Human and dog rabies prevention and control

Report of the WHO/Bill & Melinda Gates Foundation Consultation
Annecy, France
7 – 9 October 2009

World Health Organization

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Contents

Acronyms and abbreviations

ABC	animal birth control
AMRO	WHO Regional Office for the Americas
CCV	cell-culture vaccine
EPI	Expanded Programme on Immunization
ERIG	equine rabies immunoglobulin
BMGF	Bill & Melinda Gates Foundation
HDCV	human diploid cell vaccine
HRIG	human rabies immunoglobulin
ICAM	International Companion Animal Management
ID	intradermal
IM	intramuscular
IU	international unit
MAb	monoclonal antibody
NIH	National Institutes of Health
NTV	nerve-tissue vaccine
OVD	oral vaccination of dogs
PAHO	Pan American Health Organization
PCECV	purified chick-embryo cell vaccine
PEP	post-exposure prophylaxis
PrEP	pre-exposure prophylaxis
PVRV	purified Vero cell rabies vaccine
QSMI	Queen Saovabha Memorial Institute
RFFIT	rapid fluorescent focus inhibition test
RIG	rabies immunoglobulin
RVNA	rabies virus-neutralizing antibody
SMBV	suckling mouse brain vaccine
TRC	Thai Red Cross
WHO	World Health Organization

1. Opening session

The Consultation was opened by Anastasia Pantelias, representing the Bill & Melinda Gates Foundation (BMGF), and François Meslin, representing the World Health Organization (WHO), who welcomed the participants on behalf of their respective organizations. The Consultation was organized back-to-back with the first annual meeting of the International Coordinating Group of the BMGF-funded project for human and dog rabies elimination in developing countries, held at WHO headquarters, Geneva, Switzerland, from 5 to 7 October 2009. This allowed the Consultation to benefit from the participation of the national coordinators and advisers of the BMGF-funded projects in the Philippines, South Africa (KwaZulu-Natal) and the United Republic of Tanzania.

François Meslin thanked the Gates Foundation for its sponsorship. Raffy Deray kindly agreed to chair the first session on human rabies prevention, and Alexander Wandeler the session dealing with dog rabies control and elimination.

The final agenda for the Consultation and the list of participants are attached to this report as Annexes 1 and 2 respectively.

2. Human rabies prevention

Chaired by: Dr Raffy Deray, Coordinator of National Rabies Control Programme in the Philippines, National Center for Disease Prevention and Control, Department of Health, Manila

Agenda item 2.1
Shorter post-exposure prophylaxis vaccine regimens

2.1.1 "Essen": four vs five doses regimen

Presented by: Dr Charles Rupprecht, Head, WHO Collaborating Centre for Reference and Research on Rabies, Centers for Disease Control and Prevention, Atlanta, GA, USA, on behalf of the Advisory Committee on Immunization Practices Working Group on Rabies

Peer-reviewed literature, unpublished data, epidemiological reviews and expert opinion were reviewed for evidence to support a reduced (four intramuscular doses at days 0, 3, 7 and 14) vaccine schedule in healthy patients during rabies post-exposure prophylaxis (PEP) (Rupprecht et al., 2009). No increase in adverse events was identified or suspected following deletion of the final rabies vaccine dose (at day 28) of the "Essen" regimen for post-exposure prophylaxis.

Recommendations for immunization in persons with altered immunocompetence have been presented previously (CDC, 1993; CDC, 2006). Various immunosuppressive agents, drugs and illnesses can interfere with active immunity after vaccination: seroconversion that is less than ideal among immunosuppressed persons may be attributable to infection (Pancharoen et al., 2001; Tantawichien et al., 2001). Until additional evidence becomes available, prophylaxis in persons with broadly defined immunosuppression should be administered using five doses of vaccine. Serum samples can be tested for rabies virus-neutralizing antibody (RVNA) by the rapid fluorescent focus inhibition test (RFFIT) to ensure that an acceptable antibody response has developed.

Overall, previous studies indicate that PEP – combining wound treatment *plus* local infiltration of rabies immunoglobulin (RIG) *plus* vaccination – is uniformly effective when appropriately administered, regardless of whether a fifth dose of rabies vaccine is administered.

2.1.2 The one-week four-site PEP regimen("4–4–4")

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

Patients exposed to a rabid animal often travel long distances to receive PEP which, in Thailand, requires four or five visits, depending on the regimen used – two-site intradermal (ID) or five intramuscular (IM) doses. Efforts are being made to develop a PEP regimen that can be completed in one week.

Four ID injections of 0.1 ml of purified Vero cell rabies vaccine (PVRV) were administered at four sites in deltoid muscles and thighs on days 0, 3 and 7, with and without equine rabies immunoglobulin (ERIG) at a dose of 40 IU/kg (Shantavasinkul et al. 2010). A control group received the WHO-recommended Thai Red Cross (TRC) regimen (two-site ID injections on

days 0, 3 and 7 and one injection on days 28 and 90) with ERIG. Titres of RVNA were determined up to day 360.

Geometric mean titres in subjects receiving the one-week four-site ID regimen, with or without ERIG, were significantly higher than those in the control group on days 14 and 28 ($p<0.001$). All subjects in all groups had RVNA titres of 0.5 IU/ml or more on days 14 and 28. Percentages of subjects with RVNA titres ≥ 0.5 IU/ml from day 0 to day 360 were not significantly different among the three groups.

2.1.3 A four-site one-day ID PEP for previously immunized individuals

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

According to WHO recommendations, individuals previously immunized against rabies need only two IM or ID booster injections (one on day 0 and one on day 3) when re-exposed to rabies risk. Administration of RIG is not required in such patients. An earlier study had shown that patients receiving four ID injections (two over deltoids and two on thighs) of 0.1 ml of tissue culture rabies vaccine during a single clinic visit developed satisfactory antibody titres. These RVNA titres were significantly higher than those achieved with the standard two-booster dose on days 0 and 3. The four-site ID booster vaccination has been used routinely in the Queen Saovabha Memorial Institute (QSMI) since 1998.

All patients who received the four-site ID booster at QSMI were studied retrospectively. Outpatient records for 1998–2008 were reviewed (Tantawichien et al., 1999; Khawplod et al., 2002). A total of 5116 patients received the four-site ID booster; the youngest patient was 2 years old and the oldest was 83, and 2453 (48.1%) of the patients were male. The longest interval since primary rabies vaccination was 25 years. More than 65% of the 5116 patients had severe potential rabies exposures classified as category III and 253 patients (4.9%) were bitten by laboratory-confirmed rabid animals. There were no reports of human rabies deaths in this group and no patients experienced serious adverse reactions to the four-site booster regimen.

2.1.4 A four-site ID PEP regimen

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

According to Dr Warrell, WHO advice supporting the use of the ID route for PEP (ID/PEP) has not been popular mainly because:

There is a lack of confidence in low-dose PEP regimens.

ID/PEP regimens and dosages are confusing.

ID treatment may be considered inconvenient by medical staff (although patients do not object).

The eight-site method is economically viable only with vaccines of 1.0 ml per ampoule.

The use of a single IM dose for multi-dose ID purposes is an off-label use of the product in most countries.

Sharing of vaccine ampoules is necessary, making ID treatment economical only in clinics with several patients per day.

To reduce these problems a four-site regimen was chosen, which had the following features:

A large vaccine dose was given on day 0, which might be especially beneficial to patients who miss later doses (the principle of the eight-site regimen was applied).

Vaccine was given in four rather than eight sites on the first day to make vaccination both more acceptable and practicable with any size of ampoule.

The total amount of vaccine needed was the same as for the other ID regimens.

A four-site regimen was studied that consisted of four ID injections, using a whole vial of PVRV (0.5 ml/ vial) divided between the deltoid and thigh areas on day 0, two 0.1-ml doses over the deltoids on day 7, and one 0.1-ml dose over the deltoids on days 28 and 90 (Warrell et al., 2008). This four-site regimen was compared with an eight-site ID regimen (with 0.05 ml per ID site), the two-site ID regimen (0.1 ml per ID site) and the standard IM regimen in a non-inferiority immunogenicity study. All regimens used PVRV; no RIG was used. It was concluded from the study results that:

All three ID regimens were equally immunogenic and were not inferior to the IM "gold standard" method.

There was no detectable advantage of ID injections in eight sites rather than four sites on day 0 because the same vaccine dose and timing were used.

Since the eight-site regimen (from different studies using 0.1 ml per ID site and RIG) is not suppressed by concomitant RIG, and has been tested after proven exposure to rabies, the four-site regimen will not be suppressed by RIG.

This vaccine (PVRV) and regimen (used without RIG in a study conducted in the Philippines) also proved to be as immunogenic as the two- and eight-site ID regimens (Quiambao et al., 2008). In 2006, Ambrozaitis et al. studied a similar four-site ID/PEP regimen in healthy volunteers who received 0.1-ml volumes of PVRV or PCECV (purified chick-embryo cell vaccine) administered over both left and right shoulders and both deltoid regions on day 0, both deltoid regions on day 7, and one deltoid region on days 30 and 90. This latter study showed that injecting deltoid and suprascapular sites offers an alternative method for applying a four-site regimen which can be useful in populations where there is reluctance to expose the thighs.

Dr Warrell asked the Consultation to consider approving "as suitable for use with any WHO-prequalified rabies vaccine, *a four-site regimen using a whole vaccine vial* divided between the deltoid and thighs or suprascapular 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 day 28 for all categories of exposure including category III". In addition, she proposed deleting the eight-site regimen from the list of WHO-approved ID regimens.

Agenda item 2.2
Duration of immunity after vaccination

Presented by: Dr Deborah Briggs, College of Veterinary Medicine, Kansas State University, Manhattan, KS, USA.

The development of immunological memory after vaccination with cell-culture rabies vaccines (CCVs) is a critical component in the establishment of long-lasting immunity against rabies in humans (Dietzschold, 2008). Since their development more than three decades ago, modern CCVs have proved to be highly effective in preventing human rabies, both when administered as pre-exposure vaccination (PrEP) and when used in association with immunoglobulin for PEP (Briggs, 2007; WHO, 2007a). Only a handful of vaccination failures have been reported among the millions of people who have received CCVs, all of which occurred in developing countries and most of which involved deviations from the WHO-recommended PEP protocol (Wilde, 2007; Rupprecht et al., 2009). Although one death has been reported, of an individual who was previously vaccinated with a CCV and subsequently exposed to a rabid puppy (Bernard et al., 1985), this patient did not seek and was not given the WHO-recommended two-dose PEP series after the exposure occurred.

Several recently published clinical trials have shown that individuals who received 3–5 initial CCV doses will have long-term immunity, possibly lasting for decades (Naraporn et al., 1999; Gheradin et al., 2001; Suwansrinon et al., 2006; Brown et al., 2008). Published data also indicate that individuals who received their primary series up to 21 years previously evince a good anamnestic response after booster vaccination. Individuals vaccinated with a modern CCV will respond to a booster vaccination regardless of whether they have measurable antibody titres at the time the booster is administered (Horman et al., 1987; Gheradin et al., 2001).

It is clear from the literature that it is not necessary to provide routine booster vaccine doses after primary rabies vaccination for the general public living in or travelling to (*International Travel and Health*; WHO, 2009; http://www.who.int/ith/ITH2009Chapter6.pdf) areas of risk. However, for laboratory technicians, researchers, and others working in environments where there may be occupational exposure to virulent rabies virus, routine serological evaluation should continue. Any professional who is at high risk should receive one booster dose of CCV if his or her antibody titre falls below 0.5 IU/ml. Finally, all individuals who have been previously vaccinated with a CCV and are subsequently exposed to the risk of rabies should receive two doses of CCV, one on day 0 and the second on day 3 (WHO, 2005).

Agenda item 2.3
Do we need to state a vaccine potency by intradermal dose?

Presented by: Mary Warrell, Oxford Vaccine Group, University of Oxford, Oxford, England, and Beatriz Quiambao, Research Institute for Tropical Medicine, Alabang, Philippines

The relationship between antigen dose and antibody response was investigated in a limited number of immunogenicity studies. In a meta-analysis of immunogenicity studies, Sudarshan and colleagues concluded that increasing vaccine potency above 5 IU/dose did not affect the

antibody response (Sudarshan et al., 2005). Beran et al. (2005) showed that, when a PCECV with an initial potency of 5.06 IU/ml was diluted up to 16-fold, the immunogenicity of the two-site ID/PEP regimen was proportional to the antigen dose. However, there was little difference in geometric mean titres (all well above 0.5 IU/ml of serum, at around 10 IU/ml) measured at day 14 between the undiluted vaccine, the twofold dilution and the fourfold dilution (potency of 2.53 IU/ml and 1.27 IU/ml or 0.253 IU/ml and 0.127 IU/0.1 ml respectively). Täuber (1986) gave 1, 2, 4 or 8 ID injections (deltoid and thighs) of 0.1 ml human diploid cell vaccine (HDCV) on a single day. Serology showed that antibody levels increased from day 10 to day 90 with the number of injections (and thus quantity of antigen).

In reviewing the potency values of vaccines used in major ID clinical trials, it should be stressed that early dose-finding and first post-exposure ID/PEP trials used vaccines with potency ranging from 2.55 IU (HDCV) to 7.5 IU (PCECV) per vial and that PCECV potency in later studies tended to be higher (6–9.16 IU per vial). Warrell (2008) reported 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. 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, only a very small number of ID immunogenicity studies have involved vaccines with a potency equal to, or slightly higher than, the WHO minimum potency of 2.5 IU/IM dose.

Additional caution is required when considering the correlation between stated NIH (National Institutes of Health) vaccine potencies and the immunogenicity results obtained in different studies. Only large differences in NIH vaccine titres (in IU/ml) should be deemed significant, especially when those titres are measured in different laboratories (WHO, 2000). Because of its variability, the NIH test may not be able to distinguish the differences required by a specified threshold potency value per ID dose as that dose represents a fraction of a vial.

Certain countries, including the Philippines, Sri Lanka and Thailand, have requested a potency greater than the WHO-recommended value for rabies vaccine used for ID/PEP. These requests have been prompted largely by concerns over:

- the fact that many – if not all – trials on ID/PEP regimens were done using vaccines with potency much higher than the 2.5 IU/IM dose;
- the immunogenicity of 0.1 ml of a WHO-recommended rabies vaccine reconstituted in a volume of 1.0 ml; these concerns were later allayed by the results of clinical studies (e.g. Briggs et al., 2000, Quiambao et al., 2005);
- using 0.1 ml of newer rabies vaccines, some of which were recommended for ID use in the absence of proper clinical data for that route of administration.

It was the overall conclusion of this review that there is currently no evidence of a need for a potency higher than the WHO-recommended 2.5 IU/IM for vaccines shown to be immunogenic by the ID route. WHO maintains a short list of vaccines that are safe and efficacious when administered ID according to a WHO-recommended regimen. This list is different from that of WHO-prequalified rabies vaccines, which have been assessed on the basis of their production and control modalities for IM application only. National regulatory authorities are invited to consult, and adhere to, WHO recommendations when a new rabies vaccine is proposed for ID use.

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, GA, USA, on behalf of the PAHO/AMRO Center for Zoonoses, Rio de Janeiro, Brazil.

Amazonia has unique characteristics. Risks for rabies are increasing as a consequence of environmental disturbances and migration; attacks on humans by vampire bats 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 PEPs are initiated but discontinued by exposed patients. Consultations between ministries of health of Member States and PAHO/AMRO and their Collaborating Centres are focused on rabies PEP schedules that are adapted to the limited access to health care and the conditions of vaccine cold chain maintenance that prevail in Amazonia. For example, a PEP schedule of injections on days 0, 3, 7, and 14 is not possible, because intervention teams cannot maintain a cold chain after day 3 and may not come back with additional vaccine on day 7 after initiation of rabies PEP. Such schedules are unrealistic and therefore not used, as repeated access to these often transient populations is difficult – there are few roads and the cost of helicopter lifting is prohibitive. In addition, the medical community is frequently reluctant to use any schedule not recommended by WHO or to use ID schedules (even those recommended by WHO). PAHO/AMRO therefore requested the WHO Consultation to review relevant PrEP and PEP options for areas with very limited health care and access. The Consultation was asked to pay particular attention to the situation of special areas such as Amazonia, and to propose studies aimed at increasing the use of modern rabies biologicals for PEP and PreEP in high-risk areas. Research should aim at developing regimens that would be appropriate for areas at high risk of vampire bat attacks but with limited access to rabies prophylaxis. These studies should focus on schedules using current vaccines given in a reduced number of doses and longer intervals between visits as well on the development of new biologicals and schedules.

Agenda item 2.5
Optimal usage of rabies immunoglobulin (RIG)

Presented by: Dr David Anderson and based on his 2007 paper "WHO guidelines dealing with immunoglobulin use impede rabies prevention" (*Asian Biomedicine*, 1:103–107).

Dr Anderson argued that there is no rational basis for calculating the dose of RIG according to the weight of the patient. Considering that it is the RIG injected into and around the wound that is important, he suggested a modification of the WHO guidelines for PEP – in particular that no RIG be injected at sites other than bite wounds. The following conclusions and recommendations were presented by Dr Anderson:

> Numerous experimental studies point to the efficacy of local as well as systemic injections of RIG preparations 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 wolf bite experience in the Islamic Republic of Iran (Baltazar, Bahmanyar & Ghodssi,

1954) strongly supports RIG use in humans. Other conclusions regarding humans have inevitably been based on surrogate studies, looking at circulating levels of antibody.

Despite its undoubted importance, RIG 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 administered in the optimal manner to the maximum number of victims at risk. This is the basis for the local administration of RIG into wounds. If the dose can be safely reduced, cost – currently 5–10 times that of vaccine and a major factor in the gross underuse of RIG – will also be reduced.

Studies to determine the dosage of RIG, which were carried out nearly 35 years ago, resulted in systemic administration, IM, into a site distal to the wound being recommended. These studies aimed to achieve inhibitory levels of circulating antibody. In these circumstances, it made sense to calculate the dose on the basis of the patient's body weight. It has since been recognized that RIG should be given locally into and around the wound, i.e. where it is needed to neutralize virus and prevent its entering nerve endings. Later studies also cast doubt on the earlier method of dose calculation.

Human RIG (HRIG) has a longer half-life than equine RIG and this was the basis for doubling the dose of the latter. This may not be relevant when RIG is injected into and around the wound.

It is well documented that vaccine alone will protect most victims of animal bites. It is impossible, however, to predict reliably which patients will succumb to rabies if wounds are not injected with rapidly virus-neutralizing RIG. In victims with severe wounds of the face, head and hand – areas with a large supply of superficial nerves – the incubation period is especially likely to be short and treatment to fail if no RIG is used. These are the patients who will die if RIG is not instilled locally. Nevertheless, it is dangerous to assume that small wounds do not put the bite victim at risk.

Over the course of the meeting Dr Anderson proposed various amendments to the current WHO recommendations on the use of RIG, which are set out in the annex to *WHO Expert Consultation on Rabies. First report* (WHO, 2005), sections A2 and A3.2. His final proposal to the Consultation can be summarized as follows:

For passive immunization, the whole dose of RIG is given into the wound(s). The maximum total amount of ERIG administered for all individuals, regardless of body weight, should be 1000 IU (normally a 5-ml vial). ERIG may be diluted up to a volume sufficient for the effective and safe infiltration of all wounds. It is not necessary or useful to inject any residual RIG into a distal site; residual RIG may be used on another patient within 6 hours or otherwise discarded.

Agenda item 2.6
Pre-exposure rabies vaccination (PrEP) for children

Pros and cons of PrEP presented by Thiravat Hemachudha, Head, WHO Collaborating Centre for Research and Training on Viral Zoonoses, Chulalongkorn University, Bangkok, and cost-effectiveness of PrEP presented by Thiravat Hemachudha on behalf of Chirapol Sinthunawa et al., Faculty of Environmental Science, Mahidol University, Bangkok, Thailand.

2.6.1 Pros and cons of PrEP introduction

Incorporating pre-exposure rabies vaccination into EPI (Extended Programme on Immunization) is suggested for programmes in areas with a high incidence of dog rabies on the basis of the following considerations:

Effective and sustainable dog vaccination and population control have not been achieved in most places (e.g. Thailand) despite many years of disease elimination efforts, and the persisting incidence of dog rabies, especially in community dogs, remains unacceptable.

Childhood rabies PrEP should be considered in areas of high rabies prevalence where children aged under 14 years are at high risk.

Studies have shown that:

- PrEP is safe in children; 5-year follow-up showed that coadministration of rabies PrEP with DPT and inactivated poliomyelitis vaccine at 2 and 4 months and 1 year elicited satisfactory antibody titres to all antigens with no interference with other antigens used;
- IM and ID routes are equally effective after two doses (at 2 and 4 months) in producing and maintaining rabies antibody for a period of at least 5 years after first injection (Kamoltham et al., 2009)

Re-exposures are common in childhood, but if a child has received PrEP there is no need for RIG, which is costly and may not always be available; two boosters (ID or IM) on days 0 and 3 are given instead. Moreover, it is possible that boosters can be provided on a single visit (see section 2.1.3).

ID vaccination is less expensive than IM administration, requiring only 0.1 ml at 2 and 4 months.

On the other hand, incorporation of PrEP into EPI programmes may have the following negative consequences:

If compliance with PrEP is not optimal, there may be increased wastage of rabies vaccine. Although recent studies have shown immunity of some duration may be achieved even with fewer than three injections (Kamoltham et al., 2009), it is not certain that all children will receive the tow or three doses of rabies vaccine required for effective PrEP.

PrEP may contribute to ignorance of, or lack of interest in, dog vaccination and population control.

In the event of re-exposure, it may be difficult to be sure who has already received PrEP. A rapid, reliable and inexpensive test for rabies antibody may be needed to determine whether a patient with an uncertain PrEP history actually has antibody or will need a full course of PEP with RIG.

It will be virtually impossible to determine the efficacy of a universal PrEP regimen in countries where the incidence of rabies is low (for example in Thailand, with fewer than 20 human cases per year in a population of 70 million).

In addition policy-makers need to be convinced of the safety and efficacy of integrating rabies into the childhood immunization programme.

2.6.2 Cost-effectiveness of rabies PrEP

To analyse the cost–effectiveness of childhood rabies PrEP in Thailand, the authors proposed a model, shown in Figure 1, which combines the factors related to dog population size/density/turnover and dog rabies and dog population control (loops A, B and C) that influence the number of persons bitten by dogs and therefore PEP cost (in red at centre) and the cost of PrEP programmes complementing these activities (loop D in blue at right).

One factor that determines the number of rabies PEPs (or persons bitten by dogs) is the dog density (ratio of dog to human populations). Growing numbers of dog bites raise public concerns and give rise to complaints that are likely to elicit responses from the relevant authorities. These responses may include a combination of dog culling, vaccination and sterilization. The net growth rate of the dog population then declines (loops A and B of Figure 1). Loop C illustrates a similar causal relationship between biting incidence/human rabies deaths and public responses, which may be triggered by reports in the mass media. Media articles will contribute to increased public awareness/education, which may result in more dog owners voluntarily having their animals vaccinated and sterilized and in greater motivation for action by government sectors and nongovernmental organizations. PrEP may also gain support (Figure 1, loop D); then, in the event of re-exposure, individuals who have received this preventive immunization will need only rabies boosters without ERIG. In this model, the PrEP programme (loop D) consists of three ID doses of 0.1 ml provided to infants at birth and at 2 and 4 months, beginning in 2010.

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

The annual cost of rabies PEP (Tcost1) is compared with Tcost2 (representing the sum of Tcost1 and PrEP as described above); see Figure 2. The Tcost2 programme was slightly more expensive than Tcost1 (2245 vs 2027 million baht per year) (see Figure 2); by 2026, however, the two cost estimates become comparable (2622 vs 2619 million baht per year). Over time, the proportion of people requiring only rabies vaccine boosters if re-exposed increases incrementally in parallel with the number of pre-immunized children within the entire population. This scenario was based on there being 0.75 dogs per household.

Thus, total expenses would be higher for the first 15 years, all other parameters remaining unchanged; however, this period might be shortened to 13 years if the dog population declines.

Agenda item 2.7
Other advances in rabies biological products development and usage

Presented by: Dr Jean Lang, Sanofi Pasteur, Lyons, France.

The Research and Development Department of Sanofi Pasteur has a longstanding commitment to meeting increasing quality and regulatory requirements for its current rabies biological products. A new rabies vaccine technology encompassing serum- and animal origin component-free medium in Vero-cell fermentors has been evaluated. The resulting highly purified Vero vaccine (using WISTAR Rabies PM/WI 38 1503-3M strain) is inactivated by beta-propiolactone and then freeze-dried and has a potency of more than 2.5 IU per dose. The comparability of this new "VRVg" rabies vaccine to the current PVRV/Verorab is supported by extended characterization studies. Its ability to elicit a satisfactory protective humoral response has been established in animal models. Further development and clinical evaluation are under way.

In the field of passive immunization and as an alternative to RIG, a combination (CL184) of two carefully selected, fully human monoclonal antibodies (MAbs), CR57 and CR4098, is being developed in partnership with Crucell. These two MAbs have complementary specificity and functionality. Preclinical results show that the potency, breadth of neutralizing activity and in-vivo efficacy of a polyclonal RIG directed at a lethal virus can be retained in a cocktail of two MAbs. Licensing of CL184 in the main enzootic countries is planned, based on full clinical development including one pivotal protective efficacy study in confirmed category III patients (adults, adolescents and children). To date, two Phase I studies (in India and USA) and two Phase II studies (in Philippines and USA), all in healthy subjects (healthy adolescents and children in Philippines), have been performed. A total of 288 subjects participated, of whom 59 received a single IM dose of CL184 (8–40 IU/kg) alone and 136 received a single IM dose of CL184 (20 IU/kg) in combination with rabies vaccination (five IM doses according to the Essen regimen). A Phase II study in healthy adults (India) is planned before proceeding to Phase III. The clinical evaluation conducted so far confirms that CL184 may offer a safe and effective alternative to ERIG or HRIG.

Figure 1. **Multifactorial model for cost–effectiveness analysis of childhood rabies PrEP in Thailand**

Factors influencing dog population size/density/turnover and dog rabies (loops A, B and C).

Factors influencing number of persons bitten by dogs and therefore PEP cost: in red at centre.

Factors influencing cost of PrEP programmes complementing these activities (loop D in blue at right).

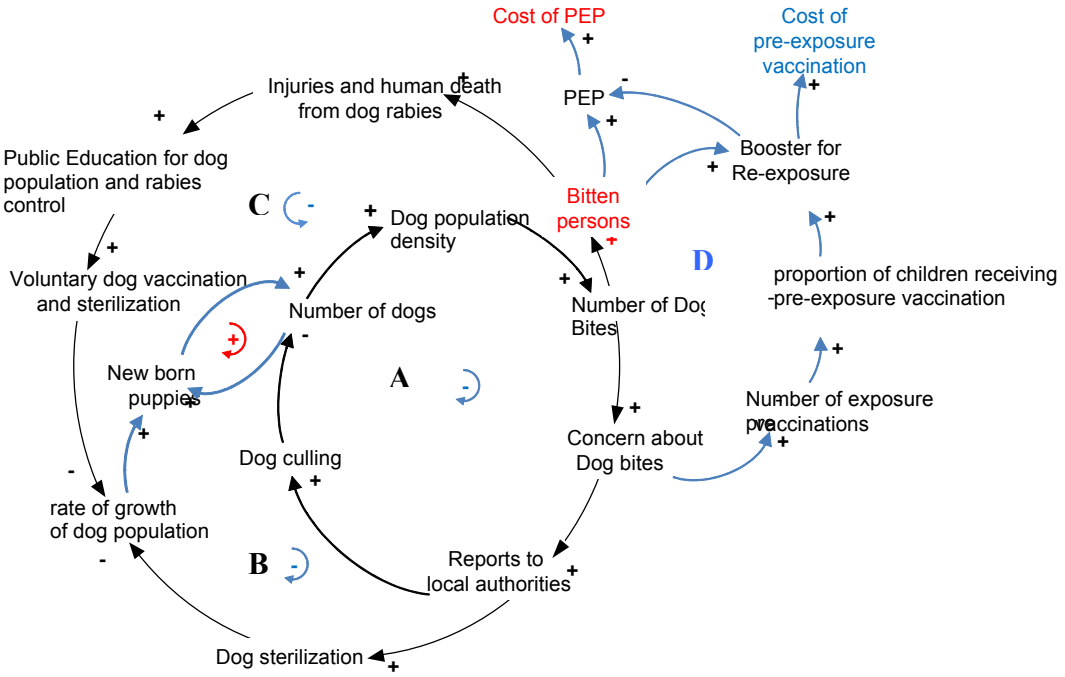
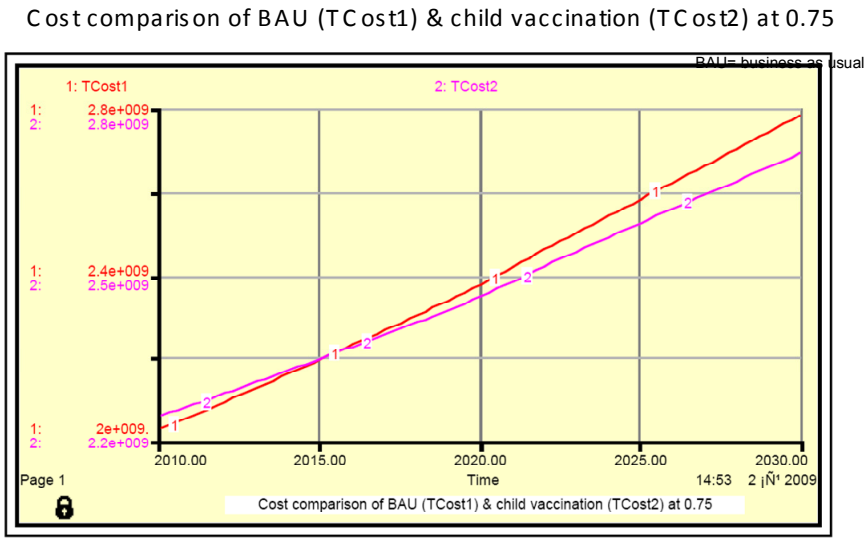


Figure 2. **Comparison of the annual cost of rabies PEP (Tcost1) with Tcost2 (representing the sum of Tcost1 plus PrEP)**



Year	2010	2020	2021	2022	2023	2024	2025	2026	2030
TCost1(e+6Baht)	2027	2377	2418	2459	2500	2541	2582	2622	2782
TCost2(e+6Baht)	2245	2461	2488	2541	2541	2567	2593	2619	2719

NOTE THAT Y AXIS SCALES ARE NOT THE SAME FOR T1 AND T2

3. Session on control and elimination of rabies in dogs

Chaired by: Dr Alexander Wandeler, Head, WHO Collaborating Centre for Control, Pathogenesis and Epidemiology of Rabies in Carnivores, Animal Diseases Research Institute, Rabies Unit, Nepean, Canada

Agenda item 3.2
Including sterilization in addition to vaccination for rabies control

Presented by: Dr Elly Hiby, Head of Companion Animals, WSPA Programme Department, World Society for the Protection of Animals, London, England

The change in size of a mammalian population over time is the sum of individuals born and immigrating into the population minus those dying and emigrating. These constituents of population dynamics must be taken into account in estimating population size and the impact of control measures: abundant theoretical literature and practical guidelines are available. Animal birth control (ABC) projects aim at reducing birth rates and will reduce population turnover, leading eventually to a reduction in population size. Other possible beneficial effects are discussed below.

Sterilizing dogs (spaying of females or neutering of males) as part of dog population management is a common intervention in many countries. The motivation for sterilization may come from a dog owner who wants to control the number of dogs owned or to reduce potential nuisance sexual behaviours, or it may come from government or an organization that aims to reduce the production of unwanted dogs at a population level. In the latter case sterilization should be targeted to female dogs that are likely either to be abandoned or to produce offspring that will not be vaccinated.

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 *Humane dog population management guidance*, available from the International Companion Animal Management (ICAM) Coalition at www.icam-coalition.org. Here, however, the focus is on sterilization only as a potential additional tool for reducing, and eventually eliminating, rabies, since a reduction in dog population may not be necessary for success in improving rabies vaccination coverage.

There are several different ways of delivering a sterilization programme. In some countries, dogs are caught on the street then sterilized, vaccinated and released. In others, owners are encouraged to bring dogs for sterilization to a central location (which can be a mobile clinic); additional help from dog handlers with suitable transportation may be offered to owners who would struggle to bring the dogs themselves. In most countries, most roaming dogs are owned (it cannot be assumed that a dog that is currently unconfined and on public property does not have an owner), and the mode of sterilization delivery will be significantly affected by their ownership status.

Sterilization usually involves surgical removal of sexual organs but there is increasing research into chemical or immunological alternatives that will be used increasingly if they are found to be safe, effective and cheaper than surgery.

The benefits of including sterilization alongside vaccination will be:

A reduction in population turnover which in turn helps to maintain herd immunity. This is especially important in 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.)

Increasing owner compliance. Owners benefit from bringing their dogs to an intervention, and hence the percentage of dogs vaccinated may increase.

Helping to maintain herd immunity by reducing the number of unowned dogs: improving health and reducing problem behaviours of individual owned dogs will reduce the chances of their being abandoned on the streets. (Abandoned – unowned – dogs may be difficult to access for vaccination.)

Reducing both the production of unwanted offspring that may otherwise be abandoned and the reproduction of unowned dogs whose offspring are likely to also remain unowned.

Reducing reproductive behaviours that put dogs at higher risk of contracting rabies as a result of increased movement of individual animals and more frequent contact between dogs.

Managers of an intervention that includes sterilization – surgical, chemical or immunological – must ensure that good standards are maintained; this will require initial training and regular refresher training of staff. There must also be consistent follow-up of cases, to help identify problems and raise and maintain standards. Costs of intervention can be reduced by high throughput but this must not be allowed to lead to falling standards: poor sterilization techniques and ineffective postoperative care can lead to dogs becoming sick or dying and this will generate mistrust of the entire intervention. Establishing a good reputation for an intervention can take time, but poor reputations will grow more quickly and can be long-lived; hence it may be better not to use sterilization at all than to perform it poorly and risk a low uptake of vaccination.

Costs of sterilization can be high. WSPA project costs vary from approximately US$ 6 to US$ 25 per dog sterilized. In addition, sterilization of some or all dogs in an area can reduce the throughput of an intervention and divert resources away from the priority of mass vaccination. Sterilization may be required for many years, alongside vaccination, if rabies is to be eliminated, and sustaining it is difficult. Ensuring an adequate budget for continuing rabies vaccination alone can be difficult enough, but adding the cost of sterilization can make sustainability impossible when many programmes are reliant on overseas funding, often from nongovernmental organizations.

The targeting of sterilization will depend on the aim of the intervention. If a particular subpopulation of dogs is expected to produce offspring that will not be vaccinated, the proportion of the total population to be targeted may be low. If the aim is only to improve owner compliance and interest in the intervention, sterilization services will depend on what owners feel they need. For situations where the goal is to stabilize or reduce the total dog population, a useful guide has been developed for establishing the required sterilization proportion for a desired rate of growth; the guide is available upon request from the author of this paper.

In conclusion, there is evidence that sterilization can be a useful addition to vaccination, helping to reduce the costs of rabies control and increase its benefits. Sterilization may also benefit

animal welfare in ways that have not been discussed in this paper but that help to outweigh the costs; for example, improved body condition score and a reduction in skin conditions have been observed in sterilized dogs in Colombo. While the use of sterilization may continue to be limited by its cost, the development of safe chemical/immunological sterilization agents holds promise for reducing that cost. Even contraceptives that remain effective for 1 year would be extremely useful: these could be applied alongside annual rabies vaccination, provided that the cost of each dose was low enough to counterbalance the added cost of having to access dogs repeatedly.

Agenda item 3.3
Role of oral vaccination of dogs (OVD) against rabies in dog rabies elimination

Presented by: Dr François Meslin, Department of Control of Neglected tropical Diseases, World Health Organization, Geneva, Switzerland

The accessibility of dogs for parenteral vaccination remains the major obstacle to effective control of dog rabies in many parts of the world. Acknowledging the inadequacies of parenteral administration for dog rabies elimination, WHO prompted studies on the oral vaccination of dogs (OVD) and the development of safe and effective vaccines and baits for OVD. *Guidance for research on oral rabies vaccines and field application of OVD against rabies* (WHO, 2007a) is a compilation of the recommendations of the WHO consultations on OVD (accessible at http://www.who.int/rabies/resources/guidelines%20for%20oral%20vaccination%20of%20dogs%20against%20rabies_with%20cover.pdf).

The new approach offered by OVD promises a significant increase in vaccination coverage (especially of free-roaming and poorly supervised dogs), both when applied exclusively and when used in combination with parenteral vaccination. 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 is a prerequisite to promoting its use in the field, and safety for non-target species, especially humans, remains the centre of WHO concern. To that end, all candidate vaccines were tested in immunosuppressed animal models and for safety in non-human primates. Guidelines were established for determining oral vaccine efficacy in laboratory dogs, for bait development and bait preference trials, and for the evaluation of bait delivery systems in the field. Three OVD delivery systems were envisaged:

- distribution of baits to owned dogs – their owners would collect the baits at a central location;
- placement of baits at selected sites where they were accessible to free-roaming dogs (so-called "wildlife immunization model"); and
- distribution of baits to dogs encountered in the street (so-called "hand-out model").

Specific guidelines were developed for implementing OVD projects and promoting further investigation of the logistics and economics of OVD.

Investigating the economics of OVD is essential, since it is highly unlikely that all resources required for elimination of dog rabies suddenly become available. Financial constraints will clearly continue to affect the implementation of control activities and new techniques must therefore be as cost-effective as possible. When targeting certain "high-risk" elements of the dog population – such as feral and free-roaming dogs – it may be possible to accept a higher cost per

dog vaccinated orally than that for parenteral vaccination (e.g. US$ 1–1.30, with 0.35 cents' worth of vaccine), since most savings accrue *after* rabies elimination. However, when comparing costs of oral and parenteral vaccination for the same dogs (e.g. the owned and "restrainable" elements of the population), costs per fully vaccinated dog by the parenteral or the oral route should be within the same range . To reduce costs further, and thereby open up new opportunities for the initiation of large-scale vaccination programmes, inexpensive and voluntary vaccine delivery systems involving communities or community leaders should be promoted.

More than 10 years after the WHO OVD group had its last meeting, OVD has still not become an operational component of any dog rabies control and elimination programme. In some countries, the major obstacle is clearly concern over safety for humans; in others the problems is largely one of economics since the cost per (imported) vaccine bait is high compared with that of parenteral vaccine. In countries that have been combating rabies by providing millions of PEPs and vaccinating millions of dogs for decades and today have only a few human cases, OVD could make the difference between a lingering public health problem and the elimination of human rabies.

4. Topics for future research in human and dog rabies prevention and control

Agenda item 4.1
New vaccine ID delivery systems

Presented by: Dr Darin Zehrung, Technical Officer, PATH, Seattle, WA, USA

The rationale for developing ID devices for delivering rabies vaccine is based on the following facts:

> ID injection using the conventional needle and syringe method is difficult to master without proper training and continual practice.
>
> In immunization programmes in developing countries, ID injections are found to be difficult to deliver in the dermis in a consistent volume
>
> There is generally poor compliance with ID PEP regimens and training standards are frequently inadequate.

New ID delivery technologies should overcome the problems outlined above by increasing the number of health care personnel who can deliver the ID vaccine and provide the flexibility needed for non-conventional PEP delivery scenarios (i.e. other than at a health facility).

The different ID delivery systems that have been tested include the PATH ID adapter, the Nanopass MicronJet™ (hollow microneedle), and the PharmaJet disposable syringe jet injector. Two of these – the ID adapter and the PharmaJet device – proved generally acceptable to health care workers in India who thought that the devices could benefit the Indian health care system.

The PATH ID adapter is a simple injection "aid" that fits onto a conventional needle and syringe and limits the angle and depth of needle penetration. It is intended to deliver any medication or vaccine indicated for ID delivery. The current design is intended for use with 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 an early prototype of the ID adapter produced adequate levels of antibodies, similar to those that follow ID delivery by conventional needle and syringe. The next steps in ID adapter development are:

- to generate preclinical and ID rabies vaccine clinical data to confirm device performance;
- to explore other potential ID research applications (e.g. yellow fever, influenza);
- further simplification and refinement of design for safety (reuse prevention feature);
- technology transfer to manufacturer based in India for market introduction and availability.

PATH is implementing a rabies research project that aims to identify and qualify appropriate ID devices with the potential for delivering a reduced dose of rabies vaccine at public health clinics in India, demonstrate the clinical feasibility of ID-capable technologies, and assess value proposition and commercialization potential. PATH is conducting an assessment in three health care facilities in Andhra Pradesh, India, to determine health care workers' perceptions of ID device acceptability, safety, and expected disposal practices.

In the near future PATH plans a Phase II clinical trial, in Hyderabad, India, of rabies vaccine delivered by ID devices (both ID adapter and PharmaJet injector) to test their safety and compare immunogenicity with that of standard needle and syringe ID delivery in healthy adult volunteers. The primary objective of the trial is to determine whether there is a significant reduction in immunological responses in the experimental device groups compared with those in the conventional vaccine administration group 14 days after receipt of the initial vaccine injection. Secondary objectives are to:

- determine whether immunological responses in the experimental device groups are inferior to those in the conventional vaccine administration group at 28 and 90 days after receipt of the initial vaccine;
- determine whether the immunological responses of any participants in the experimental device groups fall below the WHO RVNA detection threshold of 0.5 IU/ml for post-exposure prophylaxis at any time during the study (days 14–90 following receipt of first dose of vaccine);
- determine whether the experimental devices are safe for human use based on injection site reactions and systemic events;
- determine whether these experimental devices are acceptable to study participants; and
- confirm ID delivery of rabies vaccine using the experimental devices.

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

Agenda item 4.3
Current status of research on monoclonal antibodies for PEP

Presented by: Dr Marie-Paule Kieny, Director, Initiative for Vaccine Research, World Health Organization, Geneva, Switzerland

There is a critical lack of both availability and use of rabies immunoglobulins (RIGs) in countries where canine rabies is a public health problem. Indeed, only 2% of PEP 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.

Cocktails of anti-rabies monoclonal antibodies (MAbs) offer the potential of safe, efficient and cost-effective replacements for equine and human RIG. They can be produced on a large scale with high batch-to-batch consistency, reduced theoretical health risk associated with blood-derived products, and – in the case of murine MAbs – the possibility of manipulating Fc fragments so as to minimize adverse effects and prolong half-life. 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.

Agenda item 4.4
Future rabies biologicals and other tools

Presented by: Dr Charles Rupprecht, Head, WHO Collaborating Centre for Reference and Research on Rabies, CDC, Atlanta, GA, USA, on behalf of the US ACIP working group on rabies

Since the initial suggestion of the existence of rabies-related viruses during the 1950s, more than a dozen different *Lyssavirus* genotypes have been defined. 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. Laboratory, field and modelling tools should be integrated to provide potential solutions for the prediction and detection of, and intervention against, conventional and emerging lyssaviruses, particularly within the context of the challenges posed 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. Progressive rabies prevention and control, in both the developed and the developing world, requires enhanced support for relevant, innovative scientific discovery, translation and technology transfer.

Humane dog population management is a keystone in animal rabies control. Research on safe and effective approaches for rabies vaccination and immuno-contraception may provide a dual long-term solution leading to more efficacious disease elimination programmes.

Novel recombinant techniques, reverse genetics and other innovative methodologies offer great promise for the development of new rabies interventions. Such biologicals offer the opportunity for major advances in areas ranging from oral vaccination of animal rabies hosts to human prophylaxis.

Despite the unprecedented survival of an unvaccinated teenager in the USA after a bat bite in 2004, other attempts to treat human rabies cases have been unsuccessful. Relevant animal models are needed as surrogates to provide more basic insights into the pathogenesis of rabies, as well as to serve as model for demonstrating the value of various suggested modalities for their use as human therapeutics. In addition, a directed focus on antiviral strategies is needed for consideration of introduction into experimental therapy.

5. Conclusions and recommendations

Agenda item 2.1
Shorter post-exposure prophylaxis vaccine regimens

2.1.1 Essen: four vs five doses

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

- In healthy, fully immunocompetent exposed persons who receive wound care *plus* high-quality RIG *plus* WHO-prequalified rabies vaccines, a PEP vaccine regimen consisting of four doses administered IM on days 0, 3, 7 and 14 can be used as an alternative to the five-dose regimen.
- In other cases, including WHO category II exposure when RIG is not required, the use of the five-dose Essen regimen on days 0, 3, 7, 14 and 28 should continue. In addition, enhanced surveillance of patients who receive prompt PEP as recommended by WHO and who subsequently die of rabies should be strongly encouraged.

2.1.2 Four-site one-week PEP regimen ("4–4–4")

Post-exposure rabies prophylaxis given by four-site ID injections on days 0, 3 and 7 requires three visits in one week. The immunogenicity study revealed similar antibody response pattern to, but higher antibody titres than, those obtained with the TRC "2–2–2–0–1–1" ID regimen administered with or without RIG. Although this four-site one-week PEP regimen requires a total volume of 1.2 ml, which is higher than that for the two-site TRC regimen, it appears to be an interesting alternative, particularly because it reduces the number of clinic visits (and hence the cost) and the duration of a complete PEP, which is likely to improve patient compliance.

- The WHO Consultation acknowledged the promising results of the four-site one-week regimen. The Consultation decided to reassess this regimen as a possible alternative to the widely used two-site TRC regimen on the basis of the results of a well-designed "4–4–4" study to be conducted shortly.

2.1.3 Four-site one-day ID PEP for previously immunized individuals

The single-visit four-site ID booster vaccination consisting of four 0.1-ml injections – on each arm and thigh or suprascapular region – has been shown to induce an anamnestic response as good as, or superior to, that induced by the IM/ID 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 5116 patients. Although it requires twice as much vaccine as the two ID boosters at day 0 and 3, the four-site ID booster regimen is safe and effective, saves transportation expenses and loss of working time, and may reduce patient non-compliance.

- The Consultation noted the accumulated evidence and recommended the use of this single-visit four-site ID booster regimen as an alternative to the previously recommended two-visit (day 0, day 3) single-site ID or IM regimen. The decision to use one or the other regimen is the responsibility of the health care provider in consultation with the patient.

2.1.4 A four-site ID PEP regimen

The results obtained with a four-site regimen consisting of four 0.1-ml ID injections divided between the deltoid and thighs areas on day 0, two 0.1-ml ID injections over the deltoids on day 7 and one 0.1-ml ID injection over the deltoid on days 28 and day 90 were reviewed.

The Consultation considered Dr Warrell's request to approve a four-site regimen "as suitable for use with any WHO-prequalified rabies vaccine" using a whole vaccine vial divided between the deltoid and thighs or suprascapular 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 day 28 for all categories of exposure including category III.

- The Consultation noted that this proposed four-site regimen, which requires using an entire vaccine vial on day 0 for an individual patient, is not suitable for use at the dose of 0.1 ml per ID site with all currently WHO prequalified rabies vaccines approved for ID use, which was a prerequisite for endorsement.

  In order to simplify, and thus facilitate, the use of ID PEP, the Consultation recommended that the rarely used eight-site regimen be deleted from the list of WHO-approved ID regimens.

Agenda item 2.2
Duration of immunity after vaccination

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. Duration of immunity and the ability to develop an anamnestic response to a booster vaccination in previously vaccinated persons are related neither to the route of the initial vaccination series (IM or ID) nor to whether the patient received PreP or PEP. Moreover, the ability to develop an anamnestic response is not related to the time elapsed since administration of the initial vaccination series: published data indicate that persons vaccinated up to 21 years earlier will respond to a booster of rabies vaccine.

- The Consultation recommended that routine booster doses of rabies vaccine are not required for individuals living in or travelling to high risk areas who have received a primary series of PrEP or PEP with a WHO-recommended vaccine. Persons who have received either PrEP or PEP should receive the recommended short series of PEP injections (one shot ID or IM on day 0 and day 3 or alternatively four injections ID on day 0) in the event of subsequent re-exposure to a suspected rabid animal. Individuals whose occupation puts them at constant risk of exposure to live rabies virus (i.e. persons working in rabies diagnostic laboratories or rabies vaccine manufacturing facilities) should continue to have their serological titre monitored and be given a booster if it falls below 0.5 IU/ml.

Agenda item 2.3
Do we need to state a vaccine potency by intradermal dose?

The WHO-recommended minimum potency is 2.5 IU per IM dose and the WHO-recommended volume of a single dose of rabies vaccine administered per ID site is 0.1 ml. There has been concern about the varying potency that may be contained in that 0.1-ml volume because rabies vaccines are produced as single IM doses reconstituted in different volumes depending on

manufacturers[1] and because an increasing number of newly developed modern cell-culture or embryonated egg vaccines are coming onto the global market.

- 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 IM dose that have been satisfactorily assessed for their innocuity, immunogenicity and/or safety in well–designed ID PrEP and PEP clinical trials. The Consultation recommended that new vaccines with a minimum potency of 2.5 IU per IM dose be similarly assessed for ID use in well-designed clinical trials. In addition, the Consultation recommended that the national regulatory authority of any country wishing to register a new rabies vaccine, whether locally produced or imported, for ID PEP usage should ensure that adequate tests and satisfactory clinical trials (safety and immunogenicity studies) have been performed and that national requirements have been met.

The WHO Secretariat will contact the WHO group in charge of strengthening the capacity of national regulatory systems; the Developing Countries' Vaccine Regulators Network has been asked for its advice, which will be distributed to members of this Consultation. It will also bring the issue to the attention of both the Department of Immunization, Vaccines and Biologicals and the Expert Committee for Biological Standardization.

The WHO Secretariat wished to stress that:

> WHO maintains a list of vaccines proven to be safe and efficacious by the ID route using WHO-recommended ID regimens.
>
> This list is different from the list of WHO-prequalified rabies vaccines, which concerns only vaccines administered by the IM route.

Agenda item 2.4
Prevention of human rabies in vulnerable populations

2.4.1 In Amazonia

Populations of the Amazon region living in places that are especially difficult to reach and at constant risk of exposure to vampire bat rabies will benefit from modern health care for only three days or even less after rabies exposure. This is not commensurate with any of the current WHO PEP regimens.

- The Consultation strongly encouraged the development of safe and effective biologicals and protocols and their evaluation for use in 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 PEP according to WHO recommendations, the Consultation urged health authorities in African countries to facilitate the availability of, and access to, modern rabies PEP (including RIG in category III exposures) for all patients exposed to the rabies risk.

[1] Currently, rabies vaccines are reconstituted in volumes of 0.5 ml or 1.0 ml.

Agenda item 2.5
Optimal usage of RIG

The Consultation agreed that the immunoglobulin injected into wounds is of utmost importance in the management of category III exposures. In view of the lack of evidence, however, the Consultation did not endorse the suggestion that a standard maximum dose per bitten individual be defined, nor did it agree to drop mention of IM administration of any RIG at a site distant from the wound.

- The Consultation reiterated previous recommendations that RIG can be diluted if necessary to ensure infiltration of all wounds at a volume determined by the capacity of the site and sound clinical judgement. In addition, the Consultation recommended that new in-vitro and in-vivo research be encouraged to determine the quantity of RIG (in IU) required on site, with or without distal parenteral RIG administration.

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

- Concerning the ERIG sensitivity test still recommended in the first report of the WHO Expert Consultation on Rabies (TRS 931; WHO, 2005) the WHO Secretariat wished to stress the superseding recommendation of the WHO position paper on rabies vaccine (WHO, 1997b), which states that heterologous rabies immunoglobulins may carry a small risk of hypersensitivity reactions but that there are no scientific grounds for performing a skin test before administration of ERIG because testing does not predict reactions, and ERIG should be given whatever the results of the test.

Agenda item 2.6
Recommendation for PrEP for Children

The Consultation took note of the many pros and cons of incorporating PrEP into EPI programmes presented by Thiravat Hemachudha and congratulated Chirapol Sinthunawa and colleagues of the Faculty of Environmental Science, Mahidol University, for the interesting dynamic PrEP cost–effectiveness model developed for Thailand.

- The Consultation could not issue a consensual statement on that particular issue; it was obvious that further studies and deliberations are needed.

  In these circumstances, the WHO Secretariat wished to reiterate the WHO position paper on rabies vaccines (WHO, 2007b): "Pre-exposure immunization is recommended for all individuals living in or travelling to highly rabies-enzootic areas and for those exposed to rabies by the nature of their occupation. WHO encourages further studies on the feasibility, cost-effectiveness and long-term impact of incorporating CCVs in the early immunization programmes of infants and children in communities where surveillance has proven rabies to be a major problem." Rabies vaccines for large-scale public health interventions should meet the current WHO quality requirements; be safe and have a significant impact against the actual disease in the target populations; if intended for infants or young children, be easily adapted to the schedules and timing of national childhood immunization programmes; and not interfere with the immune response to other vaccines given

simultaneously; be formulated to meet common technical limitations; e.g. in terms of refrigeration and storage capacity; and be appropriately priced for different markets.

Agenda items 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 vaccination of their dogs during mass vaccination campaigns can be counterproductive – turnout may be too low for adequate vaccination coverage to be achieved. Vaccination coverage should be monitored and the impact of charging for dog rabies vaccination evaluated. A potential alternative to charging is to encourage voluntary contributions, thus avoiding any perception of coercion. If a threshold vaccination coverage of about 70% cannot be reached, dog rabies is unlikely to be controlled, resources will be wasted, and communities and field veterinary staff will lose motivation.

- The Consultation recommended that the impact on dog immunization coverage of charging owners for dog rabies vaccination, which has been shown to be negative in Africa, be further evaluated, particularly in Asian countries where a trend towards cost-recovery and further financial involvement of dog owners in rabies control is developing.

Most domestic dogs, however, are accessible to relatively simple parenteral vaccination campaigns. Effective dog vaccination campaigns can have rapid impacts on the demand for PEP, resulting in financial savings. The relationship between the incidence of dog rabies and the demand for PEP appears to vary widely across different settings. Optimizing 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 recommended that exploration of financial mechanisms by which dog rabies control could be sustained through savings in PEP be encouraged, which will probably require rabies to be managed as an integrated programme across the veterinary and public health sectors.

Education and awareness programmes can be highly effective in reducing rabies exposures.

- The Consultation recommended that more data be collected for evaluation of the cost–effectiveness of different educational methods in preventing exposures and reducing human rabies deaths.

Because there are demographic differences both between and within dog populations, the collection of preliminary data on dog demography, dog ownership and community attitudes towards dogs is advised. These data can be used to determine the most appropriate method for delivering reproduction control and can help to ensure that reproduction control resources are used to best effect. Surgical sterilization is currently the most common method but is too costly to provide a sustainable solution to dog population management in all countries where it is required.

- In this regard, the Consultation strongly encouraged 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 encouraged

development of safe, inexpensive and humane methods of permanent dog identification that do not require a dog to be anaesthetized for application.

The use of reproduction control for dogs can help in reaching and maintaining appropriate vaccination coverage. Dogs may be accessed for reproduction control either by owners delivering their dogs to some central location or by catching ownerless dogs in public areas; following sterilization, vaccination and post-operative care, ownerless dogs are released at the point of capture. This animal birth control, or ABC, is 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 recommended the inclusion of reproduction control and/or other primary veterinary health care in dog rabies control programmes as a means of increasing owner perception of the value of the intervention and hence improving owner compliance.

Oral vaccination, either exclusively or in combination with parenteral vaccination, has been shown in various settings to lead to a significant increase in dog vaccination coverage, especially of ownerless and poorly supervised owned dogs.

- The Consultation encouraged the launching of new studies on oral vaccination of dogs where the technique is integrated within current dog rabies control activities as a complementary element, particularly targeting inaccessible owned and ownerless dogs.

Agenda item 4.2
New delivery systems

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

- The Consultation recommended evaluation of ID delivery devices, examining user acceptability, logistics for PEP and PrEP vaccination, efficacy and overall cost–effectiveness.

As these devices are adopted for other immunization programmes (BCG, influenza, polio vaccine, 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 and equine immunoglobulins. These products are currently in Phase 2 clinical development, with two studies already completed in the Philippines and USA, one (human MAbs) due to start in India and another (murine MAbs) about to enter Phase 1 clinical trial in India.

- The Consultation recommended 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.

Additional agenda items

Additional recommendation for new PrEP and PEP studies

Any new PrEP or PEP regimen and any modifications of existing regimens should be evidence-based. The clinical data on which WHO recommendations are based must be derived from proper sample sizes, controls and comparison arms, endpoints and statistical analysis. Confirming results in a second study may be beneficial, although the quality of the inception study and its results are more important. Even if shown to be safe and efficacious, new regimens must have clear practical and/or economical advantage(s) over existing regimens if they are to be endorsed. New ID regimens must be applicable with all currently WHO-prequalified vaccines and/or vaccines recommended by WHO for ID use.

Four steps to replace nerve-tissue vaccines with modern rabies vaccines produced on cell culture 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-tissue vaccines (NTVs) found to be reactogenic and sometimes of low immunogenicity. Following the first WHO recommendation in 1984 to replace NTVs, many developing countries have discontinued the production and use of brain-tissue vaccines for human use and have met 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 to the effect that NTVs should be discontinued and that only cell-culture and purified embryonated egg vaccines should be used in humans (WHO, 2005). Today only a very small number of countries in Africa, Asia and Latin America are still manufacturing and using NTVs and most are looking for affordable and sustainable alternatives.

- The Consultation recommended that countries still producing or using NTVs adopt the following four-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 evaluate local conditions and assess the feasibility and cost of shifting from NTV to modern vaccines. In the implementation of this policy, serious consideration should be given to the use of the cost-saving ID regimens for rabies PrEP and PEP.

  Step 2

  Clear instructions on the provision of modern vaccines for PreEP and PEP, including indications for their use and modalities of their administration (as well as of RIG.), must be formulated in national guidelines. These guidelines should be developed by technically competent experts and based on the recommendations of the WHO Expert

Committee/Consultation on Rabies, WHO's advisory groups such as the Strategic Advisory Group of Experts (SAGE) on Immunization, updated literature, and the experience and observations of national and international experts, and should be disseminated to all centres providing PreEP and PEP. The guidelines must provide clear policies on such matters as vaccine subsidy (if any), handling of left-over vaccine, etc., and should be regularly updated.

Step 3

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

Step 4

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

6. Closing session

The Consultation was closed by François Meslin, who thanked all participants for their contributions and the various co-sponsors – particularly the Gates Foundation – for their continued collaboration and support. He indicated that the report of this Consultation, after final review by participants and editing, will be posted as a stand-alone document on the WHO web site. In addition, all recommendations contained in the report, such as the four-site one-day booster and the four-dose IM PEP, that supersede or complement the text of the 2007 WHO position paper on rabies vaccine (WHO, 2007b) endorsed by SAGE will be reviewed with the WHO Secretary of SAGE and, if considered substantial, submitted to the next meeting of SAGE in April 2010 for possible inclusion in an updated rabies vaccine position paper.

François Meslin concluded by wishing all participants a safe return to their respective countries.

References

Ambrozaitis A et al. (2006). Rabies post-exposure prophylaxis vaccination with purified chick embryo cell vaccine (PCECV) and purified Vero cell rabies vaccine (PVRV) in a four-site intradermal schedule (4-0-2-0-1-1): an immunogenic, cost-effective and practical regimen. *Vaccine*, 24:4116–4121.

Baltazar M, Bahmanyar M, Ghodssi M (1954). Prevention of human rabies: treatment of persons bitten by rabid wolves in Persia. *Bulletin of the World Health Organization*, 10:797–803.

Beran J et al. (2005). Potency requirements of vaccines administered intradermally using the Thai Red Cross regimen: investigation of the immunogenicity of serially diluted purified chick embryo cell rabies vaccine. *Vaccine*, 23:3902–3907.

Bernard KW et al. (1985). Pre-exposure rabies immunization with human diploid cell vaccine: decreased antibody responses in persons immunized in developing countries. *American Journal of Tropical Medicine and Hygiene*, 34:633–647.

Briggs DJ (2007). Human vaccines. In: Jackson AC, Wunner WH, eds. *Rabies*, 2nd ed. Amsterdam, Elsevier:505–516.

Briggs DJ et al. (2000). Antibody response of patients after post-exposure rabies vaccination with small intradermal doses of purified chick embryo cell vaccine or purified Vero cell rabies vaccine. *Bulletin of the World Health Organization*, 78:693–698.

Brown D et al. (2008). Intradermal pre-exposure rabies vaccine elicits long lasting immunity. *Vaccine*, 26:3909–3912.

CDC (1993). Recommendations of the Advisory Committee on Immunization Practices (ACIP): use of vaccines and immune globulins in persons with altered immunocompetence. *Morbidity and Mortality Weekly Report*, 42(RR-4):1–18.

CDC (2006). General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). *Morbidity and Mortality Weekly Report*, 55(RR-15):1–48.

Dietzschold B et al. (2008). Concepts in the pathogenesis of rabies. *Future Virology*, 3:481–490.

Gherardin AW et al. (2001). Early rabies antibody response to intramuscular booster in previously intradermally immunized travelers using human diploid cell rabies vaccine. *Journal of Travel Medicine*, 8:122–126.

Hampson K et al. (2009). Transmission dynamics and prospects for the elimination of canine rabies. *PLoS Biology*, 7:e53.

Horman JT et al. (1987). Antibody response after a two-year intradermal booster of rabies human diploid cell vaccine. *Journal of the American Veterinary Medicine Association*, 191:185–187.

Kamoltham T et al. (2009). Rabies PrEP in children: anamnestic immune response to PCECV booster doses up to 5 years after primary vaccination. In: *Proceedings of the second Rabies in Asia Conference, Hanoi, 9–11 September 2009* (available at: www.rabiesinasia.org/riacon2009report.html).

Khawplod P et al. (2002). Four-site intradermal postexposure boosters in previously rabies vaccinated subjects. *Journal of Ttravel Medicine*, 9:153–155.

Naraporn N et al. (1999). Immune response to rabies booster vaccination in subjects who had postexposure treatment more than 5 years previously. *Journal of Travel Medicine*, 6:134–136.

Pancharoen C et al. (2001). Failure of pre- and post-exposure rabies vaccinations in a child infected with HIV. *Scandinavian Journal of Infectious Diseases*, 33:390–391.

Quiambao BP et al. (2005). Reducing the cost of post-exposure rabies prophylaxis: efficacy of 0.1 ml PCEC rabies vaccine administered intradermally using the Thai Red Cross post-exposure regimen in patients severely exposed to laboratory-confirmed rabid animals. *Vaccine*, 23:1709–1714.

Quiambao BP et al. (2008). Rabies post-exposure prophylaxis in the Philippines: health status of patients having received purified equine F(ab')(2) fragment rabies immunoglobulin (Favirab). *PLoS Neglected Tropical Diseases*, 2:e243.

Rupprecht CE et al. (2009). Evidence for a 4-dose vaccine schedule for human rabies post-exposure prophylaxis in previously non-vaccinated individuals. *Vaccine*, 27:7141–7148.

Shantavasinkul P et al. (2010). Postexposure rabies prophylaxis completed in 1 week: preliminary study. *Clinical Infectious Diseases*, 50:56–60.

Sudarshan MK et al. (2005). Assessing the relationship between antigenicity and immunogenicity of human rabies vaccines. Results of a meta-analysis. *Human Vaccines*, 1:187–190.

Suwansrinon K et al. (2006). Survival of neutralizing antibody in previously rabies vaccinated subjects: a prospective study showing long lasting immunity. *Vaccine*, 24:3878–3880.

Tantawichien T et al. (1999). Antibody response after a four-site intradermal booster vaccination with cell-culture rabies vaccine. *Clinical Infectious Diseases*, 28:1100–1103.

Tantawichien T et al. (2001). Failure of multiple-site intradermal postexposure rabies vaccination in patients with human immunodeficiency virus with low CD4+ T lymphocyte counts. *Clinical Infectious Diseases*, 33:E122–E124.

Täuber MG et al. (1986). High rate of insufficient antibody titers after single-day immunization with human diploid-cell-strain vaccine against rabies. *Klinische Wochenschrift*, 64:518–521.

Warrell MJ et al. (2008). A simplified 4-site economical intradermal post-exposure rabies vaccine regimen: a randomised controlled comparison with standard methods. *PLoS Neglected Tropical Diseases*, 2:e224.

WHO (2005). *WHO Expert Consultation on Rabies. First report*. Geneva, World Health Organization (WHO Technical Report Series, No. 931).

WHO (2007a). *Guidance for research on oral rabies vaccines and field application of OVD against rabies*. Geneva, World Health Organization.

WHO (2007b). Rabies vaccines: WHO position paper. *Weekly Epidemiological Record*, 82:425-435.

WHO (2009). *International travel and health*, Geneva, World Health Organization:125–132 (available at: http://www.who.int/ith/chapters/en/index.html).

Wilde H (2007). Failures of rabies post-exposure prophylaxis. *Vaccine*, 25:7605–7609.

Annex 1
Agenda

Note: Names of theme leaders are underlined.

Wednesday, 7 October 2009

14:00 – 14:10	**1.**	**Opening session** (Anastasia Pantelias/François Meslin)
	2.	**Prevention of human rabies** (*Chair:* R. Deray)
		A. Active immunization
14.10 – 16:30	**2.1**	**Shorter post-exposure prophylaxis (PEP) vaccine regimens**
14:15 – 14:40	2.1.1	Essen: 4 vs. 5 doses (C. Rupprecht)
14:40 – 15:05	2.1.2	The one-week four-site PEP regimen (P. Shantavasinkul)
	2.1.3	A four-site one-day ID PEP (P. Shantavasinkul)
15:05 – 15:30	**Coffee break**	
15:30 – 16:00	2.1.4	A four-site ID PEP regimen (Mary Warrell)
16.00 – 16-30	**Conclusions/recommendations on shorter PEP regimen**	
16:30 – 17:00	**2.2**	**Duration of immunity after vaccination** (Deborah Briggs)
17:00 – 17:30	**2.3**	**Do we need to state a vaccine potency by intradermal dose?** (Mary Warrell)
17:30 – 18:00	**2.4**	**Prevention of human rabies in vulnerable populations** (C. Rupprecht)
		B. Passive immunization
18:00 – 18:30	**2.5**	**Optimal usage of rabies immunoglobulin (RIG)** (David Anderson)
18.30 – 19. 00	**Conclusions/recommendations on booster doses and potency/ID dose/RIG usage**	
19.00 – 21:00	**Cocktail party**	

Thursday, 8 October 2009

09:00 – 10:00	**2.6**	**Preventive immunization of children** (Thiravat Hemachuda)
10:00 – 10:30	**2.7**	**Other advances in rabies biological products development and usage, including cost–effectiveness studies** (representatives of the pharmaceutical industry and other partners)
10:30 – 11:00	**Coffee break**	
11.00 – 12.30	**2.8**	**Reviewing and amending current WHO guidelines for rabies PEP and PreP** (all experts)

12:30 – 14:00	**Lunch break**	
14:00 – 17:00	**3.**	**Control and elimination of dog rabies** (*Chair:* A. Wandeler)
14.00 – 14. 30	**3.1**	**Designing the most cost effective package for sustainable dog rabies control** (Sarah Cleaveland)
14:30 – 15:00	**3.2**	**Including sterilization in addition to vaccination for rabies control** (E. Hiby)
5:00 – 15.30	**3.3**	**Role of oral vaccination of dogs (OVD) against rabies in dog rabies elimination** (François Meslin)
15.30 – 16:00	**Coffee break**	
16:00 – 17:00	**Conclusions/recommendations on control and elimination of dog rabies**	

Friday, 9 October 2009

09:00 – 12:30	**4.**	**Rabies research: topics for future research in human and dog rabies prevention and control**
09:00 – 09:30	**4.1**	**New vaccine ID delivery systems** (Darin Zehrung)
09:30 – 10:00	**4.2**	**New tools for dog population management** (Michael Royals)
10:00 – 10:30	**4.3**	**Current status of research on monoclonal antibodies (MAbs) for PEP** (M. Kieny)
10:30 – 11:00	**Coffee break**	
11:00 – 11:30	**4.4**	**Future rabies biologicals and other tools** (C. Rupprecht)
11:30 – 12: 30	**4.5**	**Conclusions and recommendations on research**
12:30 – 14:00	**Lunch break**	
14:00 – 16:00	**5.**	**Final conclusions and recommendations** (all experts)
1:.00 – 16:15	**6.**	**Closing session** (François Meslin)

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