Special Report

AREB Position paper on Draft recommendations issued from the WHO-Gates Consultation on Rabies, October 7-9, 2009, Annecy, France

Dr. Amlan Goswami, Consultant Physician, Kolkata.

The Asian Rabies Expert Bureau [AREB], established in 2004, is an informal network of rabies experts from nine countries: Bangladesh, China, India, Indonesia, Pakistan, the Philippines, Sri Lanka, Thailand, and Viet Nam. The network seeks to eliminate human deaths from rabies in Asia.

Many members of the AREB were participants of the WHO-Gates Consultation Meeting held at Annecy, in France, from 7th October 2009 to 9th October 2009.

I am a member of the AREB and participated in the meeting held at Manila in the Philippines from 9th November 2009 to 12th November2009. There was a lot of discussion on the WHO Expert Consultation meeting's Draft report available with us at that time. The AREB's position in this matter [Drafted after full consultation with all participants] is being presented in this report.

General Comments

AREB members suggest that the overall strategic intent of reviewing the current WHO guidelines be clearly stated as well as the rules for adoption of new recommendations and validation of results from new studies.

New vaccination regimens for post-exposure prophylaxis (PEP)

It would be useful to ensure that the same process for the validation of results from new studies is consistently followed for the approval of new vaccination regimens, so that the decision of whether or not to approve a schedule is made in a consistent manner.

AREB members emphasize the need for clear, simplified post-exposure prophylaxis (PEP) protocols - ideally no more than two intramuscular (IM) and two intradermal (ID) regimens. Adding new PEP regimens increases the complexity of treatment, even though it can also be considered as improving its flexibility for the adaptation of PEP to various situations. More precise indications on the "gold standard" of WHO recommendations for PEP are required, as well as a flow chart with a decision-making tree, in order to help determine the most reliable PEP for different circumstances.

Strategies for rabies control

Concerning strategies for rabies control and elimination, AREB members expect the final guidelines to include comprehensive recommendations on best options. It is the responsibility of national authorities to make their own decisions according to the available resources and their national strategies and health priorities. Strong recommendations from WHO on the best rabies control strategies (independent of considerations of cost) are necessary in order to obtain financial support from national and international funding agencies for rabies control strategy implementation.

Comments Concerning Specific Items

Agenda item 2.1.1: Shorten Essen 4 doses instead of 5

In <u>healthy</u> exposed persons who receive wound care, RIG and WHO pre-qualified 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

<u>AREB comments</u>

- AREB members mentioned that an IM PEP protocol with four doses and only 3 visits (Zagreb regimen), has already been recommended by WHO and has been extensively used with success in several rabies endemic countries.
- It was underlined that the abbreviated Essen protocol should only apply to "healthy" subjects exposed to rabies. The term "healthy" should be better defined: does it mean "with a healthy immune system"? In Asia, in most exposed populations, many people may consider

themselves as healthy, while their immune system may be compromised further to malnutrition, HIV infection, or ongoing anti-malaria treatment. Since PEP is always administered in emergency situations, it is difficult to quickly define the immune status of the patient.

- Consequently, AREB members would like to propose a slightly modified wording:
- The shortened 4-dose Essen regimen is an alternative to the standard 5-dose Essen regimen, when and only when the state of health of the patient is such that it allows for an appropriate immune response, wound care is executed according to WHO recommendations, rabies immunoglobulin with documented efficacy and quality is used, and the immunization is conducted using a WHO-approved rabies vaccine.

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

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 providing another "4-4-4" study fulfilling WHO criteria* (*see below) conducted in a different country confirms these results.

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.

AREB comments

- According to the note (* - Additional agenda item: Additional recommendation for new studies), it is not quite clear whether *a single independent, statistically sound study showing safety and immunogenicity, carried out under GCP conditions and published in a peer-reviewed journal* is enough, or a second independent study is necessary.
- AREB members recognize the value of a 4-site one-week PEP regimen requiring only three visits to the rabies prevention center. Reducing the number of clinic visits would not only reduce costs for the patient but may also help increase patient compliance with complete PEP.
- AREB members look forward to reviewing the results of the confirmatory study, which is scheduled to be conducted in Pakistan, before this new PEP regimen is recommended.

Agenda item 2.1.3: Providing PEP booster in one day using 4 site ID:

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.

AREB comments

- This PEP booster protocol (one day, four sites) has been used for 10 years in Thailand. It was first published by Prof. Terapong Tantawichien four years ago; the study included over 5,000 patients who had one year follow-up. According to Prof. Thiravat Hemachudha, even one 2-site booster vaccination was shown to be enough to produce an anamnestic immune response. Nevertheless, four injections are preferable in order to guarantee an appropriate boosting effect.
- AREB members from India noted that, in India, they follow the WHO recommended protocol (two visits, on Day 0 and Day 3) for booster vaccination, and feel comfortable with this protocol.
- It was noted that no consensus was obtained within AREB on which protocol would be preferable.

Agenda item 2.1.4: the 4 site intradermal PEP 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.

AREB comments

- AREB members mentioned that several points with respect to this new PEP regimen have to be

clarified, and queried especially under what evidence this new protocol was recommended.

- It is not clear why the 8-site regimen should be "deleted". Does it mean that this regimen was not safe and efficacious? Or that is should be replaced by a simpler and more economic regimen?
- It was also noted that this new recommended regimen dramatically differs from the schedule that was initially studied and published, which also included one 0.1 mL dose at day 90.
- AREB members wonder whether an additional study was published or a different rule was applied for the 'one-week' PEP regimen (2.1.2.) and the 4-site PEP regimen.

Agenda item 2.2 Duration of immunity after vaccination:

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.

AREB comments

- AREB members agreed that the evidence showed that post-vaccination immunity is long-lasting.
- AREB members wondered whether a patient exposed to rabies, who recently received a complete series of PrEP or PEP, should receive additional booster vaccination. In Sri Lanka, a booster dose is administered when exposure to a rabid animal occurs more than six months after completion of the rabies vaccination course.
- It was, however, suggested that if there will be a 'cut-off' the decision should be based on common sense and serological analysis should be performed.
- AREB members agreed that a recommendation should be given regarding the length of interval after completion of vaccination for which a booster dose is necessary in case of rabies exposure.
- AREB members wondered whether a booster was sufficient if the patient had previously received an *incomplete* PEP (stopped because the biting dog was found to be healthy) - e.g., only 2-2-2 ID doses on days D0, D3, D7, while the updated 2-site TCR regimen requires an additional ID vaccination on day 28.

Agenda item 2.3: do we need to state a vaccine potency by intradermal dose:

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 DCVRN has been asked for their advice.**

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

[[**DCVRN is the Developing Countries Vaccine Regulator's Network – Note added by AREB]]

AREB comments

- The text in brackets : **(safety, immunogenicity, and safety studies)** should read **(safety, immunogenicity, and efficacy studies)**
- AREB members agreed that recommendations concerning this item need to be clarified. They reiterate their concern that the ID dose should be pharmaceutically defined by its potency (antigen load, IU) and not by volume, in order to define, as for any other vaccine, the minimum quantity of antigen to be injected into the patient to induce an adequate immune response.
- Although there may not currently be enough potency data, AREB members would like to know what additional data WHO would require to consider establishing an appropriate potency per ID dose.
- AREB members from Thailand, Sri Lanka and the Philippines reported that a minimum potency per ID dose was defined in their respective countries and that this regulation was effective and followed by vaccine producers, confirming its feasibility. They stress the necessity of ensuring that each patient receives the same minimum amount of antigen, independent of the brand of rabies vaccine used.
- Understanding that this issue relates more to standardization and pharmaceutical considerations than to clinical observations, AREB members request that the WHO Department of Immunization, Vaccines and Biologicals as well as Biologicals Standardization Committee directly address this issue.

Agenda item 2.6 Recommendation for PrEP for Children

...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.

AREB comments

- AREB members acknowledge that several studies and demonstration projects have shown the efficacy and feasibility of pre-exposure rabies vaccination in infants and school children, and consider that these data are sufficient for recommending PrEP in children living in areas where rabies is highly endemic.
- AREB members wonder what new data and demonstration project(s) are necessary to provide additional evidence that pre-exposure vaccination is an important part of any rabies control program and should be strongly recommended for children living in highly endemic areas.
- Considering that pre-exposure vaccination is recommended to travelers to endemic areas, this cannot be denied to children living in these areas, who obviously are at much higher risk than travelers.
- PrEP should not be introduced only after a dog rabies control has failed, but it should be introduced without delay in highly endemic areas, together with dog rabies control and reinforcement of PEP. These various options should not be used alternatively or be exclusive of each other.
- AREB members recognize that the cost and operational hurdles of such approaches represents a challenge for countries with limited resources. It is particularly important for WHO to make strong recommendations on rabies PrEP in children so that countries can raise funds from national and international funding agencies for PrEP implementation.