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Meeting report

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Preventing the incurable: Asian rabies experts advocate rabies control

1. Introduction

Rabies is a deadly disease; diagnosis is synonymous with death. Only a handful of survivors have been reported and all except one had received rabies vaccine either before or soon after the onset of illness [1,2]. Rabies, however, is a preventable disease. Even after exposure to the rabies virus, from the bite, lick or scratch of an infected animal, disease and death can be prevented by proper local wound treatment followed by immunization with safe and effective vaccines, and if necessary with administration of rabies immunoglobulins (RIGs).

In spite of this, every year 55,000 people die from rabies worldwide. 31,000 (56%) of these deaths occur in Asia, mainly (90%) in rural areas [3,4]. Children and young adults suffer the most; children under 15 years of age account for 30–50% of rabies cases in humans and the inevitable deaths that follow. An average of 31 years are lost per rabies death. Including the morbidity and mortality following side effects of nerve–tissue vaccines (NTV), rabies is globally responsible for the loss of 1.78 million disability-adjusted life years (DALYs) each year, of which 996,000 are in Asia [3,4].

In Asia, the main route of rabies virus transmission is through rabid dog bites which are responsible for 96–98% of deaths from rabies in humans—other animal species may also be infected (cats, cattle, monkeys, mongoose) and serologic evidence of infection in bats has also been documented in Cambodia [5].

In Asia, more than 2.5 billion people are potentially exposed to rabies infection; each year, an estimated 8 million people receive treatment after being exposed to animals that are suspected of rabies. The economic burden has been estimated to be US$ 563 million (96.5% of the total burden of rabies worldwide) [3,4].

Although effective and economical control measures are available and although rabies satisfies all WHO criteria for being considered as a disease of priority for control, still rabies remains a neglected disease in most Asian countries [4]. There is a lack of awareness among the public, general practitioners, and health authorities, little information available for public and healthcare professionals, a shortage of funding for modern cell-culture vaccines and immunoglobulins, and a lack of political will to control canine rabies. Rabies control in dogs is given a low priority in public health programmes—policies for reducing dog populations are extremely unpopular in Asia, and reaching dogs for vaccination and implementing control measures is difficult since most animals are community-owned or ownerless.

A group of rabies experts from seven Asian countries most concerned by the rabies situation (China, India, Indonesia, Philippines, Sri Lanka, Thailand and Vietnam) was created in 2004, constituting the Asian Rabies Expert Bureau[1] (AREB). This group met in Cebu in the Philippines in June 2004 and again in Shanghai, China in July 2005, to present and discuss the rabies situation in their respective countries, to exchange points of view, to consider specific problems encountered in their clinical practice and to find practical solutions.

2. The current situation in AREB countries

The estimated incidence of rabies (and consequent mortality) in the seven Asian countries varied from 0.03 per 100,000 population in Thailand to 2–3 per 100,000 in India, in 2004 (see Table 1). In the Asian countries considered above, a total of approximately 6 million patients received post-exposure treatment (PET) in 2004 (Table 1).

Rabies is endemic in India, but its true incidence is not known with any degree of accuracy since it is not a notifiable disease. In China, computerized reporting of rabies was established at the end of 2004, but the diagnosis is based only on clinical criteria. Data collected showed that after a decrease in rabies deaths between 1990 and 1996, the incidence has been increasing every year since 1998, with a total of 2651 reported deaths in 2004. In Sri Lanka, the rabies situation has deteriorated in areas affected by the 2004 tsunami. There is an increase in the number of ownerless and free-roaming dogs seeking food and shelter around refugee camps and the number of animal bites and the demand for post-exposure treatment have increased in these areas during the first half

[1] Details are provided in Appendix A.

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of 2005. Also the rabies diagnostic laboratory established in the southern province was destroyed in the natural disaster.

2.1. Available vaccines

Nerve–tissue vaccines are still used in some countries since their production costs are assumed to be lower. However, these vaccines are responsible for severe and long-term side effects in an estimated 0.3–0.8 per 1000 cases [3]. Patients treated with NTV are also less likely to complete the course of treatment [6]. WHO strongly recommends stopping their production and switching to modern tissue culture vaccines (TCV).

These recommendations have been followed by several countries in Asia: China banned NTV in 1981 and produces hamster kidney cell culture vaccines and purified Vero cell culture vaccines (PVRV). These locally produced vaccines have not been evaluated according to standardized procedures and consequently are not recommended by WHO. They are produced in sufficient quantities not only to respond to the domestic demand, but also to be exported to other Asian countries. However, problems in distribution (including the quality of the cold chain) often reduces rabies vaccine availability in remote, rural regions where rabies is highly endemic. Moreover, patients have to pay for the vaccine provided at public health centres, and consequently often turn to cheaper, but untrained, private general practitioners or traditional healers, who are unaware of the correct course of treatment. Thailand switched to imported TCV in 1993, Sri Lanka in 1995, and the Philippines in 1997. India stopped production of NTV in early 2005, while Vietnam still uses almost exclusively locally produced nerve–tissue vaccine (see Table 1).

In order to decrease the cost of post-exposure treatment with TCV, intradermal (ID) administration schedules, which use reduced quantities of vaccine, have been established. When administered by trained staff and following WHO recommendations, they offer adequate protection against rabies. ID administration is being increasingly used in most AREB countries, except in China and India. However, the decision to implement ID regimens has to be taken by the National Health Authorities of the individual country. A recently published pharmaco-economic study carried out in India reported that dividing the dose by half is not associated with a direct 50% reduction in total costs—the reduction was less than 20%[7].

3. The AREB objectives

Based on the analysis of the strengths and weaknesses of rabies prevention and control in Asia, AREB members have designated domains where they could help improve the situation in their respective countries, taking into account limited resources, the practicability of solutions to specific, local situations, and the need to increase awareness and availability of information on rabies. They also agreed to share their experiences, and see how successful initiatives can be transposed from one country to another. Some of the specific topics they raised are discussed below.

4. From guidelines to practical applications

WHO publishes regularly updated guidelines and recommendations for rabies treatment [8,3]. National authorities also have their own guidelines, which sometimes differ from WHO. AREB members suggested comparing the guidelines in their respective countries, and examining the possibility of harmonizing their recommendations.

4.1. Immunoglobulin shortage

The AREB experts noted that some issues specific to the situation in Asia were not addressed in the WHO guidelines. For instance, clinicians in Asia often face the problem of shortage of rabies immunoglobulins. Most patients (80–85%) that go to rabies care centres in Asia have had a category III exposure (single or multiple transdermal bites or scratches or contamination of mucous membrane with saliva), which requires treatment with both RIG and vaccine. However, in

Table 1
Estimated numbers of human deaths from rabies, post-exposure treatments and pre-exposure prophylaxis (2004)

Country	Population (million inhabitants)	Notifiable disease	No. of deaths per 100,000 inhabitants	Total no. of deaths from rabies	Post-exposure treatments			No. with pre-exposure prophylaxis
					No. of post-exposure treatments	% Treated with TCV	No. of PET with RIG	
China	1306	Yes	0.20	2651	2500000	100	(2.1%)	–
India	1027	No	2–3	20000	2300000[a]	78[a]	30000[a] (1.3%)	Very limited
Indonesia	219	Yes	0.045	99	6770	49.9	22	0
Philippines	84	Yes	0.29	248	55301	100	5241	No data
Sri Lanka	20	Yes	0.48	97	200000	100	55000	–
Thailand	63	Yes	0.03	19	351535	100	30678	No data
Vietnam	82	Yes	0.099	81	615000	10	20000	1000

[a] Data 2003.

some areas immunoglobulins are not always affordable or available in sufficient quantities and only a limited number of patients who qualify for RIG treatment can receive it (see Table 1). The WHO APCRI survey showed that only 2.1% of patients requiring a post-exposure treatment received RIG [6]. Healthcare providers are confronted with a serious dilemma when they have to select patients to receive RIG. The Expert Bureau noted that category III exposure was a very broad definition. They considered that subtypes within category III could be defined, according to the probability that the biting animal was rabid, and different treatment priorities offered. For instance, a patient bitten by a pet animal that is observable, with a history of vaccination and shows normal behaviour (i.e. the bite was provoked), could be considered as having a lower priority for receiving RIG.

However, the Expert Bureau acknowledged that these criteria are no guarantee of risk-free exposure, even a vaccinated dog could have rabies, and WHO recommendations should be followed whenever possible. In fact, various vaccines and vaccination schedules are used for the vaccination of dogs, and their effectiveness may be highly variable. Members of the Expert Bureau agreed that it would be helpful if the effectiveness of these vaccines could be further evaluated and if a unique, validated vaccination schedule could be recommended for dogs in Asian countries.

4.2. Intradermal administration of vaccines

Another topic of particular interest in Asia is the use of ID administration for modern vaccines, in order to decrease the volume of vaccine necessary for post-exposure prophylaxis. The Expert Bureau noted that ID administration could be an appropriate solution, provided that a number of precautions are respected, including adequate staff training and supervision, and strict control of the conditions and duration of vaccine storage after reconstitution. It was estimated that only dog bite centres treating at least five patients per day could be considered viable for ID post-exposure treatment since an opened vial has to be used within 6–8 h (and kept at $5 \pm 3\,^{\circ}C$ during that time). On the other hand, ID administration involves injection at multiple sites and is more time-consuming than intramuscular administration. Some rabies centres may be treating such a large number of patients that they do not have time to administer the vaccine by the ID route. The National Health Authorities of the respective countries should define, according to the capacity of the rabies centres, an upper limit – as well as a lower limit – to the number of patients treated daily, in order to be able to effectively handle ID administration of rabies vaccines.

4.3. Implementation of pre-exposure prophylaxis

Pre-exposure prophylaxis simplifies rabies treatment by eliminating the need for RIG and decreasing the number of vaccine doses needed for post-exposure treatment in the event of a subsequent exposure to the rabies virus. It may enhance immunity and protect people whose post-exposure therapy might be delayed, as well as providing protection to children with unapparent exposure to rabies. Pre-exposure prophylaxis is recommended by WHO for anyone at increased risk of exposure to the rabies virus: this applies to large segments of the Asian population. One of the problems identified during discussion was the shortage of modern TCV in some countries. The Expert Bureau agreed that mass, pre-exposure vaccination of all persons at high risk of exposure to rabies, although desirable, could not be recommended when there was not enough TCV available for post-exposure treatment. Consequently, the experts recommended pre-exposure immunization of identified groups with a higher risk of exposure, including people handling animals (veterinarians, wildlife officers, pet shop workers, taxidermists, etc.), laboratory staff exposed to rabies virus (those working in rabies diagnostic laboratories, in research or production of rabies biologicals) and health personnel working in emergency care facilities or rabies health centres.

Recognizing the enormous benefits of early vaccination of infants and young children in areas where canine rabies is endemic, the experts recommended that pre-exposure immunization, administered by the intramuscular route, be proposed as an optional vaccine for children of pre-school age. The efficacy and immunogenicity of pre-exposure immunization by ID route in children is not sufficiently documented and clinical trials should be carried out to remedy this situation. One such study is currently ongoing in the Philippines among school children aged 5–9 years. If such studies confirm sufficient immunogenicity, and if TCV is available in sufficient quantities, inclusion of pre-exposure prophylaxis into the Expanded Programme on Immunization (EPI) could be considered. For such programmes to work, it is important that good records of pre-exposure vaccination are maintained and made available, so that the immunization schedule can be completed and the treatment in cases of exposure modified.

WHO recommends that persons who have been immunized prophylactically be monitored every year (or every 6 months for those at continuous risk) by checking their rabies antibody titres. A booster injection should be given when antibody titres fall below 0.5 IU/ml. Monitoring antibody concentrations is difficult in most Asian countries; most of the areas where pre-exposure immunization is recommended do not have the facilities for regular testing of antibody titres. The question was raised as to whether it was possible to define a safe booster interval for use when antibody titres cannot be regularly checked?

4.4. Switching vaccination regimens

Post-exposure treatment can be discontinued when the biting animal remains healthy throughout a 10-day observation period. By this time patients would usually have received two or three doses of rabies vaccine. Some members of the Expert

Bureau wondered whether effective immunisation could be achieved with a 'prophylactic pre-exposure' regimen. This would avoid potential "waste" of vaccines used for injections when the subject is later shown not to have been exposed to a rabid animal. It would also provide prophylactic protection to these persons, especially children, who are at a higher risk of exposure. Advice on how to switch from post-exposure to pre-exposure prophylaxis needs to be available for those involved in immunization programmes and rabies treatment. Clinicians also need reliable advice on the schedule to be applied when a patient is bitten by a potentially rabid animal during a course of prophylactic immunization.

4.5. Increasing awareness

Members of the Expert Bureau agreed that increasing rabies awareness among Asian health authorities and policy-makers, improving training of general practitioners and health care workers, educating school children and the general public are crucial for effective rabies control. Many people die from rabies because of lack of awareness, improper wound care, and inadequate or delayed post-exposure treatment.

Some people prefer to consult general practitioners or traditional healers who are often unaware of the international and national treatment recommendations and lack adequate facilities. Moreover, many who start post-exposure treatment do not complete it. A study carried out in India showed that 79% of rabies victims did not receive any post-exposure vaccination (neither NTV nor TCV) [6]; 26% died in spite of some post-exposure prophylaxis: 11% had received NTV, and 10% had received TCV. But 85% and 79%, respectively, of these "treated" patients who died of rabies never completed the course of immunization and 99% did not receive any RIG [6].

Rabies management and control should be included in the curriculum of health care professionals. Traditional healers should also be contacted and informed. They are often the first referral of people who have been bitten—and they usually apply improper care. According to the AREB experts, they may be willing to cooperate and, if properly informed and trained, they could administer proper wound care and refer the patients to specialised rabies centres.

AREB members from the Philippines have initiated a pilot program on rabies prevention through curriculum integration in all elementary schools of the Bicol Region, in partnership with the Department of Health (DOH) and the Department of Education (DepEd), and with the financial support of Merial and sanofi pasteur. As a first step, the DOH carried out a survey on rabies awareness (knowledge, attitude and practice—KAP) in target groups; then a teaching module was designed based on the results of the survey. A pilot program was launched in November 2004, and the module was improved, following the evaluation of its impact in the pilot area. The module was launched during the 2005 Rabies Awareness Month and is being implemented in all elementary schools of the Bicol region, which has the highest number of human rabies cases. Rabies experts from the Philippines and Thailand have also published booklets and "pocket memos" containing information for health care professionals on the management and post-exposure treatment of bites from suspected rabid animals. These documents could be translated and modified for use in other Asian countries.

In order to identify the most effective ways of increasing awareness in the general population, members of the rabies expert bureau decided to test rabies awareness in their countries. As an initial step, they will establish a short questionnaire, which will be tested on patients visiting rabies treatment centres, to identify how and why they consulted the rabies centre and where they got the information from.

In order to reach their objectives, the AREB members agreed to meet at least once a year, to discuss specific practical topics related to rabies, and to publish their conclusions as position papers. They also decided to establish a network of Asian rabies experts, in order to find answers to frequently asked questions in the clinical practice.

Resolutions of the Asian Rabies Expert Bureau

The workshops and discussions held during the meeting of the Asian Rabies Expert Bureau led to the following aims and objectives:

- to hold annual, thematic meetings to elaborate consensus on practical solutions to specific problems, and publish position papers
- to promote evaluation of the safety and efficacy of locally produced TCVs, as per WHO guidelines
- to collect "frequently asked questions" and publish answers from a consensus of key opinion leaders from each of these countries
- to draft a short questionnaire to test rabies awareness and identify the best networks for dissemination of information on rabies.
- to compare guidelines in their respective countries
- to share positive experiences and adapt them to the other Asian countries, e.g. educating school children, informing and training medical doctors; elaborating "pocket memos".
- to increase rabies awareness

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Appendix A

The Asian Rabies Expert Bureau is an informal group of experts in rabies, including members from seven Asian countries

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