

## Special Report

# Report of the Eighth AREB Meeting, 5th to 7th December 2011 held at Pattaya in Thailand

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The Eighth Annual Meeting of the Asian Rabies Expert Bureau [AREB] meeting took place at Pattaya, in Thailand from 5<sup>th</sup> December, 2011 to 7<sup>th</sup> December, 2011. Initially, it was planned to be held at Bangkok on from 7<sup>th</sup> November, 2011 to 11<sup>th</sup> November, 2011. The meeting was postponed due to the floods that threatened Bangkok.

**The Asian Rabies Expert Bureau (AREB), was founded in 2004.** It is an informal network of rabies experts from 12 countries: Bangladesh, Cambodia, China, India, Indonesia, Lao PDR, Myanmar, Pakistan, Philippines, Sri Lanka, Thailand, and Viet Nam. AREB is committed to contribute to rabies elimination in Asia. AREB members meet annually to present and discuss the rabies situation in their respective countries, share experiences, and address specific problems encountered in clinical practice, and find practical solutions.

**The delegates from India were, Dr. M. K. Sudarshan** from Bangalore, **Dr. Amlan Goswami** from Kolkata, **Dr. B. J. Mahendra** from Mandya, **Dr. Gadey Sampath** from Hyderabad and **Dr. Thomas Mathew** from Thiruvananthapuram.

The meeting aimed at reviewing the current rabies situation in Asia, presenting and discussing ongoing projects in rabies prevention, and exchanging updates on the development of new rabies immunobiologicals and vaccination schedules.

Rabies is still prevalent in Asia, and since it remains largely underreported the disease burden has been underestimated. In 2005, annual human mortality due to rabies was estimated at 30 000 deaths in Asia, and 55 000 worldwide<sup>1</sup>. To get a more accurate picture of the impact of rabies, a survey was launched in 2009 by the Global Alliance for Rabies Control (GARC) and the Partners for Rabies Prevention

(PRP), with the participation of AREB. Preliminary results suggest that the global rabies death toll is actually around 70000 annually. The cost is estimated at an annual US\$4 billion, with \$500 million spent on post-exposure prophylaxis (PEP), \$160 million on dog vaccination, and \$800 million on livestock losses<sup>2</sup>.

AREB participants also reviewed some of the new studies, pilot projects and developments in rabies prevention around the world. A second global survey has recently been launched by GARC to map rabies notification status in public health systems; it started through the different Rabies Expert Bureau networks [e.g. AREB, AfroREB, MEERAB], and has now been extended to other global networks. It aims at identifying existing gaps and evaluating options in order to improve rabies notification.

## Pilot projects update

In the **francophone African region**, new dog bite management centers are being established outside the capital cities, in high rabies risk areas, in order to improve access of the population to PEP at reduced cost. The project is the fruit of collaboration between AfroREB members, municipalities and local health care authorities, with the support of Sanofi Pasteur. AfroREB members actively participate in defining new potential center locations and organizing training sessions for the personnel of newly created centers.

In **Latin America**, in most urbanized areas human rabies is close to being eliminated owing to the vaccination of domestic dogs and the implementation of other control measures<sup>3</sup>. Key to the success of campaigns in Latin America has been the central role played by the public health sector as a lead agency and community/ involvement/ empowerment in rabies control activities<sup>4</sup>. From

2004, a new predominant mode of human rabies transmission began to emerge in Latin America,

rabies prevention before and after the intervention. A record of the incidence of dog bites in participating children is being kept in order to verify how effective education is in protecting children from exposure to rabies. Midwives, village health workers and teachers are involved in data collection on rabies exposure, since they are well known to the community and are aware of the need for urgent medical attention in case of an animal bite.

In **India**, the **Adopt a Village project**, supported by GARC, the Rabies in Asia (RIA) Foundation and the Commonwealth Veterinary Association, aims to reduce the incidence of human and animal rabies through improved educational awareness and mass vaccination of dogs. It integrates for the first time both medical and veterinary actions under one umbrella for rabies prevention and control, and involves six villages (3 study and 3 control villages) outside of the city of Bangalore. Women from the community have been identified as contacts in case of dog/animal bites. They provide guidance to bite victims, take responsibility for ensuring the completion of vaccination, and participate in data collection in order to evaluate the impact of this initiative on the incidence of animal bites.

### Official recognition of rabies

In 2007, countries of the **ASEAN Plus Three** [Brunei, Cambodia, Indonesia, Laos, Malaysia, Myanmar, Philippines, Singapore, Thailand, Vietnam, plus China, Japan and South Korea] recognized rabies as a priority disease, and took the resolution to eliminate rabies by 2020. **Bangladesh** has now taken the same resolution, and **Sri Lanka** has committed itself to eliminating rabies by 2018

**Malaysia, Japan, Brunei** and **Singapore** are already rabies free, but they spend large amounts of money to prevent introduction of rabies from rabies endemic countries.

### Country profiles

In **Thailand**, human rabies incidence has dramatically decreased from 185 cases in 1995 to less than 20 annually (15 cases in 2010), mainly thanks to improved rabies awareness among the general population and healthcare professionals resulting in better management of exposures with quality PEP. However, rabies is still present in several provinces,

including Bangkok.

Rabies control programs generally include increasing public awareness and access to PEP (which is free of charge in governmental clinics), dog immunization, reduction and control of stray dogs, and establishment and enforcement of legislation on dogs. They are based on inter-sectoral collaboration and community participation. Areas are classified into three different levels based on their rabies status:

1. **Level A** areas, where no human or animal rabies deaths have been observed for 2 years. Rabies free areas are Level A areas that benefit from a strong rabies surveillance system.
2. **Level B** areas, where only cases of animal rabies have been reported (classified as risk areas).
3. **Level C** areas, where human and animal rabies cases have been recently reported (considered as high risk areas).

In Thailand, as of end 2011, 32 provinces are classified Level A, 32 provinces are Level B and 12 are Level C. Since rabies is mainly transmitted by dogs, future efforts concentrate on dog vaccination and control and reduction of the stray dog population, eventually through legislation and law enforcement.

Thailand's strategy for rabies elimination is adapted according to the status of the area and comprises 5 steps: 1) Strengthening collaboration between the regional centers of the Department of Disease Control (DDC) and the Department of Livestock Development (DLD); 2) Increasing resources at different levels of the Health and Livestock administration and other local authorities; 3) Increasing surveillance, prevention and control activities of the Ministries of Public Health and Agriculture; 4) Increasing community participation in the establishment and implementation of road maps for rabies elimination; and 5) Increasing public awareness of rabies prevention and control.

**China** has also intensified its rabies control programs. In 2005, the Chinese Ministry of Health (MOH) and the Chinese CDC established national guidelines for rabies PEP (published in 2006 and revised in 2009). More recently, a national plan to eliminate rabies by 2020 based on a One Health approach was adopted. It includes strengthening dog management and vaccination, popularizing

knowledge on rabies prevention and strengthening PEP availability - especially in the countryside.

**Rabies notification is mandatory** through the National Notifiable Infectious Diseases Reporting Information System (NIDRIS); 15 counties and 6 endemic provinces are now covered by a sentinel surveillance system. Investigation of reported cases is carried out (clinical information, exposure and PEP history) with laboratory testing and PEP monitoring, and collection of information on the reservoir. Every year, 12-15 million doses of rabies vaccine are dispensed.

In 2010, 2048 rabies cases were reported in China. This represents a 38% decrease compared to 3300 recorded cases in 2007. Rabies was reported from 23 provinces, mainly from southern China. Most cases (90%) were caused by dog bites and occurred in remote rural areas in the South. Lack of awareness and limited access to PEP are the main reasons why people, especially those in remote rural areas, often do not take any prophylactic measures against rabies after a dog bite. No wound treatment was applied to 75% of the rabies cases notified in 2010; 92% of patients did not receive timely and appropriate vaccination and 98% did not receive rabies immunoglobulin.

The number of dogs has been increasing in rural areas; 70% of households have one or more dogs in Guangxi, Guizhou, Jiangsu and Hunan, where rabies incidence is high. In 2010, the dog population was estimated at 75 to 100 million, and the dog:human ratio at 12.25:100 with dog vaccine coverage at 33%. Vaccination coverage is generally higher in cities (40-90%), while it may be as low as 3% in rural areas where rabies is endemic (and where households often have 1-4 dogs).

Rabies is endemic in 24 out of 33 provinces of **Indonesia**. In 2010, 216 rabies cases were officially notified, with 116 between January and November 2011. And dog rabies continues to spread and gain new Indonesian territories.

**Bali**, is a small, beautiful island of Indonesia (population: 3 479 800 plus over 1.6 million visitors per year), it is of great importance for tourists, was historically free of rabies. Rabies was introduced in 2008 through the import of an unvaccinated rabid dog. The initial rabies outbreak occurred in a remote village at the end of an isolated peninsula. However,

due to the lack of rabies awareness of the population and health authorities, and a lack of surveillance both in the human and animal sectors, several months elapsed before the outbreak was officially recognized and even then measures were not taken on time. Bali officials relied on exterminating dogs as their primary control strategy, dog vaccination started late, not enough dogs were vaccinated to keep the outbreak confined, and the vaccines used were of unreliable potency. Exposed people were unaware of primary wound care as well as the need for PEP and the need to vaccinate pets. Vaccines were often not available or not affordable and rabies immunoglobulin was lacking.

As on November 27, 2011, a total of 135 human rabies deaths have been reported officially in Bali: 4 in 2008, 28 in 2009, 82 in 2010, and 21 in 2011. Since the introduction of rabies in Bali through September 2011, 123 856 people have been bitten and 109 932 have received PEP. In 2011, 49 458 people were bitten and 46 675 were vaccinated.

Now, thanks to the establishment of 28 rabies prevention centers, improved vaccine availability and a large education program, dog bite victims seek treatment more frequently. The number of new human rabies cases is decreasing.

Several other Indonesian islands that were historically free of rabies have, like Bali, lost their rabies-free status. For example in Flores and Ambon (where rabies was introduced in 1997 and 2003, respectively) animal rabies is still endemic and human deaths continue to occur.

It is estimated that about 800 people die from rabies annually in **Cambodia**, for a population of 14 million<sup>8</sup>. As part of the ASEAN, Cambodia has also taken the resolution to eliminate rabies.

However, Cambodia has the highest dog : human ratio in the region (1 dog:3.1 humans), there is still no national rabies control program and the little available data on rabies stem from Institut Pasteur du Cambodge (IPC) in Phnom Penh, the only specialized centre/facility involved in rabies prevention. The IPC provided PEP free of charge from 1996 to August 2010, when it switched to a cost-recovery scheme. Few private practices deliver cell culture rabies vaccines, and those that are available are sold at a prohibitive cost (up to US\$800).

The IPC National Reference Center Laboratory is the only laboratory facility in the country for rabies diagnosis in humans and animals. According to the estimates, PEP administration at the IPC has probably prevented about 1000 rabies deaths between 1998 and 2007. Between 2000 and 2010, 168 980 bite victims (median age 15 years), mostly from the Phnom Penh province, visited the IPC for PEP. Almost 20% of these cases came with deep bites. In 2010, more than 22 000 bite victims were referred to the IPC, and 12 clinical cases were referred to the nearby hospital. Out of 322 animals examined at the IPC laboratory, 137 (42.5%) were positive for rabies (by immunofluorescence assay). Preliminary data for 2011 are comparable.

**Myanmar** has not yet established a national rabies prevention and control program, and rabies is not a notifiable disease in this country. In 2010, 205 rabies cases and 18 360 dog bite victims were registered.

Rabies PEP is administered in general hospitals; there are no specific bite management centers in Myanmar. Cell culture vaccine and RIG are available in the private sector, while the public sector still uses Semple nerve tissue vaccine (NTV).

Rabies is endemic throughout **Bangladesh**. There are about 200 000 to 300 000 animal bites annually in Bangladesh, mainly dog bites, with about 2000 human rabies deaths (for a population of 140 million). Rabies is diagnosed on clinical grounds, since laboratory facilities are very limited. Most of the 1.5 to 2 million dogs are stray and unvaccinated.

In 2011, the government prohibited production and the use of rabies NTV and scaled-up intradermal (ID) rabies vaccination with cell culture vaccines. In addition, Bangladesh has now adopted a strategy aiming at reducing rabies by 90% by 2015, and eliminating rabies by 2020. The program includes advocacy, communication and social mobilization; scaling-up modern post-exposure management to the district level; and mass dog vaccination and sterilization.

Currently, rabies control activities include a few pilot projects. One covers a rural area (Raipura, Narsingdi); it is based on advocacy, communication and social mobilization (ACSM); dog survey, and dog population management through humane killing and sterilization (Animal Birth Control - ABC). A survey of the dog population has begun in Dhaka city; it should

be followed by mass dog vaccination and surgical sterilization in the Dhaka City Corporation (DCC) and Tongi Municipality.

A Rabies Prevention and Control Centre has been established in the Cox Bazaar District General Hospital. Rabies vaccine and RIG is provided and doctors and nurses have been trained in ID administration of rabies vaccines. Mass dog vaccination has been carried out as a demonstration project. Between November 18 and 20, 2011, 3400 dogs were vaccinated (corresponding to a coverage > 80%), tagged with a red collar, and vaccination data have been entered in a GPS system. These projects receive the technical support of several organizations such as WHO, Food and Agriculture Organization (FAO) and the World Society for the Protection of Animals (WSPA).

In 2005, the government of **India** banned the production and use of NTV, which was widely used in the public sector. With the discontinuation of NTV, the availability and affordability of adequate amounts of cell culture vaccine (CCV) became a major issue with many Indian States. With the recommendations of WHO and the National Experts, the National Regulatory Authority approved the use of ID rabies vaccination with CCV in February 2006, to reduce the cost of treatment and allow for wider coverage with the available quantity of vaccine. The National Institute of Communicable Diseases (NICD) issued national guidelines on ID rabies vaccination in 2007. Only four of the eight commercially available vaccines against rabies, available in India are approved for use via the ID route, according to the updated Thai Red Cross schedule [2-2-2-0-2-0]. They are approved for use only in selected anti-rabies clinics having an appropriate number of adequately trained staff for ID inoculation. These centers must maintain the cold chain for vaccine storage and ensure an adequate supply of suitable syringes and needles for ID administration.

ID rabies vaccination has been progressively implemented in the different Indian States. In Kerala, the NICD guidelines were adapted following an expert consultation. Thirty health personnel received hands-on training at the Institute of Preventive Medicine, Hyderabad (Andhra Pradesh) and ID rabies vaccination has been implemented in eight model anti-rabies centers that also function as training centers. Communication campaigns have

been carried out. Now PEP with ID rabies vaccination is administered free of charge in 214 centers throughout Kerala. From March 2, 2009, to March 10, 2011, 76 527 bite victims received IDRIV in Kerala, and 21 centers were provided with RIG.

This switch to ID administration of CCV has been problematic in some states or areas, and there is a great need for a survey evaluating the proper implementation of ID rabies vaccination in India and its effectiveness in reducing the rabies burden. For instance, experts reported that in many centers, doctors and nurses say that they are using 'subcutaneous rabies vaccination'. If this is really the case, the immune response may be suboptimal because of the low antigen load, and therefore may not protect bite victims. It also appears that vaccines that have not been clinically tested for ID administration are used for ID rabies vaccination in some government hospitals. In some circumstances, an increased diluent volume, that has not been clinically tested, is used, which may change the vaccine characteristics.

The Association for the Prevention and Control of Rabies in India (APCRI) has started a study to monitor the effective use of ID rabies vaccination, but cooperation with some authorized centers in teaching and non-teaching institutions has proven to be difficult, when they are approached for collecting patient blood samples.

**Rabies is still not a notifiable disease in India, making evaluation difficult.** It also appears that RIG is only used in some centers, and in many cases it may be used improperly because of a lack of training of doctors and staff. APCRI's Manual on Rabies Immunoglobulin Administration, published in February 2009, appears to be very useful for the doctors working in the anti-rabies centers.

In **Pakistan**, inadequate surveillance, poor access to modern vaccines and immunoglobulin, weak political support, a lack of resources and ineffective collaboration have until now limited effective rabies control. The government supplies NTV, and RIG is rarely available or affordable. There is a lack of rabies awareness both in the population and in healthcare professionals.

A detailed analysis of data collected for the "**Survey of the Regional Rabies Situation in Eight Asian Countries**"<sup>9</sup> shows that, in Pakistan, only 27% of bite victims seeking PEP washed their

wound correctly. Wound severity was often incorrectly categorized by healthcare professionals, resulting in poor management<sup>10</sup>.

A national dog bite and rabies surveillance study supported by the WHO involves nine tertiary health centers across Pakistan, with representation of referral centers from rural and urban populations. Between 2008 and 2010, 367 rabies deaths were noted in these 9 hospitals: 267 at the Infectious Diseases Hospital in Lahore, 80 at the Lady Reading Hospital in Peshawar; 12 at the Jinnah Post Graduate Medical Center in Karachi and 8 at the Indus Hospital in Karachi. Preliminary results indicate that 77% of reported dog bites occur in urban areas, mainly in males (79%), with a peak in the 5-15 year-old age group. Less than 3% of category III wounds received RIG in rural sites, while traditional remedies were commonly used. Even in Emergency Rooms, wounds were not managed properly. However, things are changing, thanks to the dedication of a few rabies specialists who have participated in every World Rabies Day since its establishment in 2007. To raise public awareness, they have participated in radio and TV talk shows, given press conferences, and organized walks and national conferences for rabies. A two-page Resolution signed by 8 professional and non-governmental organizations was mailed to the Ministers of Health, Federal Health Secretaries, heads of various organizations and the WHO representative in Pakistan, exhorting advocacy and urging the discontinuance of NTV. At a meeting at the WHO Eastern Mediterranean Regional Office for rabies (March 2011, Islamabad), **recommendations were made to the government of Pakistan to make rabies a reportable disease**, to discontinue NTV by 2012 and replace it with CCV, to designate dog bite management centers in large towns in each province, to intensify training of healthcare professionals in correct PEP, and to include veterinarians in the dog rabies control program.

The 18th constitutional amendment announced by the government in early 2011 granted provinces greater autonomy and has devolved decision making in many sectors, including health. Punjab Province has taken the lead in rabies control. Rabies treatment centers have been established at each District Headquarters Hospital and training sessions on dog bite management and PEP have been organized by WHO and the Government of Punjab. All public

hospitals now purchase CCV and provide all bite victims at least the two initial PEP vaccine doses free-of-charge. In addition, laws relating to the vaccination of pet animals have been enacted and are being enforced, stray dog vaccination and elimination campaigns are being carried out, and the existing rabies reporting system has been strengthened in order to monitor dog bites and dog and human rabies. The Sindh Province will soon follow suit.

### **Rabies is of great risk for tourists**

Tourists are at increased risk when travelling in rabies endemic countries. They are poorly informed of the rabies risk, like to approach animals and cannot communicate with the local population due to the language barrier. When transferred to local rabies prevention centers, they often do not trust the local healthcare professionals and want to contact their GP before receiving PEP; they may receive contradictory advice from the general practitioner in their home country. For instance, a study carried out in Sri Lanka showed that less than 10% of tourists were able to communicate with their country general practitioner before initiating treatment – mainly because of the time difference between Sri Lanka and their home country; less than 7% of GPs responded to e-mails, and some patients did not come back.

### **A shortened ID regimen**

Post-exposure rabies prophylaxis schedules date back to Pasteur and Semple, over a century ago. They were burdened by the uncertainties of consistency and potency of early vaccines. There was no evidence-based knowledge of the duration of the immune responses induced. This resulted in a vaccine series timeline of up to 3 months. When new consistently potent cell and avian culture vaccines arrived in the middle of the last century, there was still uncertainty, even fear, preventing the shortening of schedules. Human diploid cell vaccines continued to be used with injection schedules lasting up to 3 months. Slowly, as reliable technology was developed to measure the antibody response for Vero cell, duck and chick embryo cell culture vaccines, and long term immunogenicity and efficacy studies were published, the duration of schedules was reduced to one month.

The current WHO approved “updated TRC-ID” still requires 1 full month and 4 clinic visits. It consists of injecting 0.1 mL of vaccine at 2 sites (deltoid and

thigh) on days 0, 3, 7 and 28<sup>3&11</sup>.

Reducing the number of clinic visits may help increase compliance to complete PEP courses. A recent study showed that ID post-exposure immunization can actually be safely and effectively completed in one week by injecting 0.1 mL of vaccine at 4 sites on days 0, 3, and 7<sup>12</sup>. This study has been recently repeated in India. Preliminary results show that both purified chick embryo cell rabies vaccine (PCEC Rabipur™) and purified Vero cell rabies vaccine (PVRV Verorab™) are safe and immunogenic from day 14 till day 180 when administered by the new shortened 'one week' ID regimen.

**The Next Generation of PVRV (PVRV-NG)** has been developed by Sanofi Pasteur with an improved and innovative manufacturing technology encompassing human and animal origin component-free cell culture medium. It still makes use of qualified Vero cell bank cell substrate and established Pitman Moore rabies virus seed strain, which is further inactivated with beta-propiolactone. Extensive characterization studies have been carried out to demonstrate the comparability of the resulting serum-free vaccine to Verorab™, showing its high level of purity and thorough consistency of molecular and structural properties. The scope of characterization includes state-of-the-art analytical methods. The ability of this serum free PVRV-NG to elicit an effective protective response has already been established in animal models. Clinical evaluation in humans is underway, and first results obtained from a multicentre study carried out in France favorably support its safety and efficacy. PVRV-NG is at least as immunogenic as Verorab™ in terms of seroconversion rates 14 days after the 3<sup>rd</sup> injection. Reactions at the injection site are less frequent in PVRV-NG recipients.

### **What is the most appropriate time interval, when boosters will be required following reexposure to rabies in previously vaccinated individuals?**

In rabies endemic areas, re-exposure to rabies is quite common, with an incidence of up to 15%. Some bites may occur during pre- or post-exposure vaccination (between the doses) or immediately after completing the regimen, when patients are supposed to have an adequate antibody level. Most of

established Asian animal bite clinics use the arbitrary cut-off of either three or six months post reliable vaccination, and consider that boosters may not be necessary during this window. This practice has, however, not been endorsed by WHO<sup>3</sup> and creates a dilemma for many physicians involved in treating cases of potential exposure in persons recently vaccinated. A review of the published literature and clinical trials suggests that booster vaccination may not be necessary for up to three months after previous pre- or post-exposure vaccination in healthy subjects who have been re-exposed to rabies: 99.93% and 99.86% of the 2795 subjects who had received prior post-exposure immunization had neutralizing antibody levels > 0.5 IU per mL at the end of the first and third month post primary vaccination, respectively. All of the 577 subjects with previous PrEP had antibody responses above 0.5 IU per mL at the end of the first and third month post-primary vaccination<sup>13</sup>.

### **Conclusions and recommendations**

AREB acknowledges the progress made in India and Bangladesh, especially concerning the switch to cell culture vaccines. They support efforts made by rabies specialists in Pakistan advocating for replacement of NTV and advocate for Myanmar to discontinue production and use of the Semple type NTV.

### **AREB advocates for rabies to be a notifiable disease in all AREB countries**

AREB recommends a holistic approach to rabies control where PrEP is introduced in children living in endemic areas, together with education and dog vaccination. After discussion, AREB participants considered that pre-exposure prophylaxis could be included in ongoing dog rabies control pilot projects, for instance in Cox Bazaar (Bangladesh), or in Kerala (India) or in a high-risk area in Sri Lanka, where a cost-benefit study could be planned. Pediatricians should be involved in the planning of such projects, in order to better define the optimal age for vaccination, integration of vaccination into EPI programs and the vaccination of schoolchildren.

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## ***Announcement***

**The APCRI Journal is published twice a year. Once in January and again in July. The APCRI Journal invites Contributions from the Scientific Community, on All aspects of Rabies and Related Matter, in the form of Original Articles and Review Articles, Brief Reports, Case Reports, Personal Viewpoint, Letters to the Editor, Notes and News, Your Questions and Book Review.**

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