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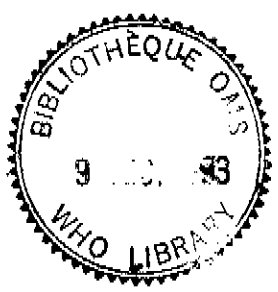
REPORT OF THE SYMPOSIUM ON RABIES CONTROL IN ASIAN COUNTRIES

Organized by the Mérieux Foundation with the co-sponsorship of the World Health Organization

Jakarta, Indonesia, 27-30 April 1993



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1. INTRODUCTION

The Symposium was officially opened by Dr Hadi M. Abednego, Director-General of Communicable Disease Control and Environmental Health (CDC), who welcomed the participants on behalf of His Excellency Professor H. E. Sujudi, Minister of Health of the Republic of Indonesia. Dr F.-X. Meslin, Chief, Veterinary Public Health unit, World Health Organization (WHO), conveyed to the audience the wishes of Dr H. Nakajima's (Director-General, WHO) for a successful Symposium and, on the Director-General's behalf, thanked the Indonesian Government for their hospitality. Dr L. Valette, Mérieux Foundation, welcomed the participants in the name of Dr C. Mérieux.

Dr Soehadji, Director General of the Ministry of Livestock and Animal Husbandry, Jakarta, chaired the first session of the Symposium.

2. COUNTRY REPORTS

2.1 Bangladesh

Bangladesh is a sub-tropical country situated in the South Asia region. It has an area of 144 000 sq. km and a human population of 110 million. No estimates have been made of the dog population, but there is a large number of stray dogs and a lower number of pet dogs.

Rabies is being considered as a priority zoonosis in Bangladesh. Sporadic incidence occurs in all parts of the country throughout the year.

Dogs, cats, jackals and other wild animals are all carriers of the disease, but in Bangladesh most of the rabies cases in both man and animals are due to dog bites.

Anti-rabies vaccine and antisera for human use are produced by the Institute of Public Health under the Ministry of Health and Family Planning. The vaccines are sold under prescription from hospitals for infectious diseases, municipalities, municipal corporations or the civil surgeons' offices at the district level. Cases of dog bites in humans are recorded in these places.

Data on post-exposure vaccine production and application were, in 1992, as follows:

> About 100 000 doses of vaccine were produced (killed phenolized); approximately 50 000 human beings received treatment and 8000 domestic animals. All cases were results of dog bites. However, many bites are not reported due to ignorance and lack of facilities.
>
> There were about 2000 human deaths. The number of deaths in animals is unknown but will probably be higher than the figure for human cases. Human Diploid cell (HDC) and Chick Embryo cell (CEC) vaccines are imported and marketed by private companies but are very expensive compared to the average income.

The Veterinary Public Health Division (VPH), and the Division of the Department of Livestock services, has initiated a country-wide rabies control programme since its establishment in 1985. Under this programme, each "thana" and municipal authority is requested to implement the programme under the supervision of staff from the livestock department.

The programme includes: a) elimination of stray dogs by municipal and "thana" authorities, b) registration and vaccination of pet dogs, and c) logistic support provided by the VPH division to the local authority which includes the supply of posters, leaflets, booklets and having film shows, meetings, seminars etc.

About 10 000 dogs are killed every year and approximately 5000 dogs are vaccinated annually using a live attenuated vaccine produced by the Livestock Department for single-dose pre-exposure vaccination. Approximately 10 000 animals are treated "post-exposure" each year.

Although canine rabies control activities have been initiated in Bangladesh, their success has been very limited due to lack of manpower, diagnostic facilities, coordination within livestock, health and local government organizations and financial support for conducting the control programme. These conditions should be improved. Epidemiological studies of rabies in Bangladesh are also very much needed to formulate an effective control programme.

Considering the present situation, Bangladesh needs to strengthen cooperation with international organizations like the World Health Organization and with neighbouring countries to share common interests and formulate effective control measures.

2.2 Cambodia

Cambodia is a small country of 9 million inhabitants located in the south-western corner of Indochina. During the second half of the 1970's dogs almost disappeared from Cambodia when the country faced starvation and killing. They re-appeared later on, and rabies has since become a serious public concern. In fact, since the mid 1980's, the number of patients who have sought medical assistance after a dog bite has been at least 4000 per year. However, the number of reported deaths due to rabies has been very low, partly because of improved post-exposure treatment delivery, and also as deaths occurring at home (see Table 1) are not usually reported to health services.

Control measures undertaken are as follows:

- Public education and publicity about rabies to promote cooperation in rabies control and proper medical treatment at the time of bite.

- Vaccines used for post-exposure treatment in humans are of tissue origin, imported from Russia and Viet Nam. Twenty to forty thousand doses of rabies vaccine are used yearly and given free of charge to the population by the Ministry of Health, through its Hygiene and Epidemiology network throughout the country.

- Immunization of dogs and cats has been initiated recently by the Veterinary Services, at a cost of US$ 5 per rabies vaccination.

There are no legislative measures to make dog vaccination compulsory, nor to eliminate stray dogs. Diagnostic laboratory facilities are not available.

TABLE 1. NUMBER OF CASES OF ANIMAL BITES AND NUMBER OF DEATHS BY DOG BITES AS REPORTED BY HOSPITALS AND HYGIENE AND EPIDEMIOLOGY NETWORK, CAMBODIA, 1982-1991

Year	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991
Cases	722	270	256	421	596	704	582	567	479	840
Deaths	6	6	3	10	9	2	1	0	12	2

2.3 China

A total number of 42 153 human deaths due to rabies were reported from 1983 to 1992. The annual number of deaths has decreased rapidly and constantly since 1990 (see Table 2).

TABLE 2: NUMBER OF DEATHS AND MORTALITY RATE DUE TO RABIES IN CHINA (1983-1992)

Year	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992
Rabies deaths	5323	6017	4109	4331	5739	4832	5156	3520	2102	1024
Mortality rate*	0.53	0.587	0.397	0.414	0.541	0.449	0.471	0.317	0.184	0.089

* Number of cases per hundred thousand people.

In 1991 rabies was concentrated mostly in nine provinces. These were Hubei, Hunan, Guanxi, Sichuan, and Guizhou (see Map 1). During the decade, Qinghai province and Tibet had not reported deaths due to rabies at all. Dog bites are the main source of disease (96.5%) and cat bites are the secondary source, comprising about 2%. Other vector species were the fox, wolf, house mouse and leopard. The main animal victims were cattle, deer, pigs, horses, donkeys, camels, sheep, bears, jackals, hedgehogs and badgers.

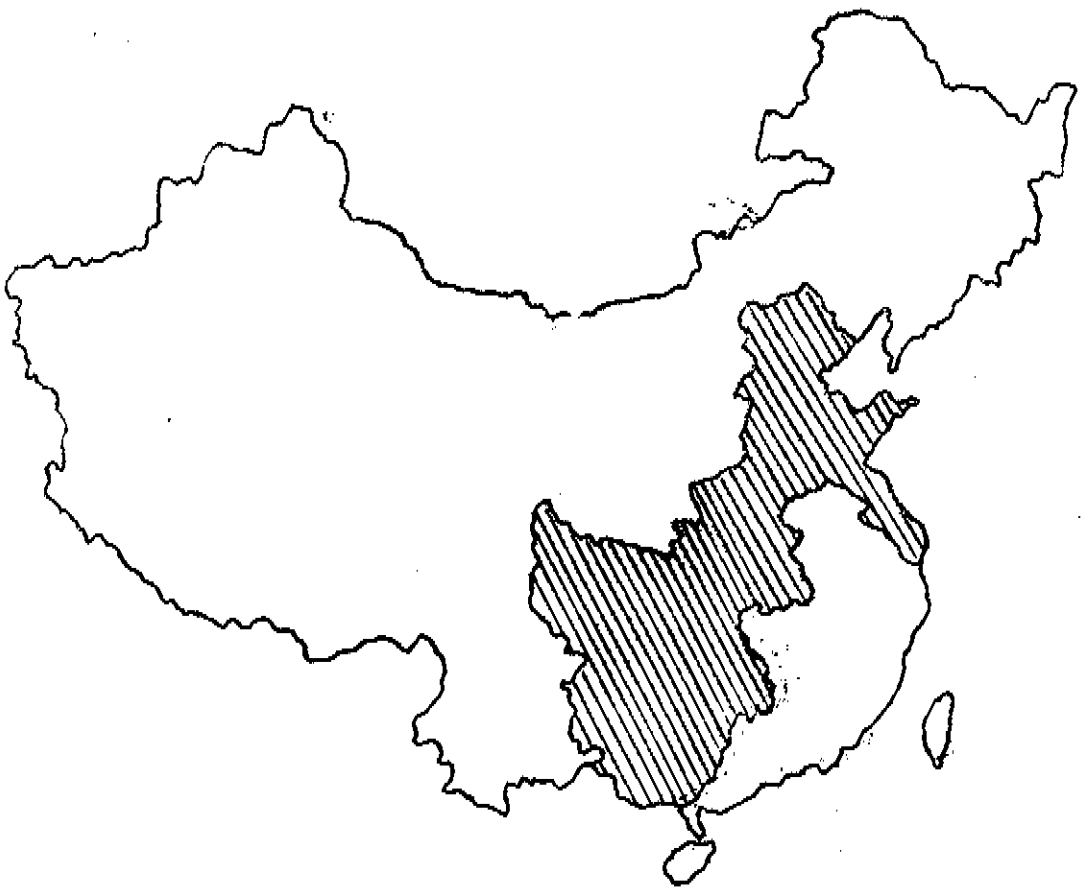
Now the human rabies vaccine used in the whole of China is produced on Primary Hamster Kidney cells (PHKC). The vaccine virus strain is Beijing aG. The NIH value of the vaccine is 2.5 I.U./dose of 2 ml. The price of a dose is about US$ 0.8-1.0. The output of human vaccine is 20 to 22.5 million doses. This amount does not satisfy national needs.

China has no national rabies control programme or coordinated organization or officials at central level. In 1992 the Public Health Ministry set up a Zoonoses Expert Consultative Committee and the Institute of Epidemiology and Microbiology of the Chinese Academy of Preventive Medicine organized six provinces to implement a surveillance programme. In the Ministry of Agriculture there is at present no organization to deal with rabies control. National data on animal rabies are incomplete although it is estimated that there are 150 million dogs in China. Animal rabies vaccines used are made from HEP and ERA strains.

The key measure for human rabies prevention is mass dog immunization to control the disease in its main reservoir. Fifty and 60 per cent of dogs were immunized in 1986 and 1987 in some local areas such as the suburbs of Kuangzhou. This coverage was increased to 80% and 90% in 1990 and 1991.

Human rabies incidence decreased from 70 cases to 1 case in 1991 in these areas. However, as this measure cannot, in general, be used in China, post-exposure vaccine application in humans should be greatly strengthened.

MAP 1. RABIES INFECTED AREA IN CHINA IN 1991



PHKC rabies vaccine has been shown to be efficacious in human beings in some rabies endemic areas like Jiangxi province, where the number of vaccinees increased from 2500 in 1981 to 107 400 in 1989. The number of human rabies cases decreased from 415 to 48. In China as a whole, where the number of persons receiving post-exposure treatment increased from 430 000 in 1981 to about 5 000 000 in 1991, the number of human rabies cases decreased from 7018 to 1014.

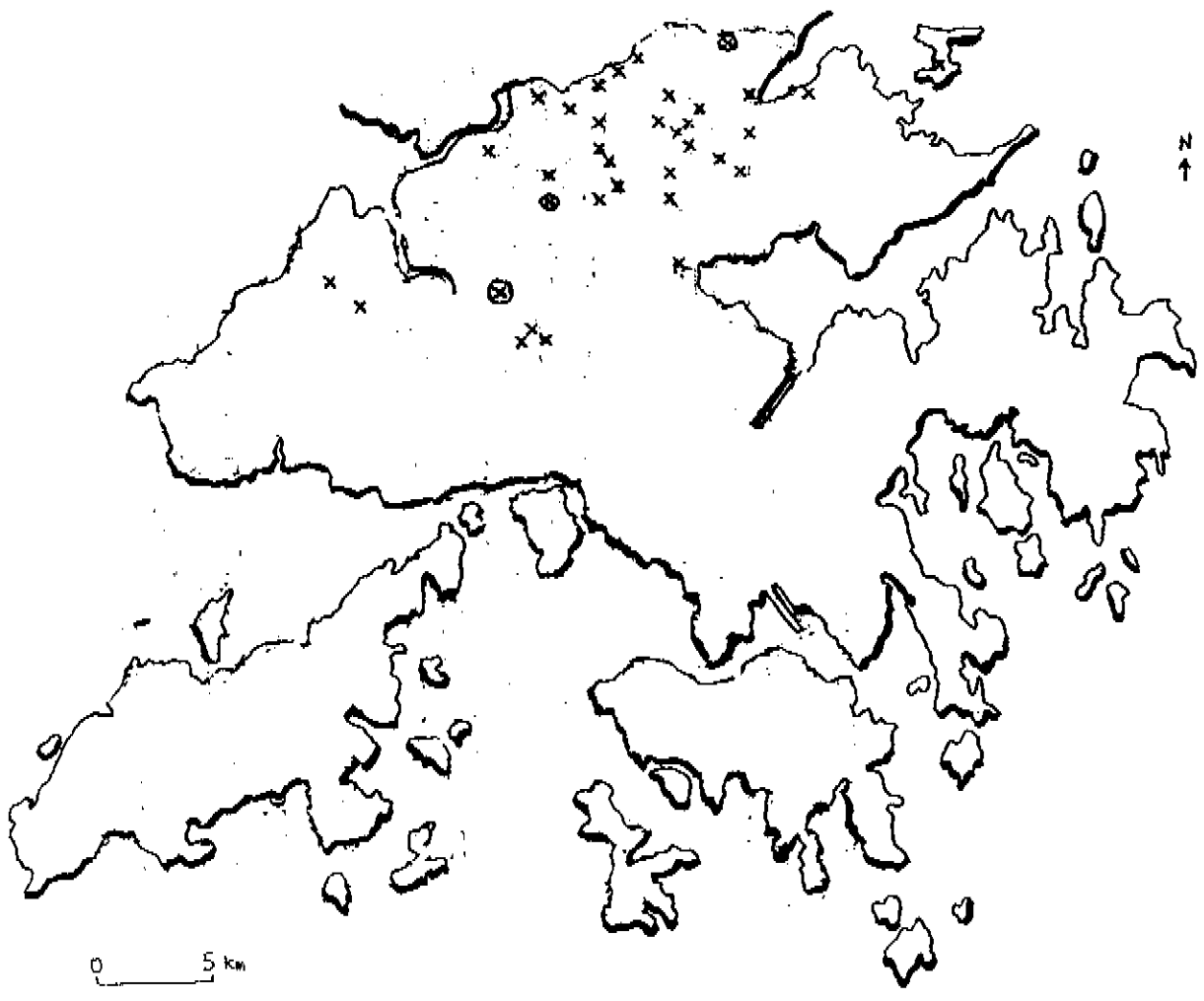
2.4 Hong Kong

Rabies was re-introduced into Hong Kong in 1980 after an absence of 24 years. On institution of active control measures, Hong Kong became rabies free again in 1988. During this period of relapse, 34 animal cases (32 in dogs, 2 in cats) and 8 human cases - which were all fatal - were recorded. The outbreak was confined to the northern areas bordering China (see Map 2), where sylvatic transmission was absent but where dogs were often kept in a semi-feral state. Dog rabies may have spilled-over from China, where a marked resurgence of rabies had been reported.

The strategy is to control the spread in animals (build up an immune belt in border areas through vaccination, mobile vaccination teams providing house-to-house service) and to prevent the disease in humans (using HDC vaccine and human anti-rabies immunoglobulin when appropriate). These are facilitated by a sound surveillance system (notification by doctors, clinics and hospitals, public investigation of bite cases, appropriate laboratory diagnostic techniques) and cooperation between veterinary and public health administrations.

A total of 44 humans exposed to laboratory confirmed rabid animals were given treatment during 1980-1988, with none contracting the disease. As for animals, a vaccination coverage of over 85% or about 35 000 dogs, has been sustained in border areas to date, while the overall territory vaccination coverage is estimated as 50% or about 90 000 dogs.

Map 2. DISTRIBUTION OF RABIES CASES IN HONG KONG (1980-1992)



2.5 India

India is a vast country with a land area of 33 million sq. km, a human population of 844 million, a livestock population of 415 million, and a dog population of 18.2 million.

Rabies is endemic in India and approximately 30 000 people die of the disease every year. Ninety-six per cent of the people seeking anti-rabies treatment are exposed by dogs. More than 500 000 people undergo anti-rabies vaccination every year. The explosion of human as well as animal populations offer chances of increased exposure to rabid animals and increased incidence of dog bite cases. The rabies positivity rate in samples originating from pet dogs has increased to about 68.2 per cent (National Institute for Communicable Diseases (NICD), New Delhi, India).

Each year 40 million ml and 90 million ml of nervous tissue vaccine (NTV) is indigenously produced in 12 centres, for human and animal use respectively. A total of 1 800 000 doses of cell culture vaccine are locally produced or imported for human use and large quantities of these vaccines are also produced and imported for animal use. Extensive studies are being carried out at NICD on the efficacy of brain tissue vaccine and cell culture vaccines in rabies post-exposure treatment as well as on pre- and post-marketing surveillance of cell culture vaccines. Allergic reactions to the vaccines and treatment failure resulting from inappropriate vaccine administration have been reported.

Apart from vaccinations, control of stray dogs is a major programme component in India. This part of the programme is entrusted to the local health authorities. Several pilot projects on dog rabies control have been started since 1984 by local authorities and the Animal Husbandry departments. However, the seizing and killing of stray dogs has not altered the rabies situation in humans or in animals.

In the absence of a comprehensive national rabies control programme, the existing control activities have minimal input in the reduction of rabies cases in animals and humans.

2.6 Indonesia

The first cases of rabies in Indonesia were reported in a water buffalo in 1884, then in a dog in 1889, and in a human being in 1894.

Of the provinces of Indonesia, twenty provinces are infected by rabies. The others are still free (Bali, Nusa Tenggara Barat (NTB), Nusa Tenggara Timur (NTT), Timor Imur, Kalimantan, Basah, Makeku, Irian Jaya).

During the last five years the numbers of cases of canine rabies has decreased in Java, Kalimantan and Sulawesi, but in Sumatra it is on the increase. The total number of cases of canine rabies in 1992 was 1199 cases, of which 1045 cases (87,1%) occurred in Sumatra, 130 cases (10.8%) in Sulawesi, 15 cases (1.3%) in Java, and only 9 cases (0.8%) in Kalimantan.

Fifty four cases of human rabies were reported from 20 provinces in 1992. The incubation period ranged from 9 days to one year with the average being two months. The duration of illness ranged from 3 to 7 days.

Rabies control in Indonesia is implemented based on government legislation and a joint decree between three ministers, namely, the Minister of Health, the Minister of Agriculture and the Minister of Home Affairs. Based on the mutual agreement between these three authorities, the eradication of rabies in Indonesia was commenced in Java and Kalimantan from 1989 to 1993 (five year plan) and then will be followed by a control programme in Sumatra and Sulawesi.

The strategies used in this programme are mass vaccination with a coverage of 70% of the dog population, elimination of stray dogs representing 30% of the population. Epidemiological surveillance and community participation are important programme components.

The objective of the programme is to eliminate canine rabies.

2.7 South Korea

In Korea, outbreaks of rabies have occurred in both domestic animals and human populations since the disease was first recorded in 1906. Thereafter, a massive rabies immunization programme of dog populations was carried out successfully, while the destruction of stray dogs was encouraged and quarantine measures on imported pet animals were strengthened. Due to these efforts towards rabies elimination, Korea has been free from human rabies since 1979 and from canine rabies since 1985 (see tables 3, 4, and 5 below).

Although the country is now free of the disease, control policies will be continued for the safety of human beings and animals.

TABLE 3. INCIDENCE OF CANINE RABIES IN KOREA

Year	Regions			Total
	Central	Yeongnam	Honam	
1980	5	0	0	5
1981	1	0	0	1
1982	(14*)	0	0	(14*)
1983	1	0	0	1
1984	0	0	0	0
1985 to date	1	0	0	1
Total	22	0	0	22

* Rabies in cattle

TABLE 4. INCIDENCE OF HUMAN RABIES IN KOREA

Year	N° of cases	Year	N° of cases
1971	2	1976	1
1972	0	1977	0
1973	1	1978	4
1974	1	1979	0
1975	13	1980 to date	0

TABLE 5. IMMUNIZATION OF DOGS AGAINST RABIES IN KOREA

Year	N° of Dogs	N° vaccinated (%)
1981	1 349 694	511 470 (37.9)
1982	1 355 439	506 434 (37.4)
1983	1 316 814	505 195 (38.4)
1984	1 272 074	482 765 (38.0)
1985	1 002 650	482 571 (48.1)
1986	1 091 536	414 816 (38.0)
1987	1 392 826	299 293 (21.5)
1988	1 931 681	255 148 (13.2)
1989	2 010 268	308 570 (15.3)
1990	1 872 841	268 327 (14.3)
1991	2 088 592	408 108 (19.5)

2.8 Laos

The People's Democratic Republic of Laos is a small country with about 4.2 million inhabitants. Animal rabies, particularly canine rabies, is endemic all over the country. Due to the weak reporting system and poor communication only some provinces including the capital, Vientiane, reported on rabies cases and sent samples for laboratory analysis to the Central Laboratory, Livestock and Veterinary Department, Ministry of Agriculture and Forestry.

TABLE 6. ANNUAL NUMBER OF SAMPLES ANALYZED AND POSITIVE FINDINGS

Year	N° of samples received for analysis	N° of positive findings
1988	90	83 (92.2%)
1989	96	89 (92.7%)
1990	107	97 (90.1%)
1991	112	102 (91.1%)
1992	144	136 (94.4%)

Source: Livestock and Veterinary Department, Ministry of Agriculture, Laos

Some activities concerning rabies control and prevention are carried out: e.g. information through various media: television, newspaper, radio and posters, etc. with emphasis on dog vaccination and human anti-rabies post-exposure treatment after contact with an animal suspected of rabies.

TABLE 7. ANNUAL NUMBER OF VACCINATED DOGS

YEAR	N° OF VACCINATED DOGS
1988	1 800
1989	3 200
1990	3 650
1991	4 520
1992	7 230

Two seminars on rabies prevention were held in 1991 and 1992 in collaboration with colleagues from the Thai Red Cross, Thailand.

TABLE 8. ANNUAL CUMULATIVE NUMBER OF PATIENTS IN VIENTIANE MUNICIPALITY AND SOME NEIGHBOURING PROVINCES (1989-1992)

YEAR	N° of bites	N° of positive tests	N° of vaccinated persons
1989	274	69 (25.18%)	273 (99.6%)
1990	208	96 (46.10%)	184 (88.46%)
1991	503	356 (70.77%)	503 (100%)
1992	820	242 (29.51%)	496 (60.48%)

In conclusion, rabies control in Laos needs to be strengthened and improved in many fields such as:

a) Health education among the population.
b) Adequate procurement of human and animal rabies vaccines.
c) Reporting and surveillance system on bites and rabies cases.
d) Capabilities of provincial diagnostic laboratories.
e) Enforcement of regulations.
f) Collaboration with neighbouring countries, as well as with international agencies for technical and equipment support.

2.9 Malaysia

Rabies is a rare disease in peninsular Malaysia. Since 1982 there have been only two confirmed cases in humans. Nevertheless, it remains a disease of concern. The disease is confined to the northern states of Peninsular Malaysia bordering Thailand. However, the states of Sabah and Sarawak in East Malaysia remain free of rabies despite the presence of the disease in Kalimantan, Indonesia. The virus has not been detected in local bats.

A major rabies epidemic occurred in Peninsular Malaysia from 1930 to 1953 (see Table 9 and Figure 1). The severity of this outbreak prompted the establishment of a National Rabies Control Programme whereby compulsory vaccination of dogs and destruction of stray dogs were instituted. Since then, only sporadic and isolated cases have been encountered and rapidly controlled. A 50-80 km immune belt was established in 1955 covering the

state of Perlis, northern districts of Kedah, Perak and Kelantan, bordering Thailand (see Figure 2). In the immune-belt area compulsory dog licensing and vaccination campaigns are undertaken on an annual basis while destruction of unlicensed and stray dogs is carried out continuously. Tables 10 and 11 summarize the number of dogs vaccinated, licensed and destroyed from 1986 to 1992 in the immune belt, as well as in Peninsular Malaysia. Regulatory measures on importation of dogs and cats have been revised and public education on rabies enhanced.

Nevertheless, issues such as the vaccination coverage, efficacy of stray dog control as well as the quarantine period still need to be resolved and improved.

The preparedness to respond immediately in the face of an outbreak, continued surveillance and prompt notification of rabies cases between neighbouring countries are vital to the success of control and eradication efforts.

TABLE 9. DISTRIBUTION OF CONFIRMED CASES OF RABIES IN PENINSULAR MALAYSIA

Year	Kedah	Kelantan	Perlis	Perak	Penang (P. Wellesley)	Pahang	Selangor	Terengganu	Negri Sembilan	Total
1930	5	3	17	14	–	–	–	–	–	39
1931	1	1	3	1	13(10)	–	5	–	–	34
1932	3	1	7	11	9	–	2	–	–	33
1933	2	2	6	4	1	–	–	–	–	15
1934	1	1	4	1	–	–	–	–	–	7
1935	3	2	5	2	–	–	–	–	–	12
1936	1	–	4	1	–	–	–	–	–	6
1937	5	1	7	2	–	–	–	–	–	15
1938	7	2	10	–	–	–	–	–	–	19
1939	2	1	3	2	–	–	–	–	–	8
1940	1	–	2	1	–	–	–	–	–	4
1941	data not available (Japanese occupation)									
1942	data not available (Japanese occupation)									
1943	data not available (Japanese occupation)									
1944	data not available (Japanese occupation)									
1945	data not available (Japanese occupation)									
1946	13	–	15	55	(5)	–	–	–	–	88
1947	56	1	9	47	(9)	1	–	–	1	124
1948	38	2	6	59	–	–	–	–	–	105
1949	42	2	7	77	(5)	–	2	–	–	135
1950	45	1	4	66	(12)	–	–	–	–	128
1951	22	4	13	84	(9)	–	2	–	–	134
1952	16	1	4	83	(1)	–	112	1	–	218
1953	–	–	–	9	–	–	6	–	–	15
1954	–	–	–	1	–	–	–	–	–	1
1955	–	1	–	1	–	–	–	–	–	2
1956	–	–	1	–	–	–	–	–	–	1
1957	2	–	–	–	–	–	–	–	–	2
1958	1	–	–	–	–	–	–	–	–	1
1959	no cases recorded									
1960	no cases recorded									
1961	no cases recorded									
1962	no cases recorded									
1963	–	–	2	2	–	–	2	–	–	6
1964	no cases recorded									
1965		1	–	–	–	–	–	–	–	1
1966	no cases recorded									
1967	no cases recorded									
1968	no cases recorded									
1969	no cases recorded									
1970	7	–	3	–	–	–	1	–	–	11
1971	no cases recorded									
1972	2	–	–	–	–	–	–	–	–	2
1973	1	–	–	–	–	–	1	–	–	2
1974	3	–	1	–	–	–	–	–	–	4
1975	1	–	–	–	(2)	–	–	–	–	3
1976	no cases recorded									
1977	–	–	1	–	–	–	–	–	–	1
1978	–	–	2	–	–	–	–	–	–	2
1979	no cases recorded									
1980	1	–	4	–	–	–	–	–	–	5
1981	1	–	2	–	–	–	–	–	–	3
1982	–	–	2	–	–	–	–	–	–	2
1983	no cases recorded									
1984	no cases recorded									
1985	–	2	–	–	–	–	–	–	–	2
1986	no cases recorded									
1987	no cases recorded									
1988	no cases recorded									
1989	1	–	–	–	–	–	–	–	–	1
1990	no cases recorded									
1991	1	–	–	–	–	–	–	–	–	1
1992	–	–	11	–	–	–	–	–	–	11
Total	284	29	155	523	76	1	133	1	1	1203

Source : Direction of Veterinary Services, Malaysia

TABLE 10. RABIES CONTROL IN DOGS: PENINSULAR MALAYSIA (including immune belt)

Year	Number of dogs		
	Destroyed	Vaccinated	Licensed
1986	41 503	4 192	127 568
1987	44 295	3 976	121 595
1988	40 692	4 232	83 345
1989	44 275	3 210	91 707
1990	51 980	4 140	223 030
1991	46 680	4 626	109 203
1992	47 736	4 948	85 685
Total	317 161	29 324	842 133

Source: Direction of Veterinary Services, Malaysia

TABLE 11. RABIES CONTROL IN DOGS: IMMUNE BELT OF PENINSULAR MALAYSIA

Year	Number of dogs		
	Destroyed	Vaccinated	Licensed
1986	18 931	4 192	8 235
1987	18 280	3 979	8 121
1988	6 570	4 232	7 002
1989	5 917	3 237	6 422
1990	4 523	4 140	5 387
1991	9 356	4 626	8 467
1992	16 706	4 936	11 542
Total	80 283	29 342	55 176

Source: Direction of Veterinary Services, Malaysia

FIGURE 1. TOTAL OF CONFIRMED RABIES CASES IN MALAYSIA (1930-1992)

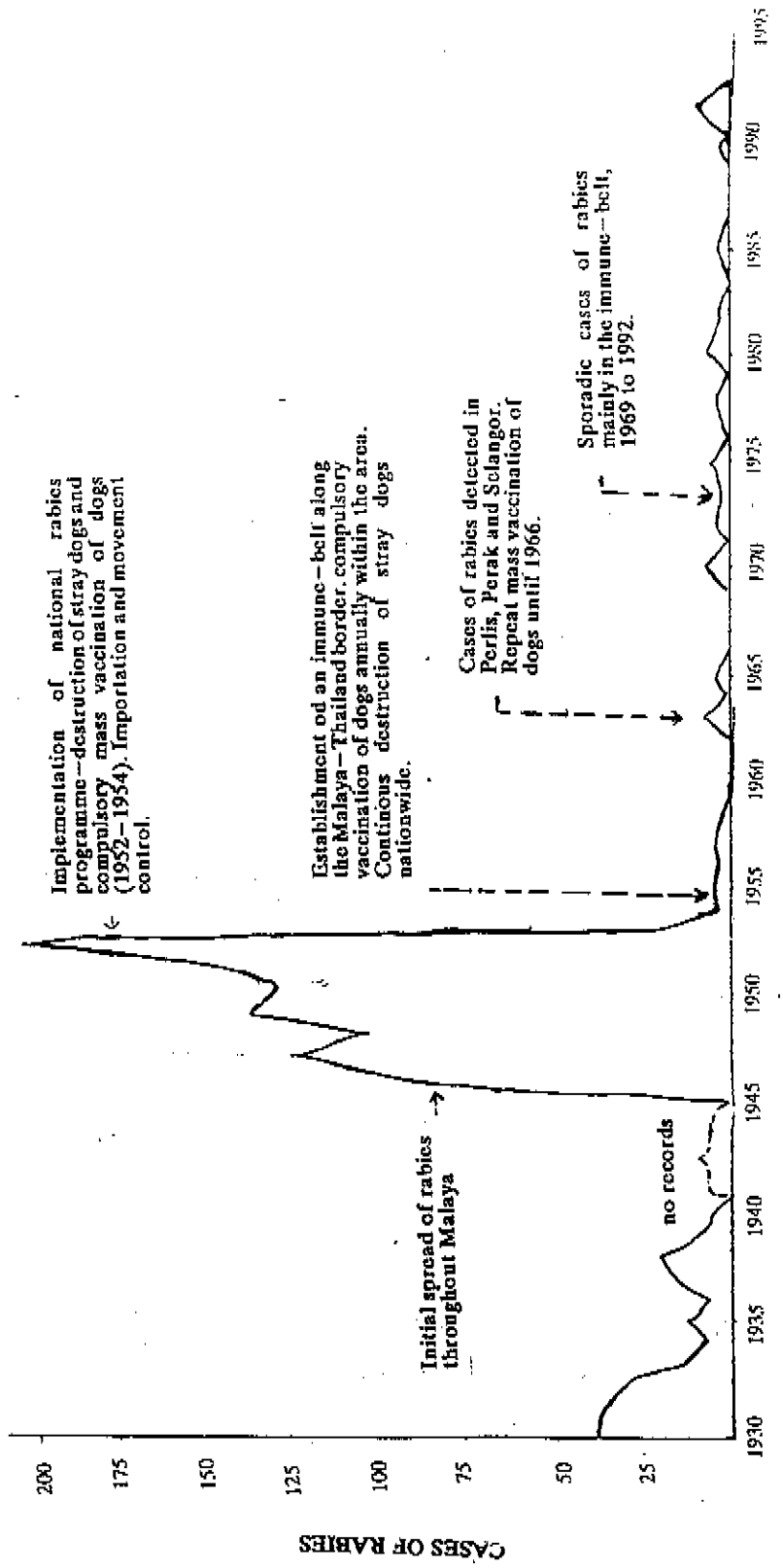
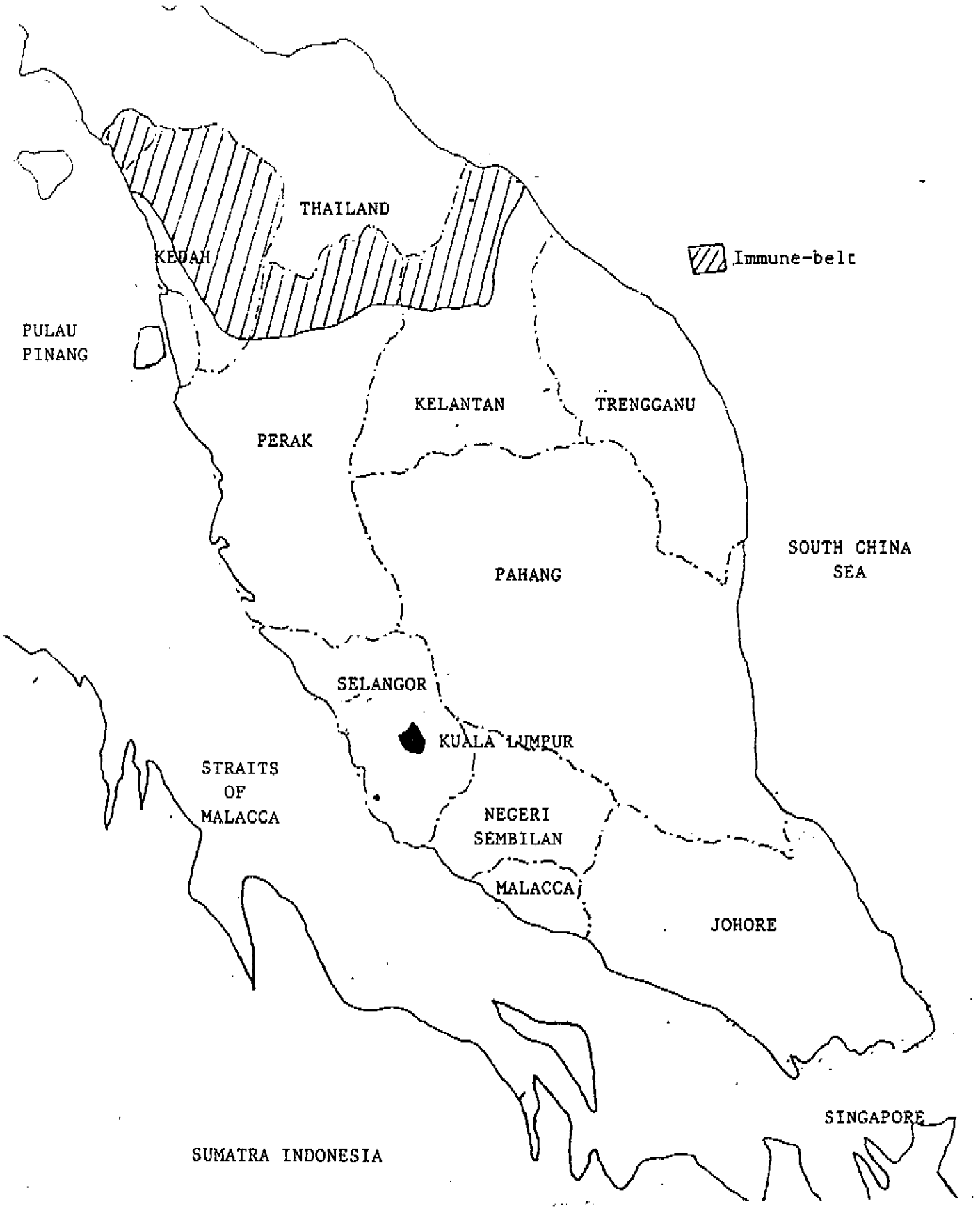


FIGURE 2. THE RABIES IMMUNE BELT OF PENINSULAR MALAYSIA



2.10 Nepal

The Kingdom of Nepal has a human population of 18 million and is bordered by China and by India. Rabies is widespread throughout the Kingdom. Over 150-200 human deaths due to rabies are reported each year. About 30 000 people receive post-exposure treatment annually. No nationwide epidemiological surveillance system exists. However, from 33 districts, 13 medical hospitals keep records of human deaths as well as ON post-exposure treatment.

About 300 000 ml and 50 000 ml of Semple vaccines containing 5% and 20% sheep brain respectively are produced locally for post- and pre-exposure immunization of dogs and other domestic animals. At present the same Semple vaccine inactivated by Beta proprolactone (BPL) is produced for human post-exposure treatment. However, about 600 000 ml of BPL inactivated brain tissue vaccines are imported from India annually for human post-exposure treatment. HDGV, PGEC, PDEV and Vero cell rabies vaccines for humans and Rabisin for pre-exposure of dogs are available in the Kingdom, but are very expensive. In one of the pilot rabies vaccination programmes in Lalitpur in 1987 about 70-80% of dogs were immunized, including stray and community dogs. There is however, no legislation for compulsory dog immunization. A project document for rabies control in Kathmandu Valley has been developed, but funds to implement it are lacking. The country is looking for external financial assistance.

At present, the National Zoonoses and Food Hygiene Consulting Centre is vaccinating pets as well as community dogs in Kathmandu Valley within the framework of an echinococcosis control programme supported by the International Development Research Centre (IDRC), Ottawa, Canada. So far, 2000 dogs have been tested for echinococcosis along with injection of Droncit, and vaccinated against rabies, free-of-charge.

2.11 Philippines

Rabies is widespread throughout the Philippine archipelago. Three hundred human cases (6 cases per million population) have been reported annually over the last decade.

About 450 laboratory-confirmed animal rabies cases are reported each year (98% of the positive are dogs). The disease is virtually confined to dogs. This is about 2% of the 25 000 dogs which are assumed to be rabid each year. Transmission is mainly from dog to dog, and from dog to man or to other mammals.

Animal vaccination has been optional and mainly performed by private practitioners at the initiative of the animal's owner. To a limited extent, vaccines are also administered in public campaigns using vaccines purchased by the government through the Bureau of Animal Industry of the Department of Agriculture.

One million doses of various modern tissue culture animal vaccines are imported annually. Half of these are administered in public campaigns by government officials.

Around 100 000 persons seek medical care following dog bites each year, and about 60% receive post-exposure prophylaxis. Approximately 75% of those receive the Semple vaccine alone. Most persons are treated without waiting for laboratory confirmation of rabies in the suspect animal.

Research activities include efforts to improve diagnostic capabilities in the country, studies on reduced regimens and dose for pre- and post-exposure immunization, as well as epidemiological and operational studies on dog rabies elimination programme implementation.

Rabies elimination is a desirable and realistic goal. The current public health and economic burden of the disease justifies the human and financial resources necessary for elimination. The insularity of the Philippines should facilitate step-wise rabies elimination.

2.12 Sri Lanka

Rabies is endemic in Sri Lanka. The dog is the most important transmitter - responsible for over 90% of cases - with cats coming second. The mongoose is the most frequent wild species found infected. Forty-nine per cent of human cases are in the age group under 20 years and 74% of victims are male.

TABLE 12. NUMBER OF RABIES CASES (PERIOD 1990-92) IN HUMANS AND ANIMALS

Data in humans			Data in animals (positive)
Year	N° of cases	Death rate per 100 000 population	
1990	154	0.89	963 (70.2%)
1991	134	0.77	846 (69.06%)
1992	112	0.64	511 (55.2%)

Source: Weekly epidemiological Bulletin and Public Health Veterinary Services

TABLE 13. RABIES CONTROL ACTIVITIES IN DOGS

Year	N° of dog vaccinations	Dog eliminations
1990	412 586	63 233
1991	336 053	102 292
1992	453 958	98 881

TABLE 14. NUMBER OF HUMAN POST-EXPOSURE TREATMENT DELIVERED - PERIOD 1989-1992

1989	15 910	(927 per one million inhabitants)
1990	35 982	(2096 per one million inhabitants)
1991	26 655	(1553 per one million inhabitants)
1992	22 189	(1293 per one million inhabitants)

Using Semple goat brain vaccine and tissue culture vaccines (Vero cell and PCEC)

2.13 Thailand

Human rabies in Thailand is steadily declining from 370 deaths (0.78 per 100 000 population) in 1980 to 96 deaths (0.17 per 100 000 population) in 1992 (see Table 15).

The real incidence of canine rabies is believed to be approximately 7500 cases per year. The dog is the predominant rabies transmitter (approximately 95% of the total number of positives).

A questionnaire survey in 1992 showed that the ratio of owned dogs to humans was 1 to 6, or 0.7 dogs per household, which gave the figure of approximately 7.6 million owned dogs for the whole country. Most of these dogs (~90%) were raised in rural communities under semi-restriction. Dogs below one year old were 27.5% of the total. Male to female ratio was 61.7 to 38.4. The reported causes of death were illness (58.9%), car accident (32.5%), being killed (4.4%), being destroyed by officials (2.88%) and rabies (1.4%).

Approximately 1.5 million dogs are vaccinated each year. Free vaccination is provided during the campaign in the summer months. During the dog vaccination campaign, the primary health care infrastructure has been very helpful.

Local production of Semple and Suckling Mouse brain vaccines (SMBV) was stopped in 1988 and 1992 respectively. Cell culture vaccines (HDCV, PCEC, PVRV, PDEV) are now available. Recommendations on improvement of post-exposure treatment services have been disseminated to all concerned.

At present, other activities beside dog immunization, including control of dog population, post-exposure treatment of humans, health education and surveillance are being strengthened. Intersectoral and intercommunity cooperation is also promoted.

It is thus generally anticipated that through these strengthening efforts, rabies will be brought under control and eliminated from the southern part of the country northward in the near future.

TABLE 15. HUMAN RABIES CASES IN THAILAND, 1982-1992

Year	Human rabies cases	
	Number	Rate per 100 000 population
1980	370	0.78
1981	339	0.70
1982	300	0.61
1983	288	0.58
1984	288	0.45
1985	210	0.41
1986	179	0.34
1987	212	0.39
1988	213	0.39
1989	212	0.38
1990	185	0.33
1991	159	0.28
1992*	96	0.17

* As of March 1993

2.14 Viet Nam

The results of the National Dog Rabies Control Programme in Viet Nam over a period of ten years (1982-1992) are given below:

- One to three million doses of live Flury vaccine were produced for the mass vaccination of dogs against rabies.

- Mass dog vaccination campaigns were carried out successfully at district and provincial level by the National Programme for Rabies control. This programme has covered 22 provinces and over 100 districts in the north.

- From 1983 to 1991, the number of vaccinated dogs increased markedly: from 30 000 in 1983 to 950 000 at the end of 1991.

- With the huge dog population (15 million), the present quantity and quality of vaccine do not suffice to control rabies in the whole country. International assistance would be highly appreciated to upgrade vaccine production technology, vaccine storage and rabies diagnostic laboratories.

In recent years, in the northern part of Viet Nam, the number of persons bitten by rabies-suspect animals and human deaths by rabies has been increasing. However, the ratio of human deaths by rabies to the number of persons immunized with rabies vaccine has reduced markedly, especially since Fuenzalida rabies vaccine started to be used. Three periods could be distinguished as shown below:

TABLE 16. NUMBER OF RABIES POST-EXPOSURE TREATMENTS AND HUMAN DEATHS DUE TO RABIES (PERIOD 1955-1991) IN THE NORTHERN PART OF VIET NAM

Periods	N° of vaccinees		N° of human rabies deaths		ratio (B/A)
	Total	per year A	Total	per year B	deaths/vaccinees (x 100)
1955-1972	120 840	6 713	2 689	149	2.2
1973-1985	360 151	27 704	2 388	184	0.7
1986-1991	690 334	115 055	2 037	339	0.3

Since 1987, in all provinces/cities in North Viet Nam, vaccinees' cards and rabies vaccination registers have been introduced to follow-up vaccinees and deaths due to rabies. Therefore data collection has become relatively complete and precise. Results have been as follows:

TABLE 17. NUMBER OF RABIES POST-EXPOSURE TREATMENTS AND HUMAN DEATHS DUE TO RABIES (PERIOD 1987-1992) IN THE NORTHERN PART OF VIET NAM

Year	N° of vaccinees	N° of deaths	Vaccinees per 100 000 inhabitants	Deaths per 100 000 inhabitants	Deaths/ Vaccinees
1987	87 463	261	298.71	0.89	0.30
1988	111 980	349	375.68	1.17	0.31
1989	108 931	317	360.44	1.05	0.29
1990	142 237	396	462.33	1.28	0.28
1991	144 692	425	462.9	1.36	0.29
1992	118 416	285	197.36	0.47	0.11

Dogs are usually the source of rabies transmission to humans (more than 97% of cases, and cats account for about 3%).

Ninety-eight per cent of human cases are reported in unvaccinated patients or in people who are vaccinated too late or treated by traditional medicine.

According to the report of the Pasteur Institute, Nha Trang, in 1990, in the Central area, the number of vaccinees was 12 502 with 5 human deaths and in 1991 the number was 13 120 with 16 deaths. In the first semester of 1992, there were 8009 vaccinees and 5 deaths.

According to the report of the Pasteur Institute, Ho Chi Minh City, in the Southern part from 1986 to 1990, there were 579 229 vaccinees bitten by animals suspected to be rabid. The annual average was 115 849 vaccinees. The number of human deaths due to rabies was 95. That is, 19 cases per year on average.

3. TECHNICAL PRESENTATIONS

3.1 Oral vaccination of foxes in France

Three different vaccinal baits have been tested on a large scale in France. The viruses used are as follows:

- SAD-B19 : a live attenuated cloned rabies strain of SAD
- SAG-1 : a low pathogenicity mutant strain of SAD Berne
- VRG : a vaccinia virus recombinant coding for the rabies glycoprotein

The baits are distributed by helicopter. Using four helicopters, 3000 km^2 can be covered in a day, at a rate of 13 baits per square kilometre. Two vaccination campaigns are organized per year, one in spring and another in autumn. After two campaigns at least 75% of foxes have consumed baits as revealed by tetracycline research in foxes; and more than 70% consumed at least two baits. Conversely, at least 93% of baits are consumed by non-target species. These results illustrate that innocuity tests in non-target species are a prerequisite for the release of a candidate vaccine in the field.

A marked decrease of rabies incidence has been observed in large areas where fox oral vaccination campaigns have been organized regularly.

Differences in the rapidity of the decrease have however been noted for the different vaccine-baits and may be linked to differences in their respective thermo-stability under field conditions.

3.2 Safety of oral rabies vaccines

Two WHO consultations defined the safety requirements and criteria to be followed when conducting field trials for oral vaccination of dogs against rabies (Geneva, 1-2 March 1989 - WHO/Rab.Res./89.32, and 21-22 July 1992 - WHO/Rab.Res./92.38. These recommendations were endorsed by the recent WHO Expert Committee on Rabies (WHO Technical Report Series No. 824).

As dogs often have a closer association with human beings, and with children in particular, the likelihood of direct exposure of humans to a vaccine-bait is higher during campaigns for the oral vaccination of dogs than in the context of wildlife vaccination. Thus, safety requirements must be more stringent in the former case.

Before any candidate vaccine is released, its safety should be proven in several animal models. Steps to be followed are outlined in Table 18.

As part of risk assessment during release the following should be carried out:

- establish an intense surveillance system for human exposure to vaccine;
- prescribe anti-rabies treatment if there has been contact between the vaccine and the mouth, nose, eyes or a wound;
- prescribe pre-exposure immunization for laboratory workers handling the vaccine.
  (The last two recommendations do not need to be applied for rabies recombinant virus which cannot induce rabies).
- characterize in treated areas, rabies isolates using monoclonal antibodies or other appropriate techniques.

Several vaccines were tested according to these recommendations. Results are presented below:

- Results of safety tests of candidate vaccines in primates (see Table 19);
- Results of the evaluation of rate of human contacts with rabies vaccine baits in France: 1 out of 10 000 baits released in the field was picked up by people often after their dogs had found them. The proportion of human post-exposure treatments following contact with a bait was 0.002%. No disease followed bait distribution.
- The steps followed in the United States for the release of VRG in the field conform with the recommendations of the United States Department of Agriculture for vaccine purity, potency, safety and efficacy.

TABLE 18. ANIMAL MODELS TO BE APPLIED ON VACCINE CANDIDATES FOR ORAL VACCINATION OF DOGS (INNOCUITY TESTS)

animal species and characteristics	minimal number	treatment	requirement
young dogs (3-6 months)	10	per os 10 x [ ]	no disease
dogs	10	per os 10 x [ ]	no sal. excr. after 3 days no latency after 6 months
Wild rodents (of each of the most common local species)	10 to 50 10 to 50	per os 0.05 ml field [ ] i.m. 0.05 ml field [ ]	less than 10 % develop sickness
5 other domestic or wild species	not specified	per os field [ ] vol. according to body weight	
primates	10	per os 10 x [ ]	no mortality during 90 days
immunocompromised primates	10	per os 10 x [ ]	no mortality during 90 days
nude mice	not specified	per os, & i.c, & i.m., ...	results to be compared with those obtained in immunocompetent individuals
SCID mice or other immunodeficient lab. model	not specified	per os, & i.c, & i.m., ...	

TABLE 19. SUMMARY OF SAFETY TESTS ON PRIMATES TO ASSESS CANDIDATE VACCINES FOR ORAL VACCINATION OF DOGS

	species	treatment	result	authors
SAD-Bern	4 baboons *Papio ursinus*	per os 107.8 TCID	2 rabid 11, 13 days	Bingham *et al.*
SAG2	5 baboons	per os 10^9 PFU	no disease at 90 days	Bingham *et al.*
VRG	24 squirrel monkeys (+ 2 controls) *Saimiri sciurus*	scarifications 10^8 PFU	no disease in 6 individuals sacrificed at day 7, 14, 21, 60	Rupprecht *et al.*
	8 chimpanzees *Pan troglodytes*	per os $10^{7.2}$ PFU	no disease at 60 days	
	the same chimpanzees + 3 (+ 2 controls)	per os 10^9 PFU	no disease at 28 days (+)	

3.3 Control of rabies in the Philippines by dog vaccination

It has been demonstrated in past vaccination campaigns that rabies can be eliminated in certain areas of the country by dog vaccination. These areas are the cities of Manila and Dumaguete and the provinces of Signijar and Guimaraz. However, the absence of sustained programmes led to the reintroduction of the disease in these areas.

The dog remains the reservoir of rabies: 98% of laboratory diagnosed animal rabies cases in the Philippines are dogs.

Embryonating egg rabies vaccines prepared with the modified live virus rabies strains, LEP and HEP were used in the past. Currently, rabies vaccines of cell culture origin are being used for the National Rabies Programme. A study of the serological responses of dogs to four brands of cell culture vaccine was made using RFFIT. It was found that 30 days post vaccination, 99.47% of the dogs vaccinated with vaccine A, 98.19% of those vaccinated with vaccine B, 100% of those vaccinated with vaccine C, and 86.4% of those vaccinated with vaccine D had antibody levels of $\geq$ 0.5 I.U.

The management structure of the National Rabies Program ensures multi-sectoral collaboration of the different government agencies involved as well as the non-governmental organizations. The contribution of the private sector both locally and internationally has been significant.

3.4 Dog rabies vaccination: recombinant poxviruses used by the oral and parenteral routes

The safety and potency in dogs of two recombinant poxviruses coding for the rabies glycoprotein gene were studied in dogs.

The vaccinia rabies recombinant (V-RG) widely used at present in the field for the elimination of fox rabies in Belgium and France, has been tested in dogs by oral and parenteral routes. The baiting system, developed for foxes may be applied to dogs. Many experiments in confined animals demonstrated the complete safety at different dosages (from $10^{6.5}TCID_{50}$ to $10^{9.5}TCID_{50}$). Protection using $10^{9.5}TCID_{50}$ against a virulent challenge was complete 18 months after bait ingestion. At a dosage of $10^{8.5}TCID_{50}$ per bait, two dogs out of three resisted challenge six months post vaccination and all dogs (five out of five) were protected against a challenge 13 months post vaccination. After ingesting two baits, all dogs were protected.

The V-RG can be used by the parenteral route, but a second poxvirus recombinant is being developed for subcutaneous administration: a canary poxvirus rabies recombinant (ALVAC RG-vCP_{65}). The safety of this virus is assured by the abortive replicative cycle of this avian virus in mammal cells (see section 3.10). All experiments demonstrated the potency of vCP_{65}. The minimum immunizing dose is $10^{6.7}TCID_{50}$ for dogs. After one inoculation, 10 out of 11 dogs were protected 2 years after immunization. Seroconversion was rapid but transitory. All vaccinated dogs were protected against challenge in spite of a lack of detectable virus neutralizing antibodies (VNA) at the time of challenge.

3.5 Impaired immune-responses in human rabies

Factors that determine rabies virulence in man are poorly understood. When symptoms develop, a fatal outcome must be expected. Studies suggest that defects in immune activation and in natural killer (NK) cell and

antibody responses in the early phase, in addition to an immunopathogenetic mechanism of T-cell dependency are responsible for rabies virulence.

Rabies virus neutralizing antibodies (VNA), regarded as the major immune mechanisms for protection, appear in the serum of only one-quarter of the patients. The fact that VNA appear as early as 3 or 4 days after clinical onset suggests that immune recognition must have developed during the incubation period. Antibodies in three antibody positive rabid patients (2 encephalitic and 1 paralytic) reacted mostly against the rabies glycoprotein (G) but not against the nucleoprotein (N). These results suggest that the rabies N protein which is an essential component for neutralizing antibody production, may be involved in the lack of, or inefficient production of rabies virus neutralizing antibody in human rabies.

Examination of cytokines showed that patients with paralytic rabies demonstrated S-IL2R less frequently than patients with encephalitic rabies (1 of 6 versus 12 of 22 respectively). It was also observed that rabies patients with paralytic rabies usually survive longer. This suggested that an immune process may affect disease presentation. IL-6 titres were high only in sera of patients with encephalitic rabies (5 of 22 compared with 0 of 6 with paralytic rabies). Six of 26 non-vaccinated rabid patients had serum antibodies during their clinical phase. Four of these antibody-positive patients presented rabies encephalitis. Proportions of cells with Lev 12 marker (B cell) were also diminished in three patients with paralytic rabies (2%, 4% and 9%) when compared to those in four patients with encephalitic rabies (15%, 20%, 20% and 22%) (normal 17 ± 3, n=18). The lack of IL-6 and diminution of circulating B cells together with a defect in nucleoprotein recognition may contribute to suppression of antibody response, particularly in paralytic rabies cases.

Study of cellular immunity by <u>in vitro</u> lymphocyte proliferation assay to rabies antigen showed that patients who have cellular responses (6 of 9) tend to die faster and present encephalitic rabies. None of the patients with paralytic rabies had such a response. This correlates with S-IL2R data and suggests that immunopathogenetic mechanisms play a role in accelerating death.

Regarding NK cell response, there was no difference in NK cell number or response as determined by a Cr^{51} release microcytotoxicity assay using K 562 target cells between rabies patients and controls. However, a significant enhancement of NK activity was observed in four rabies patients and in ten normal controls after interferon-alpha and IL-2 administration. None of the four non-fatal non-rabies encephalitic cases showed such enhancement, suggesting that NK cells of rabies patients are not fully stimulated and NK enhanced activity reflects a naive condition.

Mechanisms responsible for the lack of immune responses, particularly in patients with paralytic rabies, remain to be investigated.

3.6 <u>The experience of the Thai Red Cross in rabies prevention</u>

The Queen Saovabha Memorial Institute (QSMI) has developed an intradermal (ID) economical rabies post-exposure treatment (PET) regimen that can reduce substantially the amount of cell culture vaccine required for PET. The QSMI guidelines for PET in 1987 were endorsed by the WHO Expert Committee on Rabies in September 1991.

Semple and suckling mouse brain vaccines were abandoned in 1986 and 1988 respectively. An ID regimen using cell culture vaccines of high potency was shown to be as effective as a conventional five-dose intramuscular PET regimen in terms of production and maintenance of VNA as well as cellular immune response determined by lymphocyte proliferation test to rabies antigen. The ID regimen efficacy was tested in 100 severely exposed individuals bitten by rabid dogs. All vaccinees survived after one year. When applied together with the first ID doses of vaccine, rabies immunoglobulin (RIG) had no interfering effect on VNA development. The QSMI ID regimen (2-2-2-0-1-1) consists in 0.1 ml. injections at two sites on days 0, 3 and 7, and 0.1 ml injection at one site on days 30 and 90. As at April 1993 more than 50 000 people have been treated using this PET regimen. The ratio of ID-regimen to IM-regimen has been approximately 2:1 in a total annual number of 12 000-15 000 treatments. Approximately one-third of these vaccinees also received RIG. More than 20 000 patients received equine rabies immunoglobulin with a complication rate of less than 1%. Adverse effects following ERIG application were mild, e.g. rashes, fever, etc. None of them presented anaphylaxic shock. The use of steroids was never required.

Since 1987 QSMI has promoted PET application as soon as possible after the suspect contact and discontinuation when the dog or cat at the origin of exposure remains healthy after ten days of observation. Inquiries regarding dog behaviour at time of exposure are not considered useful. RIG must be applied regardless of the location of the bite when exposure is considered severe as judged by evidence of bleeding. As much RIG as possible should be infiltrated at and around the wound and the remaining amount should be injected deeply in the gluteal muscles.

Regarding diagnosis in animals, fluorescent antibody test (FAT) gave false negative results in 0.1%-0.2% of the positive samples examined. This figure becomes higher once specimens decompose (starting 48 hours after death). Nested PCR, a double-gene amplification technique, has been shown to be 100% sensitive without any false positives in 500 consecutive dog brain specimens. It can also detect rabies genome in specimens left at room temperature for 72 hours. This suggests that nested PCR may be applicable for use as a confirmatory test in FAT-negative specimens.

This PET protocol, and the development of an affordable ID regimen led to a successful protection of over 50 000 persons, with only a single report of PET failure in a person who sought treatment 5 days after exposure.

3.7 Rabies immune globulin (RIG) - Routine use and prospects

The three key points for proper rabies post-exposure treatment are (a) the local treatment of the wound, (b) RIG administration and (c) vaccine application. Passive immunotherapy in rabies aims at neutralizing the rabies virus at wound level before it reaches the nervous system.

The work of Balthazard and Bahamanyar in 1954 demonstrated the benefits of applying RIG together with vaccine in bitten subjects. In this study, the death rate decreased from 60% to 8.3%. A 100% survival rate was obtained using a dose of 40 I.U./kg of ERIG associated with HDC vaccine in an efficacy field trial carried out by the same authors in 1976.

In healthy volunteers, a dose of 20 I.U./kg of human RIG (HRIG) was shown to provide adequate titres and not to interfere with the active immunization using Duck embryo vaccine of high potency (Loofbourow and

Cabasso, 1971). Subsequent field trials confirmed the efficacy of HRIG-cell culture vaccine combination.

In 1992, the 8th WHO Expert Committee on Rabies recommended to apply both RIG and the vaccine, in all category III exposures. In addition, taking into account animal experiments and reported cell culture vaccine failures, it was recommended to perform local wound infiltration (if anatomically feasible) with as much as possible of the recommended dose, the rest of the dose being injected IM, intraglutally.

Sound clinical trials on RIG (human or equine) and vaccine interaction should be conducted, special attention being paid to the route of vaccine administration (e.g. intradermal), shortened vaccination schedule, dose, vaccine and batch potency.

In rabies post-exposure treatment, vaccine and HRIG (safe homologous Ig G) is clearly the best choice. This treatment may not be available or affordable in developing countries where more than 90% of the 30 000 estimated annual deaths occur.

Currently purified ERIG are safe, inducing serum sickness in less than 1% of the recipients. Efforts are underway to further improve the industrial purification process and to increase the specific ERIG activity (I.U. rabies activity/mg protein content), which is strongly linked with safety.

3.8 Dog ecology and rabies vaccination

Dog ecology studies can contribute to the evaluation of dog accessibility to different vaccination strategies. In Tunisia parenteral rabies vaccination proved to be a useful strategy to control rabies.

Seventy-five to 85% of dogs in some areas of Tunisia were accessible to parenteral (IM or SC vaccination, see Figure 3). However, ownerless dogs and owned dogs which cannot be captured and restrained are not accessible to parenteral vaccination. In Tunisia the proportion of ownerless dogs never exceeded 15% of the total dog population. Seven to 14% of owned dogs (juvenile and adult) could not be handled by their owners. The theoretical vaccination coverage of 75-85% is therefore hardly reached through parenteral vaccination under field conditions. In some areas in Tunisia vaccination coverage varying between 33 and 70% of the total dog population was observed. This coverage corresponded to 40-90% of all theoretically accessible dogs. Unmotivated dog owners as well as logistical, operational and methodological problems were responsible for the difference between theoretical and actual vaccination coverage.

Oral vaccination of dogs would permit the immunization of dogs inaccessible to parenteral vaccination. These very dogs through their behaviour are at high risk of contracting and transmitting rabies. Their immunization could be decisive as regards the eventual success or failure of a rabies control programme. The Tunisian experience showed that it is difficult for a country to maintain parenteral vaccination efforts for several years. A combination of parenteral vaccination of easily accessible owned dogs and oral immunization of inaccessible dogs whether ownerless or owned by two bait distribution techniques - bait distribution to dog owners and bait distribution in the field - would allow to reach a high and homogeneous vaccination coverage. Theoretically, only very small puppies unable to consume a bait would be excluded from oral immunization (see Figure 4).

When baits are distributed according to the Wildlife Immunization model, availability of baits to dogs may become an important limiting factor. Bait availability to dogs is determined by the level of competition for the baits between the target (dog) population, vaccinated owned dogs and non-target or other (wild or domestic animals) species.

Oral vaccination is a promising adjunct to parenteral vaccination. The development of this method is not limited to the elaboration of a functional vaccine-bait system for dogs. A careful evaluation of different safe and efficacious bait distribution techniques is also needed. In addition, efforts should be increased to establish and maintain good rabies surveillance and systematic assessment of the vaccination coverage in order to define the optimal combination of these different vaccination techniques.

FIGURE 3. ACCESSIBILITY OF DOGS TO PARENTERAL VACCINATION IN TUNISIA

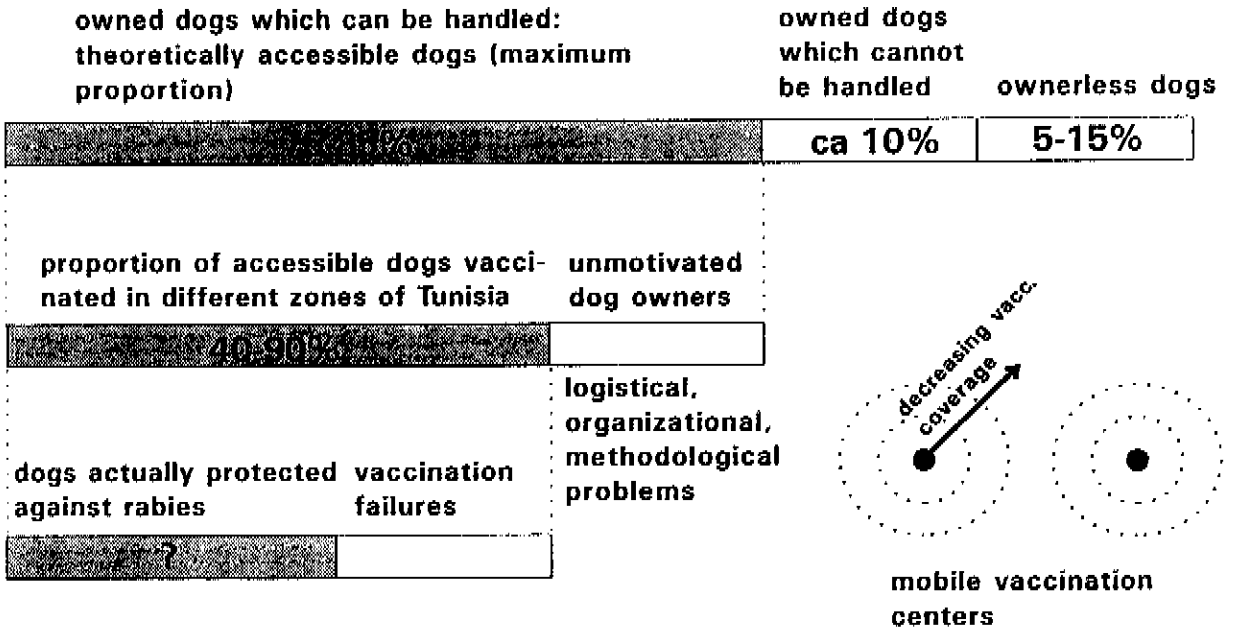
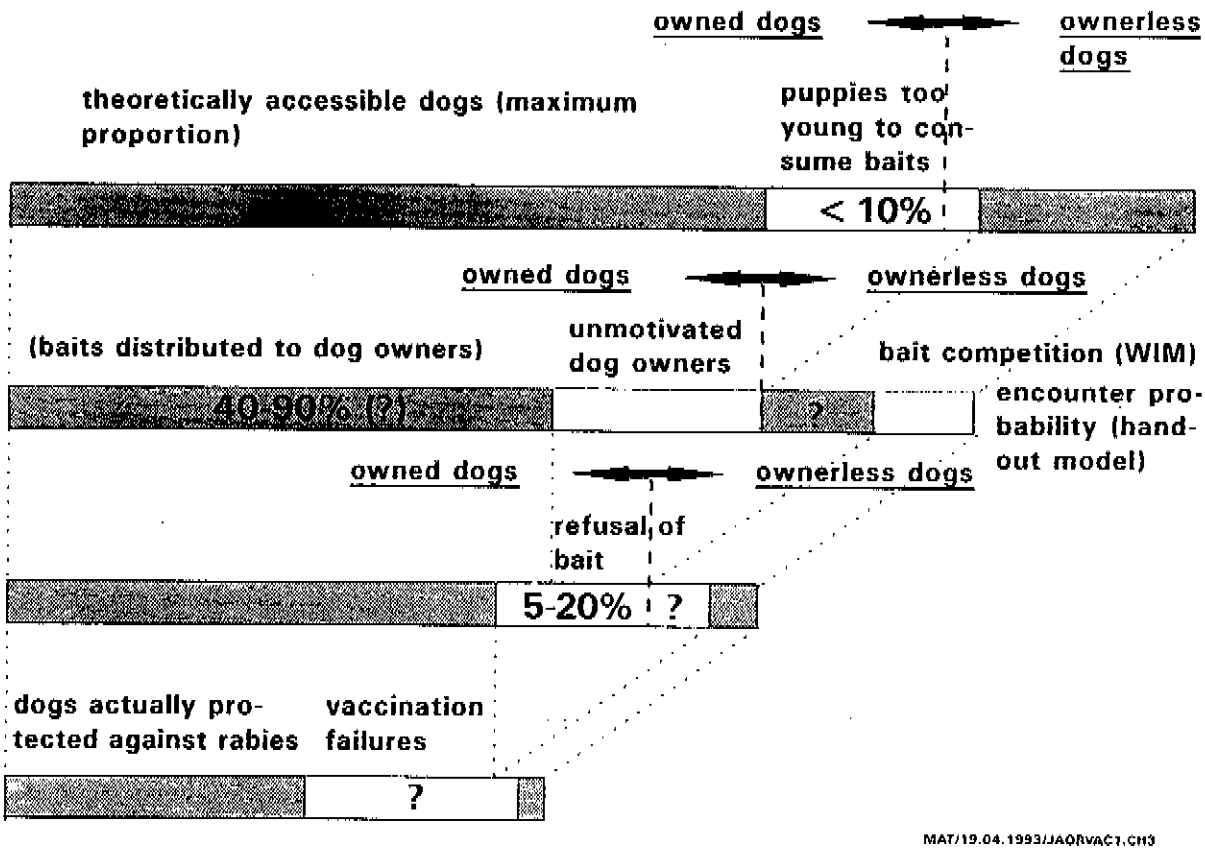


FIGURE 4. ACCESSIBILITY OF DOGS TO ORAL VACCINATION IN TUNISIA



3.9 Regimens for rabies pre- and post-exposure treatment

A critical evaluation of reduced intramuscular pre- and post-exposure immunization regimens was carried out in France.

With regard to pre-exposure regimens, a trial has been performed simultaneously comparing Purified Vero cell rabies vaccine versus Human Diploid cell vaccine and primary immunizations with two injections at (day 0, day 28) versus three (day 0, day 7, day 28) injections with a booster dose one year later. Immunogenicity was studied during five years after immunization. This trial showed that the primary immunization must be performed with three injections, particularly when PVRV is used. A booster dose one year later would appear indispensable. Further booster doses may be considered every five years after a three shots primary immunization. The additional cost of the second injection on day 7 compared to a two-injection regimen is offset by the fact that booster injections are needed less frequently. Therefore, in order to achieve a ten-year immunity, the cost/efficacy ratio would be in favour of the three-injection regimen.

With reference to post-exposure treatment, several trials have been conducted with the 2.1.1 intramuscular regimen (1 ml on two sites on day 0, and 1 ml on days 7 and 21) compared to the 5-injection intramuscular regimen. VNA probably appear more quickly (as early as day 14) but VNA titres are not

constantly maintained at appropriate levels until day 90. Simultaneous application of immunoglobulin affects the antibody response from day 14 to day 90.

The design and the results of the trials are heterogeneous. Some of them revealing methodological deficiencies. Before arriving at a definitive conclusion, further trials will probably be needed. After careful review of results of immunogenicity studies using the specific vaccine and regimen under consideration in volunteers (non-exposed) efficacy may be initiated. These trials should:

- (using a large sample (e.g. 100 per each group) compare immunogenicity and efficacy of the vaccine and regimen under test with a reference vaccine and regimen (e.g. HDC vaccine applied according to the 5 dose IM regimen);

- randomly allocate patients with the same level of exposure (e.g. category III) to the different groups (e.g. vaccine and regimen under test versus reference vaccine and schedule). Immunoglobulins may be applied according to the category of exposure selected for the trial;

- ensure homogeneity of materials, biologicals, staff, and surrounding conditions to decrease the risk of bias.

3.10 Application of a canary pox recombinant rabies vaccine in humans

Several breakthroughs in human rabies vaccines manufacturing processes have been observed, during the past decades. Different stages starting from primary cell culture vaccines to HDC and finally to continuous cell line systems (e.g. Vero cell) have brought continued improvements. PVRV has demonstrated its safety and efficacy in numerous field trials involving patients with proven rabid exposure. Attempts have been made to improve the affordability of PET by using reduced regimens alternative to the five intramuscular full dose regimen. Nowadays, PVRV is the only current vaccine that has been tested in comprehensive field tests by ID post-exposure immunization. Further progress has led to the conception of a genetically-engineered vaccine expressing the rabies glycoprotein (V-RG) that was shown to be effective in foxes and raccoons as well as in some domestic species (see section 3.4). Theoretical risks associated with the use of the vaccinia virus as a vector in humans may be avoided by using another expression system: the canary pox virus.

The safety and efficacy of canary pox virus recombinant (ALVAC RG-VCP_{65}) were studied in different animal species confirming the fact that avian pox viruses do not replicate completely in mammalian cells. This abortive replication permits the early presentation of glycoprotein to the immune system. Twenty-five volunteers were randomly administered two subcutaneous doses at four weeks' interval ($10^{3.5}$, $10^{4.5}$, $10^{5.5}$ $TCID_{50}$ respectively), or HDC vaccine (potency: 6.52 I.U. per dose).

Twenty-eight days after the second dose, all canary pox recombinant vaccine recipients had rabies neutralizing antibody levels of at least 0.5 I.U./ml. Booster injections at six months resulted in an increase in rabies antibody titres in all subjects, including those having received primary HDC immunization.

Side effects were mild and transient and consisted in tenderness and redness. They confirmed the non-replication of avian pox virus.

Pre-existing immunity elicited by either the pox virus vector or rabies glycoprotein had no blocking effect on responses to booster vaccination with HDC or ALVAC RG.

Further research should include larger scale safety and immunogenicity trials, evaluation of higher doses and other routes of administration. Promising results obtained with other canary pox virus recombinant vaccines may also modify future strategies for human vaccinations.

3.11 Rabies physiopathology

To demonstrate that rabies virus induces brain function modifications, neurobiological tests have been used to analyze brain pathogenesis mechanisms. Alterations of several neurotransmitters involved in the expression of rabies disease were studied.

Uptake and release of gamma amino butyric acid (GABA) in infected embryonic rat brain neuronal cultures were measured. Both uptake and potassium-evoked release of GABA from virus-infected neurons were modified suggesting that hyperactive or depressive behaviour in rabies may be triggered by alterations in the GABA system.

The potassium-evoked five hydroxytryptamine (5-HT) released from rat cerebrocortical synaptosomes was decreased in virus-infected samples. In contrast, an increased release of noradrenalines (NA) from infected synaptosomes suggests that infection of the CNS may induce imbalance in serotonergic and adrenergic regulatory mechanisms resulting in pathological behaviour modifications.

The reciprocal interactions of the nervous system and of the immune system during rabies virus infection have been studied. A significant down-regulation of IL-1 receptors was observed, suggesting that this cytokine may be involved in virus-induced neuronal changes.

An antiviral effect using a selected family of excitatory amino-acid non-competitive antagonists was observed. These data indicate that besides classical rabies prophylaxis methods (vaccine therapy), new experimental approaches to design neuro-active antiviral drugs may be useful.

There is accumulating evidence that neurotropic viruses can modify brain functions. Understanding how the complex homeostasis of brain functions can be altered by viral infection without necessarily inducing cell death is a prerequisite for developing a therapeutic strategy for neurotropic virus.

4. CONCLUSIONS AND RECOMMENDATIONS

4.1 Summary reports

4.1.1 Rabies situation in Asian countries

Considering the countries participating in the Symposium, three major categories can be recognized according to their current epidemiological situation:

- countries free of the disease, such as Malaysia and Korea
- countries where rabies exists only in limited areas, such as Hong Kong and Indonesia

- countries where rabies is present in most or large parts of the territory.

Among the latter category, two groups can be identified - those countries where rabies represents a significant health problem, namely India (20 000-30 000 human cases), China (1000), Bangladesh (2000), Vietnam (300), Philippines (400), Nepal (150-200), Thailand and Sri Lanka (100), where the figure in brackets represents the mean number of deaths reported annually. The total number of human deaths due to rabies in this part of the world represents, in spite of a marked reduction in the number of cases reported in some of them, a large proportion (85%) of the cases reported worldwide.

The evolution is characterized by a stable or increasing trend in many of the most heavily infected countries (e.g. India, Philippines, Bangladesh, Nepal and Viet Nam) whereas a downward trend is reported in Thailand, China and Sri Lanka. (e.g. China with a reduction from 5000 to 1000 since 1990, Thailand, from 300 annual cases to less than 100 in 1992, Sri Lanka with 100 cases per year over the past three to four years).

With regard to control strategies, large-scale dog vaccination programmes are being carried out in Sri Lanka, Thailand, Viet Nam, and to a lesser extent, in China and the Philippines. Improved post-exposure programme delivery to humans has been promoted in Thailand and China. In most other countries, activities for the control and prevention of the disease in animals and man are very limited.

4.1.2 Parenteral and oral rabies vaccination of dogs

Parenteral vaccination of dogs with inactivated vaccines of high potency leads to eradication of the disease. For example, in the city of Lima (Peru), the vaccination of 76% of dogs in 1985 was followed by the absence of any cases until 1993. In the Philippines, two islands (Siquijor and Guimaras) were similarly freed of rabies for three to eight years.

As proven by large scale trials in France and elsewhere in Europe, oral vaccination of wild carnivores leads to a significant decrease of rabies incidence. Such results have never been achieved by wildlife depopulation methods.

Despite the difficulty to extrapolate from results obtained in fox rabies control the applicability of the technique for dog rabies control, the success of the former should encourage research on oral vaccination of dogs (OVD). In this connection one should especially consider that a very high proportion (95%) of baits distributed for the fox were taken by non-target species, thus demonstrating the relevance of WHO recommendations stating that safety tests should be performed on major non-target species.

Potent rabies vaccines administered parenterally may induce only low titres of rabies neutralizing antibodies in view of the generally poor health status of dogs in Asian countries. This phenomenon was also observed following vaccination of dogs with the V-RG vaccine in laboratory dogs. These dogs, however, were well protected against a virulent challenge after 13 months.

Studies in Tunisia have demonstrated that 75%-85% of dogs may be accessible to parenteral vaccination. However, oral vaccination of dogs may become a useful supplementary method to reach that portion of the dog population that is not accessible to parenteral vaccination (ownerless dogs,

owned dogs difficult to catch and handle, as well as those belonging to unmotivated owners).

For oral vaccination of dogs, several steps should be followed:

- development of baits specific for the dog;
- demonstration of the acceptability of these baits by dogs, as well as and evaluation of bait-uptake by non-target species;
- testing according to WHO criteria, for safety of the candidate vaccines in major non-target species.

Such studies should be undertaken only in areas where good rabies surveillance, risk assessment and evaluation of vaccination coverage systems have been established and demonstrated to work efficiently over long periods of time.

4.1.3 Rabies prevention strategies and tools

Clearly, the dog is responsible for approximately 90% and greater of the associated human mortality in Asia. Consequently, human rabies may be reduced by dog rabies control. Otherwise, human rabies is almost entirely preventable by the combination of proper wound care and the prompt utilization of potent rabies vaccine with rabies immuneoglobulin.

In areas where dog rabies is hyper-endemic and the probability of dog to human transmission is relatively high, it is impractical to base post-exposure treatment (PET) initiation solely upon confinement and observation of suspect dogs. In contrast, where there is a firm history of good veterinary care, evidence of regular vaccination with a minimum of two immunizations with a potent rabies vaccine, human supervision, coupled with sound reasons for how the bite occurred, immediate treatment may not be warranted. Factors involved in human rabies despite these guidelines include an ignorance of any bite exposure, overlooking the severity of a wound, reliance upon subjective interpretation of provocation of a bite, delays in treatment, or failure to comply with WHO guidelines concerning PET.

Several potent human rabies vaccines and serum and economical/effective schedules of administration are currently available, which will gradually replace the use of the brain tissue vaccines of the past. Regardless of the particular means of PET, the kinetics of therapy in children may be different from what is known in adults.

If intradermal PET regimens are begun, attention should be paid to minimum potency equivalents of the vaccine per unit volume, administered in a schedule currently approved by WHO. The use of ERIG today appears to be associated with fewer serious complications than previously noted.

Considerations for pre-exposure immunization of certain high risk populations may improve the management of human PET.

While the FAT is the conventional reference standard for rabies diagnosis, technological advances (e.g. PCR) may provide added reliability and improvement in the near future.

Basic studies into the pathogenesis and related immunological defects of human rabies and improvements in the purity, potency, and efficacy of newer rabies biologicals (e.g. monoclonal antibodies, recombinant vaccines,

etc.) may provide important insights into the reduction of morbidity, mortality and associated costs with human rabies prevention.

4.2 Final Recommendations

4.2.1 Veterinary aspects

(a) Programme implementation

- As there is a need to further study the dog populations, research institutions at national level should initiate in as many areas as possible, dog ecology and dog accessibility studies to acquire better knowledge, especially of the size and turnover of the dog population and to appreciate the potential of parenteral and oral immunization. Basic principles for conducting such studies can be found in WHO documents on oral immunization of dogs (WHO/Rab.Res./91.37, WHO/Rab.Res./92.38 and WHO/Rab.Res./93.42).

- A comprehensive strategy for rabies control and elimination based primarily on parenteral vaccination should be developed. Attention should also be paid to the other programme components such as selective dog elimination programmes, public information and, in the future, other immunization techniques such as oral rabies vaccination.

- In many countries, dog parenteral vaccination with one dose/one shot performed during annual mass campaigns has led to a significant reduction in the number of cases of both humans and animals. Dog vaccination should consist of annual mass vaccination programmes.

Countries should develop sustainable programmes using appropriate/customized maintenance strategies. The efficiency of dog marking at time of vaccination followed by selective dog capture and elimination using humane methods should be investigated as a component of a comprehensive dog rabies control programme.

- The advantages of using local community leaders as vaccinators in mass campaigns cannot be over stressed: (a) they are recognized and respected by the community residents; (b) they are familiar with the terrain and community set-ups; (c) they speak the native dialect; (d) they are motivated to serve the community. Veterinarians should appreciate the rationale behind this approach and should adopt a more proactive role in the campaign (i.e. as trainers, programme planners and assessors).

(b) Research

- As unwanted, unowned or uncatchable dogs may play a special role in rabies epidemiology, each country should study cost-effective techniques for selective elimination of these dogs by humane means.

- The efficacy of rabies vaccine given parenterally in one dose for primo or booster vaccination should be further studied on indigenous dogs receiving the level of care most common under normal field conditions. Challenge studies would be necessary to evaluate the level of protection conferred by single shot vaccination carried out within mass campaigns.

- At present, no specific vaccine-bait systems are available for the oral vaccination of dogs. A number of vaccine candidates have fulfilled WHO requirements regarding efficacy and safety laboratory tests for target and non-target species. However, further field research projects need to be

carried out before these vaccines can be released into the environment. For countries contemplating the use of the dog oral vaccination technique as a complementary strategy to parenteral vaccination, it is recommended that the following preliminary steps be performed:

- assess actual vaccination coverage reached by parenteral vaccination;
- estimate the proportion of ownerless dogs in different areas representative of the country;
- make tests on owned dogs of the acceptance of already available or new candidate substances which could be used as baits;
- identify possible pilot areas where oral vaccination of dogs should be first used;
- intensify animal rabies surveillance in these areas.

More details can be found in the following documents WHO/Rab.Res./91.37, WHO/Rab.Res./92.38, WHO/Rab.Res./93.40, and WHO/Rab.Res./93.43.

4.2.2 Human aspects:

(a) Vaccine types and procurement:

- The Symposium reiterated the recommendation of the WHO Expert Committee on Rabies stating that whenever possible the production and use of vaccines prepared on brain tissues should be discontinued and replaced by inactivated cell-culture or embryonating egg vaccines.

- Governments should consider the use of reduced post-exposure schedules (both intramuscular and intradermal), especially in countries where vaccine costs, and therefore availability, is a major obstacle to maintaining an adequate level of rabies post-exposure treatment delivery.

(b) Research

- The priming effect in humans of new recombinant vaccine should be further studied for possible administration to groups at risk living in remote areas where vaccines are only available in short supply.

- As cases of complications following application of modern vaccines were mentioned, there is a need to further investigate and, if possible, substantiate such findings;

- The potential use of monoclonal antibodies for post-exposure treatment of humans and animals should be further studied.

4.2.3 Role of WHO collaborating centres

Currently several WHO collaborating centres are actively engaged in basic and applied research concerning surveillance, diagnosis, pathogenesis, prevention and epidemiology of rabies in domestic animals, wildlife and humans. These centres play a prominent role in providing, upon request, information, training and reference reagents to countries. Collaboration between WHO collaborating centres on rabies should be strengthened through a greater exchange of information and material. The establishment of WHO newsletters at regional and global levels would also help information exchange.

4.2.4 Promotion of regional and global activities for rabies elimination

WHO should further cooperate with Member States and regional governing bodies to initiate comprehensive rabies control programmes at national and regional levels. In this connection, the participants in the Symposium proposed and endorsed the following resolutions:

The participants from 14 Asian countries attending the Symposium on rabies control in Asia,

Recognizing the health significance of rabies in their countries, where between 25 000 and 30 000 rabies-related deaths are reported each year;

Recognizing that the presence of the disease leads to the application of millions of post-exposure treatments in humans and millions of preventive, and, in some countries, post-exposure treatment in animals, thus making rabies a very significant economic burden for their countries' economies, especially for the health and agriculture sectors;

Acknowledging the efficacy of mass vaccination of dogs and the usefulness of new economical protocols for post-exposure treatment of humans (both IM and ID) as recommended by the WHO Expert Committee on Rabies;

Acknowledging the potential of oral vaccination of dogs as an adjunct to parenteral vaccination campaigns, and ongoing research projects on new vaccines and substances for pre- and post-exposure immunization of humans;

REQUEST

(1) their governments to consider costs and benefits deriving from dog rabies control/elimination programmes and to provide increased support to activities for the surveillance and control of rabies in humans and animals;

(2) the WHO Regional Committees of the South-East Asia region (SEARO) and the Western Pacific region (WPRO) to reinforce their capabilities to meet the demands from Member States for technical assistance, and to consider the launching of a regional initiative for urban rabies control and elimination in Asia;

(3) WHO Headquarters to increase its ability to promote new concepts for human and animal rabies prevention and control and further coordinate research in this field.

ANNEX 1

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