incorporating pre-exposure rabies vaccination (PrEP) into the EPI programmes for regions with a high prevalence of canine rabies is suggested considering that:

- Effective and sustainable dog vaccination and population control have not been successful and the high prevalence of dog rabies, especially in community dogs, remains unacceptable.
- Childhood rabies PrEP should be considered for high rabies prevalence regions where there is a high risk for children < 14 years of age. Time of administering rabies PrEP may be possible by one at birth and 2 months and another at 2 and 4 months. The former with one dose at birth and another at 2 months seem plausible. The need for the third dose may not be necessary.
- Studies have shown that mass pre-exposure vaccination can be done: (a) PrEP was done safely in children in Vietnam. Five years follow up showed that co-administration of rabies pre-exposure prophylaxis with diphtheria-tetanus-pertussis (DPT) and inactivated poliomyelitis vaccine at 2, 4 months and 1 year elicited antibody concentrations to all antigens with no interference among vaccines used; (b) The intramuscular (IM) or intradermal (ID) routes were equally effective after 2 doses at 2 and 4 months in producing and maintaining rabies antibody up to 5 years.
- Re-exposures are common in childhood. There is then no need for immunoglobulin (RIG) which is very costly and usually not available where needed. Two boosters (ID or IM) on days 0 and 3 are only required. Moreover, it is possible that boosters can be provided at one visit (routine practice at Queen Saovabha Memorial Institute, manuscript in preparation).
- ID vaccination is much less expensive than the intramuscular method. It requires only 0.1 mL intradermally at 2 and 4 months. This can be modified to 2 doses: one at birth and another at 2 months. The technique of ID injection is well known and widely practiced in most developing countries (BCG at birth etc).

On the other hand incorporating PrEP into the EPI programmes may have the following negative consequences:

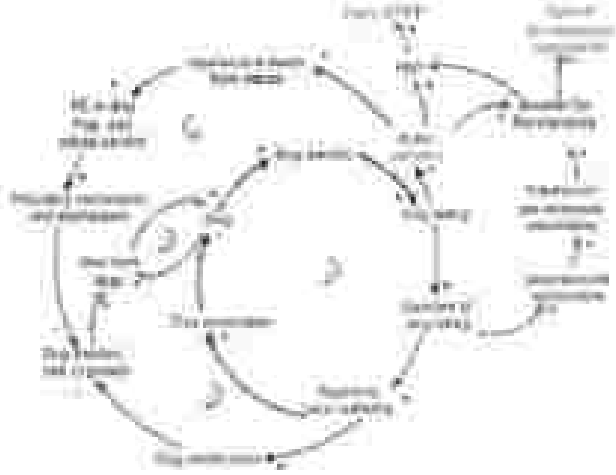
- PrEP may increase rabies vaccine wastage if compliance not optimal. Although recent studies have shown that even fewer than 3 injections will provide immunity of some duration (Kamolthiam T, presentation at Rabies in Asia meeting, September 2009), it is not certain whether all children will receive all 2 or 3 doses of rabies for PrEP. Although as many as 99% of Thai newborns receive BCG, this number may be lower by the end of 4 or 6 months for DPT and poliomyelitis vaccines (administered at 2, 4 and 6 months).
- PrEP may have an undesirable side effect. It may further aggravate ignorance or lack of interest in dog vaccination and population control. Thus, solving an old problem by starting a new one that will still be confronting our grandchildren.
- Once re-exposure happens, it may be difficult to know who has already received PrEP. Children and their parents forget.

- We may need a rapid reliable and inexpensive test for rabies antibody to determine whether a patient with doubtful history of PrEP has antibody or may need a full course of PEP with RIG.
- In countries with a low rabies incidence it will be virtually impossible to determine the efficacy of a universal PrEP regimen due to the low incidence of rabies (< 20 among 70 million in Thailand). No such study would have sufficient statistical power to be publishable in a scientific journal.
- Policy makers need to be convinced that childhood immunization is cost-effective

2.6.2 Cost-effectiveness of rabies PrEP

To analyze the cost-effectiveness of rabies PrEP in childhood in Thailand the authors proposed the model below combining activities for dog population and rabies control (loops A, B and C) influencing number of bitten persons therefore cost of PEP (in red) and cost of a pre exposure vaccination programme complementing these activities (loop D on the right).

One factor that determines the number of rabies PEPs (or persons bitten by dogs) is the dog density (ratio between dog and human population). As dog bites increase, this can raise concern among the public, resulting in complaints to relevant authorities. Responses may include dog vaccination, sterilization and elimination. The net growth rate of the dog population then declines potentially to a more manageable and controllable level (Fig 1, loops A and B). Loop C illustrates a similar causal relationship between biting incidence/rabies deaths and public responses. This may be mediated via media reporting. Increased public awareness education is promoted. It may result in more voluntary vaccination sterilization by dog owners and better motivation for action by non-governmental organization as well as persons who hold responsible positions in the government sector. PrEP may be one activity that is promoted and supported (Fig 1, loop D). This PrEP population will need only rabies boosters without the need of ERIG. The childhood immunization program was constructed giving 3 ID doses of 0.1 mL at 3 different time points (at birth, 2 and 4 months). It was delivered to all newborn since 2010.



A dynamic model was constructed on the basis of the model outlined above and simulated using STELLA program (version 9.0 available at www.hpsystems.com).

This simulation hypothesized that three-quarters of the 500,000 rabies PEP administered annually in Thailand required vaccine and ERIG. The remaining one third received only boosters (ie. those who have had prior immunization). T cost 1 represented annual cost of rabies PEP. This was compared with T cost 2, representing sum of T cost 1 and childhood immunization as mentioned above. Tangible and intangible costs were listed at the end of this draft.

Expense for T cost 2 program was slightly higher than the conventional T cost 1 (2,245 vs 2,027 million/ year) (Figure 2). These 2 numbers became comparable by the year 2026 (2,622 vs 2,519). The pre-immunized children then incrementally increased and this immunized population would be only requiring boosters if exposed. Such scenario was based on the assumption that there was a ratio of 0.75 dogs per household.

This cost-analysis showed that total expenses would be higher for the first 15 years, given that all other parameters were not modified. However, the time required for cost equivalence between T cost 2 (representing sum of T cost 1 and childhood immunization) and T cost 1 (annual cost of rabies PEP or business as usual) might be shortened to 13 years if the dog population decreases.

2.7 Other advances in rabies biological products development and usage including cost-effectiveness studies

Presented by Jean Lang, Sanofi Pasteur, Lyon, France and Fernando Borges.

No text or presentation available to the editor of this report.

Session 3 on Control and elimination of rabies in dogs

Chaired by Alexander Wandeler, Head WHO Collaborating Centre for Control, Pathogenesis and Epidemiology of Rabies in Carnivores

Agenda item 3.1:

Designing the most cost-effective package for sustainable dog rabies control

Presented by Sarah Cleveland, Glasgow University, Glasgow, the UK.

Not text or power point presentation yet available to the editor of this report.

Agenda item 3.2:

Including sterilisation in addition to vaccination for rabies control

Presented by Elly Hiby, Head of Companion Animals, WSPA Programme Department, WSPA, London, UK.

The change in the size of a mammal population over time is the sum of individuals born and immigrating into the population minus those dying and emigrating. These constituents of population dynamics all need to be taken into account when estimates of population size and the impact of control measures are made. There is abundant theoretical literature and practical guidelines available. Animal Birth Control (ABC) projects aim at reducing birth rates. They will reduce population turnover and eventually lead to a reduction of population size, and they may have other beneficial effects that are discussed below.

Sterilizing dogs as part of dog population management is a common intervention performed in many countries (sterilization is also known as spaying of females or neutering of males). The motivation for sterilization may come from a dog owner who does not want to increase the number of dogs they own or wants to reduce potentially nuisance sexual behaviours - or it may come from a government or organization that is aiming to reduce the production of unwanted dogs at a population level. It is important to note that sterilization should be considered as just one (important) part of comprehensive population management, a wider discussion of the use of sterilization in the context of a comprehensive population management programme is available in the International Companion Animal Management (ICAM) Coalition humane dog population management guidance available at www.icam-coalition.org. However this paper focuses only on sterilization as a potential additional tool to vaccination for an intervention aiming to reduce and eventually eliminate rabies. There are several different ways that a sterilization programme can be delivered. In some countries dogs are caught on the street by dog catching staff, sterilized, vaccinated and released. In other countries owners are encouraged to bring dogs for sterilization at a central point (which can be moved if using a mobile clinic), and additional help from dog handlers with suitable transportation for dogs might be offered for owners who would struggle to bring the dogs themselves. Sterilization is currently usually done via surgical removal of sexual organs but there is increasing research into chemical or immunological alternatives that if found to be safe, effective and cheaper than surgery will increase the use of this tool.

Benefits of including sterilization alongside vaccination will consist in (a) reducing population turnover and hence helping maintain herd immunity, especially important if using annual mass vaccination campaigns (see Hampson et al. 2009 for a discussion of the reduction in population level immunity in dog populations with high turnover) (b) increasing owner compliance as they gain more benefit for effort of bringing their dogs to an intervention, hence the percentage of dogs vaccinated can increase (c) helping to maintain herd immunity by reducing the number of unowned dogs that might be difficult to access for vaccination, by improving health and reducing problem behaviours of individual dogs and hence reducing abandonment (d) reducing the production of unwanted offspring that may have been abandoned and reproduction of unowned dogs whose offspring are likely to also remain unowned and (e) reducing reproductive behaviours that put dogs at higher risk of contracting rabies due to increased movement of individual animals and increased mating frequency between dogs.

Costs of sterilization can be high. WSPA project costs vary from approximately $6 USD to $25 USD per dog sterilized. In addition sterilization for some or all dogs in an area can decrease the throughput of an intervention and divert resources away from the priority of mass vaccination. The managers of an intervention that includes sterilization must ensure that good standards are maintained; regardless of the mode of sterilization used (surgical, chemical or immunological). This will require prior training of

staff and regular refresher training. Staff should also perform consistent follow-up of cases in order to help identify problems and raise/maintain standards. High throughput interventions can reduce costs but must not allow a weakening of standards. Poor sterilization techniques and ineffective post-operative care can lead to sick or dead dogs, creating mistrust in the whole intervention. In general, building a good reputation around an intervention can take time but poor reputations are comparably quick to establish and can be long lived; hence it may be better not to use sterilization at all than to perform poor sterilization and risk a low uptake for vaccination. Sustaining delivery of sterilization is problematic and may be required for many years alongside vaccination if rabies is to be eliminated. Ensuring a budget for ongoing rabies vaccination alone can be difficult enough, but adding the cost of sterilization can make sustainability impossible and many programmes are entirely reliant on overseas funding often from NGOs.

A common question posed is what proportion of the population should be sterilized if this tool is to be used? Returning to the earlier discussion about targeting sterilization, this will depend on the aim of the intervention. If there is a particular sub-population of dogs that are expected to produce offspring that will not be vaccinated, the proportion of the total population may be low. If the aim is only to improve owner compliance and interest in engaging in the intervention the sterilization services will depend on what owners feel they need. However, if the goal is to stabilise or reduce the total dog population a useful guide to establish the required sterilization proportion for a desired rate of growth has been developed and is available upon request from the author of this paper.

In conclusion, there is evidence that sterilisations can be a useful addition to vaccination as part of rabies control. There are ways of delivering sterilisation that can help to reduce costs and increase benefits to rabies control. There are also other benefits to using sterilization related to animal welfare that have not been discussed in this paper that help to outweigh costs. An example improved body condition score and a reduction in skin conditions have been observed in sterilised dogs in Colombo. However, the financial costs of sterilization might continue to limit its use. The development of safe chemical/ immunological sterilization agents is a promising area that will hopefully help tackle this issue of cost. Even contraceptives with one year effectiveness would be extremely useful as these could be applied alongside annual rabies vaccination, so long as the cost of each dose was low enough to counter the added cost of having to repeatedly access the dogs.

Item 3.3 role of oral vaccination of dogs against rabies:

Presented by François Meslin, Neglected tropical Diseases Department, WHO Headquarters, Geneva, Switzerland

As dog accessibility to vaccination by the parenteral route was reported to be the major obstacle for dog rabies control in many different parts of the world WHO since 1985, promoted research on dog populations and achievable dog immunization coverage in Africa, Asia and Latin America. Acknowledging the insufficiencies of the parenteral route for dog rabies elimination, WHO stimulated studies on oral vaccination of dogs (OVD) and the development of safer and effective vaccines and baits for OVD. WHO produced in 2007 entitled Guidance for research on oral rabies vaccines and field application of oral vaccination of dogs against rabies which is a compilation of recommendations made by the consultations on OVD organized by the Zoonoses and Veterinary Public health unit of WHO.

OVD offers new approaches promising a significant increase in the dog vaccination coverage (especially of free-roaming and poorly supervised dogs) both when applied exclusively or in combination with parenteral vaccination. Since 1986 WHO has continuously promoted international collaboration and coordinated research in OVD through an informal group of specialists associating specialised WHO collaborating centers, researchers and official representatives of potential recipient countries, as well as pharmaceutical companies. Very early on it became evident to this group that ensuring the safety of OVD (from candidate vaccine to bait and bait delivery systems) under the specific conditions prevailing in most areas with dog rabies was a prerequisite to promoting its use in the field. OVD safety for non-target species, especially humans, has remained the center of WHO coordinated activities. The group very carefully looked at different probable and also more unlikely scenarios which could lead to human exposure to a live dog vaccine.

To better assess the likelihood of these different scenarios the group requested that all candidate vaccines be tested in immuno-suppressed animal

models and for safety in non-human primates. It was further recommended that better quantitative tests be developed to measure input vaccine virus excretion and that the levels of virus excretion with time be evaluated in young puppies as the most probable excretor and transmitter of vaccine virus to humans. The group also established guidelines for determining oral vaccine efficacy in laboratory dogs and for bait development, bait preference trials and for the evaluation of bait delivery systems in the field. Three delivery systems for OVD were envisaged : the distribution of the baits to owned dogs via their owner who would collect the bait at a central location, b) the placement of baits at selected sites where they were accessible to free roaming dogs (so-called «wildlife immunization model») and c) distribution of baits to dogs encountered in the street (so-called «hand-out model»). The group worked on elaborating specific guidelines for implementing OVD projects and has promoted the further investigation of OVD logistics and economics.

Investigating economics of OVD is essential since it is very unlikely that all resources required for dog rabies elimination become suddenly available. The implementation of control activities will obviously remain under financial strain and require that new techniques be as cost effective as possible. When targeting certain « high risk » components of the dog population such as feral and free roaming dogs it may be possible to accept a cost per dog vaccinated by the oral route higher than that established for a parenteral vaccination (e.g. US$ 1 to 1.3 with 0.35 worth of vaccine) as most savings accrue after rabies elimination. However, when oral and parenteral vaccination competes for the same dog (e.g. owned and restrainable segment of the population), one should expect at least comparable costs per fully vaccinated dog. To reduce costs further and thereby open new opportunities for the initiation of large scale vaccination programmes, inexpensive and voluntary vaccine delivery systems involving communities or community leaders should be promoted. In this context, the results acquired in Tunisia by placebo bait distribution to dogs via their owners are very encouraging. This method would however necessitate modifications of regulation on the delivery and application of veterinary rabies vaccines currently enforced in many countries. It should also be kept in mind, that this move might not be well received by professional associations and governments struggling to allocate often limited budgets to competing public health problems.

In conclusion, more than 10 years after the WHO OVD Expert Group had it last meeting OVD has not yet taken off anywhere as a operationalized component of a dog rabies control and elimination programme. The major obstacle in some countries is clearly concerns over safety for humans whereas in others it is mostly an economical issue as cost per (imported) vaccine bait is high compared to parenteral vaccine. In countries which have been combating rabies by providing million of PEP and vaccinating million of dogs (mainly the same owned dogs) for decades and are today left with only a few human cases OVD would make the difference between a lingering rabies problem and human and dog rabies elimination.

Session 4 on Rabies Research: topics for future research in human and dog rabies prevention and control

Agenda item 4.1 new vaccine delivery systems

Presented by Darin Zehrung, technical officer, PATH, Seattle, USA

The rationale for ID Devices for Delivering Rabies Vaccine is based on the facts that: (a) ID injection using the conventional needle and syringe method is difficult to master without proper training and continual practice (b) among developing-country immunization programs, ID injections are found to be difficult to deliver and inconsistent. (c) in general there is poor compliance to ID PEP regimens and training standard are found to be insufficient. In that context new ID delivery technologies would overcome the above-mentioned challenges by increasing the number of health care personnel that can deliver the vaccine ID and provide flexibility for non-conventional PEP delivery scenarios (i.e. outside of a health facility).

Different systems have been tested such as the PATH ID Adapter, the Nanopass Microdot™ (hollow microneedle), the Pharmajet disposable syringe jet injector for ID delivery. Two devices (ID adapter and Pharmajet device) proved generally acceptable to health care workers who believe that the devices could potentially benefit the Indian health care system due to the ID capability

The PATH ID adapter is a simple injection "aid" that fits on a conventional needle and syringe to facilitate a successful ID injection by limiting the angle and depth of needle penetration. It is intended to

deliver any medication or vaccine indicated for ID delivery. Its current design is intended for use with the a 1 ml, insulin syringe with a fixed 29 gauge, 12.7 mm needle and will be modified to be compatible with other insulin syringes in the future. In guinea pigs, rabies vaccine delivered via the ID adapter (early prototype) produced adequate levels of antibodies, similar to ID delivery by a conventional needle and syringe. The next steps in ID Adapter development are (a) to generate pre-clinical and ID rabies vaccine clinical data to confirm device performance (b) to explore other potential ID research applications (e.g. YF, influenza) (c) further simplification and refinement of design for safety (reuse prevention feature) (d) technology transfer to India based manufacturer for market introduction and availability.

PATH is implementing a rabies research project which aims at identifying and qualifying appropriate ID devices with potential for delivering a reduced dose of rabies vaccine at public health clinics in India, demonstrating clinical feasibility of ID capable technologies and assessing value proposition and commercialization potential. In three health care facilities in Andhra Pradesh PATH conducts an ID Device User Assessment whose purpose is to determine health care worker perceptions of device acceptability, safety, and anticipated disposal practices. In the near future PATH plans to implement in in Hyderabad, India a phase II clinical trial of rabies vaccine delivered by ID delivery devices (both ID adapter and Pharma Jet injector) to test their safety and immunogenicity in comparison to standard needle and syringe ID delivery in healthy adult volunteers. The study will be conducted, partnering with Institute of Preventative Medicine (G. Sampath) and Indian Immunologicals, Ltd (Abhayrab vaccine) using the ID post-exposure prophylaxis regimen recommended by WHO (Modified 2-site Thai Red Cross regimen, 2-2-2-0-2, days 0,3,7,14,28). The study primary objectives are to determine whether there is a significant reduction in immunologic responses in the experimental device groups as compared to the immunologic responses in the conventional vaccine administration group 14 days following receipt of the initial vaccine. Secondary objectives are to determine (a) whether the immunologic responses in the experimental device groups are non inferior to the immunologic response in the conventional vaccine administration group at 28 and 90 days following receipt of the initial vaccine (b) whether the immunologic responses of any participants in the experimental device groups fall below the WHO virus neutralising antibody (VNA) detection threshold of 0.5 IU/mL for post-exposure prophylaxis at any time throughout the study (days 14 to 90 following receipt of first dose of vaccine) (c) whether the experimental devices are safe for human use based on injection site reactions and systemic events (d) whether these experimental devices are acceptable to study participants and finally to confirm ID delivery of rabies vaccine using the experimental devices.

An ID technologies value proposition analysis will be carried out consisting in an economic cost modeling from the health system perspective and an evaluation of the costs added and saved by introducing devices for ID delivery of a rabies vaccine as compared with needle and syringe. This analysis should facilitate country level decision making regarding the feasibility of introducing an alternative ID delivery technology. An analysis on manufacturing cost, a survey on willingness to pay are also required.

Agenda item 4.2: New tools for dog population management

Presented by Michael Royal, Pharmajet, USA

No text or power-point presentation available to the editor of this report

Agenda item 4.3: current status of research on monoclonal antibodies for PEP

Presented by Marie-Paule Kieny, Director Initiative for Vaccine Research, WHO Headquarters, Geneva, Switzerland.

There is a critical lack of both availability and use of rabies immunoglobulins (RIG) in countries where canine rabies is a public health problem. Indeed, only 2% of post-exposure prophylaxis treatments in India include infiltration of wounds with RIG, and there is virtually no RIG use in many African countries. This underutilization is due in part to the cost of the current high-quality products. Research on RIG alternatives is progressing and it is hoped that more readily available and affordable products could replace RIG in the future.

Anti-rabies monoclonal antibodies (MAbs) offer the potential to be a safe, efficient and cost-effective replacement for equine and human RIG products. They can be produced on a large scale with high batch-to-batch consistency, reduction of theoretical health risk associated with blood-derived products

and possibilities to manipulate Fc fragments so as to induce minimal adverse effects and prolong half-life in case of murine MAbs. No single MAb is pan-reactive with the global spectrum of Lyssaviruses and a cocktail of at least two MAbs is therefore recommended for PEP.

Conclusions and recommendations:

Agenda item 2.1.1:Shorten "Essen" 4 doses regimen instead of 5

On the basis of the available pathobiological, clinical, epidemiological and economic data presented the WHO Consultation agreed on the following recommendation:

In healthy exposed persons who receive wound care, RIG and WHO prequalified rabies vaccines a PEP regimen consisting of 4 doses of vaccine administered intramuscularly on days 0,3,7 and 14 can be used. In case of others the use of the 5 dose "Essen" regimen on days 0,3,7,14 and 28 shall continue. In addition enhanced surveillance for human cases should be strongly encouraged".

Agenda item 2.1.2: The one-week PEP regimen ("4-4-4")

Post-exposure rabies prophylaxis, given by the four-site intradermal injections on days 0, 3 and 7, requires 3 visits in 1 week. The immunogenicity study revealed similar antibody response pattern to the updated Thai Red Cross (TRC) intradermal regimen "2-2-2-0-2" regimen administered with or without RIG but with higher antibody titers. Although volume required for this one week "4-4-4" regimen is higher than the "2 sites" TRC regimen, it is more practical. It can be used as alternative regimen for the patients who cannot follow the standard schedule.

This WHO Consultation acknowledged "4-4-4" regimen promising results. The Consultation decided to consider endorsing this regimen as an alternative to the 2 site TRC provided another "4-4-4" study fulfilling WHO criteria* (*see below) conducted in a different country confirms these results.

Agenda item 2.1.3:

Providing PEP booster in one day using 4 site ID

* Generally, rabies vaccines are acceptable in volumes of 0.5 mL or 1.0 mL

The single visit four-site intradermal booster vaccination consisting of 4 injections of 0.1 mL injection on each arm and thigh or suprascapular region has been shown to induce anamnestic response equally as good as or superior to intramuscular/intradermal booster regimen on days 0 and 3. This single visit regimen has been used since 1998 at Queen Saovabha Memorial Institute in a total of 5,116 patients.

The consultation takes note of the accumulated evidence and recommends the use of this single visit four-site intradermal booster regimen as an alternative to the previously recommended two visits one-site ID or IM regimen.

Agenda item 2.1.4:

The 4 site intradermal PEP regimen

Promotion of economical rabies PEP in new areas is more likely to succeed using a single, simple highly immunogenic regimen. **This WHO Consultation considers the 4-site regimen consisting of 4 ID 0.1 ml injections using a whole vial divided between the deltoid on day 0, two 0.1 ml doses ID over the deltoids on day 7 and one 0.1 ml dose ID over the deltoid on day 28 suitable for use with any WHO prequalified rabies vaccine. The consultation recommends deleting the 8-site regimen from the list of WHO approved ID regimen.**

Agenda item 2.2

Duration of immunity after vaccination:

Considering that (a) the development of immunological memory after vaccination with cell culture rabies vaccines is a critical component in the establishment of long lasting immunity against rabies in humans (b) duration of immunity and the ability to develop an anamnestic response to a booster vaccination in previously vaccinated persons is not related to the route of the initial vaccination series (IM or ID), nor to whether the person received PrEP or PEP (c) the ability to develop an anamnestic response is not related to the amount of time after the initial vaccination series was administered as published data indicates that persons vaccinated up to 21 years earlier will respond to a booster of rabies vaccine **this consultation recommends that routine booster doses of rabies vaccine are not required for individuals that have received a primary series of PreP or PEP with**

a WHO recommended vaccine. Persons who have received either PreP or PEP as a primary series should receive the recommended booster vaccine injections in the event that they are subsequently re-exposed to a rabid animal. Individuals whose occupation puts them at constant risk of inadvertant exposure to live rabies virus (ie persons working in rabies diagnostic laboratories or rabies vaccine manufacturing facilities) should continue to have their serological titer monitored and receive one routine booster if their titer falls below 0.5 IU/ml.

Agenda item 2.3:

Do we need to state a vaccine potency by intradermal dose:

The WHO recommended volume of a single dose of rabies vaccine administered per intradermal site is 0.1 ml. There has been concern about the varying potency that may be contained in that volume of 0.1 ml as rabies vaccines are manufactured for an intramuscular dose reconstitution in different volumes* and as an increasing number of newly developed modern cell-culture or embryonated egg vaccines are coming on the global market. In many case there is insufficient clinical evidence proving these new vaccines effectiveness and safety for ID administration when they may be inadvertently injected by this route by well-meaning clinicians using a WHO recommended intradermal regimen.

Considering that (a) there are no international controls over what vaccine a country or agency may import only a list of WHO pre-qualified rabies vaccine for consideration (b) the problem may arise when a regulatory authority registers a vaccine even if not all requirements have been met (c) if the minimum potency requirement were to increase as an intended safety measure, there is no guarantee that the producers and/or National Control/ Regulatory Authorities would systematically comply the consultation stated that current data do not support indication of a specific potency for ID use for vaccines with a potency of at least 2.5 IU per intramuscular dose which have been satisfactorily assessed for their innocuity, immunogenicity and/or safety in well-designed intradermal PreP and PEP clinical trials. New vaccines should be similarly assessed in clinical trials using a minimum potency of 2.5 IU per IM dose.

In addition the consultation recommended the following :

If a country decides to register a new rabies vaccine whether locally produced or imported for intradermal PEP usage, the National Regulatory Authority should ensure that adequate tests and satisfactory clinical trials (safety, immunogenicity and safety studies) have been performed and that their national requirements have been met.

The WHO group in charge of strengthening the capacity of national regulatory systems and DCVBN has been asked for their advice.

*Currently, rabies vaccines are reconstituted in volumes of 0.5 ml or 1.0 ml.

Agenda item 2.4

Prevention of human rabies in vulnerable populations:

2.4.1 in the Amazonas

Populations of the Amazon region living in places very difficult to reach and at constant risk of exposure to vampire bat rabies, may benefit from modern health care after rabies exposure for only 3 days or even less. This is not commensurate with any of the current WHO PEP regimens. *The Consultation strongly encourages the development of safe and effective biologics and protocols and their evaluation for these unique, neglected scenarios.*

2.4.2 in sub-Saharan Africa

Considering the probable high incidence of human rabies in sub-saharan Africa and the few exposed patients who receive rabies post-exposure prophylaxis according to WHO recommendations, the Consultation urges health authorities from African countries to facilitate availability and access to modern rabies PEP (including RIG in category 3 exposures) to all patients exposed to rabies risk.

Agenda item 2.5

Optimal usage of RIG

The Consultation agreed that the immunoglobulin injected into the wounds is of upmost importance in

category 3 exposures management. The consultation however in view of lack of evidence did not endorse the suggestion to define a standard maximum dose per bitten individual or agree to drop mention of intramuscular administration of any RIG at a distant site from wound.

The consultation reiterated its previous recommendation that if necessary RIG can be diluted to ensure infiltration of all wounds at the volume which is determined by capacity of the site and sound clinical judgement. In addition the consultation recommends that new in- vitro and in-vivo research to determine adequate quantity of RIG (in IU) required on site with or without distal parenteral RIG administration should be encouraged.

Dr Madhusudana, Head of the WHO Collaborating Centre for Reference and Research on Rabies located in the National Institute of Mental Health and Neuroscience, Bangalore, India confirmed his willingness to initiate such studies.

Agenda item 2.6

Recommendation for PrEP for Children

The model proposed by Thailand (which uses as point for cost-comparison their current half a million PEP annual "consumption level - one of the highest PEP ratio per million inhabitants in the world) can only be successful and sustainable if it is acceptable to public and government in terms of efficacy and cost-benefit. It shows that the time required for cost equivalence between annual cost of rabies PEP (business as usual) + childhood immunization and annual cost of rabies PEP only may range between 13 and 15 years depending on dog population size and therefore bites. Cost equivalence is reached faster if the dog population decreases which in turn is likely to decrease the number of dog bites and reduced the motivation for initiating or maintaining such a project. It must also be recognized that there might be a paradoxical outcome when childhood immunization is implemented. Existing, already limited dog vaccination and population control efforts may then degrade further with most resources spent on PrEP vaccination. Other programmes may also suffer from such constraints and there may be less interest to realise rabies control when humans are no longer threatened as they have been immunized. It is obvious that this issue requires considerable more study and deliberation before it is recommended to already overburden health care policy makers. In countries with a low rabies incidence it will be virtually impossible to determine the efficacy of a universal PrEP regimen due to the low incidence of rabies. Policy makers on the other hand need to be convinced that childhood immunization is cost-effective.

In this context the Consultation recommended studying further the technical and economic feasibility of incorporating rabies vaccine into immunization programme for infants, toddlers and/or schoolchildren. This particularly in countries and areas where there is no shortage of vaccine for PEP and where attempts at establishing an effective and sustainable dog vaccination and population control programme have not been successful and the high prevalence of dog rabies, especially in community dogs, remains unacceptable.

Agenda item 3.1, 3.2 and 3.3 and 4.2: Control and elimination of rabies in dogs

Rabies control is a public good. In many circumstances where dog rabies continues to be a problem, charging owners for dog rabies vaccination during mass vaccination campaigns can be counter-productive as turnout may be too low to achieve an adequate vaccination coverage. Vaccination coverage should be monitored and impact of charging for dog rabies vaccination evaluated. A potential alternative to charging is to encourage voluntary contributions avoiding a perception of coercion. If a threshold vaccination coverage of ~70% cannot be reached, dog rabies is unlikely to be controlled, resources wasted, and communities and field veterinary staff demotivated. **The Consultation recommends that impact on dog immunization coverage of charging dog owners for dog rabies vaccination which has been shown to be negative in Africa is further evaluated in particular in Asian countries where a trend towards cost recovery and further financial involvement of dog owners in rabies control is developing.**

The vast majority of domestic dogs are however accessible to relatively simple parenteral vaccination campaigns. Effective dog vaccination campaigns can have rapid impacts on demand for PEP and hence economic savings. The relationship between dog rabies incidence and demand for PEP appears

to vary widely across different settings. Optimising the use of PEP is important to avoid excessive wastage and ensure the most effective use of limited resources. This provides a potential mechanism for sustaining dog rabies control, with the likelihood that, in the medium and long term, combined strategies involving effective dog vaccination and PEP will be more cost-effective in preventing human rabies deaths than PEP alone. **The Consultation recommends that exploration of financial mechanisms by which dog rabies control could be sustained through savings in PEP are encouraged, and will likely require rabies to be managed as an integrated program across the veterinary and public health sectors.**

Education and awareness programs can be highly effective in reducing rabies exposures. **The consultation recommends that more data be collected to evaluate the cost-effectiveness of different educational methods in preventing exposures and reducing human rabies deaths.**

As dog populations differ in demography, both between and within dog populations, the collection of preliminary data on dog demography, dog ownership and community attitudes towards dogs is advised. The information provided by this data can be used to determine the most appropriate manner for delivery of reproduction control and can help target reproduction control resources to best effect. Surgical sterilization is currently the most common method of reproduction control but surgical sterilization is too costly to provide a sustainable solution to dog population management in all countries where this is required. In this solution **the Consultation strongly encourages the development of new immunological or chemical sterilization or contraception tools within the constraints of human and animal safety, cost and agreed standards for application. The Consultation also** encourages development of safe, cheap and humane methods of permanent dog identification that do not require the dog to be anaesthetised for application.

The use of reproduction control for dogs can help to reach and maintain vaccination coverage. Dogs may be accessed for reproduction control via owner delivery of dogs or by catching owneless dogs from public areas, followed by sterilization and vaccination, post-operative care and release at point of capture (Animal Birth Control ABC also known as catch, neuter and release). The rationale is to reduce the dog population turnover, the proportion of young dogs in the population, breeding behaviours that may make dogs more susceptible and the number of ownerless dogs that may be more difficult to access for vaccination. **The Consultation recommends including reproduction control and/or other primary veterinary health care in dog rabies control programmes as they may increase owner perception of value of the intervention and hence improve owner compliance.**

The Consultation encourages launching new studies on oral vaccination for dogs where the technique is used as a complement to parenteral vaccination campaigns targeting particularly inaccessible dogs.

Agenda item 4.1 new delivery systems

The use of reliable intradermal delivery devices for rabies vaccination and other vaccines and drugs can have application in areas where health care workers are not accustomed to or confident with intradermal delivery by the Mantoux technique.

The Consultation recommends that evaluation of intradermal delivery capable devices be pursued examining user acceptability, logistics for PEP and PrEP vaccination, efficacy and overall cost effectiveness.

As these devices are adopted for other immunization programs (BCG, influenza, IPV etc) their application and cost effectiveness for rabies vaccination may be facilitated.

Agenda item 4.3 : current status of research on monoclonal antibodies for PEP

Results obtained in two independent research and development programmes suggest that a cocktail of two MAbs of human or murine origin represents a promising, safe and efficacious biological for use in PEP as a replacement for equine F(ab')2 fragments or human IgGs. These products are currently under Phase 2 clinical development in the Philippines and in India (human MAbs) or close to entering Phase 1 clinical trial in India (murine MAbs).

The Consultation recommends that these new products proceed as quickly as possible to safety and efficacy evaluation in humans. This will require support from the rabies research community and engagement from

stakeholders, in particular WHO and national regulatory authorities in rabies affected countries.

Agenda item 4.3 : Future Rabies Biologics & Other Tools

Since the initial suggestion of the existence of rabies-related viruses during the 1950s, more than a dozen different lyssavirus genotypes have been defined to date. The melding of studies in molecular and cellular biology, pathogen discovery, and host immunology with the population biology, ecology, and evolution of rabies at an ecosystem level, offers new opportunities for collaborative introspection. A holistic combination of laboratory, field, and modeling tools should be integrated to provide potential solutions to the prediction, detection, and intervention against conventional and emerging lyssaviruses, particularly within the context of the challenges manifested by climate change and increased globalization pressures.

The critical multi-faceted role of the laboratory in primary rabies surveillance, diagnosis, and other important biomedical functions must be highlighted, strengthened, and sustained, especially in resource limited settings. Support for relevant, innovative scientific discovery, translation, and technology transfer needs to be enhanced for progressive rabies prevention and control in both the developed and developing world.

Humane population management is a keystone to animal rabies control. Application of safe and effective rabies immuno-contraceptive research approaches to this problem may provide a dual long term solution to more efficacious disease elimination programs.

Novel recombinant techniques, reverse genetics, and other 21st century methodologies offer great promise in the development of new interventions against rabies in a one world, one health setting. Such biologics offer the opportunity for major paradigm shifts in areas ranging from oral vaccination to human prophylaxis.

Despite the unprecedented survival of an unvaccinated U.S. teenager after a bat bite in 2004, additional attempts to treat human rabies cases have not met similar success. Relevant animal models as surrogates are necessary to provide more basic insights into the pathogenesis of rabies, as well as to serve as a proof of concept of various suggested modalities for direct extension into human therapeutics. In addition, a directed focus upon anti-viral strategies is needed for consideration of introduction into experimental therapy.

Additional agenda item: Additional recommendation for New Studies

The consultation recommends that new vaccines, biologicals, vaccination schedules or methods presented for WHO approval should have undergone at least one independent, statistically sound study showing safety and immunogenicity, carried out under GCP conditions and published in a peer-reviewed journal.

Additional agenda item: Four steps to replace Nervous Tissue Vaccine (NTVs) with modern rabies vaccines produced on cell culture (CCVs) or embryonated eggs.

Considerable progress has been made in the production and use of rabies vaccines in the past two decades. Various safe regimens have been developed to reduce the cost of active immunization and to replace nerve tissues found to be reactogenic and sometimes of low immunogenicity. Following the first WHO recommendation in 1964 to replace NTVs many developing countries over the past 25 years have discontinued the production and use of brain-tissue vaccines for human use and have managed to meet their needs by importing vaccine. Other countries have developed or acquired modern technology for the production of cell-culture or embryonated rabies vaccines. In 2004 the WHO Expert Consultation issued a definitive statement saying that nerve-tissue vaccines should be discontinued and that only cell-culture and purified embryonated egg vaccines should be used in humans. Today only a very small number of countries in Asia, Africa and Latin America are still manufacturing and using brain tissue vaccines and most are looking for affordable and sustainable alternatives.

This Consultation recommends that countries still producing or using neural tissue based vaccines (NTVs) follow this 4 step strategy proposed to assist them in replacing NTVs by modern vaccines.

Step 1: Relevant national authorities usually under the leadership of national health authorities have to make the final decision to shift from NTVs to modern vaccines. After review of the safety, immunogenicity and efficacy of modern vaccines, these authorities

should then evaluate the local conditions and assess the feasibility and cost of shifting from NTV to modern vaccines. In the implementation, serious consideration should be given to the use of the cost-saving intradermal (ID) regimens for rabies pre and post exposure prophylaxis.

Step 2: Clear instructions on the provision of modern vaccines for pre-exposure prophylaxis (PreEP) and post-exposure prophylaxis (PEP) including indications for their use, modalities of their administration as well as those of RIG etc, have to be formulated in national guidelines. These guidelines should be developed by technically competent experts, based on recommendations of WHO Rabies Expert reports, WHO Advisory groups such as SAGE, updated literature, international/national experts' experience and observations and disseminated to all centers providing PreEP and PEP. The guidelines must provide clear policies on vaccine subsidy (if any), how to handle left over vaccine etc and should be regularly updated.

Step 3: A constant supply to the rabies centres of safe and effective rabies vaccines and RIG that are WHO recommended should be ensured by a central office. Once the decision to stop NTV production and use is made, procurement of modern vaccines should commence to avoid any gap in provision of treatment once the NTV supplies run out. Coordination with regulatory bodies in the registration of new rabies biologicals and in the conduct of post marketing surveillance for new rabies vaccines and RIG is also important.

Step 4: A network of specialised bite centres should be set up where staff are trained on provision of PreEP and PEP and management of adverse reactions and where supply of adequate quantities of rabies biologicals is ensured. A referral system needs to be established in order to maximize the benefit of the ID regimen and reduce the amount of leftover vaccine. A quality assurance system should also be instituted with set standards that will be followed by all centers. Importantly the provincial and municipal governments should be involved in order to support the establishment of new centers, ensure sustainability of the supply of vaccines/ RIG and other immunization supplies, and guarantee reporting, investigation of human rabies cases and monitoring of the rabies program.

ASSOCIATION FOR PREVENTION & CONTROL OF RABIES IN INDIA (APCRI)

Association for Prevention & Control of Rabies in India (APCRI) was founded on 17th April, 1998 & is registered as a scientific society under the Karnataka Societies Act S.No 439, 2000-01. It is an association of professionals, scientists & others who are committed to the elimination of rabies from India. (Goal: Rabies Free India by 2020).

Activities till date

1. **Annual Conferences on 6th July (World Zoonosis Day):**
   Kolkata (1999), Bangalore (2000), Amritsar (2001), Jaipur (2002), Bhubaneswar (2003), Kolkata (2004), Shimla (2005), Jammu (2006), Hyderabad (2007), Lucknow (2008) & Thiruvananthapuram 2009.
2. **Workshops, Seminars & Training Programmes:**
   - National workshop for APCRI debate on modern WHO approved rabies prophylaxis at NIMHANS, Bangalore (2001).
   - National seminar on "Intradermal Rabies Vaccination", IIHS, Bangalore (2002).
   - National workshop on "Developing guidelines for Rabies Prophylaxis" at Hyderabad (2006).
   - National workshop on "Rabies Prophylaxis "at Alleppey, Kerala (2006).
   - National workshop on "Rabies Immunoglobulin (RIG) Administration" at KIDS, Bangalore (2008).
   - **National Seminar on Rabies Vaccines: Important Issues, at Visakhapatnam (Vizag), Andhra Pradesh (1st March, 2009).**
3. **Publications:** APCRI Journal (Biannual) & APCRI News Letter (Biannual).
4. **WHO sponsored "National multicentric Indian rabies survey" (2004).**
5. **Awards:** APCRI was honoured with "**Chiron vaccines award 2000**" for its contribution to prevention & control of Rabies in India.
6. APCRI in association with Indian Academy of Paediatrics (IAP) and Rabies in Asia (RIA) Foundation, formulated the **IAP Guidelines for Rabies Prophylaxis in Children** (2008).
7. **Slides on "Rabies Prophylaxis – Current concepts & Recommendations"** prepared by an expert consultation (2001). Revised in 2006 & now available on www.apcri.org
8. Observed "**World Rabies Day**" on 8th September 2007 & 28th September 2008, 2009 all over the country.
9. WHO-APCRI survey on "**Post Exposure Prophylaxis modalities in India** (2007).
10. APCRI is regularly organising Zonal/ Regional conferences & CME programmes.
11. APCRI played a major role in implementation of **Intradermal Rabies Vaccination (IDRV)** in the country.
12. **Manual on Rabies Immunoglobulin (RIG) Administration published in February, 2009.**