

## Special Report

# Report of the Sixth AREB Meeting, November 2009, at Manila, Philippines

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The Asian Rabies Expert Bureau (AREB) is an informal network of experts in rabies. The members are from nine Asian countries, Bangladesh, China, India, Indonesia, Pakistan, Philippines, Sri Lanka, Thailand, and Viet Nam. The first meeting of the AREB was held at Cebu in the Philippines in June 2004. The second meeting of the AREB was held at Shanghai, in the Peoples Republic of China, in July 2005. The third meeting of the Asian Rabies Expert Bureau (AREB) was held at New Delhi in India in September 2006. The 4<sup>th</sup> meeting was held at Bangkok in Thailand, in September 2007. The 5<sup>th</sup> meeting of the AREB was held at Ho Chi Minh City in Vietnam, in November, 2008. The 6<sup>th</sup> meeting of the AREB was held at Manila, in November 2009.

AREB has met annually since 2004 to compile the projects driven during the year and challenge points of view and discuss their experiences with the aim of (a) Improving clinical practice and finding solutions adapted to the Asian situation and context; (b) Defining appropriate responses to the rabies issue in their respective countries, including quality requirements for clinical practice and biologicals; (c) Defining best clinical management practices in local situations; (d) Improving rabies awareness in their respective countries and in Asia; (e) Improving health education on rabies so that patients seek appropriate medical care immediately. (f) Improving access to quality treatments.

## Abstract

At the sixth annual meeting of the Asian Rabies Expert Bureau (AREB) held at Manila, in the Philippines, the AREB reviewed the implementation of programs for rabies prevention, control, and elimination in Asia. They strongly supported the "one health" approach, combining increased public awareness, community involvement, pre-exposure prophylaxis (PrEP) programs in children living in endemic areas, improved dog bite management and access to post-exposure prophylaxis (PEP) for humans, as well as extended dog vaccination. They called for stronger PrEP recommendations for children and clear (non ambiguous), simplified PEP regimens including modern WHO pre-qualified vaccines and, in case of category III exposures, the use of rabies immunoglobulin (RIG) or possibly monoclonal antibody combinations in the future. They renewed their support to the World Rabies Day, one of the best opportunities to increase advocacy for rabies control.

**Keywords:** rabies, prophylaxis, PrEP, PEP, rabies immunoglobulin, monoclonal antibody, rabies control programs, World Rabies Day

## Introduction

Every year, rabies kills an estimated 55,000 people worldwide, the majority (57%) of deaths occur in Asia [1]. In 2009, the Philippines was selected as the host country for the 6<sup>th</sup> meeting of the Asian Rabies Expert Bureau (AREB), which was held in Manila from 9<sup>th</sup> to 12<sup>th</sup> November, 2009.

Since its creation in 2004, AREB has met annually to review recent progress in human rabies prevention, explore new alternative strategies and methods for reducing the rabies burden, establish common initiatives, and advocate for rabies control in Asia [2-5]. In 2008, AREB published the results of an epidemiological survey that included more than 4,300 subjects in eight Asian countries, and confirmed the urgent need to increase rabies awareness in the populations exposed to the risk of rabies [6]. Currently, AREB has gained an international recognition, and was invited to participate in the Partners for Rabies Prevention Group, and to other major international meetings (the 2<sup>nd</sup> Rabies in Asia conference – RIACON

2009, Hanoi, Viet Nam, September 9-11, 2009 and the 20<sup>th</sup> International Conference on Rabies in the Americas – RITA, Quebec, Canada, October 19-23, 2009), to present its achievements. AREB has also been invited to participate in various working groups.

### 1. The Philippines at the forefront of the fight against rabies

With 250 human rabies deaths reported in 2008, rabies is considered a serious health problem in the Philippines. At least one-third of these deaths occurred in children under 15 years of age. Most cases are transmitted by dogs; 190,000 animal bites were reported to the National Center for Disease Prevention and Control (NCDPC) in 2008, 50% of which involved children.

One highlight of the Manila meeting was the enthusiastic acknowledgment of the commitment made by the Philippines government to support rabies control efforts. Dr Yolanda Oliveros, Director IV, NCDPC, Department of Health (DOH), stressed that the country strengthened its National Rabies Prevention and

Control Program by enacting it into law in 2007, with the aim of eliminating rabies by 2020, and that several pilot projects had already been initiated.

The recent launch of a project for a rabies-free Visayas, one of the three island groups in the Philippines, with a population in excess of 17 million (19% of the Philippine population) was discussed. Almost one-third of the total cases of human rabies in the Philippines occur in this region. The project, coordinated by WHO and funded by the Bill & Melinda Gates Foundation, is conducted by the Department of Health, the Department of Agriculture and the local governmental units working in collaboration. **It aims to prevent human rabies through the control and eventual elimination of canine rabies.** The strategy is based on community participation and relies on increasing dog vaccination coverage while concomitantly optimizing management of humans exposed to rabies. It also includes promotion of local community involvement, 'responsible pet ownership' and increased education on how to prevent rabies.

In Bohol (one of the Visayas Islands, with a total population of 1.4 million), the Rabies Prevention and Eradication Program is already in progress. This four-year project (2007-2010) is supported by the national government and the Bohol Provincial Government, the Alliance for Rabies Control and a private Swiss foundation. It was the first to utilize a "one health approach" to prevent and control rabies in the Philippines. A survey of the progress indicated that rabies has been successfully included in the elementary school curriculum; 71% of the dogs have been vaccinated; and 85% of the households are aware of activities related to dog rabies control. As a result of the program, no human rabies case has been reported on Bohol in 2009, whereas approximately 10 human deaths were reported annually before implementation of the program.

## **2. Pre-exposure vaccination for children living in areas of endemic dog rabies**

The main reasons why there is a higher burden of rabies in children, lies with their habit of playing outdoors, where they become particularly vulnerable to dog bites due to their close proximity with the animals and also because they exhibit provocative behavior towards the dogs and cats. Children are less intimidating to animals, due to their smaller size than the adults, and they are less able to defend them-

selves or escape when attacked. As a result, they are more prone to facial attacks and multiple bites on the head and neck regions, the most severe type of exposure with the shortest of incubation periods taken to develop rabies. Additionally, children are less likely to report animal exposures, such as licks or scratches from dogs and cats, to their parents.

Vaccination for pre-exposure prophylaxis (PrEP) of children living in areas where dog rabies is enzootic can help prevent a fatal outcome by protecting them against unreported exposures to rabies virus, and from post-exposure prophylaxis (PEP) failures due to delayed or incomplete PEP. In the case of an exposure to rabies, only two additional doses of rabies vaccine are necessary to boost the immune memory in individuals who previously received a complete pre- or post-exposure immunization course. Importantly, no rabies immunoglobulin administration is required in persons who have received PrEP.

A rabies PrEP pilot program for school children is currently under way in the province of Camarines Sur, in the Philippines. The program was initiated in the municipality of Cabusao, where the incidence of dog bites and rabies deaths in children is high. The program, which is part of the Philippines National Rabies Elimination Plan, includes education on rabies prevention during elementary school curriculum, dog vaccination, and improved access to PEP, in addition to PrEP of school children. Three years after its implementation, the success of the project is evidenced by the fact that 77% of dogs have been vaccinated and no human rabies deaths have been recorded in Cabusao in 2009. The program is being expanded to the adjacent municipalities.

AREB members agreed that the program currently implemented in Camarines Sur, in addition to the published results of the clinical trials conducted in Thailand [7] and in India [8] demonstrates that PrEP rabies vaccination of school children is safe, feasible and brings significant benefit to the community, preventing deaths in children which are avoidable. They strongly recommend PrEP for children living in areas where canine rabies is enzootic. Protecting these children through vaccination should be considered as a public health duty. Rabies PrEP is widely recommended for travellers staying only for a limited time in rabies endemic areas; the same level of protection, must be applied to children who live in canine rabies endemic areas and are at higher and constant risk.

AREB proposed to support a new comprehensive demonstration project of PrEP vaccination of school children, to be implemented in The Philippines in early 2010. The expected outcome is:

- To complement the clinical experience and confirm the feasibility of pre-exposure strategy,
- To confirm the efficacy of such programs in areas where dog rabies has not been eliminated,
- To advocate for similar policies thus lowering the burden of human rabies.

This project aims at complementing the current experience, confirming the feasibility of the PrEP strategy and evaluating its efficacy of PrEP in preventing rabies in children living in areas where dog rabies has not been eliminated.

Administration of PrEP to infants is an alternative approach to vaccinating school age children and has the advantage of protecting children at an earlier age. Clinical trials conducted in Thailand [9] and in Viet Nam [10,11] have shown that rabies vaccine can be administered at the same time as routine pediatric vaccines, e.g.; the Japanese encephalitis vaccine [9], or the combination vaccine against diphtheria, tetanus, pertussis, and poliomyelitis (DTP-IPV) [10,11]. Its integration into the Expanded Program of Immunization (EPI) would facilitate access to the targeted population and minimize operational costs. AREB members thus recommended that demonstration projects should be conducted to evaluate the feasibility of introducing rabies vaccination into the EPI in countries where the risk of rabies is high.

**PrEP implementation is not intended to eliminate the need for management of rabies exposure, nor compromise vaccine availability for PEP. PrEP programs must be coupled with complementary strategies aiming at increasing dog vaccination coverage, raising public awareness and education, and increasing access and compliance to PEP.**

In Thailand, where the number of rabies deaths decreased from 200-300 in the early 1980s to less than 20 annually nowadays, due to outstanding management of dog bite victims and use of modern cell-culture vaccines. However, the disease is not yet controlled in dogs [12]; as 500,000 bite victims still required rabies PEP in 2008. Consequently, large-scale

pre-exposure immunization of children has been advocated to further reduce the number of rabies deaths that occur mainly in children but financial barriers have hindered its implementation until now. Cost-effectiveness studies have shown that childhood immunization programs increase the total annual expense of immunization (PrEP and PEP), but the cost gradually decreases, and in the long term would be equal to that of PEP without childhood immunization [13]. Another cost analysis showed that the total expense would reach a balance after 15 years and that the time required to reach the breaking point can be shortened proportionally to the success of the dog population control.

AREB members agreed that cost-effectiveness studies as well as studies on the real burden of rabies on public health could be helpful for decision making with respect to PrEP introduction. They request WHO to strongly recommend PrEP vaccination for children living in areas where dog rabies is enzootic as this would support the effort of the affected countries in raising funds from national and international organizations for PrEP implementation.

### **3. Monoclonal antibodies as a solution to the poor accessibility of rabies immunoglobulin**

Administration of rabies immunoglobulin (RIG) is necessary for the success of PEP in cases of severe exposure (WHO category III [14]). Passive immunization using RIG provides immediate protection until the immune system can develop its own rabies virus neutralizing antibodies in response to vaccination. Nevertheless, RIG is dramatically underutilized in rabies endemic areas. This is mainly due to the fact that highly purified RIGs, prepared from human or equine serum, are in short supply and not always accessible in Asian countries. In addition, equine RIGs are often considered as 'unsafe' due to the commercialization of poorly purified or under-potent products produced locally. This creates a lack of trust from health professionals and patients even to the most modern highly purified equine RIG. Finally, RIG is also considered by some sectors as a non compulsory step of PEP (just "nice to have") due to the lack of education across all sectors of society. Data on vaccine and RIG sales in the AREB region indicates that RIGs are used in 2-10 % of the PEP, while it is estimated that 48% of rabies exposures were identified as category III in the survey completed by AREB [15].

The development of monoclonal antibodies (mAbs) may bring a solution to the RIG accessibility. AREB members discussed the combination of two human mAbs with rabies virus neutralizing activity, developed by Crucell and Sanofi Pasteur. The definitive added value of combining two antibodies is their ability to bind to two distinct epitopes on the rabies virus glycoprotein, providing a good coverage of natural rabies isolates, which may not be achieved when using a single mAb. Phase I clinical trials conducted in the USA and in India showed that the mAbs combination is safe and well tolerated when given alone or in association with rabies vaccine. Its neutralizing activity was comparable to human rabies immunoglobulin (HRIG), currently considered as the gold standard [16].

Two phase II clinical trials have been performed with these mAbs: one study in healthy adults in the USA, and another among a healthy paediatric population in the Philippines, confirming that this mAbs combination is safe and well tolerated. All participants in the studies, who were given the antibody combination, reached adequate levels of anti-rabies neutralizing activity, similar to those observed in subjects given HRIG.

AREB recognized that rabies mAbs can bring a change in the PEP for category III exposures in Asia. Since they can be produced in large quantities, they would be more largely accessible in endemic areas. **Rabies mAbs could even fully replace currently available RIGs, if their safety, immunogenicity and efficacy are established in phase III studies and if their activity against circulating rabies strains is confirmed.**

#### 4. The evolving situation in Asia

AREB acknowledged and supported the resolution to eliminate rabies by 2016 adopted by Sri Lanka, and that of the Asean plus three countries and India to eliminate rabies by 2020.

**Some Asian countries, however, have not yet adopted rabies control policies and sheep brain vaccine is still produced and/or used in Bangladesh, Pakistan and Myanmar.**

**Areas having Rabies occurrences has expanded in size, in some regions, e.g. in Bali, in Indonesia, formerly a rabies free island, where it has claimed more than 20 human lives since its introduction in 2008.**

The situation in China was presented during the AREB meeting. In this country, the number of reported human rabies cases had declined annually between 1990 and 1996, with the lowest number of cases reported in 1996 ( $n = 159$ ). Since 1997, however, the fatality rate has increased exponentially with a peak of 3,300 notified human rabies deaths in 2007. With an estimated 80-200 million dogs living in China [17], and 85-95% of human rabies cases were ascribed to dog bites, the domestic dog plays a pivotal role in rabies transmission. Human cases are reported in all provinces of China, except Qinghai, with most cases in southern China, where the human-to-dog ratio is substantially greater than in the rest of the country. A well established internet-based national reporting system is in place for notifiable diseases, including rabies and a sentinel surveillance system was established for rabies in 2005. An investigation conducted recently by the China Center for Disease Control and Prevention showed that only 32% of victims of a category III animal bite receive adequate wound treatment and 31% are compliant with the full course of vaccination, presumably because of a lack of awareness. Recently, the Ministry of Health revised the national criteria for human rabies diagnosis and the national guidelines for rabies PEP, involving additional official entities in the National Rabies Control Program.

#### 5. Practical guidelines

Reviewing the studies and proposals for new vaccination regimens, AREB members emphasized the need for clear, simplified PEP protocols - ideally no more than two IM and two ID regimens. Adding new PEP schedules increases the complexity of patient management, although this can also be considered as improving flexibility for the adaptation of PEP to specific situations. More precise indications on the "gold standard" of WHO recommendations and a flow-chart with a decision-making tree are needed in order to help choose the most reliable PEP for particular circumstances. AREB members acknowledged the promising results of a new intradermal (ID) PEP regimen, "one week, 4-site", developed by the Thai Red Cross and the Queen Saovabha Memorial Hospital in Bangkok, Thailand, that can be completed within one week (4-site ID injections on days 0, 3, and 7). With this protocol, the geometric mean titre of rabies neutralizing antibodies on days 14 and 28 was significantly higher than with the WHO approved and widely used updated Thai Red Cross (TRC) regimen (2-site ID injections on each days 0, 3 and 7,

and 28). AREB members recognized that **reducing the number of clinic visits and shortening the time to complete the PEP vaccine schedule would not only reduce costs for the patient but may also help increase compliance with the complete course of PEP.**

AREB members stressed, however, the necessity to ensure that each patient receives the minimum amount of antigen necessary for inducing an immune response, independently of the rabies vaccine used and the volume of solvent used to reconstitute it, as is the case for any other currently used vaccine. They thus consider that **the ID dose must be pharmaceutically defined by its potency (IU/ID dose), and not only by a volume, which is currently the recommendation in international guidelines.** This requires defining a standardized and reproducible measure of this potency, as recommended by biological standardization committees. AREB members from Thailand, Sri Lanka and the Philippines reported that a minimum potency per ID dose is defined in their respective countries, and that this regulation is effectively implemented and followed by vaccine producers, thus confirming its feasibility

## 6. World Rabies Day

Before ending the meeting, AREB members renewed their support to the World Rabies Day. Held on September 28<sup>th</sup> each year, this initiative aims to strengthen rabies public awareness, prevention and control and mobilize resources for carrying out these activities. In 2009, events were reported for World Rabies Day in 105 countries, and over 200 countries visited the related website to download educational information. This worldwide event is the best opportunity to advocate for rabies control. In Pakistan, World Rabies Day was used in 2007 and 2008 to raise rabies awareness among the general public. This year, the focus was put on health care givers with the theme "Managing dog bites the right way saves lives" Thanks to these efforts, rabies surveillance has begun in Pakistan, and an increasing number of rabies centers are using modern cell-culture vaccines. Similar actions can be observed all around the world, making realistic the objective to reach a "rabies free world" [18,19].

## Acknowledgements

The Asian Rabies Expert Bureau (AREB), an informal network of experts in rabies from Asian countries, acknowledges the support of Sanofi Pasteur in its activities.

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## Association for Prevention & Control of Rabies in India (APCRI)

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

### Goal: Rabies Free India by 2020.

#### Activities till date

1. **Annual Conferences** on 6th July (World Zoonosis Day) or near about (On Saturday and Sunday only): Kolkata (1999), Bangalore (2000), Amritsar (2001), Jaipur (2002), Bhubaneswar (2003), Kolkata (2004), Shimla (2005), Jammu (2006), Hyderabad (2007), Lucknow (2008), Thiruvananthapuram (2009) and New Delhi (2010).
2. **Workshops, Seminars & Training Programmes:**
  - \* National workshop for APCRI trainers in modern WHO approved rabies prophylaxis at NIMHANS, Bangalore (2001).
  - \* National seminar on "Intradermal Rabies Vaccination", KIMS, Bangalore (2003).
  - \* National workshop on "Developing guidelines for Rabies Prophylaxis" at Hyderabad (2006).
  - \* National workshop on "Rabies Prophylaxis" at Alleppey, Kerala (2006).
  - \* National workshop on "Rabies Immunoglobulin (RIG) Administration" at KIMS, Bangalore (2008).
  - \* National Seminar on Rabies Vaccines: Important Issues, at Visakhapatnam (Vizag), Andhra Pradesh (1st March, 2009).
  - \* National Workshop on Development of IEC Material on Prevention of Rabies for School Children and Public at Mysore, Karnataka ( 20th & 21st March, 2010).
3. **Publications** : APCRI Journal (Biannual) & APCRI News Letter (Biannual).
4. **Research** : WHO sponsored "National multicentric Indian rabies survey" (2004).
5. **Award** : APCRI was honoured with "Chiron vaccines award 2000" for its contribution to prevention & control of Rabies in India.
6. APCRI in association with Indian Academy of Paediatrics (IAP) and Rabies in Asia (RIA) Foundation, formulated the IAP Guidelines for Rabies Prophylaxis in Children (2008)
7. Slides on "Rabies Prophylaxis – Current concepts & Recommendations" prepared by an expert consultation (2001), Revised in 2006 & now available on [www.apcri.org](http://www.apcri.org)
8. Observed "World Rabies Day" in 8th September, 2007, 28th September 2008 and 28th September, 2009 all over the country.
9. WHO-APCRI survey on Post Exposure Prophylaxis modalities in India (2007).
10. APCRI is regularly organizing Zonal/ Regional conferences & CME programmes.
11. APCRI played a major role in implementation of Intradermal Rabies Vaccination (IDRV) in the country.
12. Manual on Rabies Immunoglobulin (RIG) Administration published in February, 2009.

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