

Executive summary

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The epidemiology of human and animal rabies in Asia was reviewed during the Fourth International Symposium on Rabies Control in Asia, together with the existing programmes for prevention and control. The discussions were centred on newly available tools and strategies for control and on their optimal use in the specific context of Asia. Recommendations were drawn up, and resolutions were adopted.

Epidemiology of rabies in humans and animals in Asia

Rabies in humans

The available data on cases of human rabies and post-exposure treatment are presented in *Table I*. Centralized, well-equipped laboratories with trained staff are found in many Asian countries, but lack of awareness by both health professionals and the public and difficulties in communication obviate the collection of complete information about the real nationwide incidence of human rabies, particularly in countries with remote and/or mountainous areas, such as the Lao People's Democratic Republic, Myanmar, parts of China and archipelagos such as Indonesia and the Philippines. In Thailand, which has good laboratory diagnostic facilities and where health professionals are well aware of the problem of rabies, the number of human cases diagnosed by both laboratory analysis and clinical observation remains quite low (27%). As might be expected, the highest estimates of the number of human deaths from rabies are from countries with the largest populations and very limited activities in rabies prevention and control, such as Bangladesh, India and Pakistan, where it is estimated that a total of 40,000 deaths occur each year. In addition, these countries have weak surveillance systems, so that the true numbers can be expected to be even higher.

In some countries with reliable surveillance systems and where effective control measures have been applied (at least over a part of their territory), significant decreases in the numbers of deaths from rabies have been observed over the past few decades. In Thailand, the number of deaths due to rabies has decreased steadily, from 370 in 1980 (0.78 per 100,000) to 185 in 1990 (0.33 per 100,000) and 57 in 1998 (0.1 per 100,000). In Viet Nam, the number of deaths decreased by 76%, from 500 deaths/year

Table 1. Estimated numbers of human deaths from rabies per year and numbers of post-exposure treatments given in 2000.

Country	No. of deaths per year (estimated)	No. of post-exposure treatments in 2000 (estimated)
Bangladesh	2,000	60,000
Cambodia	20	12,000
China*	150-350	5,000,000
India	30,000	1,500,000
Indonesia*	> 100	8,000
Lao People's Democratic Republic	< 20	3,000
Malaysia*	0	Unknown
Myanmar	500-1,000	5,000
Nepal	> 100	25,000
Pakistan	2,000-5,000	69,000
Philippines*	300-600	68,500
Sri Lanka*	100-120	80,000
Thailand*	50-70	200,000
Viet Nam	~ 100	600,000

* Countries in which only modern cell-culture vaccines are used.

(0.6 deaths/100,000 inhabitants) in the early 1990s to less than 50 deaths (< 0.1/100,000 inhabitants) in 1999-2000. China, which has succeeded in drastically decreasing the number of human deaths from rabies over the past decades, has observed a recent increase: about 5,500 deaths from rabies were observed each year in the 1980s; the number dropped to 160 in 1996, but since 1997 has increased again to 200-250 deaths per year. In the Philippines, a 20% increase in the number of human deaths from rabies has been observed over the past 5 years. These increases may reflect real trends or increasingly effective surveillance.

Animal species involved: the major role of dogs

The main route of transmission of the rabies virus is through the bite of rabid dogs. In China, the Philippines, Thailand and Viet Nam, where the animal species responsible for fatal human cases are recorded, dogs are responsible for 94-98% of deaths.

Optimal conditions for the surveillance of rabies in animal species are met in only a few countries. In certain countries, the rabies status of animals remains unknown over large areas, often because of their remoteness and a lack of trained staff and of appropriate and sustainable systems for sample collection, preservation and shipping. This is true for parts of most of the countries represented at the Symposium. Nevertheless, several countries have made real progress in surveillance of animal rabies during the past five years. In other countries, despite the availability of basic laboratory facilities, equipment and training, the number of rabies cases reported in animals is inadequate for use as a basis for designing and initiating a rabies control programme. These countries include Bangladesh, Cambodia, India, the Lao People's Democratic Republic, Mongolia, Nepal and Pakistan; however, their capacity to diagnose rabies still differs.

In most countries, ministries of agriculture give priority to livestock production, and information on the dog population is usually poor. Dog populations can usually be categorized into three groups: owned dogs, community dogs (living in public areas and fed by the population) which can be reached by control measures under certain condi-

tions and ownerless dogs which usually escape control programmes. According to a survey of the dog population of Bangkok, Thailand, carried out in 1999, there were approximately 650,000 dogs, 20% of which were ownerless. The total estimated dog populations are 1 million in Cambodia, 6 million in Thailand, 10-16 million in Viet Nam (80% in rural areas, 20% in cities), and 25 million in India.

It is usually in countries where rabies surveillance is insufficient that animal species other than the dog are suspected of maintaining the disease; these species include mongoose, wolf, jackal and bat. Although the involvement of wild species in the maintenance of rabies cannot be ruled out, it remains a hypothesis that has not been confirmed in those Asian countries such as Malaysia, Japan, and parts of Indonesia, where dog rabies was eliminated, sometimes a long time ago (*e.g.* in Japan in 1957) through implementation of strict control measures.

Old and new vaccines for post-exposure treatment

Most patients who die from rabies were either not treated or did not receive proper post-exposure treatment. Many dog bites in children are not reported, may go completely unrecognized or may be discovered late by both parents and health care providers. Consequently, exposed children often do not receive post-exposure treatment at all, are not treated in a timely fashion or receive incomplete post-exposure treatment.

Modern rabies vaccines produced on cell cultures or embryonated eggs are safe and effective. Some Asian countries have begun to use modern rabies vaccines, either imported or produced locally. China has been producing a rabies vaccine prepared on primary hamster kidney cells since 1980. It is the most widely used rabies vaccine in the country, with 25-30 million doses produced and approximately 5 million post-exposure treatments provided annually. In Thailand, discontinuation of sheep brain vaccine (Semple vaccine) production in 1989 and of suckling mouse brain (Fuenzalida) vaccine in 1993 and the importation of increasing quantities of modern vaccines have played a major role in the drastic reduction in the number of cases of human rabies in that country.

A similar decision was taken in Sri Lanka and the Philippines, in 1995 and 1997, respectively. In Indonesia, post-exposure treatment over the past 10 years has been carried out mainly with imported cell-culture vaccines.

However some Asian countries where canine rabies is endemic still produce and use nervous tissue vaccines. Sheep brain vaccine (Semple vaccine) represents most of the rabies vaccine used in Pakistan, an estimated 70% of rabies vaccine doses used in Bangladesh and 45% of those used in India today. In Viet Nam, a vaccine based on suckling mouse brain is that used predominantly. These vaccines have low antigenicity and immunogenicity and are consequently less effective than cell-culture vaccines. They require repeated visits to the hospital (for daily injections into the abdominal wall for 7-21 days and booster doses, depending on the vaccine type and exposure characteristics) and administration is painful. Local and loco-regional side-effects (urticaria, rash) are often associated with their use. Consequently, patients often abandon treatment. Sheep brain vaccines may also induce neurological complications (in 1/1,200 to

1/3,000 treatments), which, in severe cases, may lead to death (in about 25% of these cases).

These vaccines, which are usually provided free of charge in these countries, are administered mainly to the poorer segment of the population. With increasing public awareness about rabies and knowledge that modern vaccines provide better protection and safety, health staff in major public and private hospitals or rabies vaccination centres face an increasing demand for better vaccines from all layers of the society, including the most vulnerable groups. In Bangladesh, where nervous tissue vaccines are still used, the number of doses used increased less rapidly than those of modern vaccine during the past 5 years. In India, brain tissue vaccines represented about 90% of all vaccine doses used in the mid-1980s, 50% in 1995 and about 45% today, whereas the total number of brain tissue vaccine doses used remained stable.

The Seventh WHO Expert Committee on Rabies, which met in 1983, recommended discontinuation of the use of brain tissue vaccines and particularly of the Semple-type vaccine, which was first produced in 1911. This recommendation was reiterated in 1992 by the Eighth Expert Committee. Local production and use of these vaccines is, however, still widespread, particularly in Africa, Asia and Latin America. The recent emergence of new prion diseases further emphasizes the need for a ban on animal brains as a substrate for human and veterinary vaccines.

Although the main reason for using brain tissue vaccines is their lower production cost, it has been shown that this cost and those for storage and administration are underestimated. In contrast, the cost of modern vaccines has been decreasing continually, owing to market forces, scaled-up production and increasing demand. The Symposium provided an opportunity to review validated, economical intradermal immunization protocols, which require only 40% of the quantity of modern vaccine needed when given intramuscularly, as an alternative safe route for modern post-exposure treatment and a possible way of at least partially fulfilling the requirements of these countries with respect to modern rabies vaccines in view of their lower cost.

Participants in the Symposium urged countries still producing brain vaccines to discontinue their production within the next 5 years and in the meantime to investigate the possibility of collaborative establishment of cell-culture vaccine plants destined to satisfy regional needs. They also recommended that plans be elaborated for provision of cell-culture vaccine for post-exposure treatment and that, with the assistance of WHO, relevant personnel be trained in the intradermal administration of cell-culture vaccine.

A shortage of rabies immunoglobulins

Most patients in Asia who have received single or multiple transdermal bites do not receive the necessary rabies immunoglobulin, both because of a permanent global shortage and because of its high price, which makes it unaffordable to most patients in countries where canine rabies is endemic.

Systematic vaccination of infants and children could be a solution to these problems in countries or areas where canine rabies is still endemic and has not been controlled by conventional methods. Pre-exposure vaccination of infants and children against ra-

bies would eliminate the need for rabies immunoglobulin and decrease the cost of post-exposure treatment in the event of subsequent exposure to rabies virus. Data presented at the Symposium confirmed that post-exposure treatment of previously vaccinated persons does not require immunoglobulin, and modern rabies vaccines given intramuscularly or intradermally are safe and immunogenic in infants when associated with the vaccines of the Extended Programme of Immunization. Consequently, the participants in the Symposium urged governments to consider early vaccination of infants and children in countries where canine rabies has still not been controlled and to encourage pre-exposure vaccination for anyone who can afford it in all dog rabies-infected countries.

Rabies control in dogs: a requirement for rabies prevention in humans

Control of rabies in dogs remains the only long-term, cost-effective means of eliminating or preventing most human cases. Human public health preventive measures should be paralleled by programmes for dog rabies control.

What are the most effective strategies? Selective destruction of dogs, widespread control of their reproduction, systematic immunization by injection and/or the oral route? How should these measures be combined? How acceptable are they to the people concerned? Strategies for dog population management and control must be adapted to the cultural and social habits of each country or area. In Asia, as in many other parts of the world, dog population reduction policies are extremely unpopular.

Comprehensive programmes for dog rabies control must combine:

- legislation and community collaboration to control the trade and movement of dogs and to hold dog owners responsible and accountable for their animals;
- actions to limit the availability of food to stray dogs, and neutering programmes to stop dog population growth at the source;
- vaccination of at least 75% of the total dog population and education of veterinarians, health professionals and related professional groups and populations at risk.

Countries including China, Indonesia, Malaysia, the Philippines, Sri Lanka, Thailand and Viet Nam, have dog control activities, all over their territory or in localized areas. Elimination of ownerless dogs is rarely practised on a large scale in these countries and usually affects an insignificant proportion of the entire dog population. The conventional approach consists in mass parenteral vaccination of dogs, with efforts to improve vaccination coverage each year. In Malaysia, dog vaccination is carried out within an 'immunity belt' along national borders; in the Philippines, a pilot rabies elimination programme is currently being conducted in the Visayas; in Viet Nam, the programme is focusing on the most heavily populated urban areas (such as Hanoi, Ho Chi Minh City and the Mekong Delta region). In these countries and areas, dog vaccination coverage is estimated to range from 10% to 94%. This wide range illustrates the need to enhance the efficacy of mass vaccination campaigns in many places but also that high coverages can be achieved if certain conditions are met.

Support should be given to vaccination systems that reach all categories of dogs. Oral vaccination with vaccine-loaded baits should be conducted as a complement to parenteral vaccination where a significant proportion of the dog population cannot be im-

munized by injection. In order to increase vaccination coverage, India, the Philippines, Sri Lanka and Thailand are considering the use of oral vaccination. Studies of the dog population have been conducted for this purpose in the Philippines, Sri Lanka and Thailand. The effectiveness of the approach has been demonstrated in limited experimental field trials in Sri Lanka.

Sustainable elimination of dog rabies, which is the only definitive solution to the problem of rabies in humans, requires strong commitment by all the important sectors, such as public health, veterinary and environmental services. Such cooperation has led to the initiation of national programmes for human and animal rabies control and elimination which have resulted in a drastic reduction in the number of cases of rabies in humans in Latin America.

The participants in the Symposium urged WHO to organize a formal meeting with ministers of health and agriculture or livestock from those Asian countries where the estimated human rabies burden is highest, in order to secure the commitment of all national services dealing with rabies, without which no major breakthrough in rabies control will occur.

Conclusions, recommendations and resolutions

Treatment and prevention of human rabies

Two workshops were organized as part of the Symposium programme to discuss major aspects of the treatment and prevention of human rabies. The first workshop addressed pre- and post-exposure treatment of rabies. It was facilitated by Dr H. Wilde, Dr J. Lang and Dr F.-X. Meslin. Dr Wilde presented a new version of a video film on pre- and post-exposure treatment of rabies that had been prepared for the training of health care personnel. It was well received by the participants. This was followed by a short introductory presentation that addressed issues related to pre-exposure immunization of infants and small children, and the latest revision of the WHO recommendations on post-exposure treatment, especially with regard to intradermal administration of rabies vaccines and the management of immunosuppressed individuals. The second workshop was entitled 'Moving away from the use of brain tissue vaccines in humans?' and was facilitated by Dr Naseem Salahuddin and Dr F.-X. Meslin. The conclusions and recommendations of the two workshops are given below.

Conclusions

- Rabies immunoglobulin is in critically short supply in developing countries where canine rabies is endemic.
 - The cost of nervous tissue vaccine production is increasing; *e.g.* the price of sheep vaccine has increased threefold and that of β -propiolactone by fivefold, and the price of thiomersal has increased in India.
 - The lack of rabies immunoglobulin means that severe exposure to rabies will be unavoidably fatal in some patients. This could be prevented by pre-exposure vaccination.
 - No human deaths from rabies have been reported in persons who have received both preventive immunization and post-exposure vaccination according to relevant WHO-approved schedules.
 - In one study, addition of purified Vero cell rabies vaccine to the diphtheria, pertussis and tetanus (DPT) vaccines in the Expanded Programme of Immunization did not in-

terfere with the immune response to the DPT antigens, and all of the vaccinated infants developed an immune response to rabies antigen.

- Pre-exposure immunization to prevent rabies in infants and children would eliminate the need for rabies immunoglobulin and decrease the cost of post-exposure treatment in the event of subsequent exposure to rabies virus.
- Professionals in human and animal health and the general public should be educated in the prevention and control of rabies.

Recommendations

- The production and use of nervous tissue vaccine should be abandoned (*see Resolution 1*).
- Asian countries that need large quantities of rabies immunoglobulin (RIG) should consider producing it domestically, as neighbouring countries that do produce it usually do not have sufficient supplies for export, and the shortage at the global level can be expected to become more severe.
- The general population should be made aware that rabies immunoglobulin might not be available. In order to improve the quality of prophylaxis and reduce the need for rabies immunoglobulin, pre-exposure vaccination should be encouraged for anyone who can afford it. Government hospitals where intradermal vaccination is practised could provide such protection economically. The recipient should keep a record of the vaccination.
- A new strategy for rabies control should be developed that would include early vaccination of children living in areas where canine rabies has not been controlled.
- Viable alternatives to rabies immunoglobulin, including monoclonal antibodies, should be sought.
- Professionals in animal and human health should receive continuing education on rabies prevention and control. The video film on pre- and post-exposure treatment produced by the Mérieux Foundation, the Thai Red Cross and the WHO Collaborating Centre in Queen Saovabha Memorial Institute should be further edited and made available to all countries of the Region for teaching health care personnel.

Control of animal rabies

Two workshops were organized as part of the Symposium programme to discuss the major aspects of animal rabies control. The first workshop was entitled "How successful have dog vaccination campaigns been so far? Is oral vaccination of dogs a viable solution?" It was facilitated by Dr K. Stöhr, Dr A. Belotto and Dr G. Bishop. A second workshop was held on "Responsible dog ownership: An adapted concept for dog population management in Asian countries?" The workshop was facilitated by Ms J. Leney from the World Society for the Protection of Animals, who presented a video film showing various aspects of the subject, including animal welfare. The conclusions and recommendations issued by the participants are as follows.

Conclusions

- No major breakthrough in animal rabies control will occur without a significant increase in the political commitment of the relevant national authorities.
 - In countries where dogs are the main reservoir, vaccination of dogs is the most cost-effective, viable solution for completely preventing rabies in humans.
 - Sustainable vaccination of dogs requires the long-term, committed involvement of all important sectors, such as public health, agricultural and veterinary services.
 - Assessment of the size and structure of the dog population is a prerequisite for planning parenteral and oral vaccination campaigns.
 - Dog population reduction activities are usually not well accepted by communities in Asia.
 - Neutering- or vaccination-and-release programmes have usually been well accepted by communities. However, they have not stopped the complaints about noise nuisance and attacks on people and livestock.
 - The key principles of dog population management are:
 - vaccination of stray dogs whenever possible;
 - legislation to control trade and movement of dogs;
 - legislation to hold owners responsible and accountable for their dogs;
 - reduction of food sources and neutering programmes to stop population growth at the source; and
 - education of children and adults in the population and of veterinarians and other professionals.

Recommendations

- National responsible officers for rabies, health care personnel, nongovernmental organizations and the general public, with the support of regional and international organizations, should strive to elicit strong political commitment and support for rabies elimination at the highest level in the country.
 - Dog vaccination should be promoted as the main tool for eliminating canine rabies. Oral vaccination should be used as a complement to parenteral vaccination when a significant segment of the dog population cannot be reached with parenteral vaccines.
 - Comprehensive dog population management schemes should be initiated, which incorporate the five key principles listed above.
 - When neutering- or vaccination-and-release programmes cannot be implemented efficiently owing to a lack of resources, education of dog owners and municipal personnel should be enhanced to engender more responsible attitudes.
 - Dog populations should be assessed during planning of the programme. Censuses targeting 'stray' dogs (ownerless, community or even owned dogs) in particular should

be conducted at regular intervals before the programme is implemented. Surveys of other indicators of human health and welfare, such as the number of bites, deaths, other diseases and attitudes, should also be carried out.

Resolutions

Three resolutions were produced by the participants, addressing the three major subjects that were tackled during the workshops: the production and use of nervous tissue vaccines; early immunization of children, and rabies control initiatives in Asia. The three resolutions were discussed and finally endorsed by the Symposium of Friday 9 March 2001.

Resolution 1

The Symposium,

acknowledging:

- the efficacy and safety of modern cell culture vaccines;
- the recommendation of the seventh and eighth WHO Expert Committees on Rabies (1983 and 1992) to discontinue use of nervous tissue vaccines, particularly Semple vaccine;
- that the costs of production, storage and use of Semple-type vaccines are underestimated; and
- the decreasing cost of modern cell culture vaccines and of active immunization, especially by the intradermal route, in most countries where dog rabies is endemic,

considering:

- the definitive changeover in certain countries of the region from nervous tissue-based to cell culture-based vaccines for human use, and the constant diminution of the use of nervous tissue vaccine reported in other countries of the region;
- the increasing demand from the general public for safer, more efficacious biological products; and
- the existence in countries where nervous tissue vaccines are still produced of double standards, whereby these products are administered mainly to the poorer segment of the population,

urges:

countries still producing nervous tissue vaccine to

- discontinue its production by 2006;
- investigate the possibility of collaborative establishment of a cell culture vaccine plant destined to satisfy regional needs; and
- plan provision of cell culture vaccine-based post-exposure treatment for rabies;

and WHO to

- continue to advocate strongly the replacement of nervous tissue vaccine by modern, safe, efficacious rabies vaccines; and

- assist Asian countries to develop alternative policies for modern post-exposure treatment for rabies, in particular by training relevant personnel in the intradermal administration of cell culture vaccine.

Resolution 2

The Symposium,

recognizing that:

- rabies is a vaccine-preventable disease for which safe, efficacious vaccines are available;
- about 40% of the estimated 40,000 deaths from rabies in Asia occur in children under 15 years of age;
- most deaths from rabies occur in children who were not treated or received inadequate post-exposure treatment, usually because of a shortage of rabies immunoglobulin;
- post-exposure treatment of previously vaccinated persons does not require immunoglobulin or other treatment; and
- modern rabies vaccines given intramuscularly or intradermally have been demonstrated to be safe and immunogenic in infants when associated with the major vaccines of the Expanded Programme of Immunization,

urges governments:

- to consider early vaccination of infants and children in countries or areas where canine rabies has not been controlled by the use of conventional methods, by studying the feasibility of incorporating rabies vaccine into immunization programmes for infants and/or schoolchildren; and
- to initiate, monitor and evaluate carefully designed pilot projects wherever possible.

Resolution 3

The Symposium urges WHO to establish an informal group consisting of rabies experts, representatives of countries in Asia where rabies is prevalent, representatives of companies that manufacture rabies vaccines and other relevant partners to:

- advise WHO on the best strategies for the control and elimination of rabies in humans and dogs in Asia, particularly with respect to the availability and affordability of human as well as animal vaccines and rabies immunoglobulin and alternative biologicals for passive immunization;
- propose new strategies for the control of rabies, particularly in Asia; and
- advocate the prevention and control of rabies worldwide.