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Geneva, 24–30 September 1991

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1. Introduction

The WHO Expert Committee on Rabies met in Geneva from 24 to 30 September 1991. Opening the meeting on behalf of the Director-General, Dr R. Henderson, Assistant Director-General, pointed out that rabies continues to be a major health hazard in many countries in Africa, South America and Asia, and an economic burden for both developed and developing countries, in spite of recent advances in diagnosis, human post-exposure treatment, the production of vaccines for human and veterinary use and the control of rabies in dogs and wild animals.

1.1 Recent advances

Since the last meeting of the WHO Expert Committee on Rabies in September 1983 (*1*), many advances have been made in basic and applied research on the disease. In particular, the Committee noted the application of molecular biology techniques, not only in the laboratory but also in field control operations, as in the oral immunization of foxes in Canada and Europe and in trials for the oral immunization of racoons in the USA. The Committee also reviewed the new strategies for controlling canine rabies that had been developed by the WHO regional programme for the elimination of urban rabies in Latin America and the interregional project for human and canine rabies control in developing countries, which was supported by the Arab Gulf Programme for United Nations Development Organizations (AGFUND) and WHO. The Committee also noted that several consultations and regional conferences on these subjects had been held and a number of training seminars had been organized. These advances were taken into account by the Committee in formulating its recommendations. The Committee urged rabies control authorities and research groups to take note of these recommendations and to revise their policies and procedures accordingly. Further details on subjects summarized in the present report may be found in the WHO document *Guidelines for dog rabies control* (*2*) and in *Guidelines for dog population management* (*3*), prepared by WHO and the World Society for the Protection of Animals (WSPA).

1.2 Canine rabies

In view of the need for a special initiative for canine rabies control, the Committee expressed its support for the conclusions of the WHO Consultation on the feasibility of global control and elimination of urban rabies (*4*), and urged rabies control authorities and funding agencies to take the necessary measures to eliminate rabies.

1.3 Laboratory techniques in rabies

The draft of the fourth edition of the WHO monograph *Laboratory techniques in rabies* (*5*) was reviewed by the Committee. The Committee commended this book as an excellent source of information on the

laboratory aspects of rabies. The revised edition, which is referred to frequently throughout the report, will contain many new chapters dealing with recent procedures, and include updated descriptions of techniques described in the previous edition.

2. Advances in rabies research

2.1 Monoclonal antibodies and the classification of rabies and rabies-related viruses

Since the early 1980s, monoclonal antibodies have been used extensively in identifying rabies virus strains and in diagnosing human and animal rabies (*6-11*).

Monoclonal and polyclonal antibody studies of rabies isolates from many animal species worldwide have led to the following classification of the rabies group of Rhabdoviridae, genus *Lyssavirus:*

> Serotype 1: prototype strain Challenge Virus Standard (CVS); includes the majority of field viruses isolated from terrestrial mammals as well as isolates from insectivorous bats in North America and haematophagous bats in Latin America; also includes fixed virus laboratory strains.
>
> Serotype 2: prototype strain Lagos bat, first isolated from pooled brains of bats in Nigeria (Lagos-bat 1), then from a bat in the Central African Republic (Lagos-bat 2) and from a bat in Guinea and a cat in Zimbabwe (Lagos-bat 3).
>
> Serotype 3: prototype strain Mokola, first isolated from shrews in Nigeria and then from a human (Mokola 1); further isolates have been obtained from shrews in Cameroon (Mokola 2) and in the Central African Republic (Mokola 3) and from dogs in Zimbabwe (Mokola 5).
>
> Serotype 4: prototype strain Duvenhage, first isolated from a human in South Africa (Duvenhage 1), and then from bats in South Africa (Duvenhage 2) and Zimbabwe (Duvenhage 3).

A number of viruses still remain to be typed. These include the recently identified European bat lyssaviruses (EBL) isolated from *Eptesicus serotinus* bats (EBL 1) and *Myotis* bats (EBL 2), as well as isolates from humans exposed to bats in Finland and Ukraine (*9-11*).

2.2 Molecular biology of the rabies virus

Over the past decade, considerable progress has been made in understanding the structure of lyssaviruses.

The virions or virus particles have a bullet-shaped structure with an average length of 180 nm and a diameter of 75 nm. Each particle contains a helical nucleocapsid surrounded by a lipid bilayer. The outer surface is covered with spike-like projections, 10 nm in length, anchored in a lipid bilayer. Five proteins have been identified following disruption of rabies virus with sodium dodecyl sulfate. The ribonucleoprotein contains the genomic RNA associated with three internal proteins, the transcriptase (L)

(M_r = 190000), the nucleoprotein (N) (M_r = 55000), and a phosphoprotein (NS) (M_r = 38000). These proteins, together with the RNA, form an active RNA complex, which controls both transcription and replication. The other structural proteins are the matrix protein (M) (M_r = 26000), which is located on the inner side of the virus envelope, and the glycoprotein (G) (M_r = 67000), which forms the surface projections. The complete amino acid sequences of these five proteins have been deduced from the primary nucleotide sequences of cloned rabies genome and individual mRNA transcripts.

Both rabies virus and rabies-related viruses have the same genomic structure. The virion contains an unsegmented and non-polyadenylated negative-stranded RNA genome. Although complete nucleotide sequences of all the five rabies genes have been determined for several fixed rabies strains, this information is not available for field virus strains.

Of the five proteins, the G and N proteins are the most extensively characterized. The G protein is the only viral antigen that induces virus-neutralizing antibodies; it is also a target for virus-immune T helper cells and cytotoxic T cells. Rabies virus-neutralizing antibodies directed against the G protein appear to be an important component in the immune response to rabies. Antigenic determinants in the G protein recognized by rabies virus-specific B and T cells have been identified, and synthetic peptides incorporating these antigenic determinants offer an approach to the development of vaccines against rabies.

Of the three proteins that form the helical nucleocapsid in conjunction with the RNA, the N protein represents the major internal protein of the virus. Analysis of the primary nucleotide sequence of the N protein gene of several rabies virus strains has demonstrated an exceptionally high level of conservation, reflected by a high degree of antigenic homology between rabies and rabies-related virus strains in the ribonucleoprotein. The N protein has been shown to be a major antigen, capable of inducing T helper cells that cross-react between different rabies and rabies-related viruses. The finding that ribonucleoprotein can confer protective immunity may have clinical significance for immunization against heterologous virus strains.

Since the G and N proteins are the major antigens capable of inducing immunity against lethal rabies infection, both should logically be included in the development of genetically engineered vaccines. Both proteins have been expressed in a variety of prokaryotic and eukaryotic expression systems (see section 2.4). The capacity to produce large quantities of genetically engineered rabies virus proteins will provide research teams with new tools for diagnosis and vaccine development.

2.3 Molecular epidemiology

Recent progress in research on the molecular genetics of lyssaviruses suggests that powerful tools for the identification of rabies viruses may be

available in the future. Cloning and sequencing techniques together with other techniques such as the polymerase chain reaction (PCR) have been successfully applied to the rabies virus and may lead to the characterization of certain regions of the viral genome.

The PCR technique, however, is not yet sufficiently developed for the routine diagnosis of rabies and should only be carried out by molecular biology laboratories with the necessary facilities and expertise.

2.4 Research in vaccine development

Since the last meeting of the Committee in 1983, significant progress has been made in the preparation and delivery of vaccines to animals and humans, including a major shift to the use of cell culture for vaccine preparations.

2.4.1 *Candidate vaccines*

Advances in cloning and gene expression have resulted in the production of many unique recombinant rabies vaccines, which have been tested for possible use in animals and humans. These recombinant vaccines include the following groups.

Orthopoxviruses

A rabies G-protein orthopoxvirus recombinant has been characterized extensively and used for oral immunization of foxes and racoons in several countries (see sections 4.3.2 and 4.4.2). This vaccine is not considered suitable for human immunization because of safety considerations in the use of live vaccinia virus. Another vector, racoon poxvirus, has been used for preparing a recombinant vaccine containing the G and N proteins; this vaccine is an effective oral immunogen in racoons, foxes and dogs.

Other poxviruses may be safer for human vaccination; these include avipoxes such as canary pox, and vaccinia attenuated through the removal of 18 genes accounting for the virulence of the virus. In one study, human volunteers injected with vaccine prepared from canary poxvirus and rabies G protein produced a level of virus-neutralizing antibodies equal to that observed in subjects injected with a standard tissue-culture vaccine. Moreover, orthopox vectoring may permit the incorporation of several antigens (e.g. measles, mumps, rubella, rabies, pertussis) into a single vaccine, which would reduce the medical facilities required for human prophylactic immunization.

Baculoviruses

Both rabies G-protein and N-protein baculovirus recombinants are now available and could be considered for the production of rabies vaccine for immunization of animals. Although the purification of N protein from the baculovirus recombinant may be too complicated and too costly for the production of a reasonably priced vaccine, it may be possible to use N

protein for human vaccination if sufficient amounts are generated by mammalian cells transfected with the recombinant.

Adenoviruses

Human and animal adenoviruses are also sufficiently large to accommodate foreign genes. When inserted into the adenovirus genome, the complementary DNA (cDNA) of rabies glycoprotein gene is expressed on the surface of infected cells, but not on the virion surface. Such vaccines would be especially useful to protect animal species that have been difficult to immunize with existing oral vaccines, such as dogs and skunks. A recombinant vaccine prepared by inserting the cDNA of rabies glycoprotein gene into human adenovirus 5 has been found to be immunogenic in a variety of animals, including skunks, racoons, foxes and dogs. Since dogs tend not to chew baits much before swallowing them, the vectored vaccine should, ideally, be resistant to the low pH conditions in the stomach and infect the intestinal tissues.

No recombinants have yet been prepared using canine adenoviruses as vectors, but preliminary studies indicate that these viruses may be suitable candidate vaccines for various species (e.g. skunks, foxes, racoons, mongooses and dogs) and studies are continuing in several laboratories worldwide.

Other recombinant vaccines

BCG (bacille Calmette-Guérin) and attenuated salmonellae are also potential candidate vectors for preparing rabies vaccines. Extrachromosomal and integrative expression vectors carrying the regulatory sequences for the major BCG heat-shock proteins have been developed which could allow expression of rabies virus G or N protein.

Other mechanisms by which antigens may be delivered to the immune system are summarized in section 13.

2.4.2 *Safety aspects*

Further development of recombinant rabies vaccines will increase the number of prototypes constructed in different vectors and proposed by different authors or manufacturers. Strict observation of international safety norms (*12-14*) will be required before field testing.

A number of rabies vaccines have induced virus-neutralizing antibodies when fed to dogs. These include both attenuated vaccines, such as SAD and SAG_1 (a derivative of SAD virus), and recombinant vaccines, such as those prepared from vaccinia and racoon poxvirus. To date none of these vaccines have been sufficiently developed for field testing in dogs, although considerable time and effort have gone into testing their safety and efficacy. Standard procedures for testing the safety and efficacy of candidate vaccines have been developed (*15*). Since children or even adults may come into contact with oral rabies vaccines intended for canine

use, any vaccine to be field tested must first be carefully examined for safety in selected non-target species to address the question of possible hazard to humans.

2.5 New substances for post-exposure treatment and new post-exposure vaccination regimens

2.5.1 *Monoclonal antibodies*

Research is continuing on the possible use of monoclonal antibodies for post-exposure treatment of humans and animals (*11*). In a recent study, monoclonal antibodies were shown to protect Syrian hamsters against rabies when given intramuscularly 24 hours or more after intramuscular challenge with a field strain. Although these antibodies were of murine origin, murine antibodies have been used extensively in the treatment of cancer patients over the past decade, without any significant side-effects being reported. However, recombinant DNA techniques are now available to prepare chimeric (murine-human) antibodies and also to "humanize" monoclonal antibodies of murine origin. Moreover, following cloning and sequencing of these latter antibodies, it is possible to have them expressed in vectors such as baculovirus.

2.5.2 *Interferon and interferon-inducers*

Both exogenous interferon preparations and "interferon-inducers" have been shown to be highly effective in reducing mortality in laboratory mice and subhuman primates challenged intramuscularly with a field virus strain. Neither interferon nor interferon-inducers appear to suppress the virus-neutralizing antibody response induced by vaccination. In addition, it has been shown that recombinant α-interferon administered with vaccine can be as effective as exogenous interferon and vaccine in reducing rabies mortality in subhuman primates. Exogenous interferon has already been shown to be effective in a patient given a corneal transplant from a person with rabies; further studies are in progress.

2.5.3 *New post-exposure vaccination regimens*

A variety of new vaccination schedules have been evaluated in humans in an effort to reduce the number of vaccinations and amount of vaccine required after exposure to rabies. One of these schedules, the 3-1 schedule, is an abbreviated multisite regimen consisting of three vaccine doses applied in the deltoid muscle of the right and left arm at day 0, and one dose applied at day 7. Application of the 3-1 regimen to human volunteers produced an early and elevated cellular (starting 6 hours after vaccination) and humoral (starting at day 5) immune response. When this regimen was combined with administration of anti-rabies human immunoglobulin, however, the initial antibody response was suppressed, although subsequent titres reached expected levels after 2 weeks.

3. Diagnosis[1]

3.1 Clinical diagnosis

Rabies in animals and humans is still diagnosed on the basis of clinical signs and symptoms in many areas of the world.

Clinical diagnosis of rabies in animals is, however, sometimes difficult, and rabid dogs may be judged to be uninfected, which could result in danger to humans; equally, persons bitten by animals with other diseases or conditions (such as distemper) could be vaccinated against rabies unnecessarily. Clinical diagnosis of rabies in humans can also be difficult, since patients may present with a paralytic or Guillain-Barré-like syndrome. Signs of brain involvement are spasms in response to tactile, auditory, visual or olfactory stimuli (e.g. aerophobia, hydrophobia), alternating with periods of lucidity, agitation, confusion, and signs of autonomic dysfunction. These spasms occur at some time in almost all rabid patients in whom excitation is prominent, but spontaneous inspiratory spasms usually occur continuously until death; their presence often facilitates clinical diagnosis. Excitation is less evident in paralytic rabies, and phobic spasms appear in only 50% of these patients. During the early stages of paralytic rabies, notable signs include myoedema at percussion sites, usually in the region of the chest, deltoid muscle and thigh, and piloerection.

Side-effects following the inoculation of adult or suckling-mouse brain rabies vaccines are occasionally misdiagnosed as rabies and a test for antibody to myelin basic protein may be useful in identifying such patients. Great care needs to be exercised before a diagnosis of rabies is made on clinical grounds.

Since imported cases of human and animal rabies have been noted in rabies-free countries (or rabies-free areas of infected countries), the Committee emphasized that rabies must be included in the differential diagnosis of all persons who present with signs of neurological involvement.

3.2 Laboratory diagnosis

3.2.1 *Postmortem diagnosis of rabies in animals and humans*

Antigen detection

The fluorescent antibody (FA) technique is a rapid and sensitive method for diagnosing rabies infection in animals and humans. The test is based upon microscopic examination, under ultraviolet light, of impressions, smears or frozen sections of tissue after treatment with anti-rabies serum or globulin conjugated with fluorescein isothiocyanate.

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[1] Details of the procedures mentioned here are given in Meslin F-X, Kaplan MM, Koprowski H, eds. *Laboratory techniques in rabies*, 4th ed. Geneva, World Health Organization (in preparation).

Bilateral impressions (or smears) of tissue samples from the hippocampus (Ammon's horns) and brain stem are recommended for increased sensitivity of the test; some laboratories also stain samples of cerebellar tissue.

An enzyme-linked immunosorbent assay (ELISA) called rapid rabies enzyme immunodiagnosis (RREID) was developed for the diagnosis of rabies, based upon the detection of rabies virus nucleocapsid antigen in brain tissue. Since the antigen can be visualized with the naked eye, the test can be carried out (with the aid of a special kit) under field conditions.

RREID is a rapid technique which can be especially useful for epidemiological surveys. The test may be used to examine partially decomposed tissue specimens for evidence of rabies infection, but it cannot be used with specimens that have been fixed in formalin. It should be noted, in addition, that the FA test may yield positive results when the RREID is negative.

Virus isolation in vitro

Virus isolation may be necessary for confirming the results of antigen detection tests and for further characterizing the isolate.

Murine neuroblastoma (NA C1300) cells are more susceptible to rabies field virus infection than any other cell lines tested. Virus isolation in cell culture (with neuroblastoma cells) is at least as efficient as mouse inoculation for demonstrating small amounts of rabies virus. It also reduces the time required for diagnosis from 10-15 days to 2 days, eliminates the need for experimental animals, and is considerably less expensive to perform. This technique is not feasible in every laboratory, however, and intracerebral mouse inoculation is still a useful test in the laboratory diagnosis of rabies. Suckling mice (less than 3 days old) are more susceptible to rabies than weanling or adult mice and should be used whenever possible. The observation period may be shortened by FA examination of brains of inoculated mice killed 3-4 days (or more) after inoculation.

Virus identification using monoclonal antibodies: epidemiological considerations

To date, several hundred lyssavirus isolates from humans, domestic animals, and wild animals in Africa, the Americas, Asia and Western Europe have been compared using monoclonal antibodies. These studies demonstrate that rabies virus can be distinguished from other lyssaviruses and that rabies isolates from a given geographical area or species have unique reactivity patterns both in the nucleocapsid and glycoprotein components of the virion. In relatively simple ecosystems, a few principal carnivore hosts (e.g. wild canids) serve as primary rabies reservoirs. In Canada and the USA, field rabies viruses are maintained in "compartments" in specific geographical regions by species such as foxes, skunks, racoons and bats; transfer of the disease to other species is

relatively unimportant for maintenance of infection. Striking differences are apparent between viruses isolated from bats and those isolated from terrestrial carnivores, which confirm previous epidemiological findings.

Detection by molecular techniques

The use of molecular probes and the polymerase chain reaction is not currently recommended for the routine diagnosis of rabies.

3.2.2 *Intra vitam diagnosis of rabies in humans*

The choice of techniques for *intra vitam* diagnosis varies greatly according to the stage of the disease; antigen detection is generally sensitive during the first few days, while virus-neutralizing antibodies in cerebrospinal fluid and serum usually tend to appear after 7-10 days of illness.

Viral antigen may be detected by FA in corneal impressions or skin biopsies from patients with rabies; however, FA-positive specimens are more common during the final stages of the disease. Skin biopsies are usually taken from the nuchal area of the neck, with hair follicles containing peripheral nerves. Corneal impressions (*never* scrapings) are taken from patients with encephalitis by lightly touching the central part of the cornea with a microscope slide.

The quality of the samples – both corneal impressions and skin biopsies – is paramount; they should be refrigerated immediately after collection and until the test is carried out.

Nevertheless, the sensitivity of the FA technique for *intra vitam* diagnosis is limited:

- Rabies antigen has been demonstrated in corneal impressions taken from patients and naturally and experimentally infected animals. However, while a positive result is indicative of rabies, a negative result does not rule out the possibility of infection.
- Although rabies antigen may be detected in skin biopsies at the onset of clinical signs, the proportion of positive results tends to increase as the disease progresses. With nuchal skin biopsies, only some patients show positive results, especially during the early phase of clinical illness. Nevertheless, the overall sensitivity of FA is higher with skin biopsies than with corneal impressions.

Rabies virus may be isolated in cell culture (see page 8) from certain body tissues and fluids, especially saliva and cerebrospinal fluid.

Saliva samples should be maintained frozen after collection; the contents of the swab should be expressed in the collection medium, the swab removed and the specimen sent frozen for further examination. Biopsy material and cerebrospinal fluid should be frozen after removal. Under no circumstances should preservatives be added to the collection medium.

On rare occasions, it will be necessary to examine brain biopsies for evidence of rabies antigen or virus; these should preferably be tested for

antigen using the FA technique. However, the virus may be absent from biopsies, saliva or cerebrospinal fluid, even during the late stages of the disease.

Antibody titration

Neutralizing antibodies in the serum or cerebrospinal fluid of non-vaccinated patients may be measured either by the mouse serum neutralization test (MNT) or by the rapid fluorescent focus inhibition test (RFFIT). The Committee recommended that, where possible, the MNT be replaced by the RFFIT, since the latter test is more rapid and at least as sensitive as the MNT.

An enzyme-linked immunosorbent assay (ELISA) using purified rabies glycoprotein has been used to determine virus-neutralizing antibody levels in the serum of several species, including humans. The test can be carried out (with the aid of a special kit) in the field and provides results within a few hours. It also appears to be quite reproducible. Nevertheless, the sensitivity of the test is limited; the measurement may include a variety of antibodies in addition to virus-neutralizing antibodies.

4. Rabies vaccines

4.1 General considerations

Considerable progress has been made in the production and use of rabies vaccines during the past decade. However, the availability of rabies vaccines of very high immunogenicity and safety is a goal that remains to be achieved in many areas of the world. The use of vaccines prepared in cell culture should replace those derived from brain tissue as soon as possible.

Strict quality controls must be used in vaccine production ("in-process controls") and strict safety and potency tests must be performed on the final product by national authorities. When appropriate, serological testing should be carried out on a sample of vaccinated animals and people to assess vaccine immunogenicity under field conditions. All cases of rabies occurring in vaccinated subjects should be fully investigated: in addition to vaccination failure related to sub-potent vaccines, rabies virus variants and rabies-related viruses must be considered as possible causes of death.

There is an urgent need to reduce the cost of cell-culture vaccines for both human and animal use. For countries initiating cell-culture vaccine production, substantial savings may be effected if human and animal vaccines are jointly produced. In the field of animal vaccines, new oral vaccines are needed to immunize various wildlife species and dogs.

Virus strains used for the production of rabies vaccine must be carefully selected, and periodic checks must be carried out on the antigenic identity of these virus strains as well as on the identity and purity of the cell lines used. Strains used for the production of vaccines must have been shown to

protect against local field rabies virus infections. It is important that WHO Collaborating Centres serve as sources of vaccine seeds, as reference laboratories for examination of strains and for training in control techniques (see section 6).

Various fixed rabies strains are used for the production of inactivated rabies vaccines:

- Paris Pasteur strain of rabbit fixed rabies virus; also adapted to Vero cells;
- PV-12 strain of Pasteur rabbit fixed rabies virus; also adapted to BHK-21 cells;
- Pitman-Moore[1] (PM) (ATCC VR-320) strain of fixed rabies virus, adapted to human diploid, primary dog kidney, Vero and Nil-2 cells;
- CVS-27[1] (Challenge Virus Standard) (ATCC VR-321) mouse-brain strain of fixed rabies virus; also adapted to BHK-21 cells;
- CVS-11[1] (ATCC VR-959) Kissling strain, adapted to BHK-21 cells;
- LEP[1] (40-50 passages) (ATCC VR-138) Flury chick embryo-adapted rabies virus; also adapted to primary chick embryo cells and to BHK-21 cells;
- HEP[1] (227-230 passages) (ATCC VR-139) Flury chick embryo-adapted rabies virus; also adapted to primary chick embryo cells;
- Kelev (100 passages) chick embryo-adapted rabies virus;
- ERA[1] (Evelyn Rokitniki Abelseth) (ATCC VR-332) strain of SAD virus, adapted to porcine kidney cells; also adapted to BHK-21 cells;
- SAD (Street-Alabama-Duffering) virus, adapted to BHK-21 cells;
- Vnukovo-32 strain of SAD virus, adapted to primary hamster kidney cells;
- Beijing strain of fixed rabies virus adapted to primary hamster kidney cells.

The description of the production techniques for most of the vaccines discussed below are given in *Laboratory techniques in rabies*, 4th ed. (*5*).

4.2 Vaccines for humans

4.2.1 *New development in brain-tissue vaccine production*

The Fuenzalida-Palacios technique for the preparation of suckling-mouse brain vaccine has been modified in an attempt to reduce further the level of encephalitogenic substances in the final product. Vaccines are now prepared using mice no older than one day at the time of inoculation. Centrifugation of the brain suspension at 17 000 *g* for 10 min is still recommended.

[1] Available on request from the American Type Culture Collection (ATCC), 12301 Parklawn Drive, Rockville, MD 20852, USA.

4.2.2 *Purified duck-embryo vaccine*

Fixed virus is grown in embryonating duck eggs and inactivated by ß-propiolactone. The purified vaccine offers the same immunogenicity and safety as modern cell-culture vaccines.

4.2.3 *Cell-culture vaccines*

Vaccines prepared in cell culture are now widely available, and have been shown to combine safety with high immunogenicity. Several types of cell cultures are used for human rabies vaccine production: (i) primary cells (hamster kidney, dog kidney or chick embryo fibroblasts); (ii) diploid cell lines (human or rhesus monkey origin); and (iii) continuous cell lines (Vero cells).

Advances in biotechnology, such as the culture of continuous cell lines on microcarriers in fermenters, have made possible the production of rabies vaccines on an industrial scale and reduced costs.

Continuous cell lines (such as baby hamster kidney cells (line 21)) are currently used for the production of animal rabies vaccines. Because high yields of rabies virus are produced, concentration of the virus is not required. These cell lines might be acceptable for the production of low-cost rabies vaccines for human use in the future provided they meet the requirements for human vaccines prepared in continuous cell lines published by WHO (*16*).

4.2.4 *Potency requirements*

The Committee emphasized the importance of checking the potency of every vaccine batch before its release. Highly purified, modern rabies vaccines for human use should have a minimum potency, as measured by the NIH test, of 2.5 IU per dose (*16, 17*). Suckling-mouse brain vaccines for human use should have a minimum potency of 1.3 IU per dose (*1*), regardless of the number of doses required for full post-exposure treatment. The Committee also recommended that the WHO Expert Committee on Biological Standardization should consider revising the requirements for rabies vaccines for human use to state that the national control authorities may release vaccines with potencies below the recommended minimum, provided these vaccines have been shown to elicit an adequate level of virus-neutralizing antibodies in humans (see section 6 and Annex 1).

4.3 Vaccines for animals

4.3.1 *Nerve-tissue vaccines*

Inactivated nerve-tissue vaccines may be produced from the brains of lambs or newborn mice. Such vaccines have been shown to be effective in mass canine immunization programmes in North Africa (lamb brain vaccines) as well as Latin America and the Caribbean (suckling-mouse brain vaccines).

4.3.2 *Cell-culture vaccines*

Vaccines for parenteral use

Selection of vaccine type. Modified live-virus (MLV) and inactivated vaccines can be produced in cell culture, using either primary cells or continuous cell lines. The seed virus/cell systems vary considerably between different manufacturers. Increasing use of inactivated vaccines for animal immunization can be expected as a result of recent improvements in vaccine production techniques.

The duration of immunity and safety are especially important when a vaccine is being selected for use in a mass vaccination campaign. Use of vaccines that will provide stable and long-lasting immunity is recommended, because it constitutes the most effective method of controlling and eliminating the disease in animals. Regardless of the vaccine used, it must be administered properly to provide the desired protection.

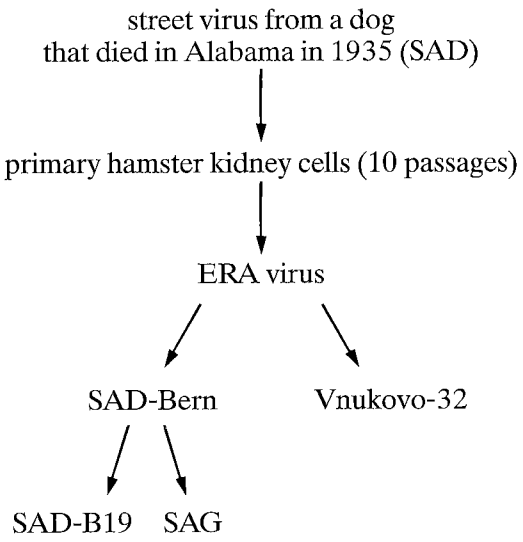
Combined vaccines. Use of combined vaccines will certainly lead to a wider range of immunoprophylactic strategies against different microbial pathogens, and has already led to a simplification of the vaccination calendar. No indication of competitive inhibition of the immune response has been reported for combined vaccines, but each new product should be investigated for its overall immunogenic potency. Attention should be paid to all vaccine components, including rabies antigen.

Combined vaccines are already used for the immunization of dogs and cats. Several different antigens are incorporated in canine rabies vaccine, such as canine distemper, canine hepatitis, leptospirosis and canine parvovirus. Combined rabies vaccines for cats may include various other antigens such as feline panleukopenia virus, feline calicivirus and feline parvoviruses. A combined rabies and foot-and-mouth disease vaccine is available for use in cattle, sheep and goats.

Vaccines for oral administration

Modified live-virus vaccines. Several types of modified live-virus vaccines have been proposed for the oral immunization of animals in the past 20 years; however, only five have proved suitable for use in the field for vaccination of foxes (Canada and Europe) and racoon dogs (Finland). All these vaccines are derivatives of the original SAD virus (for safety considerations, see section 4.4.2).

The origin of these viruses is shown overleaf.



Recombinant vaccines. A recombinant vaccinia virus expressing the glycoprotein gene of rabies virus (VRG) has been developed by inserting the cDNA of the glycoprotein of ERA strain into the thymidine kinase gene of the vaccinia virus (Copenhagen strain).

When administered orally (by direct instillation in the mouth or in a bait) to young and adult foxes or racoons, a dose of 10^8 $TCID_{50}$ (median tissue-culture infective dose) of VRG elicits high titres of virus-neutralizing antibodies and confers protection against a severe rabies challenge.

4.3.3 *Potency requirements*

The Committee suggested that inactivated veterinary vaccines with a potency of less than 1.0 IU per dose, as measured by the NIH test, should not be licensed or released unless an adequately designed experiment has demonstrated a duration of immunity of at least one year in the species for which the vaccine is to be used.

The potency of live and inactivated vaccines should be ascertained at intervals after they have been distributed. Inactivated vaccine, even in liquid form, and lyophilized modified live-virus vaccines are relatively stable when stored under proper conditions. To verify that storage conditions are adequate, it is recommended that samples from the field that are approaching their expiry date be tested using the methods applied to newly manufactured products.

Minimum potency requirements for oral vaccines for immunization of wild animals have not been generally established, although the median effective doses (ED_{50}) of various modified live-virus and recombinant vaccines are known.

To test the efficacy of candidate vaccines for oral immunization, sufficient numbers of target animals should be maintained under captive conditions, given the vaccine and challenged with the virus. The potency of the vaccines should be standardized to quantifiable levels (e.g. plaque-forming units/ml, $TCID_{50}$/ml). Once efficacy has been demonstrated in the target species under laboratory conditions (see reference *15*), the vaccine should be administered in a bait identical to that to be used in field trials. Serial dilutions of test vaccine will determine the ED_{50}. Animals should then be held for a minimum of 6-12 months prior to a challenge with a field strain administered by the intramuscular route; the interval between vaccine administration and challenge depends on the turnover rate of the target species. Potency estimates should not be based entirely on the ability of the vaccine to induce virus-neutralizing antibodies in the target species; environmental stability tests are also necessary to demonstrate that vaccine potency is retained under field conditions (see section 6 and Annex 1).

4.4 Safety

4.4.1 *Vaccines for parenteral use*

Safety requirements have been adopted by the WHO Expert Committee on Biological Standardization (*16, 17*).

Several types of safety tests for inactivated rabies vaccines have been prescribed by national authorities. These tests are described in *Laboratory techniques in rabies*, 4th ed. (*5*).

In view of the hazard of encephalitogenic reactions, the discontinuation of nerve-tissue vaccines should be considered.

Vaccine that contains living virus should not be employed in humans; the absence of living virus in inactivated vaccines must be confirmed by the most sensitive tests available.

The finished vaccine must not contain detectable levels of ß-propiolactone or any other inactivating agent, except in the case of Semple vaccine, where phenol may be allowed in the final product. No antibiotics should be added to rabies vaccines for human use.

The Committee recommended that purity testing should encompass not only the seed virus material but also the cell cultures and other biological ingredients used in vaccine manufacture. The Committee recommended that new rabies vaccines for animals be tested for safety by direct inoculation in the species for which they are to be used. The numbers of animals available for this type of testing will ordinarily be insufficient to demonstrate unusual virus-host reactions, and any reported vaccine-associated problems arising during field use should be reported to the appropriate national and international authorities and rigorously investigated.

4.4.2 *Vaccines for oral immunization of wild and domestic animals*

Modified live-virus vaccines

Laboratory studies. Four SAD-related vaccines (ERA, SAD-Bern, SAD-B19, and Vnukovo-32) are pathogenic for adult mice (by the intracerebral, intramuscular and oral routes), and for many other rodent species. They do not appear to be pathogenic for North American and European carnivores and other large mammals when they are given by the oral route, except in the case of skunks.

SAG vaccine is a deletion mutant of SAD developed using selected monoclonal antibodies. SAG vaccine is pathogenic neither for adult mice nor for any wild rodents tested by the oral, intramuscular or intracerebral routes; however, it is pathogenic for suckling mice when given by the intracerebral and oral routes.

Field studies. The SAD-Bern vaccine has been used in plastic capsules stapled to chicken head baits. Between October 1978 and October 1990, 1.3 million such baits were distributed in Switzerland. Continual surveillance led to the detection of three cases of vaccine-induced rabies. No other vaccine-related deaths were noted in over 900 animals examined.

The SAD-B19 vaccine has been widely used in the field. Between 1983 and 1990, over 20 million baits containing this virus were distributed in Europe (including Belgium, France, Germany, Italy and Luxembourg) with no reported deaths among non-target species.

Between 1989 and 1990, 250 000 doses of SAG_1 virus were used in baits distributed in France and Switzerland. No vaccine-induced rabies cases were noted in these countries.

Between 1990 and 1991, about 800 000 baits containing ERA vaccine were distributed in Canada for the oral immunization of foxes.

In addition, field trials are being conducted in the former USSR, in which tens of thousands of baits containing the Vnukovo-32 strain have been distributed.

Safety assessment for target and non-target species. The candidate vaccine strain should be characterized according to procedures recommended for rabies vaccines for veterinary use (*17*).

The vaccine chosen should not produce any disease in 10 young (3-6 months old) animals belonging to the target species when administered orally at 10 times the dose recommended for field use.

The possibility of excretion of vaccine virus in the saliva of the animals described above should also be examined. Following immunization, swabs should be taken daily. No virus should be present after 3-4 days. Any virus recovered should be characterized using monoclonal antibodies.

In addition, where feasible, at least 10 and if possible 50 of each of the most common local rodent species should be given the field dose of vaccine (i.e.

the dose which is contained in a bait) orally and intramuscularly (this may require use of different virus concentrations and volumes for different species, depending on their weight and size). No more than 10% of the animals so vaccinated should exhibit sickness or die from rabies.

Relevant local wild or domestic animal species that may take baits should also be given the field dose of vaccine orally in a volume adapted to body weight (*12*).

Any rabies virus isolated from animals in vaccination areas should be examined using monoclonal antibodies to ensure that no vaccine-induced rabies has occurred.

Recombinant oral vaccines

The development of recombinant DNA technology has initiated a new era in rabies control. Recombinant vaccines cannot exhibit residual pathogenicity caused by rabies because they contain only single non-virulent gene products.

The majority of the safety requirements for modified live-virus vaccines are also applicable to recombinant vaccines.

The recombinant virus that expresses the glycoprotein gene of rabies virus (VRG) shares many basic properties with parental vaccinia virus but differs in other ways which make the vector virus safer. The deletion of the thymidine kinase gene dramatically decreases the pathogenicity of the vaccine for mice when it is given by the intracerebral and intraperitoneal routes. In addition, no viral spread from currently known sites of viral replication has been observed, and oral vaccination of dozens of animal species, including wild animals, has not revealed any residual pathogenicity.

Studies conducted over the past 8 years have shown that the VRG vaccine is not pathogenic in over 10 avian and 35 mammalian species, including the majority of rabies reservoir hosts. Regardless of the vaccine dose or route of administration, the vaccinated animals have remained clinically normal, with no overt gross or histopathological lesions. Following oral administration, the VRG vaccine is cleared relatively quickly (e.g. within 48 hours). No abortifacient, teratogenic, or oncogenic side-effects have been noted. Large-scale field trials in foxes have been conducted with the VRG vaccine in Belgium and France and limited trials have been carried out in racoons in the United States; no adverse effects have been reported to date. Between 1988 and 1990, more than one million doses of VRG vaccine were distributed in baits in Belgium and France for fox vaccination. Other candidate recombinant vaccines (e.g. using racoon poxvirus or human or canine adenovirus as vector) should undergo comprehensive safety tests before the initiation of field trials (see section 2.4.2).

In all cases the use of genetically engineered rabies vaccines should comply with national and international biosafety recommendations.

5. Reference materials and virus strains

5.1 International reference preparation of rabies vaccine

Until 1978, rabies vaccines were calibrated against the second International Reference Preparation (*18*), a lyophilized, ultraviolet-inactivated, infected brain suspension which, on reconstitution with 8 ml of distilled water, corresponded to a 10% brain suspension. An aliquot of 1 ml of the reconstituted preparation was considered to represent one immunizing human dose and to have an antigenic value of 1.

The use of International Units (IU) for Rabies Vaccine was introduced in 1978 (*19*), when the WHO Expert Committee on Biological Standardization established the third International Reference Preparation of Rabies Vaccine. The activity assigned to the contents of each ampoule was 10 IU. The third International Reference Preparation compared to the second International Reference Preparation in that one International Unit was equal to the former antigenic value of one. Thus, 1 ml of the third International Reference Preparation reconstituted using 10 ml of diluent per ampoule had the same potency as 1 ml of the second International Reference Preparation reconstituted using 8 ml of distilled water per ampoule.

The International Standard for Rabies Vaccine is the fourth reference material. It was prepared in human diploid cell culture and was established in 1983 with a defined potency of 7.8 IU per ampoule (*20*).

Since the stocks of this International Standard for Rabies Vaccine are being depleted, a replacement International Standard, prepared in Vero cells, is under consideration.[1]

National laboratories are urged to prepare their own national reference rabies vaccine, which should be calibrated against the International Standard. The national reference preparation should be supplied to routine production laboratories within the country. Where it is not possible to establish a national reference vaccine, reasonable amounts of the International Standard can be supplied to countries wishing to establish the (relative) potency of a production batch of vaccine to be used as a national reference.

National reference vaccines should be used to estimate the potency of every production lot of vaccine by standard procedures, as described in *Laboratory techniques in rabies*, 4th ed. (*5*). The National Institutes of Health (NIH) test is recommended for calibrating national reference vaccines and determining the potency of vaccines to be released. The Habel test is no longer considered suitable for calibration.

[1] The WHO Expert Committee on Biological Standardization established this vaccine as the fifth International Standard for Rabies Vaccine in October 1991, with a defined potency of 16 IU per ampoule (*21*).

5.2 International standard for anti-rabies serum

The first International Standard for Rabies Immunoglobulin was established in 1984, with a potency of 59 IU per ampoule (*22*). Preparations for its replacement are already under way since it is envisaged that the stocks will be depleted in about 4-5 years time.

The quantitative assay of anti-rabies antibody preparations is described in *Laboratory techniques in rabies*, 4th ed. (*5*). It should be noted that, whereas some laboratories have had problems with the virus-neutralization test in mice (MNT), fewer difficulties have been reported with the rapid fluorescent focus-inhibition test (RFFIT) in cell cultures.

National control laboratories should establish reference sera of a specified potency, in terms of IU per ml, to be used routinely for *in vitro* and *in vivo* neutralization tests. It is suggested that the potency of anti-rabies reference immunoglobulin be determined in comparative studies carried out at the national reference centre and at least one of the WHO Collaborating Centres concerned with rabies.

5.3 Reference reagents for diagnostic purposes

Monoclonal antibodies against the various antigenic determinants of the nucleocapsid and glycoprotein of rabies virus have been prepared in several WHO Collaborating Centres (see section 2.1). These antibodies can differentiate between the different virus types and subtypes. In particular, they can be used to identify wild strains of rabies virus originating from different geographical locations and reservoir species, as well as fixed strains used for rabies vaccine production. Limited panels of monoclonal antibodies and reference reagents may be available from WHO Collaborating Centres for specific research projects, or the strains to be characterized may be submitted to one of these centres for identification.

5.4 Seed virus strains

At regular intervals, monoclonal antibodies and genome sequencing should be used to check the identity of virus strains maintained in individual laboratories and used for vaccine production. A list of the major vaccine strains is given in section 4.1.

6. Procedures for licensing and release of inactivated tissue-culture vaccines

6.1 General considerations

The Committee once again emphasized the importance of determining the potency of every batch of production vaccine before its release. Furthermore, whenever appropriate, quality control of the final product

should also be carried out by independent laboratories. These control laboratories should test vaccines by recognized procedures.

Encouragement should also be given to the establishment of regional quality-control laboratories. Countries that do not have the facilities to carry out tests on each individual vaccine batch should seek the assistance of a WHO Collaborating Centre.

International requirements for testing the potency of rabies vaccines for human and veterinary use have been described, including current procedures for the release of rabies vaccine batches (*5*, *16*, *17*).

6.2 Tests for licensing

6.2.1 *Vaccines for human use*

Vaccines for human use should satisfy the minimum potency requirements as described in section 4.2.4 and Annex 1. In addition, the induction of neutralizing antibodies in non-exposed persons should be studied. Following immunization with the vaccine using a recognized immunization schedule, the level of induction and persistence of neutralizing antibodies should be no less than that observed following immunization with a vaccine of proven efficacy. Once the results have been carefully analysed, efficacy trials should be conducted in exposed persons.

Induction of neutralizing antibodies should be determined using either the mouse neutralization test (MNT) or the rapid fluorescent focus inhibition test (RFFIT); the antibody titres should be measured, using the same challenge virus strain, in sera from vaccinees who received either the vaccine of proven efficacy or the vaccine under test. The challenge virus strain should be in common use.

6.2.2 *Vaccines for veterinary use*

Vaccines for veterinary use should satisfy the minimum potency requirements as described in section 4.3.3 and Annex 1. In addition, an efficacy trial should be carried out: following immunization, an acceptable proportion (usually 80%) of vaccinated animals should be protected against a field rabies virus challenge that kills at least 80% of the controls; protection should also be demonstrated at the end of the validity period claimed by the producer. The minimum number of animals to be used in each group (vaccinated and non-vaccinated) should be determined by the national control authority but in no case should be less than 10 for dogs and cats and 5 for larger animals. In addition, neutralizing antibody levels prior to challenge should be determined.

6.3 Tests for "in-process" control

The NIH test may be used for in-process control. However, since 1984, *in vitro* tests for the determination of the antigen content of rabies vaccine have been further developed and used for the control of the production

process. These tests are much simpler than the NIH test and avoid the use of laboratory animals. Examples include the antibody-binding test (ABT), enzyme-linked immunosorbent assay (ELISA) and the single radial immunodiffusion test (SRD); all of these tests are potentially suitable for determining the antigen content of non-adjuvanted vaccines. Both glycoprotein and nucleocapsid protein content can be determined by the ELISA. (For individual techniques please refer to *Laboratory techniques in rabies*, 4th ed. (*5*).)

6.4 Potency test for batch release

Potencies should be determined by the NIH test and expressed in IU per dose. Potency requirements for human and veterinary rabies vaccines are described in sections 4.2.4 and 4.3.3. Annex 1 provides guidance for the use of antigen quantification tests for the release of human and veterinary rabies vaccines.

7. Prevention of rabies in humans

7.1 General considerations

In view of the extremely high fatality rate of human rabies, the prevention of rabies infection after exposure is of the utmost importance. Major advances have been made in the safety and potency of rabies vaccines. The Committee reiterated, as stated in its 1983 report (*1*), its support for the trend to limit or abandon completely – where economically and technically possible – the production of encephalitogenic brain-tissue vaccines, and strongly advocated the production and use of inactivated cell-culture rabies vaccines in both developed and developing countries. After exposure, prevention of infection is virtually assured by immediate treatment of the wound and post-exposure prophylaxis with one of the recommended regimens of rabies immunoglobulin (RIG) and cell-culture vaccines (see sections 7.3 and 7.5 and Annex 2). If cell-culture rabies vaccine is not available, brain-tissue vaccine (preferably suckling-mouse brain vaccine) of proper potency may be administered. There are as yet no inexpensive vaccines available for mass pre-exposure vaccination and individual pre-exposure immunization should therefore be considered for all persons at high risk of exposure.

7.2 Pre-exposure immunization

Vaccines of cell-culture origin are preferable for pre-exposure immunization of humans, since they are safer and more effective than nerve-tissue vaccines (see section 4).

Pre-exposure immunization should be offered to persons at high risk of exposure, such as laboratory staff working with rabies virus, veterinarians, animal handlers and wildlife officers, and other individuals who are living in or travelling to areas where rabies is endemic.

Such immunization should preferably consist of three full intramuscular doses of tissue-culture rabies vaccine of potency at least 2.5 IU per dose given on days 0, 7 and 28. (A few days' variation is not important.) The presence of virus-neutralizing antibodies in vaccinated individuals should be ascertained, where feasible, using serum samples collected 1-3 weeks after the last dose. For adults, the vaccine should always be administered in the deltoid area of the arm. For young children, the anterolateral area of the thigh is also acceptable. The gluteal area should never be used for vaccine injections, since administration in this area results in lower neutralizing antibody titres.

Tissue-culture or purified duck-embryo rabies vaccines of potency at least 2.5 IU per dose have been shown to induce adequate antibody titres when carefully administered intradermally in 0.1 ml volumes on days 0, 7 and 28. After reconstitution of the vaccine, the entire volume should be used as soon as possible. Separate syringes and needles must be used for each dose. Intradermal application of the vaccine is of special interest in areas where economic constraints limit vaccine availability. However, pre-exposure immunization with human diploid cell (HDC) vaccine administered intradermally should, whenever possible, be performed before starting antimalarial prophylaxis, since virus-neutralizing antibody titres have been shown to be lower in patients receiving chloroquine phosphate. When this is not feasible, HDC vaccine should be administered intramuscularly.

Periodic booster injections are recommended for persons at continuing risk of exposure to rabies. The following guidelines are recommended for determining when boosters should be administered:

All persons who work with live rabies virus in a diagnostic, research or vaccine production laboratory should have a serum sample tested for rabies virus-neutralizing antibodies every 6 months and a booster administered when the titre falls below 0.5 IU/ml. Responsible authorities should ensure that all staff are properly immunized.

All other persons at continuing risk of exposure to rabies should have a serum sample tested for rabies virus-neutralizing antibodies every year; a booster should be administered when the titre falls below 0.5 IU/ml.

A rabies vaccination pre-exposure certificate should be filled in and given to the vaccinee, indicating the type of vaccine used, the manufacturer, lot number, schedule used, antibody titre (if tested), and any allergic reactions that may have occurred (see Annex 3).

7.3 Post-exposure treatment

7.3.1 *General considerations*

The combination of local treatment of the wound, passive immunization with rabies immunoglobulins (RIG) and vaccination is recommended for all severe exposures (category III) to rabies (see Annex 2). Prompt and

thorough cleansing of the wound, and administration of purified equine or human rabies immunoglobulins (ERIG or HRIG) and cell-culture rabies vaccine immediately after exposure virtually guarantee complete protection, and the risk of post-exposure treatment complications is much lower than with brain-tissue vaccines. Pregnancy and infancy are never contraindications to post-exposure rabies vaccination. Since prolonged incubation periods have been noted, persons who present for evaluation and treatment even months after having been bitten should be dealt with in the same manner as if the contact occurred recently.

Factors that should be considered in deciding whether or not to initiate post-exposure treatment are:

- the nature of the contact;
- the presence of rabies in the area where the contact occurred or from which the animal involved came;
- the species of the animal involved;
- the vaccination and clinical status of the animal involved, the type of vaccine used and the availability of the animal for observation;
- the results of laboratory testing of the animal for rabies, if available.

An apparently healthy dog or cat that bites a person may or may not justify the initiation of treatment, depending on the perceived risk. If the animal involved is a recognized rabies vector in the area where the contact occurred, initiation of treatment should never await the results of laboratory diagnosis. If the animal is suspected of being rabid, immediate euthanasia and laboratory examination of the brain should be performed. Wound treatment must be completed and serum and vaccine therapy instituted as soon as possible after any exposure. If the species involved is unlikely to be infected with rabies, treatment may be deferred pending the outcome of laboratory testing provided that diagnosis can be made within 48 hours. A report from a reliable laboratory indicating a negative result usually justifies cessation of treatment.

If the animal involved is a dog or cat, it should be kept under observation, preferably under veterinary supervision, for 10 days. Treatment may be discontinued if the dog or cat remains healthy during this period. The Committee suggested, however, that people in contact with animals other than cats and dogs that are suspected of being rabid should receive full post-exposure treatment unless the animal is available and can be killed humanely and examined for rabies in a reliable laboratory immediately.

7.3.2 *Local treatment of wounds*

The Committee emphasized the importance of prompt local treatment of all bite wounds and scratches that may be contaminated with rabies virus, even if the person presents after a prolonged period.

Recommended first-aid procedures are immediate thorough flushing and washing of the wound with soap and water, detergent or other substances of proven lethal effect on rabies virus (see Annex 2). People who live in

rabies-infected areas should be educated in simple local wound treatment and warned not to use procedures that may further contaminate the wounds. If possible, suturing of wounds should be avoided; however, if suturing is necessary, anti-rabies immunoglobulin should be infiltrated around the wound. Other treatments, such as administration of antibiotics or anti-tetanus procedures, when indicated, should follow the local treatment.

7.3.3 *Administration of rabies immunoglobulin*

Rabies immunoglobulin (RIG) should be given for all category III exposures, irrespective of the interval between exposure and beginning of treatment. Two kinds of rabies antibody preparations may be used: human rabies immunoglobulin (HRIG) and equine rabies immunoglobulin (ERIG). A skin test must be performed prior to the administration of ERIG. As much as possible of the recommended dose (20 IU/kg of body weight of HRIG or 40 IU/kg of body weight of ERIG) should be infiltrated around the wounds if anatomically feasible. The remainder should be administered intramuscularly (into the gluteal region) in a single dose and followed by a complete course of vaccine.

Rabies immunoglobulin of human origin (HRIG) is available in some countries; however, it is expensive and only limited amounts are available.

Rabies immunoglobulin of equine origin (ERIG) is available in many countries and is considerably cheaper than HRIG. Most of the currently available preparations of ERIG are highly purified and quite safe; however, a skin test should always be carried out prior to its use.

7.3.4 *Vaccine administration*

The vaccination schedule recommended in a given situation depends on the type and potency of the vaccine available.

Brain-tissue-derived vaccines

The Committee did not recommend any particular vaccination schedule. In countries where brain-tissue vaccines are used, the national authorities should recommend a schedule of immunization that has been shown to induce an adequate level of protection.

Tissue-culture rabies vaccines or purified duck-embryo vaccine

The potency of these vaccines should be of at least 2.5 IU per single human dose. All these vaccines are considered equally safe and effective when used properly. They should be applied according to the following schedules:

Intramuscular schedules: One dose of vaccine should be administered on days 0, 3, 7, 14 and 30. All intramuscular injections must be given into the deltoid region or, in small children, into the anterolateral area of the thigh muscle. Vaccine should never be administered in the gluteal region.

In the abbreviated multisite schedule, the 2-1-1 regimen, one dose is given in the right arm and one dose in the left arm at day 0, and one dose applied intramuscularly in the deltoid region on days 7 and 21. The 2-1-1 schedule induces an early antibody response and may be particularly effective when post-exposure treatment does not include administration of rabies immunoglobulin.

Intradermal schedule: One dose (0.1 ml) should be given at each of two sites, either the forearm or the upper arm, on days 0, 3 and 7, and one dose at one site on days 30 and 90. This regimen considerably lowers the cost of vaccination against rabies, as the total volume of vaccine required is much less than that required for intramuscular regimens. Separate syringes and needles must be used for each dose. Intradermal injections should be administered only by staff who have been trained in this technique. Vaccine vials should be stored between 4 °C and 8 °C after reconstitution and the total contents should be used as soon as possible.

7.4 Certificate of post-exposure treatment

A certificate of post-exposure rabies treatment should be filled in and given to each vaccinee (see Annex 3).

7.5 Post-exposure treatment of previously vaccinated persons

Local treatment of wounds should always be carried out (see section 7.3.2). On the basis of the information now available, the Committee recommended that persons who have previously received full pre- or post-exposure treatment with a potent cell-culture vaccine should be given only two booster doses, either intramuscularly or intradermally, on days 0 and 3, but no rabies immunoglobulin.

Persons who have previously received pre- or post-exposure treatment with vaccines of unproven potency, and those who have not demonstrated an acceptable rabies neutralizing antibody titre, should receive a complete post-exposure course, including rabies immunoglobulin if indicated.

7.6 Complications of anti-rabies treatment

7.6.1 *Anti-rabies immunoglobulin*

It has been shown that purified equine rabies immunoglobulin products cause adverse reactions in 1-6% of vaccinees, even when sensitivity tests are performed prior to their administration. Unpurified anti-rabies sera should be avoided whenever possible.

7.6.2 *Nerve-tissue vaccine*

Repeated inoculations of homogenates of brain tissue may induce immune responses to some neural antigens. In the case of Semple-type vaccine, these neurological complications are attributed to myelin basic protein and some of the ganglioside and phospholipid constituents. Though properly

prepared suckling-mouse brain vaccines contain virtually no myelin, neurological complications still occur, but at a much lower rate than with adult nerve-tissue vaccines.

Patients who develop neurological complications from Semple-type vaccines have higher levels of rabies virus-neutralizing antibodies than vaccinees without complications. Dexamethasone is beneficial in managing such reactions, but significantly depresses the virus-neutralizing antibody level, even when a full vaccination schedule is repeated, using a cell-culture vaccine. The Committee therefore suggested that such patients should receive twice the normal amount of cell-culture vaccine when dexamethasone is given.

7.6.3 *Cell-culture vaccines and purified duck-embryo vaccine*

These vaccines have not been causally associated with serious adverse effects. Mild serum sickness-like and urticarial reactions have occasionally been observed following booster doses of some of these vaccines.

8. Treatment of confirmed rabies in humans

Although rabies in humans almost inevitably ends in death, a few instances of recovery have been recorded. All these patients had received immediate post-exposure treatment using either duck-embryo or suckling-mouse brain vaccines. The diagnosis in these patients was based upon the demonstration of high levels of rabies virus-neutralizing antibodies in serum and spinal fluid; however, no rabies antigen was detected.

The following measures have also been tried in clinical rabies, but without any evidence of effectiveness: administration of vidarabine; multisite intradermal vaccination with cell-culture vaccine; administration of α-interferon and rabies immunoglobulin by intravenous as well as intrathecal routes; and administration of anti-thymocyte globulin, high doses of steroids, inosine pranobex, ribavirin and the antibody-binding fragments of rabies immunoglobulin G.

The clinical course of the disease, with either excitation or paralysis as the predominant symptom, is of short duration and entails much suffering. Patients remain conscious, often aware of the nature of their illness, and are usually extremely agitated, particularly when excitation is predominant. This is compounded by the fact that they become isolated because of the perceived risk of transmission of the disease through contact. Although rabies transmission from person to person has never been documented, it could theoretically be possible, since secretions may contain the virus. Nursing staff should therefore be informed of the potential risk of contamination (especially during intensive care) and should wear goggles, mask and gloves. Patients should be sedated with appropriate tranquillizers.

If contamination does occur through the skin or mucous membranes, the nursing staff should receive post-exposure treatment.

In spite of the extremely poor prognosis of human rabies, suitable tertiary care centres should be encouraged to continue with new experimental efforts to treat rabies patients. The nursing and medical staff of such centres should be offered pre-exposure immunization.

The Committee expressed concern about the risk of transmission of rabies through corneal transplants. Organs of patients with any neurological disease should not be used for transplantation.

9. National programmes for the control of rabies in dogs

9.1 Introduction

In over 80 countries, rabies is still prevalent in its most dangerous reservoir, the dog population. Each year approximately 4 million people in these areas receive treatment after exposure to rabies and over 30 000 people die after being bitten by rabid dogs. In more than 99% of all human rabies cases, the virus is transmitted from dogs, and over 90% of people who receive rabies post-exposure treatment live in areas of canine rabies.

Effective veterinary vaccines that provide a considerable duration of immunity have been developed; however, mechanisms to ensure their worldwide availability still need to be defined.

Up to the 1960s, an increasing number of countries reported the elimination of canine rabies reservoirs from their territories. With the exception of a few areas in Latin America, the Caribbean and Europe, this process, however, came to a standstill until the 1980s, when a number of successful field projects were initiated or reactivated under the aegis of WHO.

Canine rabies is almost entirely limited to developing countries. Control measures such as confinement of dogs on owners' premises, capture and removal, and dog population control have widely failed to be adopted and maintained in these countries. Much of the problem has been in failure to understand the relationship of dogs to the society, and attempts to impose rabies control approaches that have been successful in many developed countries. However, dog population immunization programmes adapted to the social structure are now feasible and are being developed in several countries. In order to reach a high proportion of the dog population, such programmes must be based on the local ecology of the dog population, on understanding of the local society, on coordination of the related sectors of society and on culturally adapted education for the control of rabies. Dog elimination programmes by themselves are not effective in rabies control (see Annex 4).

Studies coordinated by WHO on dog populations have shown that, in parts of North Africa, Latin America and Asia, up to 75% of the total dog population is accessible to parenteral immunization. This is usually high enough to break the rabies transmission cycle.

The Committee recognized the significant reduction in the number of human deaths due to rabies achieved by the PAHO/AMRO coordinated programme for the elimination of urban rabies in the Americas since its inception in 1983, as well as by the AGFUND/WHO coordinated programme for the control of human and canine rabies in developing countries during the period 1985-1988. Rabies has been spreading through canine populations in wide areas of sub-Saharan Africa during the past two decades and is becoming more common in other continents with increasing urbanization, density and mobility of human populations. Control programmes are inadequate in the absence of comprehensive schemes aiming at the elimination of the disease. The number of persons requesting post-exposure rabies treatment is also increasing; in some countries it has almost doubled over the past 10 years. This increase in demand is mainly due to greater public awareness regarding the safety and potency of rabies vaccines and immunoglobulins, together with a lowering of the costs of these products.

The social and economic significance of post-exposure treatment is often overlooked by national authorities in areas where the number of human rabies deaths has become negligible, but where post-exposure treatments remain at a high level.

There are three basic elements to any programme for the control of rabies in dogs and other domesticated animals. Their priorities will depend on the social, cultural, and economic factors prevailing in each region, country or community. The basic elements are: (a) epidemiological surveillance (section 9.2); (b) immunization (section 9.3); and (c) dog control (section 9.4). They will require community participation, managerial skills and legislation. Further technical and managerial information for planning, implementing and evaluating national programmes for the control of rabies in dogs is given in Annex 4.

9.2 Epidemiological surveillance

Surveillance of rabies is the basis of any programme for rabies control. Epidemiological data should be collected, evaluated, processed and mapped whenever possible and disseminated rapidly. Such data are essential both to physicians in deciding whether to initiate post-exposure treatment and to veterinarians in deciding what measures to adopt towards the animal responsible for the contact.

This information is also required for planning, organizing and implementing rabies control programmes.

The surveillance of rabies has at present reached a satisfactory standard in

only a few countries and this has a direct bearing on the treatment of exposed persons and on rabies control activities in animals. National authorities should be encouraged to collect more systematically the available data on rabies, including clinical records, and to ensure rapid exchange of information, after collation and processing, between different administrative sectors and levels. This would permit them to analyse the epidemiology of rabies in their area, to plan appropriate control procedures and to pass the appropriate information to authorities in other countries. National authorities should be aware that, even in areas where laboratory support is inadequate or lacking, valuable information can still be obtained from clinical observations. Countries are urged to adopt or establish regional and international systems of rabies reporting (see section 12.1). International collaboration in surveillance is particularly important, especially for the investigation of rabies outbreaks and identification of the rabies virus strains involved, in view of increased international travel and transfer of animals.

9.3 Mass parenteral vaccination campaigns

Mass canine vaccination campaigns have been the most important measure applied for controlling rabies in developing countries. At least 75% of the dog population in each community should be vaccinated within a month. In areas where the dog population turnover is rapid, it may be necessary to carry out a mass vaccination campaign each year. However, if the effective immune period of the vaccine is longer and the system for identifying vaccinated dogs can be trusted to last more than one year, the advantage of vaccinating only the dogs entering the population after the last campaign should be considered, with revaccination of dogs vaccinated during the last campaign at intervals of about 2 years.

In order to plan, execute and evaluate a mass vaccination campaign, an estimate of the dog population is required (see Annex 4). If possible, a census or a study based on a sample of the dog population should be carried out before starting the campaign or in connection with the first phase of the campaign.

For mass canine vaccination campaigns, the use of inactivated rabies vaccine is recommended. The management of inactivated vaccine in the field is easier than that of live vaccine, since it is less sensitive to changes in temperature. Furthermore, accidents of self-inoculation do not represent any risk for the vaccinator.

With inactivated vaccine, all dogs and cats taken to the vaccinator should be vaccinated, regardless of their age, weight or state of health. Puppies less than 3 months old should be given a vaccine booster at 6 months of age. For live vaccines in particular, the manufacturers' instructions should be strictly followed. (See Annex 4 for parenteral vaccination of other animal species.)

The use of coloured tags or coloured plastic collars individually adjusted

to each dog has proved useful in identifying vaccinated dogs and has contributed to the success of vaccination campaigns by motivating owners to take their pets for vaccination. It has also been useful in evaluating the vaccination coverage rate, particularly during the initial phase of the campaign.

Three basic approaches have been used, either alone or in combination, in carrying out mass vaccination campaigns: house-to-house visits, fixed vaccination posts, and mobile clinics. The choice of approach will depend on the specific community and the decision should be taken at the local level.

Research carried out by WHO between 1981 and 1988 as part of the AGFUND/WHO project for the control of human and canine rabies in developing countries revealed that:

- whether owned or not, very few dogs (generally less than 10-15% of the dog population) are able to avoid being caught;
- dog removal programmes (in which stray dogs are captured and humanely killed) are ineffective, as well as costly;
- vaccination coverage rates of 75% or higher can be attained, although this requires special efforts in mobilizing community participation, conducting health systems research and providing support services for vaccination campaigns (*23*).

High vaccination coverage was attained through strategies consisting of well-designed short-term educational campaigns, mass dog vaccination and marking, followed a few days later by vaccination of dogs that were missed during the first campaign. In some countries this was combined with the removal of unmarked dogs. In others, adequate population coverage was achieved without dog marking or a second round of vaccination. Informational campaigns and involvement of the community in planning and carrying out these programmes were major factors in their success (see Annex 4).

Fixed vaccination points or mobile clinics should be situated within the communities or neighbourhoods they are intended to serve. Experience has shown that such posts will be sufficiently attended only from distances of less than 500 m or about 10 minutes' walk.

9.4 Dog population management

The Committee expressed its appreciation of the long-term engagement of WHO in developing methodologies related to dog ecology and dog population management. Considerable experience has been gained in projects coordinated by WHO in Ecuador, Nepal, Sri Lanka and Tunisia and other ecological studies conducted in South America and Asia. However, data collection, health systems and operational research need to be continued in other areas and countries with different social and ecological conditions.

On the basis of the results obtained so far in these studies, the Committee recommended drastic changes in rabies control policies as compared with those previously adopted and practised by most national authorities and communities. There is no evidence that removal of dogs has ever had a significant impact on dog population densities or the spread of rabies. The population turnover of dogs may be so high that even the highest recorded removal rates (about 15% of the dog population) are easily compensated for by increased survival rates. In addition, dog removal may be unacceptable to local communities. Therefore, this approach should not be used in large-scale control programmes unless ecological and sociocultural studies show it to be feasible.

Several methods to estimate dog population densities based on questionnaire surveys and capture/mark/re-observe studies are available (*2*, *23*, *24*). A combination of these two methods allows collection of accurate information on the whole dog population and its subpopulations, defined in terms of confinement levels or other parameters. Whereas density estimates based on simple capture/mark/re-observe studies using uniform marking (collars, dyes) are usually adequate in rural areas, more complex study designs involving differential or individual marking are recommended in urban and suburban areas in order to compensate for variations in re-observation probability (*15*). Questionnaire surveys conducted in the community can be useful where residents recognize the dogs present in their communities.

Three practical methods of dog population management are recognized: movement restriction, habitat control and reproduction control. Further information is given in Annex 4.

9.5 International cooperation

The Committee expressed its appreciation to WHO for supporting activities in rabies surveillance, prevention and control, and stressed the need for further strengthening of the cooperation and collaboration of WHO with its Member States in rabies control.

Technical cooperation among countries should concern the following closely interrelated elements:

- rapid diagnosis and development of appropriate surveillance for immediate post-exposure treatment in people and disease control in animals;
- technical cooperation in planning, implementing and evaluating national programmes;
- promotion and coordination of control programmes involving neighbouring countries in their border areas;
- development and transfer of technologies for the production and control of modern safe and potent vaccines for use in animals and humans;
- rabies research;
- provision of training or short-term expertise as required.

The Committee appreciated the efforts of WHO to promote the above elements and to establish an inventory of resources and needs for efficient control of rabies (*4*).

In view of the promising results obtained so far through operational research projects coordinated by WHO, the Committee urged WHO, in collaboration with donor agencies and vaccine manufacturers, to develop its programme for the control of human and canine rabies further.

The Committee recommended that, in this context, four major programme components should be taken into account:

1. The planning and management of community, district, national and regional rabies control programmes.
2. Cooperation with various institutions and the pharmaceutical industry in the provision of vaccine, including promotion of the transfer of technology for rabies vaccine production to developing countries, whenever feasible, and technical cooperation in programme planning and management to ensure proper vaccine delivery.
3. Promotion of funding by bilateral and multilateral agencies and other donor agencies, within the framework of technical cooperation or humanitarian aid.
4. Coordination of international services in collaboration with the Food and Agriculture Organization of the United Nations, the International Office of Epizootics (OIE), and nongovernmental organizations such as the International Union for Conservation of Nature and Natural Resources (IUCN), the World Society for the Protection of Animals (WSPA) and the World Wide Fund for Nature (WWF).

WHO and WHO Collaborating Centres and affiliated institutions (see Annex 5) should cooperate with governments and national institutions to achieve the above goals.

10. Control of rabies in wild animals

10.1 Epidemiology and ecology of rabies in terrestrial host species

10.1.1 *Foxes*

Red foxes (*Vulpes vulpes*) are responsible for the maintenance and spread of rabies in the subarctic and north-eastern parts of North America, in subarctic Asia, and in central and eastern Europe. Antigenic differences between rabies isolates from foxes originating from North America and Europe can be detected with monoclonal antibodies.

A rabies epidemic has recently been reported in foxes in southern Arabia; rabies cases had, until then, been rare and sporadic in this area.

Red foxes are members of the family Canidae. They are omnivores, scavenging and preying on small vertebrates and invertebrates, and they

can survive on refuse provided by humans. Their generalist foraging behaviour enables them to reach high population densities in and around human habitations. Female foxes give birth to one litter per year in the spring, after a gestation period of approximately 52 days. The average litter size is about 5 puppies per female, which reach sexual maturity at about 9 months of age. Their high reproductive capacity ensures rapid recovery of populations decimated by hunting, gassing, trapping or disease. Young foxes may leave the family territory at about 6 months of age, with usual dispersal distances of between 10 and 50 km.

The above features ensure the maintenance of initial rabies epizootics, and of subsequent enzootics in fox populations. Chains of intraspecific transmission are rare in species other than the main hosts and, when they do occur, are usually short. No substantial evidence has been presented to support the hypothesis that small mustelids or rodents serve as reservoirs of the disease in nature.

10.1.2 *Mongooses*

Thirty-six species of mongooses (Viverridae) are distributed throughout Africa and parts of Asia. Sporadic cases of mongoose rabies have been reported from many African countries; in South Africa, the yellow mongoose (*Cynictis penicillata*) is the main reservoir of rabies. The small Indian mongoose *Herpestes auropunctatus* is an important reservoir and vector of rabies in Cuba, the Dominican Republic, Grenada, Haiti and Puerto Rico; in Grenada, mongooses appear to be responsible for all the recorded rabies cases. Mongooses do not appear to serve as major reservoirs or transmitters of rabies in Asia.

Mongoose trapping and poisoning campaigns in the Caribbean have been expensive and only temporarily effective.

10.1.3 *Arctic reservoirs*

Rabies has been reported in Canada, Greenland, Norway (Svalbard Islands), the United States of America (Alaska) and the former USSR. Iceland and Sweden remain free of rabies.

In the Arctic rabies has been reported in the arctic fox (*Alopex lagopus*), the red fox (*Vulpes vulpes*) and various other species. The principal vector in the regions where epizootics have been reported is the arctic fox, which also inhabits the pack ice of the Arctic Ocean during winter months. The incidence of rabies in the arctic and subarctic regions increases periodically every 3-5 years, synchronous with the population density cycle of the arctic fox. In many areas this fox is principally dependent on arvicoline rodents as prey, especially lemmings (*Lemmus* spp. and *Dicrostonyx* spp.) (*25*).

Rabies control measures such as the destruction of rabid animals and the reduction of host populations through trapping or shooting programmes

are not feasible in most of the Arctic. A more effective approach would be to carry out mass oral immunization programmes.

10.1.4 *Racoon dogs*

The racoon dog is a vector of rabies in northern Poland and western parts of the former USSR. An outbreak of rabies in this species occurred in south-eastern Finland in 1988; the disease was eliminated through oral vaccination in 1989.

The depth of the snow cover and length of winter appear to constitute climatic limits for the racoon dog to expand its habitat into the far north and arctic regions of Europe. This implies that the racoon dog is not a usual reservoir for arctic rabies.

Very few racoon dogs behave aggressively towards humans, but a considerable number of rabid racoon dogs have been found attacking, fighting with, or killed by dogs. This implies that rabid racoon dogs might constitute a greater potential risk to human health and domestic animals than rabid foxes.

10.1.5 *Racoons*

The racoon (*Procyon lotor*) first emerged as a major reservoir for wildlife rabies in North America from a well-defined epizootic in peninsular Florida during the 1950s. During the 1970s, racoon rabies was restricted to the south-eastern USA. A secondary focus of racoon rabies began in the mid-Atlantic region of the USA in 1977, which has now expanded to include most of New England.

No clear seasonal, sexual or age-related factors have been identified during these outbreaks. Incubation periods of racoon rabies measured in experimental infections in racoons have ranged from 2-3 weeks to more than 3 months, with morbidity periods (interval between onset of symptoms and death) of 1-7 days. Clinical signs in racoons range from sudden death without prior abnormalities to furious rabies.

10.1.6 *Skunks*

During the 19th century, the spotted skunk (*Spilogale putorius*) was recognized as a rabies reservoir in the central United States. Since then, the striped skunk (*Mephitis mephitis*) has become the predominant wildlife rabies reservoir in this area. Following the elimination of canine rabies in the United States in 1961, more cases of rabies have been reported in the striped skunk than in any other species, and it has also been the major source of rabies exposure to domesticated animals, especially cattle.

10.1.7 *Wildlife species in urban areas*

Although skunks, foxes and racoons are important rabies vectors in certain rural areas of North America, the disease is also present in those

species in certain urban areas. Rabies has been prevalent in skunks (*Mephitis mephitis*) and foxes (*Vulpes vulpes*) in many urban areas of southern Ontario, Canada since the early 1960s, particularly Toronto. The ubiquity and abundance of racoons and other wild carnivores, combined with their ability to adapt to a variety of urban ecosystems, and the tolerance of human communities towards them, mean that these species will represent unique problems to urban rabies control in the Americas. This will be especially true in large metropolitan areas (e.g. Baltimore, Toronto, Washington DC), where the density of affected wildlife populations has led to an increasing number of cases of exposure in humans and domestic animals.

10.1.8 *Jackals*

There are five species of jackals (*Canis* spp.) in Africa and Asia. In Africa, jackals are the major wildlife rabies vector. They are highly susceptible to rabies and can excrete very high levels of the virus in the saliva. Although infected animals usually display the furious form of the disease, some manifest excessive tameness and will wander into homesteads.

Most cases of rabies in jackals occur in epizootics, which take place in cycles of 4-8 years. Jackal rabies is usually, but not always, coincident with dog rabies.

10.2 Rabies in bats

10.2.1 *Vampire bats in the Americas*

Although massive outbreaks of rabies in cattle were noted in the 1910s, the relationship between bites from vampire bats and cattle rabies was not demonstrated until 1918. Human rabies attributed to bites from vampire bats has mainly been reported from Guyana, Mexico and Trinidad and, more recently, from Bolivia, Brazil and Peru, with an apparent increase in these latter countries during the last few years.

Vampire-bat rabies can be controlled by vaccination of cattle and administration of anticoagulant to vampire bats, either by direct application of substance on the backs of captured bats or by the intramuscular injection of warfarin to cattle. Whenever possible, individuals in high-risk areas should be protected by pre-exposure vaccination. Every person bitten by a vampire bat should receive proper post-exposure treatment (see section 7).

10.2.2 *Insectivorous bats in Europe and North America*

Rabies was first reported in insectivorous bats in 1953, in Florida, USA. Since then the disease has been diagnosed in a variety of insectivorous species in several countries in North America and Europe; since 1985, most rabies cases in insectivorous bats in Europe have been in *Eptesicus serotinus*. Human rabies caused by insectivorous bats is uncommon, with

thirteen cases reported in Canada and the United States and two cases reported in Europe.

Transmission of the rabies virus from insectivorous bats to terrestrial animals is sporadic in the USA and has not been demonstrated in Europe.

The generally low prevalence of rabies in bat populations does not justify specific control measures. Given their status as endangered species, destruction of bat colonies should be avoided. Nevertheless, people in rabies-infected countries should be informed of the risk of infection, to ensure that every person bitten by an insectivorous bat receives appropriate treatment.

10.3 Rabies in rodents

Examination of tens of thousands of wild and synanthropic rodents in endemic rabies areas in the Americas and Europe has revealed only rare instances of rodent rabies infection, indicating that these animals do not serve as reservoirs of the disease in nature.

10.4 Elimination of rabies in wild animals

Programmes to control and, eventually, to eliminate wildlife rabies have, until recently, focused on efforts to decrease the population levels of disease hosts. The recently developed oral rabies vaccination technique is being more and more widely used and has been shown to be effective under a variety of field conditions.

10.4.1 *Reduction of animal populations*

The maintenance of rabies in an animal species population requires intraspecific contact between infected vector animals, which in turn requires a high population density. The objective of wildlife reduction is to lower the population density below the threshold necessary to maintain the disease within that population. Classical reduction techniques include hunting, trapping, poisoning and den-gassing, but programmes based on these techniques almost never achieved sufficient reduction of the vector populations to allow elimination of the disease. Where such programmes are carried out, vector populations may be rapidly replenished by an influx of animals from neighbouring areas. Where hunting is carried out, it may be possible to carry out active rabies surveillance by analysing brain specimens from animals that have been killed. However, wildlife reduction techniques should not be carried out on a large scale.

Mass killing of carnivores can also cause an increase in their prey populations and, when prey species are considered a pest (e.g. rodents), these "costs of ecological disruption" may not be welcome.

10.4.2 *Current field trials for oral immunization of wild animals*

Europe

The first large-scale field trial for immunization of foxes, using chicken-head baits containing a modified live rabies vaccine (SAD-Bern strain), was initiated in October 1978 in Switzerland. The technique has been expanded to the entire Swiss territory and most of the country is now free of rabies. Foci of rabies persist, however, in the north-eastern part of the country at the border with France. The Swiss chicken-head bait was also used in trials in parts of the Federal Republic of Germany before 1985, and in Italy and France in 1986 and 1987 respectively; it was replaced by manufactured (Tübingen) baits containing the SAD-B19 virus strain as vaccine in large-scale trials conducted subsequently in these countries. The elimination of fox rabies from large areas of the Federal Republic of Germany and parts of Belgium and France, as well as more limited areas of Finland, Italy and Luxembourg, has confirmed the efficacy of oral immunization. In eastern Europe, oral vaccination projects have been initiated in Czechoslovakia, in border areas with Austria and Germany, and in Slovenia, in border areas with Italy; Hungary, Poland and parts of the former USSR are planning to initiate such schemes.

In Belgium, France, Luxembourg and parts of Germany, baits are now distributed using small planes and helicopters.

Since 1990, a vaccinia recombinant rabies vaccine in a fishmeal polymer bait has been used in large-scale trials in Belgium and France.

A field trial for oral immunization of racoon dogs and foxes against rabies was initiated in autumn 1988 in southern Finland, the main target species being the racoon dog. Rabies was eliminated from these populations within 12 months.

North America

Since 1980, Canada has been developing an aerial baiting programme for the large-scale distribution of rabies vaccine baits for red foxes, using a manufactured bait containing a plastic blister pack filled with ERA-BHK_{21} vaccine. Baits are delivered from an aircraft at densities of 20 baits per flight km, at ground speeds of up to 300 km/h. In 1990, 573 000 baits were distributed over 26 000 km^2, and an acceptance rate of up to 74% was noted in red foxes.

In the USA, the first field trial for oral vaccination of wild animals was carried out in 1990 on Parramore Island, Virginia, using the vaccinia recombinant rabies vaccine in a fishmeal polymer bait adapted to the racoon. The first trial on continental USA was initiated with the same vaccine bait in Pennsylvania in 1991.

10.4.3 *Planning, implementation and evaluation of oral rabies vaccination programmes*

The principles for initiating and continuing fox oral vaccination campaigns are now well established in Europe and have led to the elimination of rabies in the fox and other host species (e.g. racoon dogs) in some areas. However, specific strategies may need to be developed for the control of rabies in foxes and other major host species in certain countries.

Oral immunization of wild animals has become the essential tool of programmes for the control and elimination of rabies in wild animals. Basic requirements for planning, implementing and evaluating large-scale field trials for oral immunization of wild animals have been elaborated by WHO (*12, 25, 26*).

Programme planning

Data collection. Programmes for the control of wildlife rabies should include assessment of both target and non-target species of wildlife populations, in order to select the most effective baiting methodology available.

Capture, mark, release and recapture studies can generate reliable estimates of population densities in relatively small areas, provided a number of preconditions are met concerning the dynamics of the populations under study and the proportion of animals that are marked and re-observed.

Ecological studies of the target and non-target species population should also be conducted prior to the implementation of the control project to ensure that the target species is present in the proposed control area. The presence of threatened or endangered vertebrate species in the area should also be ascertained and the composition of the non-target species populations should be determined, especially for those species most likely to compete with the target species for bait uptake. If the above information is either inadequate or unavailable, the minimum relative abundance of the target species in the area (in relation to non-target species) should be determined.

Project planning. Project planning must precede the distribution of baits, and related administrative activities will vary in structure and detail depending upon political and other variables. Planning and organization are vital to the success of the project.

A project proposal must include background information on the area to be covered using the oral rabies vaccination technique, estimated costs and benefits of the project, when it will be carried out, safety considerations, methods for post-baiting evaluation and relevant data on the target population. The proposal should be distributed to institutions concerned with rabies well in advance for consideration and evaluated by a scientific committee. Upon request, WHO may help in providing the necessary expertise.

Epidemiological data based on reliable surveillance and laboratory studies of rabies cases in target and non-target species must be available before field trials can be initiated.

If several geographical locations are available for the implementation of field trials, priority should be given to those surrounded by natural barriers and/or where community cooperation and logistic support can be relied upon. The rabies situation in neighbouring areas should also be taken into account. The selected areas should be readily accessible to central government veterinary or medical services. Areas should be selected according to the incidence of wildlife rabies or the number of rabid pets and domestic animals and human exposures. The size of the area to be covered by the project should not be less than 2000 km^2.

Fox rabies vaccination campaigns initiated between rabies epizootics and during the decreasing phase of epizootics have been shown to be more successful and less expensive than those carried out during the increasing phase.

Implementation

The project should be based on a comprehensive plan that justifies it, describes the objectives, technical and organizational details and budgetary requirements, and defines the responsibilities of the collaborating institutions.

Surveillance data on fox rabies in western Europe indicate that two vaccinations per year, administered over a period of 2 years, are currently required to control the disease. Additional vaccinations may be necessary to eliminate rabies from some areas. Other areas may require different strategies.

Establishment of "immune belts" (buffer zones where fox vaccination campaigns are carried out regularly) should be considered for protection of rabies-free areas.

Implementation of oral immunization projects will require:

- Community participation, to be encouraged through information, promotion campaigns and, in some instances, training for baiting and disease surveillance.
- Awareness of the campaign among medical and veterinary practitioners so that they can take appropriate measures in case of accidental exposure to the vaccine. A medical/veterinary advisory group should also be established at national level.
- Sampling of specimens under appropriate conditions. Trained personnel and laboratory facilities should be available to carry out the tests for evaluation of bait uptake and seroconversion rates, and to diagnose rabies.
- Assignment of specialists to investigate the epidemiological situation in both humans and animals before, during and after the implementation

of the project, and to report to the responsible authorities on a regular basis. After each campaign, evaluation of the results is of the utmost importance in order to define future strategies.

Evaluation of oral vaccination programmes

Most field trials with oral vaccination employ three methods of evaluation: testing for the occurrence of a biomarker (usually tetracycline), which is incorporated into the bait, in the target species; examining sera from the target species for rabies virus-neutralizing antibody; and analysing the incidence of rabies in animals before and after the programme.

The first two techniques allow relatively rapid assessment of a vaccination programme, but accumulated knowledge is not yet sufficient to relate these measures directly to the probability of controlling rabies. Whenever feasible, only freshly collected sera should be used for virus-neutralizing antibody titration. Assessment of rabies incidence provides a direct measure of success, but must be carried out over several years and over large areas.

Surveillance plays an important part in the planning, implementation and evaluation of rabies control programmes. Before vaccination, rabies surveillance is usually satisfactory, particularly when incentives (e.g. bounties) are granted to encourage hunters to provide specimens of captured animals for examination. Generally, surveillance is also sufficiently intensive during vaccination campaigns, particularly where hunters and wildlife services are engaged in follow-up examinations of bait uptake and seroconversion of the vaccinated animals and provided active sampling is supported by granting appropriate hunting incentives.

However, experience in Europe has shown that the intensity of surveillance activities decreases as successive cycles of oral vaccination campaigns are completed. Adequate surveillance is most important during this phase since, on the one hand, residual foci of rabies need to be rapidly detected, and on the other, the absence of rabies needs to be verified.

In order to promote active rabies surveillance in areas where oral vaccination campaigns have been successful, procedures for international certification of the rabies-free status should be established. In some European countries, certification requires that no rabies cases should be reported during a minimum of 2 consecutive years in an area of at least 5000 km^2, from where at least 8 foxes per 100 km^2 are collected annually and examined in the laboratory.

The Committee stressed the need for reinforced rabies surveillance in oral vaccination areas and requested governments to consider and adopt certification procedures based on the above example.

International cooperation in oral vaccination programmes

International cooperation in border areas is essential at all levels to achieve effective vaccination programmes. Neighbouring countries should

carefully coordinate their activities along common borders. If field trials reach a country border, local administrative staff from both countries should coordinate their efforts. WHO may be particularly helpful in assisting in the coordination of rabies vaccination programmes involving borders between countries.

Oral rabies vaccination generates new epidemiological concerns. For this reason, planning, implementation and evaluation of field trials should be coordinated with the assistance of at least two independent WHO Collaborating Centres.

In the future, consideration should be given to the establishment, under the auspices of WHO, of a group of consultants for assisting countries in the preparation and submission to funding agencies of their project proposals for oral rabies vaccination programmes. This group could also collaborate with countries during the subsequent implementation and evaluation of their programmes.

11. International transfer of animals

Almost all governments have official requirements for the international transfer of animals. Rabies is one of many diseases that may be imported if major precautions are not taken. When animals are imported from countries where rabies is known to exist, recipient countries usually have rules that vary from total prohibition of importation to unrestricted entry.

The following sections take into account recent knowledge concerning rabies vaccination and immune response mechanisms; the epizootiology of rabies, particularly in wild animals and its transmission to dogs and cats; and the incidence of the disease in both exporting and importing countries.

11.1 International transfer recommendations

All animals of all species in international transit should:

- be transported in separate sealed units so that removal of the animals breaks the seals;
- have valid certificates of the animal's health and, when applicable, of the rabies-free status of the country of origin signed by the national veterinary authorities in the country of origin;
- have a valid international certificate of vaccination against rabies signed by the veterinary authorities in the country of origin;
- have an import licence (specifying details of transport requirements) prepared by the national veterinary authorities in the country of destination, if required.

The measures suggested below and guidelines for the possible reduction of quarantine and other requirements (without creating undue risk of introducing rabies to an importing country) should not preclude the application of more stringent requirements by government authorities.

11.2 Rabies-free and rabies-infected areas

A rabies-free area may be defined as one in which an effective import policy is implemented and, in the presence of adequate disease surveillance, no case of indigenously acquired rabies infection has been confirmed in humans or any animal species at any time during the previous 2 years. Conversely, an area can be considered to be rabies-infected if an indigenously acquired rabies infection has been confirmed in humans or any animal at any time during the previous 2 years.

11.3 Considerations in establishing requirements for the entry of dogs and cats through international transport

The following must be considered in establishing national, state or regional requirements:

- The incubation period of rabies is variable. Regulations must consider that it may be as long as 4–6 months.
- The pathogenesis and immune response resulting from rabies infection in immature animals, e.g. puppies, are inadequately defined. Full quarantines should always be required for their entry.
- Immune responses of animals vary depending on the type of vaccine, age at vaccination, number of doses and condition of the animals. Two doses of vaccine at least 6 months apart provide greater protection than does a single dose.
- Animals vaccinated during the incubation period may develop antibodies without the progression of the disease being affected.
- Current serological tests such as the rapid fluorescent focus inhibition test and the mouse serum neutralization test are highly sensitive, but false-positive results may occasionally occur, especially with dog sera. Two tests on separately collected sera would give a more reliable indication of the presence and level of immune response than would one test.
- Misidentification of animals on vaccination certificates or of serum samples may occur, or data may be recorded incorrectly. Precautions must be taken to avoid such mistakes.
- Rabies-related viruses and lyssaviruses other than rabies have been recognized in several countries. Animals infected with such viruses may behave differently from those infected with rabies, and respond differently to rabies vaccines. No transmission of lyssaviruses other than rabies virus by dogs or cats has been reported and the risk of transmission of these viruses, especially to pets, is considered very low.

11.4 International transport of dogs and cats between rabies-free countries or areas

If the origins of these animals can be documented and all international transit recommendations and national requirements are met, direct intercountry movement of animals should be unrestricted.

11.5 International transport of dogs and cats from rabies-infected countries to rabies-free countries or areas

It is recommended that dogs and cats be quarantined at the country of destination for 4-6 months in facilities approved and supervised by the government veterinary service. If the quarantine period is 4 months, the animals may be subject to movement restrictions to be specified by the national authorities for an additional 2 months, with monthly certification of health and immediate notification of any unusual behaviour, including biting.

Countries currently free from rabies that reduce quarantine requirements increase the possibility of importing the disease, depending on the epidemiological situation (e.g. pattern of dog or wildlife rabies) and intensity of rabies surveillance and control in the country of origin.

Where strict quarantine measures are impractical, the following measures are recommended:

Dogs and cats to be transported should be required to have at least two vaccinations, one not earlier than 3 months of age and another at least 6 months later (3-6 months prior to embarkation), and should be accompanied by official certificates including dates, animal identification and address at times of vaccination (see Annex 6). On arrival, the animals should be held in official quarantine until completion of two positive serological tests on sera collected at least 4 weeks apart. Animals yielding two positive tests and certified healthy should remain under home confinement for 10 weeks, and should be presented to the local veterinary authorities nearest the place of residence of the owner. Animals with a negative serological test should be quarantined for at least 4 months.

11.6 Special exemption for guide dogs for the blind

Certified guide dogs for the blind already present in rabies-free countries or areas should be permitted to accompany their owners into rabies-infected countries if the dogs are vaccinated with an approved inactivated vaccine and demonstrated to have an adequate virus-neutralizing antibody titre prior to departure. Such dogs should be allowed to remain outside the rabies-free country for a maximum of 6 months, and to re-enter the country without quarantine if the owners affirm that the dogs were continuously confined or on a leash while in infected areas, and if antibody titres are reconfirmed upon return.

11.7 International transport of livestock, zoo, research and show animals from rabies-infected to rabies-free countries

Countries that are free from rabies should either prohibit the importation of certain species of mammals, in particular Carnivora and Chiroptera, or permit their entry only under licence, subject to quarantine in premises and under conditions approved by the government veterinary service.

Entry may be permitted for limited periods or for life. The use of animals for exhibits or for experiments should be permitted only after quarantine for 4 months.

In view of the increase in the number of reported rabies cases in wild animals acquired as pets, national authorities should control the trade in such animals because of this potential source of human exposure. The keeping of such animals as pets should be discouraged. Adequate quarantine measures should be adopted for at least 4 months, combined with vaccination with inactivated vaccines.

11.8 International transport of any animals from rabies-free to rabies-infected countries or between rabies-infected countries

Such animals should meet all international transfer recommendations. If transported from rabies-free to rabies-infected countries they should be vaccinated at least 2 weeks prior to embarkation. If transported between two rabies-infected countries they should be vaccinated at least 2 weeks before embarkation or vaccinated on arrival in the country of destination.

12. Exchange of information and training in rabies

12.1 Collection of epidemiological data

The Committee was pleased to note that the *World rabies survey*[1] had been computerized and that issues would now be produced on an annual, rather than a biennial, basis. The database would be helpful in analysing global trends of the disease as well as regional changes, especially in regions where no surveillance systems had been established.

The Committee noted with satisfaction the increasing geographical coverage of the *Rabies bulletin Europe* prepared by the WHO Collaborating Centre for Rabies Surveillance and Research in Tübingen, Germany, as well as the efforts of the Pan American Institute for Food Protection and Zoonoses (INPPAZ) of WHO/PAHO in producing high-quality reports on rabies surveillance in the Americas. The Committee stressed that national authorities should be aware of the surveillance activities carried out by international organizations and institutions concerning the occurrence and control of rabies (see Annex 7).

Events of urgent interest, such as the appearance of the disease in previously rabies-free countries, should be systematically reported to WHO for publication in the *Weekly epidemiological record*. The

[1] Unpublished document; available on request from the Division of Communicable Diseases, World Health Organization, 1211 Geneva 27, Switzerland.

Committee stressed the importance of this mode of dissemination of information and urged responsible officers from such countries or territories to send their reports promptly to WHO for circulation.

The Committee was in favour of the establishment of a WHO Collaborating Centre working specifically on rabies epidemiology using modern techniques for virus identification and typing and producing and/or distributing panels of monoclonal antibodies to national laboratories.

The Committee also noted the joint and individual efforts of FAO, the International Office of Epizootics and WHO in the collection and dissemination of statistics on rabies in animals and humans in the *Animal health yearbook*, the *Bulletin of the International Office of Epizootics* and the *World health statistics annual*.

The case-record form recommended by the Committee, which may be found in Annex 8, has proved very useful in the compilation of rabies statistics. The information gained from the careful keeping of such records is of great use, not only to the recording institute, but also to national and international authorities concerned with rabies. Since many problems associated with the prevention and treatment of paralytic accidents, serum sickness, and the efficacy of post-exposure treatment remain to be solved, the periodic compilation and analysis by WHO of results obtained in different countries is of great value in assessing the effectiveness of the measures employed. The Committee urged, therefore, that the recommended case-record form, or a suitable modification such as the form developed by the Pan American Institute for Food Protection and Zoonoses (INPPAZ), be used in all anti-rabies treatment centres and that close collaboration with WHO be maintained.

12.2 Seminars, group training and fellowships

Regional and interregional seminars and training courses in the planning and management of zoonoses control programmes, held by WHO, PAHO and their specialized centres, have continued to include rabies.

In addition, research training grants and fellowships have been provided to individuals involved in field control projects or rabies vaccine production units and diagnostic laboratories to improve their knowledge of advances in rabies control. Stressing the importance of these activities in promoting the adoption of recommended and improved methods of control, the Committee urged countries where rabies is prevalent, as well as WHO, in collaboration with FAO, to continue to give high priority to the training of workers in all aspects of rabies control. Particular efforts should be made by national services to train project staff in all managerial aspects of programme planning, formulation, implementation and evaluation, as well as in data collection, processing and management using computer technology.

Specially trained auxiliary workers could be extremely valuable in field control operations, especially in mass campaigns. Their training should be part of any training programme in rabies.

13. Conclusions and recommendations

13.1 General recommendations

1. Further studies are required on the biology and evolution of rabies virus (e.g. phylogeny and mechanisms of host adaptation), diagnostic methods, and prevention and treatment of the disease. The use of the polymerase chain reaction (PCR) technique as a potential tool in the routine diagnosis of rabies requires further study. In particular, the suitability of brain-tissue specimens obtained from the field for examination by PCR should be assessed. In addition, the combination of PCR with partial sequencing and enzyme restriction patterns for differentiating between different antigenic groups and characterizing virus types and subtypes (for fixed and field strains) should be investigated.
2. Genome sequencing and monoclonal antibodies should be applied to characterize rabies field isolates and to obtain further information on the phylogeny of the virus, using phenetic or cladistic analysis.

13.2 Pathogenesis of rabies

1. Studies on the pathogenesis of rabies virus infections should be continued, especially in relation to the mechanisms of latency. Molecular biology techniques may be useful to detect the viral genome and trace the differential expression of viral proteins. Advances in neurobiology will probably lead to a better understanding of the pathogenesis of rabies and may open new avenues to the treatment of clinical rabies. It is now feasible to perform X-ray diffraction studies on crystallized rabies virus proteins; the resolution of the tridimensional structure of these proteins may reveal the structure of antigenic determinants and, possibly, the mechanism of antigen-antibody interaction. These studies could also indicate how rabies viral proteins interact with each other and with the genomic RNA and permit the development of new anti-rabies drugs.
2. Further studies on cell and host specificity are also required. The mechanisms by which the virus adapts to changes in host populations (e.g. in relation to turnover, density and social structure) are still unknown. Molecular biology studies combined with ecological and epidemiological field studies and computer modelling are expected to lead to new insights regarding these mechanisms.

13.3 Vaccines for human and veterinary use

1. New recombinants will be developed for use as live vaccines or as expression systems for the production of viral antigens. Rabies glycoprotein gene could be complemented with other viral genes (e.g. rabies nucleoprotein gene) to enhance antigen expression and recognition, or with mammalian genes to increase cellular and humoral responses in vaccinees. The possible role and application of antisense nucleotide sequences should be investigated. The use of peptide vaccines should also be studied. One possible mechanism of overcoming the strict human leukocyte antigen (HLA) restriction requirements for peptide recognition by T cells would be to identify peptides recognized by commonly occurring HLA haplotypes. Another approach would be to prepare a vaccine containing multiple T cell determinants recognized by different individual HLA haplotypes.
2. The development of an inexpensive rabies vaccine suitable for mass pre-exposure immunization of populations at risk should be investigated.
3. The control of rabies through mass vaccination of the main hosts (dogs, wild carnivores and bats) still needs improvement; further studies should be conducted on animal ecology and epidemiology, as well as vaccine and bait-delivery systems.
4. In view of the promising preliminary results obtained using a new intramuscular challenge test in mice for testing vaccine potency, collaborative studies should be initiated to evaluate its accuracy and reproducibility.

13.4 Post-exposure treatment

Studies aimed at reducing post-exposure treatment schedules in humans should be continued. Work is also needed on development of effective and inexpensive post-exposure treatment schedules for valuable animals (domestic and wild). Monoclonal antibodies might be applicable for use in both animals and humans; for human use, "humanized" murine or genetically engineered monoclonal antibodies might be required.

13.5 International transfer of dogs

Alternative options for the international transfer of dogs should be investigated, in order to reduce the need for and hardships of quarantine. These studies should, in particular, assess the reliability of new methods for measuring the immune status of dogs over long periods and for identifying them. If the results warrant changes in present regulations, WHO should consider convening a consultation on this subject.

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[1] Unless otherwise stated, unpublished documents have been prepared by the World Health Organization, Geneva, and are available on request from the Division of Communicable Diseases, World Health Organization, 1211 Geneva 27, Switzerland.

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Annex 1

Suggestions for the use of antigen quantification tests for the release of human and veterinary rabies vaccines

This annex provides guidance for the use of *in vitro* tests for the release of batches of human and veterinary vaccines produced according to a standardized operating procedure (SOP). Requirements for correlation between the NIH test and *in vitro* tests will need to be established by national licensing authorities. Collaborative studies are being initiated to validate the various *in vitro* antigen quantification tests as a substitute for the NIH test for the release of vaccine batches. When these studies are completed, a re-evaluation of the procedure indicated below will be made. This procedure may eventually have to be considered by the WHO Expert Committee on Biological Standardization.

1. General considerations

Problems related to potency testing using the NIH test have been examined during a number of WHO meetings (*1-3*). Although the conditions for performing the NIH test have been specified, results from assays in which identical vaccines are tested may differ markedly among laboratories. Furthermore, some vaccines of proven efficacy do not meet the requirements for rabies vaccines published by WHO (*4, 5*), as measured by the challenge test in mice. Since Challenge Virus Standard (CVS) is recommended as the challenge strain for the NIH test, vaccine prepared with viruses other than the Pasteur strains and tested in mice challenged with CVS may appear to be of lower potency than expected.

In vitro tests have been used successfully for in-process controls as well as for predicting potency values of vaccines for release (see section 6.4 of the main report).

Preliminary results of studies using *in vitro* tests for the control of the vaccine production process indicate that such tests may be suitable for the release of vaccine batches in the future, thereby reducing animal testing, provided certain conditions are fulfilled. In these tests a product-specific reference vaccine (PSRV) should be used as the reference material.

2. Product-specific reference vaccine (PSRV)

2.1 *Definition*

In order to have a product-specific reference vaccine (PSRV) preparation available for use in future testing, a final lot of vaccine should be set aside which has been shown: (a) to induce an adequate and sustained level of neutralizing antibodies in humans (i.e. comparable to that shown for vaccines of proven efficacy), or (b) in animals, to protect the target species against a virulent challenge (see section 6.2 of the main report).

2.2 *NIH potency values*

The potency of the PSRV should be determined against the International Standard for Rabies Vaccine using the NIH test with a CVS challenge; it should not be less than 2.5 IU/dose for vaccines for human use or 1.0 IU/ml for vaccines for animal use. National control authorities may, however, consider licensing vaccines with potencies below this minimum, provided these vaccines have been shown to elicit an adequate level of neutralizing antibodies in humans or, in animals, to protect a vaccinated host after challenge.

2.3 *Antigenic content of the PSRV*

The antigenic composition of the PSRV is determined using *in vitro* tests. Since different antigenic fractions have been shown to contribute to the protective efficacy of rabies vaccine, the glycoprotein and nucleoprotein content of the PSRV (the two major antigenic components) should be established.

3. Suggested procedures for the use of antigen quantification tests for batch release

3.1 *Correlate in vitro and in vivo test results*

A satisfactory correlation should be established between the NIH test and the antigen quantification test; this should be done on at least 10 vaccine batches. The NIH potency of each of the 10 batches should be at least equal to that determined for the PSRV, and the potencies of the 10 batches should be statistically homogeneous. It is expected that the antigen content of vaccines to be released on the basis of an *in vitro* test should not be less than that of the PSRV.

The PSRV should be included as reference material in all tests for NIH potency and/or antigen content to be carried out on all further batches. If batch release is based on *in vitro* tests, the antigen content of the vaccine should be expressed in relation to the antigen content of the PSRV.

3.2 *Maintain a standard operating procedure*

Since *in vitro* tests measure antigen content and not immunogenicity, the Committee recommended that the standard operating procedure (SOP) should be well defined and regularly monitored to ensure consistency in preparation of the vaccine. This includes measuring, for example, the antigen titres of the harvest prior to inactivation. Whenever the SOP is modified, a satisfactory correlation between NIH test values and antigen content of at least 10 vaccine batches should be established before vaccines are released on the basis of antigen content tests.

4. Tests under development

Studies have been initiated to develop potency tests in mice involving

vaccination followed by peripheral challenge with rabies virus. In one such test (the CDC test), mice are given an intramuscular injection containing 0.1 ml of vaccine, followed 4 weeks later by a peripheral challenge. Such challenge procedures more closely mimic natural exposure than does intracerebral challenge and may in the future replace the NIH test.

Recombinant vaccines containing only the rabies virus nucleocapsid protein can be tested by measuring the level and persistence of anti-nucleocapsid protein antibodies when indicated. However, it may be important to measure the induction of cellular immunity against rabies virus. Although tests are available that can measure parameters such as the *in vitro* proliferation of lymphocytes, or can detect the presence of specific cytokines, these tests are difficult to perform and to interpret; they are therefore not currently recommended for routine use.

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[1] Unpublished documents coded VPH and WHO/Rab.Res. are available on request from the Division of Communicable Diseases, World Health Organization, 1211 Geneva 27, Switzerland.

Annex 2

Guide for post-exposure treatment[1]

The recommendations given here are intended as a general guide. It is recognized that, in certain situations, modifications of the procedures laid down may be warranted. Such situations include exposure of infants or mentally disabled persons and other circumstances where a reliable history cannot be obtained, particularly in areas where rabies is enzootic, even though the animal is considered to be healthy at the time of exposure. Such cases may be treated as category II or III (see section 2).

As indicated in section 2, post-exposure treatment, which consists of local treatment of the wound, followed by vaccine therapy (with or without rabies immunoglobulin) should be initiated immediately with contacts of categories II and III. Treatment may be discontinued if the animal involved (dog or cat) remains healthy throughout an observation period of 10 days; or if the animal is killed humanely and found to be negative for rabies by laboratory examination. Any biting animal suspected of being rabid should be immediately killed humanely and tissues examined using appropriate laboratory technique(s). Modification of the recommended procedures would be indicated in a rabies-free area where animal bites are encountered. In areas where canine or wildlife rabies is epizootic, adequate laboratory and field experience indicating that there is no infection in the species involved may justify local health authorities in not recommending specific anti-rabies treatment.

Practice varies concerning the volume of vaccine per dose, the number of doses recommended in a given situation and the route of administration.

Tissue-culture or purified duck-embryo vaccines of potency at least 2.5 IU per dose should be applied according to the following schedules:

Intramuscular schedules: One dose of the vaccine should be administered on days 0, 3, 7, 14 and 30. All intramuscular injections must be given into the deltoid region or, in small children, into the anterolateral area of the thigh muscle. Vaccine should never be administered in the gluteal region.

In the abbreviated multisite schedule, the 2-1-1 regimen, one dose is given in the right arm and one dose in the left arm at day 0, and one dose applied in the deltoid muscle on days 7 and 21. The 2-1-1 schedule induces an early antibody response and may be particularly effective when post-exposure treatment does not include administration of rabies immunoglobulin.

Intradermal schedule: One dose (0.1 ml) should be given at each of two sites, either the forearm or the upper arm, on days 0, 3 and 7, and one dose at one site on days 30 and 90. This regimen considerably lowers the cost of vaccination against rabies, as the total volume of vaccine required is less

[1] It is strongly recommended that this guide be reproduced only in its entirety.

than that required for intramuscular regimens. Separate syringes and needles must be used for each dose. Intradermal injections should only be administered by staff who have been trained in this technique. Vaccine vials should be stored between 4 °C and 8 °C after reconstitution and the total contents should be used as soon as possible.

For brain-tissue vaccines, national authorities should recommend a schedule of immunization that has been shown to induce an adequate level of protection.

Combined immunoglobulin-vaccine treatment is considered by the Committee as the best specific systemic treatment available for the post-exposure prophylaxis of rabies in humans, although experience indicates that vaccine alone is sufficient for minor exposures (category II). Immunoglobulin should be given in a single dose of 20 IU per kg of body weight for human anti-rabies immunoglobulin, and 40 IU per kg of body weight for heterologous (equine) immunoglobulin; the first dose of vaccine should be inoculated at the same time as the immunoglobulin, but in a different part of the body. Sensitivity to heterologous immunoglobulin must be determined before it is administered. The physician should be prepared to deal with anaphylactic shock reactions.

Treatment should be started as early as possible after exposure, but in no case should it be denied to exposed persons whatever time interval has elapsed.

1. Local treatment of wounds involving possible exposure to rabies—recommended in all exposures

First-aid treatment

Since elimination of rabies virus at the site of infection by chemical or physical means is the most effective mechanism of protection (see section 7.3 of the main report), immediate washing and flushing with soap and water, detergent or water alone are imperative (this procedure is recommended for all bite wounds, including those unrelated to possible exposure to rabies). Then apply either ethanol (700 ml/l) or tincture or aqueous solution of iodine.

Treatment by, or under direction of, a physician

Treat as described above and then:

- apply anti-rabies immunoglobulin by careful instillation in the depth of the wound and by infiltration around the wound;
- postpone suturing of the wound; if suturing is necessary, ensure that immunoglobulin has been applied locally as described above;
- where indicated, begin anti-tetanus treatment and administer antimicrobials and drugs to control infections other than rabies.

2. Guide for post-exposure treatment

Category	Type of contact with a suspect or confirmed rabid domestic or wild[a] animal, or animal unavailable for observation	Recommended treatment
I	Touching or feeding of animals Licks on intact skin	None, if reliable case history is available
II	Nibbling of uncovered skin Minor scratches or abrasions without bleeding Licks on broken skin	Administer vaccine immediately.[b] Stop treatment if animal remains healthy throughout an observation period[c] of 10 days or if animal is killed humanely and found to be negative for rabies by appropriate laboratory techniques
III	Single or multiple transdermal bites or scratches Contamination of mucous membrane with saliva (i.e. licks)	Administer rabies immuno-globulin and vaccine immediately.[b] Stop treatment if animal remains healthy throughout an observation period[c] of 10 days or if animal is killed humanely and found to be negative for rabies by appropriate laboratory techniques

[a] Exposure to rodents, rabbits and hares seldom, if ever, requires specific anti-rabies treatment.

[b] If an apparently healthy dog or cat in or from a low-risk area is placed under observation, the situation may warrant delaying initiation of treatment.

[c] This observation period applies only to dogs and cats. Except in the case of threatened or endangered species, other domestic and wild animals suspected as rabid should be killed humanely and their tissues examined using appropriate laboratory techniques.

Annex 3

Suggested rabies vaccination certificate for humans

The vaccination certificate below is provided as a model for copying. It should be kept carefully by the vaccinee with his or her personal health documents. Blank forms should be supplied by the manufacturer of the vaccine.

RABIES VACCINATION CERTIFICATE Page 1

Name _____

Date of birth _____

Signature _____

Address _____

_____

_____

PRE-EXPOSURE VACCINATION

Primary vaccination:

Date	Dose/route of administration	Type of vaccine (origin/batch no.)	Vaccination centre	Signature of physician

Serum titre, if determined: _____

Booster:

Date	Dose/route of administration	Type of vaccine (origin/batch no.)	Vaccination centre	Signature of physician

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1. Serum or rabies immunoglobulin (human origin):

Date	Dose (IU)	Origin

2. Vaccine:

Date	Dose/route of administration	Type of vaccine (origin/batch no.)	Vaccination centre	Signature of physician

Annex 4

Technical and managerial considerations in planning, implementing and evaluating a national programme for the control of rabies in dogs

1. Ecological and social considerations

1.1 *Collection of dog population data*

Before any programme is initiated, data should be obtained on patterns of dog ownership, relationship of animals to human society, population density, age structure and turnover, habitat, relationship of dogs to other reservoir species, etc. Cultural factors modify the dog's influence on the environment and on human health. They not only include dog-keeping practices and people's and society's attitudes towards dogs, but also numerous other aspects of culture, from handling of refuse to settlement patterns. Wide variations exist in the relationship of dogs to human society throughout the world and the success of a canine rabies control programme in a specific country will depend largely on its adaptation to local ecological and social patterns. Procedures for the collection of dog population data are described in *Guidelines for dog rabies control* (*1*) and *Guidelines for dog population management* (*2*).

Dogs may be divided into four distinct groups, according to their degree of dependence on human care (for food, shelter and companionship) and also the level of restriction or supervision imposed on the dog by humans:

Restricted or supervised dogs are fully dependent on their owners and fully restricted or supervised. They are considered as the property of, or part of, a specific household to which they provide economic or social value. In rabies control programmes, these dogs may be vaccinated and/or confined to their owner's premises.

Family dogs are fully dependent on their owners, but their movements are only partially restricted. In rabies control programmes, these dogs are usually accessible for vaccination.

Neighbourhood or community dogs are partially dependent on humans and partially restricted or unrestricted in movement. They are accepted by residents as belonging to the community and obtain food and/or harbourage, at least during part of the year, from more than one household. Depending on the society, such dogs may be vaccinated or removed.

Feral dogs are independent and unrestricted in movement. They may be found individually or in packs. They are usually not wanted by residents of the community and can usually be removed without objections from the public.

The term "owned dog" should be used only in connection with measures exerted on dog populations such as licensing, movement restrictions

and/or vaccinations. "Owned dogs" are those having at least one referral household and include restricted, family and neighbourhood dogs.

The term "stray dog" should be used only to define a dog that is not in compliance with local rabies control regulations. A dog found straying may be a feral dog, an abandoned or lost animal, or merely a free-roaming animal belonging to a category having at least one referral household (i.e. a family or community dog).

Data on dog population size and distribution and on accessibility of dogs are essential in planning vaccination and dog removal programmes and in evaluating results. In many countries, male dogs predominate among owned dogs. The availability of food and harbourage for dogs has great bearing on the structure and turnover of family, neighbourhood and feral dog populations. Dog habitats include residential areas, markets, refuse dumps, industrial areas, warehouses and dock areas, which may support or partially support large numbers of dogs, and where specific methods for rabies control must be applied (see section 1.2).

Where other animal species that are able to transmit the disease may interact with canine reservoirs, e.g. jackals, they must be included in any ecological assessment. Other reservoirs may exist in wild animals, e.g. in racoons, skunks, foxes, mongooses, bats and other wild animals in local areas; while important in the overall ecology of animal transmission of rabies, the maintenance of the disease in these species seems to be independent of the reservoir in dogs.

1.2 *Practical methods of dog population management*

Three practical methods of dog population management are recognized:

Movement restriction. This is very important during an anti-rabies campaign in a given locality. Confinement of dogs on owner's premises, use of leashes and muzzles and obedience training are effective, but require active community participation and/or pressure by local authorities.

Habitat control. Dog populations are more vulnerable to control of their habitat than they are to direct manipulation of their numbers. The size of the populations of family, neighbourhood and feral dogs is regulated by the amount of available feed and harbourage. Storage and removal of household refuse and cleaning up of other feed sources and harbourage in residential areas, cleaning of markets and rubbish dumps, and exclusion of dogs from abattoir and fishing areas and from industrial and warehouse sites can effectively reduce the dog populations. Effective community education is essential.

Reproduction control. The simplest and most widely applied method of reproduction control is to prevent mating by restraining or confining bitches in heat. Other methods (e.g. hormone injections and sterilization) are more costly and need to be carried out or supervised by professional staff (*2*). Consideration must be given to the possibility of control areas

being re-populated by immigrating dogs. An effective, cheap contraceptive for dogs is still much needed. At present, there are no commercially available, safe, effective substances that cause permanent sterility in dogs when administered orally.

Capture and removal of dogs are no longer considered effective direct control measures. Indirect benefits may be obtained by selective elimination of unvaccinated dogs that are not in compliance with control regulations and may accumulate around markets, abattoirs and food industries. Removal of such dogs should be considered only if other dogs can be prevented from filling these ecological niches. A free community service should be available for sheltering and, if necessary, for eliminating unwanted puppies and adult dogs.

The principal aims of dog population management are development of more responsible public attitudes towards their dogs, control of reproduction and regulation of dog movement. The promotion of responsible dog ownership should be an important component of any rabies control programme.

1.3 *Dog registration*

The feasibility of dog registration depends not only on logistic and organizational capacities, but also on the dog population itself. The high turnover rate typical of dog populations in developing countries renders dog registration a difficult task. Registration should not automatically be associated with fees or taxes, as in some countries this measure may discourage the community participation required for rabies control.

1.4 *Cats*

Cats, although closely associated with dogs in both urban and rural ecosystems and although often infected by rabid dogs, do not play an important role in the maintenance of chains of infection. In general, feline rabies disappears as the disease is brought under control in the dog population. However, cats may play a significant role in the transmission of rabies from its reservoir in dogs or other animals to humans. Therefore, whenever feasible, control measures should also be applied to cats.

2. Vaccine administration

2.1 *Parenteral immunization of different animal species*

Dogs. The Committee recommended that all dogs receive their primary vaccination at the age of 3 months and a booster approximately 1 year later.

In mass campaigns in which inactivated vaccines are used, it may be appropriate to vaccinate dogs of all ages, although no assurance can be given for sufficient protection of puppies less than 3 months of age.

Certificates of vaccination, including ages of animals, should be issued to their owners.

In continuing programmes, and in rabies-endemic and endangered rabies-free areas, booster inoculations should be given at regular intervals, according to the type of vaccine. Where revaccinations are conducted as community campaigns (see section 9.3 of the main report), the frequency must be based on the effective immune period, the vaccination coverage previously achieved and the dog population turnover. In some cases, annual community vaccination campaigns will be required to maintain a 70% immunity level throughout the year.

Cats. Cats may be effectively immunized with inactivated vaccines. They should receive their primary vaccination at approximately 3 months of age and a booster 1 year later with the dose recommended by the manufacturer of the vaccine used.

Other species. Rabies in cattle remains a serious economic problem in certain areas of the world, notably in Latin America. Focal vaccination of cattle is recommended in many of the countries where vampire-bat rabies or wild animal reservoirs such as skunks or racoons are a problem. Under certain conditions of canine or wildlife rabies, mass vaccination of cattle may be indicated for economic or public health reasons. As with other species, inactivated vaccines are preferable.

In areas of vampire-bat rabies, additional measures to control vampire-bat populations should be taken (see section 10.2 of the main report).

The Committee strongly recommended that attenuated live rabies vaccines should not be used in any species of animal until the safety and efficacy of the vaccine for the species in question has been determined. Vaccines containing inactivated virus may safely be used in most species. Wild animals in zoos or exhibitions should be vaccinated with inactivated rabies vaccine, although the vaccine efficacy in many of these species has not been determined.

2.2 *Oral immunization of dogs*

When safe oral vaccines for immunization become available (see section 2.4 of the main report), oral immunization could be used to achieve a 75% coverage of dog populations in areas where parenteral vaccination may be difficult.

It should be emphasized that the baits containing the oral vaccine must be acceptable to the dogs while at the same time delivering an immunizing dose of vaccine. Various baits have been tested for acceptability (compared with commercial dog biscuits), including sponge baits, chicken heads, corn-meal and fish-meal polymer baits. Such baits should be made repugnant to humans.

In addition, the strategies for bait distribution must be studied to ensure immunization of at least 75% of the canine population; these strategies will

probably vary in different countries and even in different areas of a country, so that each ecological situation should be studied independently. This assumes that a proper study of the dog population has been made to ensure that an adequate number of baits will be assigned to the dogs in the given area. Instructions for designing protocols for testing baits and bait-delivery systems have been developed for dogs and wildlife species (*3, 4*).

3. Handling of dogs and cats bitten by rabid animals

The Committee strongly recommended that unvaccinated dogs, cats and other pets bitten by a known rabid animal should be destroyed immediately. Those bitten by animals of suspect or unknown status should be restrained and maintained under veterinary control for 6 months.

If the animal has been vaccinated previously (and its vaccination certificate is available) and can be identified with certainty (e.g. by a tattoo), it should be revaccinated immediately and restrained (leashed and confined) for at least 90 days. Post-exposure vaccination of a previously unvaccinated animal is of uncertain effectiveness and should be discouraged.

4. Legislation

Legislation must be enacted, giving powers for all the procedures included in the national programme for the control of human and canine rabies. In addition, the legislation should: (a) specify the conditions under which vaccine, vaccination and other services will be provided to the owners of animals; (b) specify the institutions responsible for case-reporting, control and disposal of dogs, and other prescribed measures to be carried out at local, community, district or national level; and (c) as far as appropriate, describe the responsibilities of the various governmental sectors and services.

When preparing rabies legislation, attention should be paid to possible counter-productive effects associated with its enforcement; for example, over-stringent regulations for removal of the dog population may give rise to adverse public reaction and opposition to the control programme, and establishment of dog vaccination fees may deter dog owners from having their dogs immunized.

5. Planning and management

Various strategies and managerial approaches to control canine rabies have been tested under field conditions during the past decade. Some of them have been shown to be effective in several areas with different geographical characteristics and different cultural, religious and socio-economic backgrounds.

Sustained financing of a rabies control programme is essential for its

success. Cost-benefit and cost-effectiveness analyses should be performed prior to development of rabies control programmes to study their feasibility and to select the best strategy. These analyses should include: (a) calculation of the direct and indirect annual costs of human pre-exposure and post-exposure vaccination and of expenses related to cases of human and animal rabies; (b) the annual costs of existing control measures (e.g. dog vaccination, dog removal) which have not eliminated rabies; and (c) the estimated costs of implementing a programme for the elimination of rabies in dogs and the effects of such a programme in both the medium and the long term on all other costs.

5.1 *Community rabies control programmes*

Rabies control programmes will be successful if they are in the interests of the local communities. The medical and veterinary public health authorities, community representatives, and other interested third parties involved in running a programme must all agree on objectives, conditions and plans of action aimed at eliminating the disease and maintaining rabies-free areas.

To ensure high coverage of the dog population, a programme promotion plan is required. The promotional campaign should be conducted through traditional health education at the local level, with support from the mass media through national and state broadcasts. It is recommended that vaccination be offered free of charge for the animal owners. The cost of the campaign may be shared between the various government sectors, nongovernmental organizations, national agencies and the community.

The sustainability of community-based programmes is frequently undermined by over-reliance on external resources. If external inputs remain low, communities are more likely to consider the programme as their own.

Accordingly, local programmes should mobilize the participation of the following groups: local councils; community administrative and technical officers; medical and veterinary services; health committees and community health workers; religious and civic groups; schools and adult education organizations; practitioners of traditional medicine, birth attendants and midwives.

However, some resources, such as diagnostic services, vaccines and syringes, may need to be provided by higher administrative levels.

The following actions should be considered by communities that do not possess specialized professional services:

1. Designation of a local committee and person responsible for community activities in rabies control.
2. Identification of local resources and establishment of a network of collaborating civic groups and individuals, including primary health care workers.

3. Establishment of a plan of action for a community programme in rabies surveillance and control and in dog population management. This plan should be prepared with the appropriate governmental services.
4. Implementation and evaluation of the programme under the supervision of the community council in close cooperation with higher administrative services.

5.2 *Intersectoral and intercommunity cooperation*

The effectiveness and sustainability of rabies control programmes at district level are strengthened by intercommunity collaboration. This collaboration may extend to other disease control programmes and include case notification, diagnostic services, technical expertise in planning and education, specialized service staff, cold chains, vaccines and equipment.

Since intersectoral collaboration at the provincial and district level should support community activities, committees for programme coordination should be established at these levels; these should include representatives of health-related committees as well as representatives of other ministries and organizations.

One objective of such committees will be to formulate and implement local action plans. Such plans may include:

- epidemiological surveillance by case notification and specimen collection and transport for laboratory examination;
- education and information schemes;
- vaccination and dog population management;
- development of proposals for programmes covering larger geographical areas up to national programmes and international schemes of cross-border cooperation;
- reporting to higher national administrative services.

Intersectoral and intercommunity cooperation may lead to reductions in costs through the sharing of resources. Examples of shared resources include diagnostic laboratories in Mexico and the Philippines, and cold chains for heat-labile vaccines in southern Sudan for the immunization of children and for rinderpest control in cattle.

The most effective methods of increasing the level of public knowledge involve informational meetings with community leaders, health workers, civic groups, teachers and schoolchildren; the basic messages may also be transmitted through popular informational material such as magazines, comics and leaflets.

Information regularly broadcasted through mass media may supplement these meetings. Locally recruited and trained educators and communicators could significantly contribute to programme development.

5.3 *Comprehensive national programmes*

The Committee recommended a step-wise development of comprehensive national programmes for canine rabies control in line with established principles of zoonoses control (*1*, 5-7). These include:

- Establishment of an interministerial committee on rabies control.
- Designation of a national programme director.
- Identification of resources and development areas for personnel, materials and management.
- Review and, if necessary, revision of legislation.
- Formulation of the national programme for rabies control, and endorsement at government level (see *1*, 5-7).
- Establishment of an institutional framework, if not already existing, including components of community-based activities.
- Assessment of programme needs.
- Mobilization of resources.
- Implementation of the programme, harmonizing phases of development within a clearly specified time-frame in respect of geographical coverage, technologies and personnel.
- Monitoring, periodic evaluation and review of the programme.

An important task of a national programme director should be to promote community initiatives through the provision of technical assistance where necessary. Other tasks concern the provision of diagnostic services, technological support, vaccines and educational schemes for implementation at community level.

References[1]

1. *Guidelines for dog rabies control* (unpublished document VPH/83.42, Rev.1).
2. *Guidelines for dog population management* (unpublished document WHO/Zoon/90.166).
3. *Report of the Second WHO Consultation on oral immunization of dogs against rabies, Geneva, 6 July 1990* (unpublished document WHO/Rab.Res./91.37).
4. *Report of a WHO/APHIS Consultation on baits and baiting delivery systems for oral immunization of wildlife against rabies, Fort Collins, CO, 10–12 July 1990* (unpublished document WHO/Rab.Res./90.36).
5. *Bacterial and viral zoonoses. Report of a WHO Expert Committee with the participation of FAO.* Geneva, World Health Organization, 1982 (WHO Technical Report Series, No. 682).

[1] Unless otherwise stated, unpublished documents have been prepared by the World Health Organization, Geneva, and are available on request from the Division of Communicable Diseases, World Health Organization, 1211 Geneva 27, Switzerland.

6. *WHO Expert Committee on Rabies. Seventh report.* Geneva, World Health Organization, 1984 (WHO Technical Report Series, No. 709).

7. *WHO/FAO/ISS guiding principles for planning, organization and management of public health programmes* (unpublished document ISS/WHO/FAO-CC/IZSTR 90.11).

Annex 5

Addresses of international institutions for technical cooperation in rabies control

The following WHO Collaborating Centres and other international organizations and institutions are prepared to collaborate with national services on request:

Zoonoses centres

The Director
Pan American Institute for Food Protection and Zoonoses (INPPAZ)
Calle Talcahuano 1660
1640 Martinez
Provincia de Buenos Aires
Argentina

Tel.: (01) 798 9393
Fax: (01) 112 328

The Director
Mediterranean Zoonoses Control Centre
PO Box 3904
10210 Athens
Greece

Tel.: (01) 639 9367
Fax: (01) 638 0163
Telex: 222 670 MZCC GR

International centres for biological standards, reference preparations and reference reagents

Department of Biological Standardization
State Serum Institute
80 Amager Boulevard
DK-2300 Copenhagen S
Denmark

Tel.: 32 683 268
Fax: 32 683 868
Telex: 31 316 SERUM DK

Collaborating and related reference centres

Rabies

The Director
WHO Collaborating Centre for Control, Pathogenesis and Epidemiology of Rabies
Rabies Unit, Pathology Section
Animal Diseases Research Institute (ADRI)
Agriculture Canada
801 Fallowfield Road, PB 11300
Station H, Nepean K2H 8P9
Ontario
Canada

Tel.: (0613) 998 9320 Ext. 4831
Fax: (0613) 952 8072

The Director
WHO Collaborating Centre for Reference and Research on Rabies
Pasteur Institute
28 rue du Docteur Roux
F- 75724 Paris Cédex 15
France

Tel.: (01) 45 688 755
Fax: (01) 43 069 835
Telex: PASTEUR 250 609 F

The Director
WHO Collaborating Centre for Rabies Surveillance and Research
Rabies Laboratory
Federal Research Institute for Animal Virus Diseases
Postfach 1149
D-W-7400 Tübingen
Germany

Tel.: (07071) 6031/32/33
Fax: (07071) 603 201
Telex: 17 707 131

The Director
WHO Collaborating Centre for Rabies Epidemiology
National Institute of Communicable Diseases
22 Shamnath Marg
Post Box 1492
Delhi 110 054
India

The Director
WHO Collaborating Centre for Training in Rabies Vaccine Production and Quality Control
Rabies Division
Pasteur Institute of India
Coonoor 643 103 (Nilgiris)
India

Tel.: 21 250, 21 846
Telex: 853 203 PIIC IN
Cables: LYSSA, COONOOR

The Director
WHO Collaborating Centre for Reference and Research on Rabies
Rabies Department (Research and Production)
Pasteur Institute of Iran
69 Pasteur Avenue
13164 Teheran
Islamic Republic of Iran

Tel.: (021) 669 8714
Telex: 214 265 IPIN
Cables: Institute Pasteur, Rabies

The Director
WHO Collaborating Centre for Reference
and Research on Rabies
Institute of Poliomyelitis and Viral
Encephalitides
Academy of Medical Sciences of the
Russian Federation
Kievskoe Šosse 27 km
Moscow 142 782
Russian Federation

The Director
WHO Collaborating Centre for Rabies
Diagnosis, Research and Training
Virus Research Institute
Department of Medical Sciences
Ministry of Public Health
88/7 Soi Bumrasnaradura Hospital
Tivanonda Road
Nonthaburi 11000
Thailand

The Director
WHO Collaborating Centre for Research
on Rabies Pathogenesis and Prevention
Queen Saovabha Memorial Institute
Thai Red Cross Society
Division of Science
1871 Rama IV Road
10330 Bangkok
Thailand
Tel.: (02) 252 6117
Fax: (02) 254 0212
Telex: 82 535 TRCS BKKTH

The Director
WHO Collaborating Centre for Reference
and Research on Rabies
Rabies Laboratory
Center for Infectious Diseases
Centers for Diseases Control
1600 Clifton Road
Atlanta, GA 30333
USA
Tel.: (0404) 639 1050
Fax: (0404) 639 3163
Telex: 549 571 CDC ATL

The Director
WHO Collaborating Centre for Reference
and Research on Rabies
The Wistar Institute of Anatomy
and Biology
36th Street at Spruce
Philadelphia, PA 19104
USA
Tel.: (0215) 898 3703/4
Fax: (0215) 898 3995
Telex: 710 670 0328

The Director
WHO Collaborating Centre for Research and Training in Veterinary Public Health
School of Veterinary Medicine
Bischofsholer Damm 15
D-W-3000 Hanover 1
Germany

Tel.: (0511) 856 8768/69
Fax: (0511) 856 7685
Telex: 922 034 TIHO D

FAO/WHO Collaborating Centre for Research and Training in Veterinary Public Health
Indian Veterinary Research Institute
Modular Laboratory Building
Izatnagar 243 122
Bareilly (U.P.)
India

Tel.: 72 965
Telex: 577 205 IVRI IN
Cables: VETEX

The Director
WHO/FAO Collaborating Centre for Research and Training in Veterinary Public Health
Laboratorio di Parassitologia
Istituto Superiore di Sanità
Viale Regina Elena 299
I-00161 Rome
Italy

Tel.: (06) 444 0097
Fax: (06) 446 9823
Telex: 610 071 ISTISAN I

The Director
WHO Collaborating Centre for Tropical Veterinary Public Health Programme and Training
School of Veterinary Medicine
Tuskegee Institute
Tuskegee, AL 36088
USA

Tel.: (0205) 727 8174
Fax: (0205) 727 8177

The Director
WHO Collaborating Centre for Veterinary Public Health Systems Research and Analysis
Tufts University School of Veterinary Medicine
Department of Medicine, Section of International Veterinary Medicine
200 Westboro Road
North Grafton, MA 01536
USA

Tel.: (0508) 839 5302
Fax: (0508) 839 2953

The Director
WHO Collaborating Centre for Research and Training in Zoonoses
China National Centre for Preventive Medicine
P.O. Box 5
Changping, Beijing
China

Tel.: (01) 444 267
Telex: Beijing 9083

The Director
WHO Collaborating Centre for Research on Borreliosis
Reference Laboratory of Lyme Borreliosis
Institute of Hygiene and Epidemiology
Srobarova 48
100 42 Prague 10
Czechoslovakia

Tel.: (02) 731 241
Telex: 122 662

The Director
WHO Collaborating Centre for Research and Management in Zoonoses Control
Laboratoire d'Etudes sur la Rage et la Pathologie des Animaux sauvages
Centre National d'Etudes vétérinaires et alimentaires (CNEVA)
B.P. 9
F-54220 Malzéville
France

Tel.: (083) 292 608
Fax: (083) 293 313
Cables: CNEVA 54 220 Laboratoire

The Director
WHO Collaborating Centre for Reference and Research on Bacterial Zoonoses
Research Institute for Bacterial Animal Diseases
Naumburger Strasse 96 a
D-O-6909 Jena
Germany

Tel.: (03778) 419 200
Fax: (03778) 419 228

The Director
WHO Collaborating Centre for Reference and Research on Neurological Zoonoses
Institute for Medical Virology
University of Essen
PO Box 10 21 41
D-W-4300 Essen 1
Germany

Tel.: (0201) 793 414
Fax: (0201) 723 5929
Telex: 857 9573 KLIES D

The Director
WHO Collaborating Centre for Prevention and Control of Zoonoses
The Kovlenko Institute for Experimental Veterinary Medicine of the Russian Federation
Kuzminky
Moscow 109 472
Russian Federation

Tel.: (095) 377 8492

The Director
WHO Collaborating Centre for Zoonoses
Central Research Institute of Epidemiology of the Russian Federation
Ministry of Health
Novogireevskaya 3 a
Moscow 111 123
Russian Federation

Tel.: (095) 176 7953/
176 0219

The Director
WHO Collaborating Centre for Reference and Research on Parasitic Zoonoses
Institut für Parasitologie der Veterinärmedizinischen und der Medizinischen Fakultät
University of Zürich
Winterthurerstrasse 266 a
CH-8057 Zürich
Switzerland

Tel.: (01) 365 1380
Fax: (01) 363 0478
Telex: 55 575 UNIZI

The Director
WHO Collaborating Centre for Reference and Research on Viral Zoonoses
Institute of Veterinary Virology
University of Bern
P.O. Box 2735
CH-3000 Bern
Switzerland

Tel.: (031) 274 413
Fax: (031) 274 534

The Director
WHO Collaborating Centre for Reference and Training on Enteric Zoonoses
Department of Microbiology
College of Veterinary Medicine
University of Missouri
Columbia, MO 65211
USA

Tel.: (0314) 882 3083
Fax: (0314) 882 2950

Chief, Veterinary Public Health Division of Communicable Diseases World Health Organization 1211 Geneva 27 Switzerland	Tel.: (022) 791 2575 Fax: (022) 791 0746 Telex: 415 416 Cables: UNISANTE GENEVE
Regional Director WHO Regional Office for Africa PO Box No. 6 Brazzaville Congo	Tel.: 833 860 Fax: 831 879 Telex: 5217/5364 Cables: UNISANTE BRAZZAVILLE
Regional Director WHO Regional Office for the Americas/Pan American Sanitary Bureau 525, 23rd Street NW Washington, DC 20037 USA	Tel.: (0202) 861 3200 Fax: (0202) 223 5971 Telex: 248 338/440 057 Cables: OFSANPAN WASHINGTON
Regional Director WHO Regional Office for the Eastern Mediterranean PO Box 1517 Alexandria 21511 Egypt	Tel.: (03) 482 0223 Fax: (03) 483 8916 Telex: 54 028 Cables: UNISANTE ALEXANDRIA
Regional Director WHO Regional Office for Europe 8 Scherfigsvej DK-2100 Copenhagen Ø Denmark	Tel.: 39 171 717 Fax: 31 181 120 Telex: 15 348 Cables: UNISANTE COPENHAGEN
Regional Director WHO Regional Office for South-East Asia World Health House Indraprastha Estate Mahatma Gandhi Road New Delhi 110 002 India	Tel.: (011) 331 7804 Fax: (011) 331 8607 Telex: 316 5095 Cables: WHO NEW DELHI
Regional Director WHO Regional Office for the Western Pacific PO Box 2932 Manila 1099 Philippines	Tel.: (02) 521 8421 Fax: (02) 521 1036 Telex: 27 652 Cables: UNISANTE MANILA

Director
Animal Production and Health Division
Food and Agriculture Organization of the United Nations (FAO)
Via delle Terme di Caracalla
I-00100 Rome
Italy

Tel.: (06) 57 971
Fax: (06) 57 973 152
Telex: 610 181
Cables: FOODAGRI ROME

Director-General
International Office of Epizootics (OIE)
12 rue de Prony
F-75017 Paris
France

Tel.: (01) 42 274 574
Telex: 642 285
Cables: INTEREPIZOOTIES PARIS

Director-General
Arab Organization for Agricultural Development
Sharia El Gamaa
Khartoum
Sudan

The President
Commission of the European Communities (CEC)
200 rue de la Loi
B-1049 Brussels
Belgium

Tel.: (02) 235 1111
Telex: 21 877
Cables: COMEUR BRUXELLES

The Secretary-General
Organization of African Unity (OAU)
PO Box 3243
Addis-Ababa
Ethiopia

Tel.: (01) 157 700
Telex: 21 406
Cables: OAU ADDIS ABABA

Nongovernmental organizations

The Secretary-General
International Council for Laboratory Animal Science (ICLAS)
Department of Physiology
University of Kuopio
70211 Kuopio
Finland

Tel.: (071) 163 080
Fax: (071) 163 410

International Union for the Conservation of Nature and Natural Resources (IUCN)
Avenue du Mont-Blanc
1196 Gland
Switzerland

Tel.: (022) 649 114
Fax: (022) 642 926
Telex: 419 605

World Society for the Protection of Animals (WSPA)
Park Place, 10 Lawn Lane
London SW8 1UD
England
Tel.: (071) 793 0208
Fax: (071) 163 410

World Wide Fund for Nature (WWF)
Avenue du Mont-Blanc
1196 Gland
Switzerland
Tel.: (022) 649 111
Fax: (022) 644 238

Annex 6

International rabies vaccination certificate for dogs and cats

The vaccination certificate below is provided as a model for copying.

CERTIFICAT INTERNATIONAL DE VACCINATION ANTIRABIQUE Page 1
POUR CHIENS ET CHATS/INTERNATIONAL RABIES VACCINATION CERTIFICATE FOR DOGS AND CATS

I. Propriétaire/Owner

Nom et adresse
Name and address _____

_____

_____

II. Signalement/Description

Espèce
Species of animal _____

Age ou date de naissance (si possible)
Age or date of birth (where known) _____

Sexe
Sex _____

Race
Breed _____

Robe
Colour _____

Type de pelage et marques/Signes particuliers
Coat type and marking/Distinguishing marks _____

_____

_____

N° d'identification dermographique (s'il y a lieu)
Tattoo no. (where present) _____

III. Vaccinations

Le soussigné certifie avoir vacciné contre la rage l'animal décrit à la page 3, comme il est indiqué ci-aprés. Au moment de la vaccination, l'animal a été reconnu en bonne santé.

The undersigned declares herewith that he or she has vaccinated the animal described on page 3 against rabies, as shown below. The animal was found to be healthy.

(1) Date	(2) 1. Nom du vaccin 2. Type: vivant ou inactivé 1. Name of vaccine 2. Live or inactivated	(3) 1. Laboratoire d'origine 2. N° du lot 1. Manufacturing laboratory 2. Batch no.	(4) Signature et cachet du vétérinaire Signature and stamp of veterinary surgeon	(5) Authentification officielle[a] Government authentication[a]
	1 _____	1 _____		
	2 _____	2 _____		
	1 _____	1 _____		
	2 _____	2 _____		

Autres vaccinations/Other vaccinations

Date	Vaccine utilisé Vaccine used	N° du lot Batch no.	Signature et cachet du vétérinaire Signature and stamp of veterinary surgeon

[a] Voir Section V: Passage de frontière — 3e paragraphe/See Section V: Frontier crossing — 3rd paragraph.

Pays d'origine
Country of origin _____

Pays dans lesquels l'animal a séjourné, selon les déclarations du propriétaire (indiquer les dates)/Countries visited by the animal as declared by the owner (give dates)

_____

_____

_____

_____

Notes:

Le présent certificat ne dispense pas de l'application des autres dispositions en vigueur pour l'entrée dans certain pays. Prière de lire la Section V.
This certificate may not be sufficient to meet all the entry requirements of the countries of destination. Please read Section V.

Autorisation d'imprimer délivrée par: [a]
Printing authorized by: [a]

Pour être valable, le présent certificat doit porter un numéro perforé à chaque page.
To be valid, this certificate must bear a number perforated on each page.

[a] Indiquer l'autorité nationale responsable/Indicate the responsible national authority.

V. Passage de frontière/Frontier crossing

1. Le propriétaire de l'animal doit, avant de se rendre à l'étranger avec celui-ci, s'assurer des conditions sanitaires imposées par les autorités du pays de destination, le présent certificat ne dispensant pas de l'application des autres dispositions en vigueur dans certains pays.
   The owner of the animal must, before going abroad with it, make sure of the veterinary requirements laid down by the authorities of the country of destination, as this certificate may not be sufficient to meet all the requirements of the country of destination.
2. Le présent certificat est valable à partir du trentième jour et jusqu'à la fin du douzième mois après la date de la première vaccination; dans le cas d'une revaccination au cours de la période de validité, pendant les douze mois qui suivent la date de la revaccination.
   This certificate is valid from the 30th day until the end of the twelfth month after the date of the first vaccination; in the case of revaccination within the validity period, for 12 months from the date of revaccination.
3. Si le vétérinaire dont la signature et le cachet figurent dans la colonne (4), page 2, n'est pas un vétérinaire agréé, la contresignature et le cachet d'un vétérinaire de l'autorité nationale responsable doivent être apposés dans la colonne (5).
   If the veterinarian signing and stamping column (4) on page 2 is not an authorized veterinarian, his or her signature must be authenticated in column (5) by the signature and stamp of a veterinarian of the responsible national authority.
4. Le présent certificat doit être imprimé et complété en français et en anglais, et si nécessaire, dans la langue du pays d'origine.
   This certificate must be printed and completed in French and English and, if necessary, the language of the country of origin.

Annex 7

Programmes and centres responsible for international surveillance and information exchange on rabies

The Committee stressed that national authorities should be aware of all the major regular surveillance activities carried out by international organizations and institutions concerning the occurrence and control of rabies. The following list of organizations and publications may not be complete but includes some purely statistical reports as well as information exchange services dealing with particular scientific developments and epidemiological events.

1. World Health Organization (WHO)

20 Avenue Appia
1211 Geneva 27
Switzerland

Tel.: (022) 791 2111
Fax: (022) 791 0746
Telex: 415 416
Cables: UNISANTE GENEVA

Weekly epidemiological record (WER) (weekly)
World health statistics annual
World rabies survey[1] (annual)

2. Food and Agriculture Organization of the United Nations (FAO)

Via delle Terme di Caracalla
I-00100 Rome
Italy

Tel.: (06) 57 971
Fax: (06) 57 973 152
Telex: 610 181
Cables: FOODAGRI ROME

Animal health yearbook, FAO-OIE-WHO (annual)

3. Pan American Health Organization

WHO Regional Office for the Americas/Pan American Sanitary Bureau (PAHO/WHO)

525, 23rd Street, NW
Washington, DC 20037
USA

Tel.: (0202) 861 3200
Fax: (0202) 223 5971
Telex: 248 338
Cables: OFSANPAN
WASHINGTON

Epidemiological bulletin (bimonthly)

[1] Available on request from the Division of Communicable Diseases, World Health Organization, 1211 Geneva 27, Switzerland.

Pan American Institute for Food Protection and Zoonoses (INPPAZ)

Calle Talcahuano 1660
1640 Martinez
Provincia de Buenos Aires
Argentina

Tel.: (01) 798 9393
Fax: (01) 112 328

Epidemiological surveillance of rabies for the Americas (monthly)

4. International Office of Epizootics (OIE)

12 rue de Prony
75017 Paris
France

Tel.: (01) 44 151 888
Fax: (01) 42 670 987
Telex: 642 285
Cables: INTEREPIZOOTIES PARIS

Statistiques O. I. E. (annual)
Bulletin of the International Office of Epizootics (monthly)

5. WHO Collaborating Centre for Reference and Research on Rabies

Rabies Laboratory
Center for Infectious Diseases
Centers for Disease Control
1600 Clifton Road
Atlanta, GA 30333
USA

Tel.: (0404) 639 1050
Fax: (0404) 639 3163
Telex: 549 571 CDC ATL

Rabies information exchange (biannual)

6. WHO Collaborating Centre for Rabies Surveillance and Research

Rabies Laboratory
Federal Research Institute
for Animal Virus Diseases
Postfach 1149
D-W-7400 Tübingen
Germany

Tel.: (07071) 6031
Fax: (07071) 603 201
Telex: 17 707 131

Rabies bulletin Europe (quarterly)

7. Mediterranean Zoonoses Control Center (UNDP/WHO)

P.O. Box 3904
10210 Athens
Greece

Tel.: (01) 639 9367
Fax: (01) 638 0163
Telex: 222 670 MZCC GR

Information circular (quarterly)

8. WHO Collaborating Centre for Collection and Evaluation of Data on Comparative Virology

Institute of Medical Microbiology,
Infectious and Epidemic Diseases
Veterinary Faculty
University of Munich
Veterinärstrasse 13
D-W-8000 Munich 22
Germany

Tel.: (089) 21 802 527/528
Fax: (089) 21 802 597

Information from animal virus data bank (on request)

Annex 8

Suggested case-record form for human exposure to rabies

The form below is provided as a model for copying.

SUGGESTED CASE-RECORD FORM FOR HUMAN EXPOSURE TO RABIES Page 1

Case no. _____ Referred by _____

Person bitten

Name _____ Date of bite _____

Age _____ Geographical locality of biting episode

Sex _____ _____

Home address _____ Site(s) of bite on the body _____

_____ Nature of bite _____

Single ☐ Mild ☐

Multiple ☐ Moderate ☐

Severe ☐

Other persons, if any, bitten by the same animal (Names and addresses)

1. _____
2. _____
3. _____
4. _____

Treatment

Local wound treatment _____

Vaccine: ***Serum:***

Size or quantity of individual dose _____ Dose _____

Route of administration _____ Date administered _____

Dates administered _____ Source of serum: Human ☐ Animal ☐

Type of vaccine (phenol- or UV-inactivated, etc.) _____ Results of sensitivity test: Positive ☐ Negative ☐

Manufacturer and Lot no. _____ Manufacturer and Lot no. _____

_____ _____

Previous rabies vaccine application? _____ Previous serum treatment? _____

Date _____ Type _____ Date _____ Type _____

Were there complications of treatment? If so, specify treatment of undesirable sequelae and outcome _____

_____

Status of exposed person after 6 months:

Alive ☐

Died of rabies ☐

Died of other causes ☐

Unknown ☐

Date of death _____

Status of other persons bitten by the same animal, if known

1. _____
2. _____

Biting animal

Kind of animal _____

Description:

Breed _____ Age _____ Sex _____ Weight _____

Animal vaccinated against rabies? _____

If so, type of vaccine _____ Date _____

Outcome:

Under observation ☐

Outcome during ___ days:

Signs of rabies ☐

Healthy ☐

Died ☐

Killed ☐ Escaped ☐

Results of laboratory examination:

	Positive	Negative
Fluorescent antibody test	☐	☐
Negri bodies	☐	☐
Animal inoculation	☐	☐
Other tests	☐	☐

World Health Organization Technical Report Series

Recent reports:

No.		Sw.fr.*
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