WHO Expert Consultation on Rabies

Third report

World Health Organization

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WHO Position Paper on Rabies Vaccines
Weekly Epidemiological Record, 2010, 85: 309-320

WHO Expert Consultation on Rabies. Second report.
Geneva, World Health Organization, 2013
WHO Technical Report Series, No. 982

WHO Expert Consultation on Rabies. First report.
Geneva, World Health Organization, 2005
WHO Technical Report Series, No. 931

WHO Expert Committee on Rabies. Eighth report.
Geneva, World Health Organization, 1992
WHO Technical Report Series, No. 824

Laboratory Techniques in Rabies. Fourth edition.
Geneva, World Health Organization, 1996

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Abbreviations and acronyms

ASEAN	Association of South-East Asian Nations
CCEEV	concentrated, purified cell culture and embryonated egg-based rabies vaccine
CSF	cerebrospinal fluid
DALY	disability-adjusted life–year
DHIS2	District Health Information Software, version 2
DRIT	direct rapid immunohistochemical test
ELISA	enzyme-linked immunosorbent assay
FAT	direct fluorescent antibody test
FAVN	fluorescent antibody virus neutralization
GARC	Global Alliance for Rabies Control
mAb	monoclonal antibody
OIE	World Organisation for Animal Health
ORV	oral rabies vaccination
PAHO	Pan American Health Organization
PARACON	Pan-African Rabies Control Network
PEP	post-exposure prophylaxis
PrEP	pre-exposure prophylaxis
RABV	rabies virus
REDIPRA	Meeting of the Directors of National Programs for the Prevention and Control of Rabies in the Americas
RFFIT	rapid fluorescent focus inhibition test
RIG	rabies immunoglobulin
RT-PCR	reverse transcriptase polymerase chain reaction
USA	United States of America

1.   Introduction

The WHO Expert Consultation on Rabies met in Bangkok, Thailand, on 26–28 April 2017. Dr Thiravat Hemachudha (Faculty of Medicine, Chulalongkorn University), Dr Jedsada Chokdamrongsuk (Director-General, Thailand Department of Disease Control) and Dean Suthipong Wacharasindhu (Faculty of Medicine, Chulalongkorn University) welcomed participants, emphasizing the importance of rabies as a preventable disease, which causes tens of thousands of deaths worldwide every year. Dr Chokdamrongsuk outlined Thailand's commitment to eliminating human deaths from rabies by 2020.

Dr Bernadette Abela-Ridder (Neglected Zoonotic Diseases, WHO) described the impact of neglected tropical diseases such as rabies on poor and disadvantaged populations and the benefits of investing to improve health systems. Health and well-being for all people at all ages is the third United Nations Sustainable Development goal, which includes ending the burden of neglected tropical diseases such as rabies by 2030 and achieving universal health coverage by ensuring equal, affordable access to high-quality health services for all. Rabies, a preventable zoonotic disease, is a good indicator of a successful health system and a model for "one health" collaboration. The launch of the Global Rabies Framework in 2015 celebrated the proof of concept that rabies can be eliminated in various settings and the shared goal of reaching zero human deaths from rabies by 2030, worldwide.

Dr Thiravat Hemachudha and Dr Christine Fehlner-Gardiner were appointed Chairs, and Dr Susan Moore and Ms Joss Kessels were appointed Rapporteurs of the Consultation. The participants are listed in *Annex 1*.

The information in this report should be considered the most current data on rabies prevention and control, and it supersedes that of the report of the second WHO Expert Consultation on Rabies, published in 2012 (*1*).

2.   The burden of rabies

Information on disease burden is widely used to set public health priorities, allocate resources for disease prevention and assess the impact and cost–effectiveness of interventions (*2*). This section focuses on dog-mediated rabies as the major cause of human rabies.

2.1   Methods for estimating the burden of rabies

Human deaths from rabies are significantly underreported in many parts of the world. To account for this, a probability decision-tree model has been used to estimate mortality in Bhutan (*3*), Cambodia (*4*) and the United Republic of Tanzania (*5*) and in Africa, Asia (*6*) and globally (*7*). Empirical studies for making these estimates include community surveys (*8*), large-scale verbal autopsy surveys (*9*), active surveillance and contact tracing (*9*), with Monte Carlo simulation used to propagate uncertainty (*7*).

Standardized metrics such as the disability-adjusted life–year (DALY) incorporate premature mortality and disability due to disease; as rabies is rapidly fatal, disability accounts for a minimal part of the disease burden. In the few places in which nerve tissue vaccines remain in use, they contribute to vaccine failure and cause severe side-effects that can last for 4–7 months in 0.03–0.08% of cases (*6*).

The most recent comprehensive estimate of the burden of rabies includes productivity losses due to mortality or morbidity (expressed as DALYs), direct costs such as those of rabies vaccines and immunoglobulins, and indirect costs such as transport and loss of income incurred by patients. Livestock losses and the costs of surveillance and preventive measures such as dog vaccination were also included (*7*).

Rabies is a neglected disease. In places where there is no organized control or surveillance, data are weak. Poor surveillance, underreporting, frequent misdiagnosis and the absence of coordination among all the sectors involved are likely to lead to underestimation of the size of the burden. In the absence of specific data, clustering of countries on the basis of epidemiological, socioeconomic and geographical criteria has been used to extrapolate estimates (*7*); and better surveillance and strengthened regional and global reporting systems would increase the accuracy of estimates and the impact of control programmes (*10*). Country-specific studies of the burden and better surveillance (see *section 11*) are encouraged to obtain more reliable global estimates.

2.2 Estimated global human burden of rabies

Fig. 1 shows the global burden of dog-transmitted human rabies.

Figure 1
Global burden of dog-transmitted human rabies
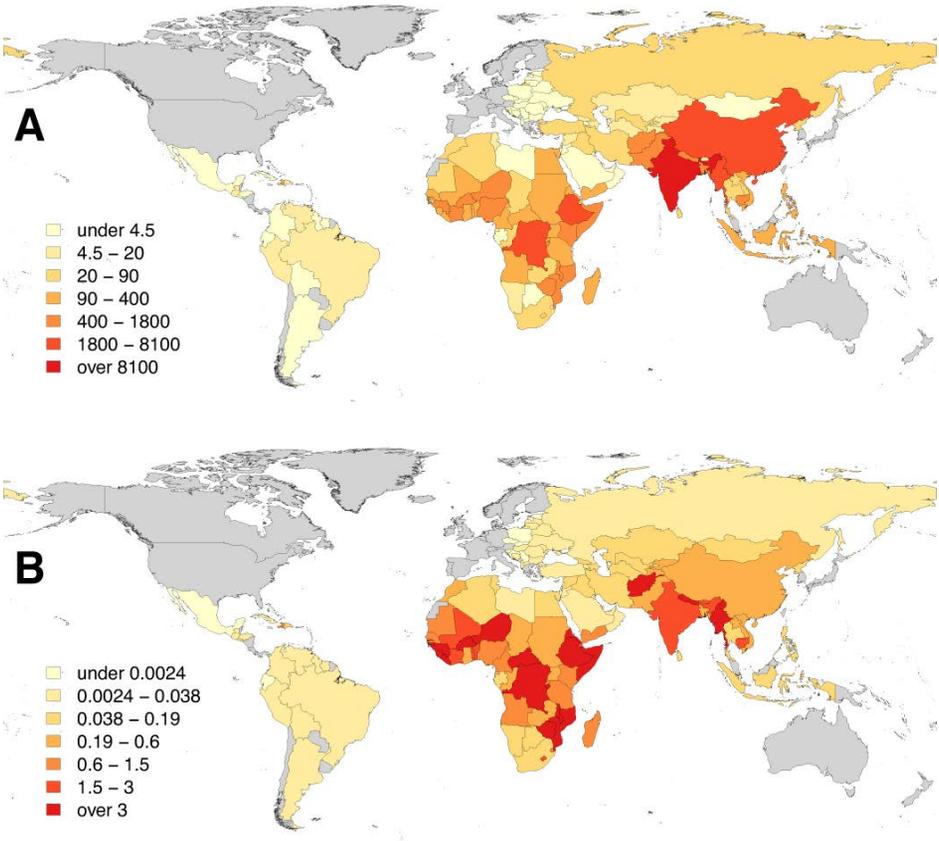
A: Human deaths from rabies; B: Death rates per capita (per 100 000 population); countries shaded in grey are free from canine rabies

Source: reference *7*

2.2.1 Countries that are free of dog rabies

A country is defined as free of dog rabies if no indigenously acquired dog-mediated rabies cases have been confirmed in humans, dogs or any other animal species for at least 2 years (see *section 12* for a full case definition). Dog-mediated rabies has been eliminated from western Europe, Canada, the United States of America (USA), Japan and some Latin American countries. Australia and many Pacific island nations have always been free from dog-mediated rabies. Such countries may still report imported cases (*11*), however, and incur costs for maintaining freedom from disease, for surveillance of endemic transmission of RABV in wildlife and/or bats and for pre- (PrEP) and post-exposure prophylaxis (PEP) for people living in or travelling to areas endemic for dog-mediated rabies (*12*).

2.2.2 Countries in which dog rabies is endemic

Latin America and the Caribbean

The numbers of cases of human and dog rabies have decreased significantly in this region as a result of sustained control (*13*). Between 2013 and 2016, dog-mediated human rabies was reported only in Bolivia, Brazil, the Dominican Republic, Guatemala, Haiti, Honduras, Peru and Venezuela (*14*). In 2016, 10 deaths due to dog-mediated rabies were reported in the Americas – 8 in Haiti and 2 in Guatemala (*14*), and 23 deaths were reported due to rabies in species other than dogs, with 3 in Brazil, 2 in Colombia, 1 in Guatemala, 2 in Mexico and 15 in Peru. Nerve tissue vaccines continue to be produced for human use in Argentina and Bolivia and for animal use in Bolivia, El Salvador and Honduras (*Table 1*).

Table 1

Countries in which nerve tissue vaccines for humans or animals remain in production

Target for use	Country
Humans	Algeria, Argentina, Ethiopia
Humans and animals	Bolivia
Animals only	El Salvador, Honduras, Zambia

Source: reference *14*

Asia

An estimated 35 172 human deaths (59.6% of global deaths) and loss of approximately 2.2 million DALYs occur per year in Asia due to dog-mediated rabies (*7*). India accounts for the most deaths in Asia (59.9% of human rabies deaths) and globally (35% of human rabies deaths). Estimates have been made of the use of nerve tissue vaccines in Bangladesh, Myanmar and Pakistan; however, their use has been discontinued in these countries since 2011, 2013 and 2015, respectively. The cost of PEP is highest in Asia, with estimates up to US$ 1.5 billion per year (*18*). Despite widespread underreporting and uncertain estimates, rabies is a major burden in Asia, particularly for the rural poor.

Africa

In Africa, an estimated 21 476 human deaths occur each year due to dog-mediated rabies (36.4% of global human deaths), with a loss of 1.34 million DALYs (*7*). Human nerve tissue vaccines remain in production in Algeria and Ethiopia (*Table 1*) (*17*). In one global cost study, Africa was estimated to spend the least on PEP (3.28% of the global non-human mortality cost) and have the highest cost of human mortality (45%), indicating that many lives could be saved if access to PEP was improved or the prevalence of dog-mediated rabies reduced (*15*).

Central Asia and the Middle East

The disease burden due to dog-mediated rabies is estimated to be 1875 human deaths and 14 310 DALYs in Central Asia and 229 human deaths and 1875 DALYs per year in the Middle East (*7*).

2.2.3   Bat rabies

Although bat rabies accounts for a relatively small proportion of human cases worldwide, it now accounts for the majority of human rabies cases in the Americas (*13,16*). In North America, this is due to a reduced propensity of people to seek PEP after interactions with bats than after bites from terrestrial carnivores; however, more rabid bats than rabid raccoons were recorded in the USA for the first time in 2015, signalling either an increasing prevalence of bat rabies or higher levels of reporting (*17*). In most other parts of the Americas, haematophagous bats are the primary source of human rabies cases. Vampire bat rabies is also a major cause of livestock mortality, affecting both subsistence and commercial farmers throughout the range of this bat (from Argentina and Uruguay to northern Mexico) (*18*). In Africa, Asia and Oceania, bat-related

human rabies cases remain rare but may be underreported because of limited surveillance and characterization of viruses. Bat lyssaviruses other than rabies virus are described in sections 3 and 10.

2.3 Global burden of rabies

The number of human deaths globally due to dog-mediated rabies is estimated to be 59 000 annually, with an associated loss of 3.7 million DALYs (*7*). The majority of deaths are estimated to have occurred in Asia (59.6%) and Africa (36.4%) (*Table 2*), and most DALYs were due to premature death (> 99%) and a few to adverse events after administration of nerve tissue vaccines (0.8%). The overall economic cost of dog-mediated rabies was estimated in a probability decision-tree model to be US$ 8.6 billion (95% confidence interval, 2.9–21.5 billion) (*7*). An enhanced verbal autopsy survey within the Million Deaths Study suggested that 12 700 deaths (95% confidence interval, 10 000–15 500) were due to furious rabies (see *section 4*) in India in 2005. The survey did not include cases of paralytic rabies (*19*).

Major costs associated with dog-mediated rabies vary by region. They include losses in productivity due to premature death (55% of total costs), the cost of PEP (20%) and direct costs to the medical sector and bite victims (20%). Spending on dog vaccination is, however, < 1.5% in most areas endemic for dog-mediated rabies, except in Latin America where 17% of costs are allocated to dog vaccination (*7*). For individuals, life-saving PEP may be hugely expensive, equivalent to 3.87% of gross national income for a person in Asia (31 days' wages for the average Asian) and to 5.80% for a person in Africa (51 days' wages for an average African) (*1*). These figures may considerably underestimate the true cost for high-risk populations, i.e. the rural poor. Livestock losses also disproportionately affect those who rely on livestock for their subsistence and livelihood.

At present, most of the burden is borne by people who can least afford it. Improving the availability of PEP could reduce the number of human deaths but is costly. The incidence of dog-mediated rabies can be reduced by sustained mass dog vaccination, and the cost of PEP will decrease with time if risk is assessed appropriately (see *section 12*) (*20*). National dog vaccination programmes and better access to PEP will require consistent, sustained commitment but will have widespread health benefits, particularly for the poorest communities in the world.

Table 2

Estimated numbers of deaths from rabies (with 95% confidence intervals) in various areas of the world

Year of estimate	Reference or source	Methods	Africa	China	India	Other Asian countries	All Asia	All Asia and Africa	World
2003	(8)	Multi-centre study (community surveys and hospital records)			20 565 (16 931–24 198)				
2003	(6)	Probability decision-tree approach	23 700 (6 900–45 900)	2336 (565–5049)	19 713 (4 192–39 733)	9489 (2281–19 503)	30–000 (8100–61 400)	55 270 (23 910–93 057)	
2005	(19)	Verbal autopsies			12 700 (10 000–15 000)				
2010	(21)	National surveillance data		2213					
2010	PRP	Probability decision-tree approach	23 800 (21 000–28 000)	7450 (2 000–13 000)	16 450 (6 000–27 000)	10 550 [a] (6 000–14 000)	34 500 (14 000–54 000)	58 300 (35 000–82 000)	61 000 (37 000–86 000)
2015	(7)	Probability decision-tree approach	21 502	6 002 (1 000–11 000)	20 847 (7 000–55 000)	8 126 [a]	37 045	58 547	59 000 (25 000–159 000)

PRP, Partners for Rabies Prevention

[a] Excluding Central Asia

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3. Classification of lyssaviruses

3.1 Distinguishing features of lyssaviruses

Rabies is an acute encephalitis caused by lyssavirus infection (*1*). The etiological agents of rabies encephalitis belong to the *Mononegavirales* order, the Rhabdoviridae family and the *Lyssavirus* genus (*2*). Lyssaviruses have a 12-kb non-segmented RNA genome of negative polarity that encodes five viral proteins (3′ to 5′): a nucleoprotein (N), a phosphoprotein (P), a matrix protein (M), a glycoprotein (G) and an RNA-dependent RNA polymerase (or large protein, L). The lyssavirus particle is shaped like a bullet, 100–300 nm long and 75 nm in diameter. It is composed of two structural and functional units: an internal helical nucleocapsid and an external envelope. The nucleocapsid consists of a ribonucleoprotein complex comprising the genomic RNA and tightly bound N protein and the L and P proteins. The nucleocapsid is active for transcription and replication: the N-RNA template is processed by the L protein, which contains most of the RNA polymerase activities, and its cofactor, the P protein. The lipid envelope is derived from the host cytoplasmic membrane during budding. Knobbed G protein spikes (5–10 nm long and about 3 nm in diameter), consisting of three glycosylated ectodomains that bind the virions to host cell receptors, protrude through the virion membrane. The M protein forms oligomers that bind to the outside of the nucleocapsid, giving rigidity to the virion structure and providing a binding platform for the viral G protein and the envelope membrane (*3, 4*).

3.2 Criteria for differentiating lyssaviruses

Until the 1950s, RABV was considered unique. Identification of serologically related viruses in Nigeria – Lagos bat virus from a pteropodid bat and Mokola virus from a shrew – showed, however, that the structure of this virus group was more complex, and the terms "rabies-related viruses" and "rabies serogroup" were introduced (*5*). Another serologically related virus, Duvenhage virus, representing a fourth serotype, was isolated from a man who died of rabies after a bite from an insectivorous bat in 1970 in South Africa (*6*).

The viruses regularly isolated from bats in the Americas and Europe since the 1950s were related serologically to Duvenhage virus and were initially included in the Duvenhage serotype (*7*). Later, use of monoclonal antibodies (mAbs) made it possible to refine the classification of the "rabies serogroup" (*8*). European bat lyssaviruses were not only distinguished from the African Duvenhage virus but also separated into two distinct serotypes, temporarily called "biotypes" (*9*). This differentiation was later supported by gene sequencing and phylogenetic

analysis. Extensive phylogenetic studies of the diversity of rabies-related viruses led to creation of the operational term "genotype", which has subsequently been used widely in the scientific literature (*10*). New genotypes were identified, and quantitative criteria for their differentiation were proposed (*11, 12*).

To accommodate the growing variety of "rabies-related" viruses, the genus *Lyssavirus* was established under the auspices of the International Committee on the Taxonomy of Viruses. The name of the genus was derived from Greek mythology: Lyssa (Λυσσα) was a goddess or spirit of rage, fury, raging madness and frenzy. The "genotypes" served as a basis for the taxonomy of lyssavirus but were refined to satisfy the official rules of the International Committee, which apply to more complex entities, such as viral species. Most recently, the nomenclature of the genus was updated to define each species as a distinct lyssavirus (*2, 13*).

The demarcation criteria for lyssavirus species include (*13, 15*):

- genetic distance, with a threshold of 80–82% nucleotide identity for the complete N gene, which provides better quantitative resolution than other genes, or 80–81% nucleotide identity for concatenated coding regions of the N+P+M+G+L genes. In general, all isolates belonging to the same species have higher identity values than the threshold, except the viruses currently included in the Lagos bat lyssavirus species. Some authors have therefore suggested that this species be subdivided into several genotypes (*14*). In the absence of other sufficient demarcation characteristics, however, Lagos bat lyssavirus has not been separated into several species, as the representatives segregate into a monophyletic cluster in most phylogenetic reconstructions;

- topology and consistency of phylogenetic trees obtained with various evolutionary models;

- antigenic patterns in reactions with nucleocapsid mAbs (preceded by serological cross-reactivity and definition of lyssavirus serotypes with polyclonal antisera); and,

- when available, additional characteristics, such as ecological properties, host, geographical range and pathological features.

3.3   Present structure of the *Lyssavirus* genus

Currently, the International Committee on the Taxonomy of Viruses recognizes 14 *Lyssavirus* species (*Table 3*). The genus has been subdivided into three phylogroups on the basis of genetic distances and serological cross-reactivity (*Fig. 2*).

Table 3

Viruses currently included in the genus *Lyssavirus*

Continent	Geographical distribution of isolates	*Lyssavirus* species	Mammalian species most frequently infected	Phylo-group, vaccine protection?	Human fatalities reported?
All	Terrestrial mammals worldwide except in Australia, Antarctica and several islands; bats in the New World only	Rabies lyssavirus	All mammals, predominantly dogs	I/Y	Yes, 59 000 human deaths/ year
Africa	United Republic of Tanzania	Ikoma lyssavirus[b]	*Civettictis civetta*	III/N	No
	Central African Republic, Ghana, Kenya, Nigeria, Senegal, South Africa; travellers returning to France from Egypt or Togo	Lagos bat lyssavirus	Numerous frugivorous bat species and occasional spillover to domestic dogs and cats	II/N	No
	Cameroon, Central African Republic, Ethiopia, Nigeria, South Africa, Zimbabwe	Mokola lyssavirus	Shrews (*Crocidura* spp.), domestic cats and rodents	II/N	Yes, 2
	Kenya	Shimoni bat lyssavirus[b]	Commerson's leaf-nosed bat	II/N	No
	Kenya[c], South Africa	Duvenhage lyssavirus	Undefined	I/Y	Yes, 3
	Zimbabwe	Duvenhage lyssavirus	Egyptian slit-faced bat	I/Y	Yes, 3

Europe	France, Germany, Spain	European bat 1 lyssavirus	Serotine bat	I/Y	Yes, 2
	Finland, France, Germany, Luxembourg, Netherlands, Switzerland, United Kindom	European bat 2 lyssavirus	Daubenton's bat	I/Y	Yes, 2
	France, Germany, Poland	Bokeloh bat lyssavirus	Natterer's bat	I/Y	No
	Spain	Lleida bat lyssavirus[b]	Common bent-winged bat	III/N	No
	Finland	Kotolahti bat lyssavirus[e]	Brandt's bat	I	No
Eurasia	Kyrgystan	Aravan lyssavirus[b]	Lesser mouse-eared bat	I/Y	No
	China[d], Russian Federation	Irkut lyssavirus	Greater tube-nosed bat	I/Y	Yes, 1
	Tajikistan	Khujand lyssavirus[b]	Whiskered bat	I/Y	No
	Kenya, Russian Federation[e]	West Caucasian bat lyssavirus[b]	Common bent-winged bat	III/N	No
Australasia	Australia	Australian bat lyssavirus	Black flying fox and related spp.	I/Y	Yes, 3
			Yellow-bellied sheath-tailed bat		
Asia	Sri Lanka	Gannoruwa bat lyssavirus	Indian flying fox	I/Y	No
	Taiwan	Taiwan bat lyssavirus[e]	Japanese house bat	I/Y	No

[a] More than 50 bat species have been implicated in RABV infection in the Americas; only.

[b] Only a single isolate described.

[c] Case reported from The Netherlands, but exposure occurred in Kenya.

[d] Not yet classified as lyssaviruses by the International Committee for Taxonomy of Viruses

[e] Serological evidence of infection in Kenya

Figure 2
Diversity of bat associated lyssaviruses
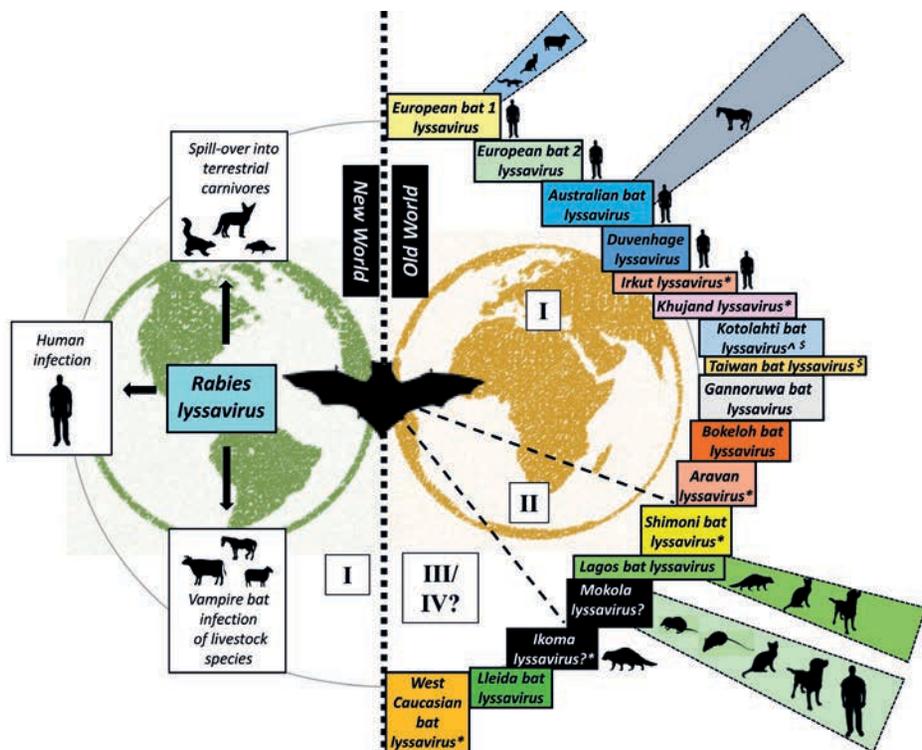
Roman numerals refer to antigenic phylogroups. Pictograms represent spillover events where reported.
* Denotes single isolation only; ^ represents no isolate available; ? No reported association with bat species; and
$ Not yet classified by ICTV within the lyssavirus genus.

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Phylogroup I contains the rabies lyssavirus (RABV), European bat-1 lyssavirus, European bat-2 lyssavirus, Bokeloh bat lyssavirus, Duvenhage lyssavirus, Australian bat lyssavirus, Aravan lyssavirus, Khujand lyssavirus and Irkut lyssavirus. Phylogroup II contains Lagos bat virus, Mokola virus and Shimoni bat virus, and phylogroup III includes West Caucasian bat lyssavirus and Ikoma lyssavirus.

A further two viruses that are likely to be classified within the lyssavirus genus have also been described. Gannoruwa bat lyssavirus was isolated from *Pteropus medius* bats in Sri Lanka and is closely related to RABV and Australian

bat lyssavirus (*15*). Further, the full genome of another novel lyssavirus, Lleida bat lyssavirus, has been characterized from a common bent-winged bat in Spain (*16*). While Gannoruwa bat lyssavirus will probably be classified into phylogroup I, Lleida bat lyssavirus is highly divergent and clusters with the phylogroup III viruses Ikoma lyssavirus and West Caucasian bat virus. Two cases of another novel lyssavirus, Taiwan bat lyssavirus, have been reported in Japanese house bats (*Pipistrellus abramus*) on Taiwan; more genetic data for this virus are required before it can be proposed as a separate lyssavirus species (*17*), and, as with Kotolahti bat lyssavirus isolated in Finland, it should be further characterized before formal classification.

The continuing identification of lyssaviruses in bats has led to the hypothesis that all lyssaviruses originated in bats. While bats have been identified as the reservoir hosts for 15 of the 17 recognized and proposed species of lyssaviruses, neither Mokola nor Ikoma lyssavirus has been detected in bat species, and their reservoir host remains to be determined (*17*).

Lyssaviruses show broad antigenic cross-reactivity at the nucleocapsid level, mainly because of sequence conservation of the N protein. Therefore, similar reagents can be used for diagnosis by immunofluorescence. The ectodomain of the G protein (which carries the main antigenic sites) is more variable, and there is cross-neutralization among lyssaviruses of the same phylogroup (amino acid identity in the ectodomain, > 74%) but not between phylogroups (amino acid identity in the ectodomain, < 62%). Experimental evidence indicates that the available vaccine strains, all of which belong to RABV species in phylogroup I, are ineffective against infection with lyssaviruses in phylogroups II and III.

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4. Pathogenesis

Most of the available information on pathogenesis is for RABV, although that of other lyssaviruses is probably similar (see *section 3*). RABV enters the body through wounds or by direct contact with mucosal surfaces; it cannot cross intact skin. RABV may replicate in muscle or other local tissues after exposure and gains access to motor endplates and motor axons to reach the central nervous system (*1–5*). Virions are carried in transport vesicles (*6*) to the central nervous system exclusively by fast retrograde transport along motor axons, with no uptake by sensory or sympathetic endings (*1–3, 5*). Viruses can also enter motor axons in peripheral nerves directly during a penetrating injury (*1, 3, 4*). In some bat variants, viral propagation may also occur via sensory nerves due to skin tropism

(3, 7, 8). The incubation period varies from 5 days to several years (usually 2–3 months; rarely more than 1 year), depending on the amount of virus in the inoculum, the density of motor endplates at the wound site and the proximity of virus entry to the central nervous system (3–5). Muscle-specific micro-RNA may contribute to this eclipse phase by suppressing viral transcription and replication in the muscle (9, 10). The estimated speed of virus migration depends on whether it moves by centripetal retrograde axonal transport or centrifugal spread. In centripetal retrograde axonal transport, migration is fast, with speeds of 5–100 mm/day or even faster, because neuronal populations of the same synaptic order located at various distances, e.g. 10 µm to 2 cm, are infected simultaneously (1, 5). Conversely, centrifugal spread is slow, as it is probably mediated by passive diffusion rather than active transport (1–3, 5).

The first rapid centripetal phase leads to wide transneuronal transfer within the central nervous system and to infection of dorsal root ganglia via their central connections with the initially infected motor neurons and spinal interneurons (1–3, 5). The virus then moves centrifugally from the central nervous system via slow anterograde axoplasmic flow in motor axons to the ventral roots and nerves and peripheral sensory axons of the infected dorsal root ganglia, leading to infection of muscle spindles, skin, hair follicles and other non-nervous tissues, such as salivary glands, heart muscle, lung and abdominal visceral organs via their sensory innervation (3–5). By the time of clinical onset of rabies, the virus is widely disseminated throughout the central nervous system and probably to extra-neural organs (11).

The first specific clinical symptom is neuropathic pain at the site of the bite. This is caused by virus replication in dorsal root ganglia and inflammation induced by cellular immunity (12). Human rabies can manifest as a spectrum of disease, from furious to paralytic manifestations, which cannot be correlated with a specific anatomical localization of RABV in the central nervous system (12–14). The major clinical signs are probably due to site-specific responses (14); functional neuronal impairment also explains coma. Electrophysiological studies with pathological correlates show that peripheral nerve axonopathy or myelinopathy is responsible for weakness in paralytic rabies (7, 12). Preferential entry via the motor route explains why subclinical anterior horn cell dysfunction precedes sensory loss in furious rabies and is initially localized at body segments corresponding to the site of the bite, progressively spreading to other locations (3, 5, 12). The same considerations apply to prodromal symptoms and signs in paralysed patients (3–5). Diffusion tensor imaging in cases of dog-mediated paralytic rabies show that neural tract integrity is compromised at the brain-stem level, limiting viral propagation to the forebrain (5, 15, 16). A viral immune evasive strategy with blood–brain barrier integrity prevents eradication of the virus in the central nervous system (4, 16–21). There is no evidence of immune suppression or accelerated neuronal death in rabies-infected patients (15, 16).

Rabies with atypical clinical and/or neuroimaging features is seen increasingly (*4, 22–26*). Whether this is due to atypical virus variants, a host immune response or large doses of virus inoculum (as in the case of organ transplantation from rabies-infected donors) is unknown. Without intensive care, death occurs within 7–10 days of the appearance of clinical symptoms (*5, 7*).

4.1   References

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5. Diagnosis

Rabies is an acute, progressive encephalitis caused by a lyssavirus. Clinical diagnosis of encephalitis can be difficult, and laboratory methods should be used to confirm a diagnosis when possible. During the past decade, significant progress has been made in laboratory methods, including clinical case confirmation by the demonstration of viral antigens, antibodies and amplicons. At a minimum, each country should have a national reference laboratory with the capacity for rabies diagnosis by currently recommended techniques (*1–3*). Where such expertise is lacking, support for training and reference diagnostic capability can be obtained from WHO collaborating centres (*section 13.1.3*), reference centres of the World Organisation for Animal Health (OIE) and FAO reference laboratories (see *section 13*).

5.1   Standard case definitions for rabies

Countries should use standard definitions for rabies, supported by laboratory-based surveillance of suspected cases in humans and animals. A suspected clinical case of rabies in humans is defined as: an acute neurological syndrome (i.e. encephalitis) dominated by forms of hyperactivity (furious rabies) or paralytic syndromes (paralytic rabies) progressing towards coma and death, usually by cardiac or respiratory failure, typically within 7–10 days of the first signs if no intensive care is instituted. These may include any of the following: aerophobia, hydrophobia, paresthesia or localized pain, dysphagia, localized

weakness, nausea or vomiting (*4*). One or more of the following laboratory criteria should be used to confirm a clinical case:

- presence of viral antigens in samples (e.g. brain tissue, skin);

- isolation of virus from samples in cell culture or in laboratory animals;

- presence of viral-specific antibodies in the cerebrospinal fluid (CSF) or serum of an unvaccinated person; and/or

- presence of viral nucleic acids in samples (e.g. brain tissue, skin, saliva, concentrated urine).

Cases of rabies are classified as:

- suspected: a case that is compatible with a clinical case definition;

- probable: a suspected case plus a reliable history of contact with a suspected, probably or confirmed rabid animal (see *Table 16* in *section 11*);

- confirmed: a suspected or probable case that is confirmed in the laboratory.

A template for recording data on possible exposure to rabies is given in *Annex 2*.

5.2   Clinical diagnosis

A presumptive diagnosis of rabies is simplified when an individual presents with a compatible illness and has documented exposure to an animal confirmed as rabid in a laboratory. Classical signs of rabies include spasms in response to tactile, auditory, visual or olfactory stimuli (e.g. aerophobia and hydrophobia) alternating with periods of lucidity, agitation, confusion and signs of autonomic dysfunction (*5*). Spasms may occur in rabid patients in whom excitation is prominent. Spontaneous inspiratory spasms can occur continuously until death, and their presence may facilitate a clinical diagnosis. Excitation is less evident in paralytic rabies, and phobic spasms may appear in only 50% of such patients. During the early stages of paralytic rabies, notable signs may include myoedema at percussion sites, usually in the region of the chest, deltoid muscle and thigh, piloerection and fasciculations.

In the absence of a history of exposure or typical symptoms, a diagnosis of rabies on clinical grounds alone may be difficult and often unreliable. Some patients can present with atypical rabies, including a paralytic or Guillain-Barré-like syndrome or other atypical features (*5*). Atypical rabies occurs quite

commonly and may contribute to misdiagnosis and under-reporting of cases. Detailed clinical information on patients with atypical rabies, especially cases associated with exposure to bats or other wildlife, has been reported (*6*).

Magnetic resonance imaging, performed with adequate precautions for potentially infectious patients, can be helpful (*5, 7*). Abnormal, ill-defined, mildly hypersignal T2 images involving the brain-stem, hippocampus, hypothalamus, deep and subcortical white matter and deep and cortical grey matter are evident, regardless of clinical type. Gadolinium enhancement may appear clearly only in later stages, when patients lapse into a coma. Such patterns can help differentiate rabies from other viral encephalitides, not in terms of location, but in the appearance of the T2 image and in the pattern of contrast enhancement, when compared with consciousness status (*7*). Computerized tomography of the brain is of little diagnostic value.

Without adequate epidemiological scrutiny and laboratory confirmation, rabies may be misdiagnosed and death ascribed to other, more common and familiar causes of encephalitis (e.g. cerebral malaria in malaria-endemic regions) (*1*). Rabies should be included in the differential diagnosis of all patients who present with unexplained, acute, progressive viral encephalitis, even in areas where the disease is rare, as it can occur locally in wildlife (such as bats, mongooses, foxes and jackals; see *section 10*), can be acquired during travel to enzootic areas, and because imported cases of human and animal rabies continue to occur *(1, 4)*. As transmission of RABV to recipients of solid organ transplants has been described, all potential organ donors who present with compatible encephalitis should be screened and tested to determine whether they present an infectious risk by examining suitable ante- or post-mortem specimens by recommended laboratory methods (*1*).

5.3   Biosafety, sampling and specimen transport for laboratory diagnosis

5.3.1   Biosafety

Rabies has the highest case fatality rate of any currently recognized infectious disease. Therefore, safety is of paramount importance when working with lyssaviruses. In general, biosafety level 2 safety practices are adequate for routine laboratory activities such as handling animals, necropsy and collection, preparation and processing of samples (*2, 3*). The basic facility design should be adequate to allow for these practices, and precautions must include personal protective equipment (e.g. clothing, gloves, eye protection) and pre-exposure rabies vaccination. Activities that may require a biosafety level 3 classification include production of large quantities of concentrated virus, procedures that

may generate aerosols (e.g. homogenization of tissue suspensions) and work with newly isolated lyssaviruses for which the effectiveness of current prophylaxis is not known. All national safety guidelines for working with infectious agents should be followed.

5.3.2   Sampling for intra-vitam diagnosis in humans

Secretions, biological fluids (such as saliva, CSF, tears, serum) and some tissues (such as skin biopsy samples, including hair follicles at the nape of the neck) can be used to diagnose rabies during life (*1, 2*). Although serum and CSF may not be very sensitive specimens for ante-mortem diagnosis, particularly in the early course of illness, a positive result provides valuable diagnostic information. The samples that afford the highest diagnostic sensitivity are at least three saliva samples, taken at intervals of 3–6 h, and skin biopsies (including hair follicles). Ideally, samples should be stored at −20 °C or less.

5.3.3   Sampling for post-mortem diagnosis in humans and animals

Brain tissue is the preferred specimen for post-mortem diagnosis in both humans and other animals (*2, 3*). In many situations, it may not be possible to remove the brain for post-mortem sampling because of factors such as family consent or practical and biosafety issues related to removal of animal brains in the field. Some of these challenges can be overcome by collecting samples with effective, well-established techniques that require less invasive post-mortem routes (*3*), such as through the orbit or foramen magnum.

A diagnostic sample can be collected without opening the skull, for example by introducing a 5-mm drinking-straw or a 2-mL disposable plastic pipette into the occipital foramen in the direction of an eye or using a trocar to make a hole in the posterior wall of the eye socket and introducing a plastic pipette or straw. Samples can be collected from the rachidian bulb, the base of the cerebellum, the hippocampus, the cortex and the medulla oblongata. When a straw is used, it should be pinched between the fingers to prevent material escaping on withdrawal.

Ideally, brain tissue should be kept refrigerated or frozen until testing. If this is not possible, samples can be preserved at ambient temperature in a 50% glycerine–saline solution. Freezing of samples in glycerine is not recommended. The glyercine must be removed by washing prior to testing, and acetone fixation is not recommended before the direct fluorescent antibody test.

Examination of chemically fixed specimens for viral antigens can be both sensitive and specific if appropriate tissues and tests are used but is not recommended for routine diagnosis. If specimens are received in formalin, the

duration of brain fixation should be approximately 7–14 days before embedding in paraffin. Wet tissue specimens should be transferred from formalin to absolute ethanol for subsequent molecular diagnosis and antigen detection.

For molecular studies and genetic characterization of viral strains, the impregnation of brain tissue or body fluid suspected of infection with RABV on filter paper containing proper inactivating chemicals allows safe, stable, cost–effective shipment of samples at ambient temperature. Effective viral inactivation should nevertheless be ensured before shipment.

5.3.4 Transport of samples

Diagnostic specimens should be frozen or refrigerated, depending on the sample type. A cold chain should be maintained after sampling, as described above. Specimens for diagnosis of rabies should be shipped according to national and international regulations to avoid exposure (*8*). Packing instructions are given in the WHO recommendations on transport of infectious substances (*8*). Information on the appropriate International Air Transport Association shipment classification can be found on the Association's website (http://www.iata.org/publications/dgr/Pages/index.aspx).

5.4 Laboratory techniques for post-mortem diagnosis of rabies in humans and animals

A definitive, reliable diagnosis of rabies can be made only by appropriate laboratory methods. The basic techniques are described in the WHO *publication Laboratory techniques in rabies* (*2*) and the OIE *Manual of diagnostic tests and vaccines for terrestrial animals* (*3*). Standard diagnostic tests for rabies are summarized in *Table 4*. Information on additional tests since the WHO publication in 1996 and the OIE Manual, including indications for and the performance of each test, is given in *Table 5*. The diagnostic tests are also described briefly in the following sections. Participation in routine quality management is strongly recommended when any of the laboratory techniques described is used (*2, 3*). An updated laboratory manual will be published by WHO in 2018.

Table 4
Standard diagnostic tests for rabies

Species (time of test)	Antigen detection		RNA detection		Virus isolation		Antibody detection	
	Sample[a]	Test[b]	Sample	Test	Sample	Test	Sample	Test
Human (ante-mortem[c])	Skin/hair follicles	FAT	**Skin/hair follicles Saliva** Tears CSF	RT-PCR[d]	Saliva Tears CSF	**RTCIT** MI	Serum CSF	**RFFIT FAVN-test** IFA ELISA
Human (post-mortem)	**Brain** Skin/hair follicles	**FAT DRI**T IHC	**Brain** Skin/hair follicles	RT-PCR	Brain	**RTCIT** MI	NA	NA
Animal (post-mortem)	Brain	**FAT DRI**T IHC	Brain	RT-PCR	Brain	**RTCIT** MI	NA	NA

Abbreviations: CSF, cerebrospinal fluid; DRIT, direct rapid immunohistochemical test; ELISA, enzyme-linked immunosorbent assay; FAT, direct fluorescent antibody test; FAVN, fluorescent antibody virus neutralization; IFA, indirect immunofluorescence; IHC, immunohistochemistry on formalin-fixed samples; MI, mouse inoculation test; NA, not applicable; RTCIT, rabies cell culture inoculation test; RT-PCR, reverse transcriptase-polymerase chain reaction

[a]   If more than one sample type is listed, the one(s) shown in bold have highest diagnostic sensitivity.

[b]   If more than one test is listed, the one(s) in bold are preferred.

[c]   Positive results in ante-mortem samples are diagnostic, but negative results do not rule out rabies.

[d]   RT-PCR may be in the conventional or real-time format.

Table 5

Rabies diagnostic tests introduced since publication of the WHO *Laboratory techniques in rabies* (2) in 1996

Test	Target	Sample type	Objective	Laboratory	Advantages	Disadvantages	Comments
Direct rapid immuno-histochemistry test (DRIT) (*10, 25*)	Viral protein (nucleo-protein)	Brain	Primary post-mortem diagnosis; enhanced surveillance	Central and local network	High sensitivity and specificity; involves light microscopy of central nervous system impressions collected from mammals with suspected rabies; rapid; suitable for surveillance under field conditions; requires biotin-labelled monoclonal or poly-clonal antibodies either from OIE or WHO reference laboratories or self-produced	Requires basic laboratory equipment, reagents and training. No commercial products available	Under consideration as another equal OIE-recommended primary post-mortem diagnostic test; broad choice of antibodies allows detection of all known lyssaviruses; in routine use in North America for enhanced surveillance of wildlife rabies in oral vaccination programmes
Indirect rapid immuno-histochemistry test (IRIT) (*17, 26*)	Viral protein	Brain	Antigenic typing of confirmed cases	Central reference and local network	Provides confirmation of canine RABV identity by mAb typing under light microscopy; such panels are widely available from the WHO collaborating centres	As above	Typing of antigenic variants has been widespread throughout Latin America in dog-mediated rabies elimination programmes

Test	Target	Sample type	Objective	Laboratory	Advantages	Disadvantages	Comments
Immuno-chroma-tographic test for RABV detection (i.e. lateral flow devices) (12, 14)	Viral protein (nucleo-protein)	Brain	Screening for RABV in domestic and wild animals	Central and local network	Low technological requirement; low containment requirement; can be use at point of sampling; suitable for surveillance under field conditions	Much better standardization and quality control of some kits required	Cannot substitute for currently recommended reference techniques but may be helpful in countries where surveillance is lacking
RT-PCR (conventional and real-time) (16, 27, 28)	Viral RNA	Ante-mortem (e.g. saliva, nuchal skin, CSF, tears, corneal wash) and post-mortem tissues (e.g. central nervous system)	Primary diagnosis; viral variant typing	Central reference laboratory	High sensitivity and specificity; ante-mortem diagnosis of human rabies to confirm clinical diagnosis and patient management, institution of barrier nursing and PEP to close contacts; can also be used for post-mortem confirmation in brain tissue (human or animal); amplified material can be sequenced for further virus characterization.	High technological requirement; sensitivity depends on the type of specimen collected; ~100% with nuchal skin biopsy and at least three saliva samples; if these requirements are not fulfilled, a negative test result does NOT rule out a diagnosis of rabies; stringent quality assurance and ideal preservation of the sample are required.	Obtaining brain tissue continues to be a challenge in human rabies diagnosis; therefore, such tests may be the only feasible ones, especially for ante-mortem testing

Test	Target	Sample type	Objective	Labora-tory	Advantages	Disadvantages	Comments
Competi-tive ELISA (kits) (29, 30)	Host antibody (animal)	Serum; sera adsorbed on filter paper; muscle extract	Detection and quan-tification of RABV antibodies; measure-ment of antibody response to vac-cination; sero-sur-veillance	Central and local network	Good repeatability be-tween laboratories; con-trolled supplier; internal controls; not species-specific; easy, rapid collection directly in the field without the need for needles, syringes or vacutainer tubes	Requires some basic laboratory equipment; may require additional validation steps [a]	Currently available kit is validated for meas-urement of antibody response to dog vaccina-tion and wildlife oral rabies vaccination, not for human antibodies
Indirect ELISA (kits) (23)	Host antibody (human, animal)	Serum, plasma	Detection and quan-tification of RABV antibodies; measure-ment of antibody response to vac-cination; sero-sur-veillance	Central and local network	ood repeatability between laboratories; controlled supplier; internal controls	Requires some basic laboratory equipment; may not be useful for all species; may require additional validation steps;[a] may detect only certain isotypes (e.g. IgG) of RABV antibod-ies	May be useful for confirming immune response in exposed per-sonnel or during PEP in immune-compromised patients or when major deviations from recom-mended PEP schedules occur; can be used in serosurveys

Test	Target	Sample type	Objective	Labora-tory	Advantages	Disadvantages	Comments
Immuno-chroma-tographic test for RABV antibod-ies (i.e. lateral flow devices) (*31*)	Host antibody (animal)	Serum	Screening for RABV antibod-ies, e.g. response to vac-cination; sero-sur-veillance	Central and local network	Low technological requirement; low con-tainment requirement; can be use at point of sampling	Screening test only for determination of hu-moral immune response to rabies vaccination	Useful in dog-mediated rabies vaccination campaigns or local vaccination clinics in areas where equipment required for RFFIT, FAVN or ELISA is not available

a Correlation with neutralizing antibody levels may depend on homology between the kit antigens and the RABV vaccine strain, as well as host genetics. Determination of appropriate cut-off levels requires validation for the purpose of testing.

5.4.1   Viral antigen detection

The fluorescent antibody test (FAT) is a rapid, sensitive, specific method for diagnosing rabies in animals and humans (*2, 3, 9*) and is the gold standard for diagnosis. The accuracy of the test depends, however, on variables such as the expertise of the examiner, the quality of the anti-rabies conjugate and functional equipment, including the fluorescence microscope, and the quality of the sample. The test is based on microscopic examination of impressions or smears of brain tissue after incubation with anti-rabies polyclonal globulin or broadly cross-reactive mAbs conjugated with fluorescein isothiocyanate. The diagnostic conjugate should be of high quality, and the appropriate working dilution for optimal performance and detection of virus-specific antigens should be determined. Impressions (or smears) of samples from the brain-stem and/or cerebellum are recommended to ensure high sensitivity of the test. The hippocampi (Ammon's horns) may also be included but are not necessary for a definitive diagnosis.

Other methods for the detection of lyssavirus antigens, such as enzyme-linked immunosorbent assays (ELISAs) and the direct rapid immunohistochemistry test (DRIT), have provided consistently reproducible results in multiple laboratories. Extensive evaluation of DRIT has shown that its sensitivity and specificity are comparable to those of the FAT (*10, 25*). The DRIT allows rapid on-site testing by light microscopy and should facilitate decentralized epidemiological surveys, especially if the reagents become commercially available. The Consultation recommends the DRIT as an alternative to the FAT for improved, decentralized, laboratory-based surveillance.

Typical intracytoplasmic inclusions in formalin-fixed brain tissue can be detected in neurons by validated immunohistochemical methods (*11*); however, formalin fixation of brain tissue is not a suitable method for routine diagnosis, because it delays the test results and is less sensitive than the FAT or DRIT.

Lateral flow tests have been developed for rapid detection of RABV antigens under field conditions, and some show good results (*12–14*), although adequate validation according to international standards is still required (*2, 13*). Nevertheless, such tests may be useful in surveillance in situations in which shipment of samples to laboratories is difficult or laboratory diagnostic facilities are lacking; it may also improve the engagement of front-line staff in rabies surveillance.

5.4.2   Virus isolation

Virus might have to be isolated to confirm the results of antigen detection tests and for further amplification or characterization of an isolate (*2*). Lyssaviruses

can be isolated in cell cultures, such as neuroblastoma cells, or by intracranial inoculation into suckling mice. Virus isolation in animals should be replaced by alternative methods, whenever possible. Murine neuroblastoma cells (e.g. NA C1300) are more susceptible to field isolates of lyssavirus than other cell lines tested (*2*). Virus isolation in neuroblastoma cell culture is at least as efficient as animal inoculation, especially for small quantities of virus. Cell culture isolation also reduces the time required for diagnosis, from 10–21 days with the mouse inoculation test to only 2–4 days. If the conditions are not optimal, however, such as decomposed brain, false-negative results may be obtained. When cell culture facilities or molecular methods are not available, animal inoculation can be used. If a rapid answer is required, suckling mice (< 3 days old) are preferred to weanling or adult mice, because they are more susceptible than older animals. The observation period may be shortened by inoculation of sufficient mice to enable sequential killing and examination of brains by the FAT, starting 4 days post-inoculation (*15*).

5.4.3 Viral RNA detection

Molecular methods, such as the reverse transcription polymerase chain reaction (RT-PCR) and other amplification techniques, play an increasingly important role in many countries (*16, 17*). If brain tissue is available, the FAT or DRIT should be used for primary diagnosis of viral antigens (*2*). Molecular techniques can be used for confirmatory testing and epidemiological surveys in laboratories with strict quality control procedures and with experience and expertise in using such techniques. They can also be used for ante-mortem diagnosis in humans. Use of robust positive or in-process controls is strongly recommended.

5.5 Techniques for ante-mortem diagnosis of rabies in humans

Many laboratory methods can be used to confirm a clinical case of rabies while the patient is still alive (*1*); however, use of ante-mortem techniques for the diagnosis of rabies in animals is strongly discouraged. The sensitivity of a technique for diagnosing rabies varies widely according to the stage of the disease, immunological status, intermittent viral excretion and the training of the technical staff. While a positive, validated result is indicative of rabies, a negative result does not necessarily rule out the infection.

A diagnosis of rabies in a patient suspected of having the disease is valuable for multiple reasons, including: specific characterization of the causative agent and of the potential source of infection, especially when a history of exposure

to an animal is lacking; identification of other people who may have been exposed to the same animal during the public health investigation; application of appropriate measures for infection control to prevent exposure from contact with the patient; administration of PEP to people exposed to the patient's infectious secretions; case closure and grief counselling with family members; consideration of experimental therapeutic options; monitoring of viral loads and patient response if treatment is given; less invasive techniques for documenting the human burden of disease, given the infrequency of autopsies; and indication of another infectious agent if the test results are negative.

5.5.1   Viral antigen detection

Viral antigens can be detected with the FAT in skin biopsy samples or hair follicles from patients with clinical rabies (*18*). The results are independent of the antibody status of the patient, and specimens may be positive during the early phase of the disease. Skin samples are usually taken from the nuchal area of the neck, with hair follicles containing peripheral nerves. Examination of several sections may be required to detect viral antigens around the base of hair follicles. The quality of the samples is of paramount importance, as the absence of follicles decreases the sensitivity of the test. This technique may not be practicable in all settings, because a cryostat is required to prepare frozen sections of skin; detection of viral RNA may be preferable if equipment is lacking (*16, 27, 28*). The FAT of corneal impressions is rarely reliable in most clinical settings, and it is not recommended as a routine test because of the risk of corneal scarification, particularly in patients with causes of encephalitis other than rabies. Immunochromatographic methods have been developed to detect RABV antigens directly in brain tissue from animals (*12*), but they require standardization and stringent quality control before their application in human ante-mortem diagnosis.

5.5.2   Viral antibody detection

Given the pathogenesis of the virus, it is difficult to use serological tests in ante-mortem diagnosis of rabies in humans, as RABV-specific antibodies may be present in serum and CSF only during the late stage of human infection.

Virus neutralizing antibodies in the serum of unvaccinated patients or in CSF can be measured with a virus neutralization test, such as the rapid fluorescent focus inhibition test (RFFIT) and the fluorescent antibody virus neutralization (FAVN) test (*19*). The sensitivity of such assays for ante-mortem diagnosis is, however, low, as virus neutralizing antibodies tend to appear only, on average, 7–8 days after clinical symptoms first appear. Viral antibodies are infrequently found in CSF, depending in part on the clinical stage of the disease. Antibody (IgG subclass) titres against RABV G protein measured by qualified ELISA have

been shown to correlate well with those measured by virus neutralization, and ELISA is easier to perform routinely (*20, 21*). ELISAs will not, however, detect IgM rabies-specific antibodies that are first produced upon exposure. Rapid detection of antibodies (IgG and IgM) to other viral antigens, (e.g. nucleoprotein) may also be useful, as they may appear before neutralizing antibodies (*4*).

5.5.3   Viral RNA detection

Molecular detection methods are highly sensitive for rabies diagnosis (*1, 2*). As with all laboratory methods, they require standardization and stringent quality control. Lyssavirus RNA can be detected and amplified from many biological fluids and tissue samples (e.g. saliva, CSF, tears, skin, concentrated urine and hair follicles). Serial samples should be tested, as the virus is excreted intermittently. The highest sensitivity is seen with skin biopsies (including hair follicles) and saliva.

5.5.4   Virus isolation

In ante-mortem diagnosis, isolation of virus from saliva or other biological samples is ideal for obtaining an unequivocal diagnosis and virus characterization (*1–3*). The success rate depends in part on the immunological status of the patient (virus is more likely to be isolated from people without antibodies), the intermittence of viral excretion and the number of consecutive passages in cell culture. Specimens may contain no infectious virus even during the late stage of the disease. Liquid specimens or swabs should be frozen after collection, the content of the swab having been expelled into the collection medium. Under no circumstances should preservatives be added to the collection medium.

5.6   Measuring antibody response to rabies vaccination in humans

The RFFIT virus neutralization assay and the FAVN test are recommended for measuring post-vaccination immune responses and for determining whether booster vaccination is necessary, because they have been correlated with protection in animal studies (*19, 22*). Virus neutralization assays are used to determine the level of protective antibodies in immunocompromised patients, in evaluating new vaccines or vaccination schedules and for deciding whether to give boost vaccination when the neutralizing antibody level is critical on the basis of individual risk factors.

ELISAs can be useful for routine screening to determine whether an immune response developed after pre- or post-exposure vaccination, as they are easy to perform (*21*). Measurement of binding antibodies with an ELISA and measurement of neutralizing antibodies with a RFFIT or an FAVN test are

inherently different, and the results should be interpreted with this understanding (*23*). Post-vaccination antibody (IgG subclass) titres against RABV glycoprotein measured by qualified ELISA have been shown to correlate well with those measured by virus neutralization (*21*). Before a commercially available kit is used, its performance characteristics (i.e. appropriate cut-off level, sensitivity and specificity) should be evaluated under local conditions (*23*). The limitations of kits, such as species specificity, immunoglobulin class detected and linear range, should be considered and evaluated in respect of the purpose of the monitoring programme (*22*).

Participation in quality assurance and proficiency programmes is recommended to ensure the validity of the results from laboratories that perform rabies serology by the RFFIT, the FAVN test or ELISA.

5.7 Measuring antibody response to rabies vaccination in animals

The RFFIT, FAVN test and qualified ELISAs can be used to measure post-vaccination immune responses in animals (*19, 22*). This is important when there is any uncertainty about the quality of the vaccine, vaccine storage (e.g. maintenance of the cold chain) or the effectiveness of vaccine delivery. Post-vaccination samples should be tested at the time, or close to the time, at which peak titres are expected (approximately 4 weeks post-vaccination). Serological results from samples collected after this time may be difficult to interpret, as antibody titres can wane rapidly even though animals are still protected against infection. As a result of the variable and potentially rapid rate of decline in antibody, serosurveys conducted more than 4 weeks after vaccination are not recommended for monitoring post-vaccination coverage or population immunity (*19, 24*). The RFFIT (*32*) and FAVN (*19*) assays are recommended for the purposes of international animal movement and trade (*3*). Both virus neutralization (e.g. RFFIT, FAVN test) and ELISA are suitable for monitoring the antibody response of vaccinated animals in the framework of rabies control.

ELISAs are available in kit format and may be indirect or competitive. Use of an ELISA is acceptable after qualification of the assay for the purpose of testing. As mentioned above, before a commercially available kit is used, its performance characteristics should be evaluated under local conditions. .

5.8 Virus identification with molecular techniques: epidemiological considerations

Thousands of lyssavirus isolates from humans, domestic animals and wildlife have been characterized with antigenic and molecular techniques, resulting in basic identification and classification of lyssaviruses and the

demonstration that virus isolates from a given geographical area or species have unique genetic sequences. In most cases, these differences can be used to identify the principal animal reservoir (e.g. bat, dog, fox, mongoose) and to infer the source of infection when a definitive history of exposure is lacking (*1, 2*).

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6.   Management of patients before and after death

6.1   Management of patients with rabies

Rabies is considered an overwhelmingly fatal disease, with tens of thousands of rabies deaths each year and only a few documented survivors. Worldwide, a probably underestimated 59 000 patients die of suspected or confirmed rabies each year (*1*). The vast majority of these deaths occur in poor, rural communities in Asia and Africa, where there is a high incidence of dog-mediated rabies and where people may find difficulty in accessing timely, affordable, adequate PEP.

Most of these patients are managed, at least initially, in peripheral or even village health centres, where human and material resources for basic wound care and rabies prevention are often extremely limited or absent. There is no effective curative treatment for rabies once clinical signs have appeared. Almost all patients with rabies will die.

An algorithm to guide management of human cases of confirmed or suspects rabies is proposed in *Fig. 3*.

Figure 3
Proposed algorithm to guide management of cases of confirmed or suspected human rabies
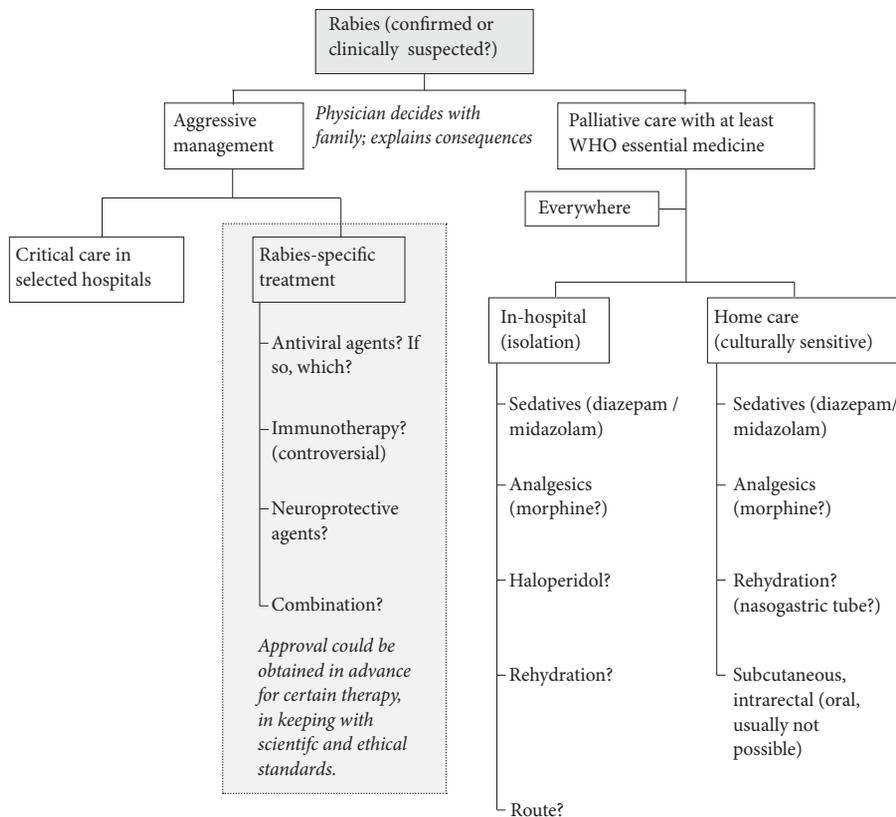
From references *2–5*

6.2   Palliative management of patients with rabies

Most patients with rabies remain conscious and are aware of the nature and outcome of their illness. They are usually extremely agitated, particularly when excitation predominates ("furious" rabies). Furthermore, they are often isolated, when possible, because of the perceived risk of transmission of RABV through contact. Unfortunately, in some countries, many rabies patients are turned away from hospitals and receive terminal care only from their families. Hospital care for patients with clinical rabies is advisable when possible, in order to reduce their suffering and ensure that they receive adequate, respectful palliative care.

Although almost all patients will die, health care providers still have an essential role to play in providing prompt, effective, holistic, compassionate, culturally sensitive management. This can be done even with extremely limited equipment and drugs (*4*). In view of the inevitability of death in most cases, treatment should be focused on comfort, with heavy sedation (barbiturates, morphine) and avoidance of intubation or life-support measures, especially once the diagnosis is certain (*1*).

The majority of patients with rabies are not candidates for aggressive therapy in a critical care unit (see *section 6.4*). Palliative care of these patients, whether in a hospital or at home, must be integral to all guidelines on rabies prevention and management. Palliative care should be accessible to patients with rabies (and other terminal illnesses) in every health care setting, and health care providers must be trained to deliver effective palliation. Some resources and a WHO guide for palliative care (including essential drugs) are available on WHO's webpage on palliative care (*6*).

Patients with confirmed rabies should receive adequate hydration, sedation and care in an appropriate medical facility, preferably in a calm, draft-free, quiet room, with suitable emotional and physical support (*4, 7*). The privacy, dignity and cultural needs of patients should be respected. Preserving the capacity of the family to communicate with patients in their dying moments must be a priority. The diagnosis should be discussed with the family as soon as possible after it has been made.

Benzodiazepines such as diazepam are effective for sedation and muscle relaxation and can be given subcutaneously, intravenously or rectally. Lorazepam and midazolam are alternative benzodiazepines. Morphine may be administered for analgesia subcutaneously or intravenously, but it is often difficult to access in very peripheral centres. The major tranquilizer haloperidol has been recommended for restlessness, agitation, hallucination and aggression (*8*), but some physicians avoid its use because of its adverse effects and because sedation is less easily controlled than with other drugs. Excessive salivation can be treated with anticholinergic agents such as scopolamine. Drugs should be titrated to avoid excessive sedation requiring intubation.

Repeated intravenous or subcutaneous morphine or benzodiazepines are effective in relieving the severe agitation, anxiety and muscular spasms that afflict patients with furious rabies (*1*). Once furious rabies has been diagnosed, invasive procedures should be avoided.

Palliative care for patients with rabies is best delivered in a hospital, with intravenous drug delivery to minimize disturbance and distress. Rabies is not a contagious disease that is likely to cause an outbreak during patient care, and human–human transmission has been documented only in exceptional circumstances, such as organ transplantation (see *section 8.3.2*). When patients with rabies and/or their families request discharge or refuse admission (e.g. for cultural or religious reasons), health care teams should consider ambulatory palliation (medication and personal protective equipment). If transport is required, non-intravenous administration or medication that can be continued by routes other than parenteral (including through a nasogastric tube or intrarectally) might be preferred. A requirement for transport may be an additional reason for the health care team to initially prefer lighter sedation (*4*).

6.3   Recommendations for health care personnel and family members of patients with rabies

Most patients with rabies die, and families that seek care should be informed and counselled to receive the news of the patient's impending death. Care of people in whom rabies is diagnosed may cause anxiety among medical and nursing staff, relatives and friends providing non-medical care and in the media and the public. Human rabies does not pose a risk to health care staff if routine precautions are taken, especially during intubation and suctioning.

PEP should be provided for health care personnel considered to be at risk, after careful assessment, and they should be reminded of the importance of adhering to barrier nursing and wearing personal protective equipment (standard precautions, including wearing gloves, glasses and mask in case a procedure generates splashes), as recommended for all infectious diseases. Hospitals that are likely to receive rabies patients can consider PrEP for health care staff who may be involved in their management (see *section 8.2*).

PEP may sometimes be necessary for the partners of patients, as close contact and sexual intercourse in the early stages of the disease pose a hypothetical risk for transmission (infectious RABV is present in saliva); however, no reports have clearly established human-to-human transmission.

People exposed to the same biting animal should be identified and should receive adequate PEP. The pathobiology and epidemiology of RABV indicate that the risk of an infant contracting rabies from breastmilk is similar to that of drinking milk from a rabid animal: it does not pose a relevant public health risk (see *section 8.3.2*).

6.4 Survivors of rabies and "aggressive" treatment protocols

Survival has been well-documented in at least 15 cases (*9*). In all but one case, the survivors received one or more doses of rabies vaccine before the onset of clinical rabies. Survivors of rabies have an immune response associated with development of neutralizing anti-RABV antibodies in the serum and CSF.

Current "aggressive" protocols, such as the Milwaukee protocol (*11*), do not reliably result in survival without severe sequelae. In exceptional cases, aggressive management may be considered. It should be undertaken in reference centres with well-trained teams who have experience or have conferred with experts in managing patients with rabies, using ethically pre-accepted protocols, after discussion with the family and a collegial decision, and only after other life-threatening but curable diseases (differential diagnoses for rabies encephalitis) have been ruled out.

6.4.1 Intensive care (symptomatic treatment)

The first documented survivor of rabies, reported in 1969, received only intensive care without intubation (*10*). Since successful treatment in 2004 of an adolescent in the USA, a treatment approach known as the Milwaukee protocol (*11*) has been used several times, with no well-documented success to date (*12*). In the past few years, six well-documented cases of survival (albeit with severe neurological deficits) have been reported in India (*13, 14*), and survival for several weeks after the onset of symptoms is increasingly being documented. This may be attributed to greater awareness of rabies and better access to critical care facilities in countries endemic for rabies.

An aggressive clinical management approach is associated, however, with a high risk of failure and is difficult to apply, especially in resource-limited settings. Therefore, only a small minority of patients with rabies who remain alert or have a mildly depressed sensorium may be considered candidates for an aggressive approach. Whether it can be applied is determined essentially by timely access to adequate resources, including critical care facilities and a competent team (*3*). Several patients who had early development of serum and CSF antibodies but no demonstrable virus or viral RNA (suggesting the virus had been cleared from the system) survived after receiving intensive care but remained in a vegetative state. These factors are, however, highly unreliable for predicting outcome (*1, 15*).

In considering use of a possible "aggressive" treatment modality for a patient with rabies, the following should be kept in mind (*1*):

- Rabies is almost invariably fatal, but a very small number of people have recovered, albeit with severe sequelae in the majority of cases, which will probably have a terrible, long-lasting impact on the patients and their families and carers.

- Most survivors, with or without treatment, had a vigorous early immune response. Although cases due to bat virus more frequently developed antibodies in serum and/or CSF, this was not the true in dog-mediated rabies cases. Most of the cases due to bat virus did not survive.

- At present, it is not possible to predict reliably which patients are likely to recover.

- Carefully planned and validated studies conducted in an ethical manner to identify management protocols, procedures for immunomodulation and new medications, including antiviral drugs, are encouraged.

- Treatment of human rabies must be reasonably considered to be safe and not further harm the patient.

6.4.2 Rabies-specific treatment

Agents that promote the entry of drugs, antibodies and immune effector cells across the blood–brain and blood–spinal cord barriers, which remain intact during the non-comatose phase (*1*), and agents that clear virus from non-neural organs (especially the heart) may be useful. Research is under way on antiviral agents that are effective against rabies, but they must be proven to be reasonably safe and not cause further harm (*17–19*). An approved drug for use in humans against RNA virus infections in general has become available and may be of benefit in some cases of rabies (*20, 21*). In any event, salvage treatment protocols should be delineated and submitted to ethical boards for approval before clinical teams use them in patients.

6.5   Management of the bodies of patients who have died of rabies

The body of a patient suspected to have died of rabies should be labelled as infectious but not as "contagious" (no airborne or droplet transmission). The risk of transmission to others is extremely low if standard precautions are observed (*22*). Blood does not contain RABV, but the virus is present in many other tissues and fluids, such as those of the central nervous system and salivary glands (*1*). If embalming or autopsy is performed, it should be undertaken carefully, with appropriate precautions and personal protective equipment. Tissues and body fluids should be disposed of in the same manner as for other infectious diseases. The body of the deceased should be allowed to be buried or cremated, depending on their religious practice.

6.6   Transmission via organ transplantation

RABV is present in many tissues in the terminal stages of disease, and caution should be exercised before transplanting organs from people who have died with neurological symptoms and signs of rabies. Several cases of rabies due to organ and tissue transplantation have been documented (*23–25*). Testing for common or highly fatal infections should be balanced against the urgency of transplanting a viable organ. Corneal transplantation, which is common in developing countries, should not be performed without ruling out whether the deceased could have died from rabies.

6.7   References

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7.   Vaccines and rabies immunoglobulins for humans

Since their development more than four decades ago, concentrated, purified cell culture and embryonated egg-based rabies vaccines (jointly referred to as CCEEVs) have proved to be safe and effective in preventing rabies. These vaccines are intended for both PrEP and PEP and have been administered to millions of people worldwide (*1*). Prompt administration of CCEEVs after exposure, combined with proper wound management and simultaneous administration of rabies immunoglobulins where indicated, is almost invariably effective in preventing rabies, even after high-risk exposure (*1*) (see *section 8*).

7.1   Vaccine types

Human rabies vaccines include:

- cell culture vaccines: purified chicken embryo vaccine, purified Vero cell rabies vaccine and human diploid cell vaccine (see *section 7.1.1*);

- duck embryo vaccine (see *section 7.1.1*); and

■ nerve tissue vaccines (see *section 7.1.2*). WHO recommends discontinuation of nerve tissue vaccines, because they induce severe adverse reactions and are less immunogenic than other vaccines

Currently, three human rabies vaccines are WHO prequalified: Rabavert® and Rabipur® produced by GSK and Verorab® (cell culture vaccine) produced by Sanofi Pasteur. Two additional rabies vaccines are being assessed for WHO prequalification.

7.1.1 Rabies vaccines based on cell culture and embryonated eggs

CCEEVs are produced by propagating RABV in cell substrates such as human diploid cells, Vero cells, primary chick or duck embryo cells or embryonated duck eggs. *Annex 3* gives an overview of currently available human rabies vaccines and their producers.

After growth in cell culture (or embryonic egg), the viral harvest is concentrated, purified, inactivated and lyophilized. In some CCEEVs, human albumin or processed gelatine is used as a stabilizer. Human rabies vaccines are not supplied in multidose vials for intramuscular or intradermal injection, and those prequalified by WHO do not contain preservatives such as thiomersal. The shelf-life of these vaccines is ≥ 3 years, provided they are stored at 2–8 °C and protected from sunlight. After reconstitution with sterile diluent, the vaccines should be used immediately or within 6 h if kept at + 2–8 °C (*2*), as partially used vials of rabies vaccine may become contaminated.

Rabies vaccines for humans should meet WHO recommendations for characterization, production and control, as set out by the WHO Expert Committee on Biological Standardization (*3*). The current WHO recommendations apply only to inactivated rabies vaccines produced in cell culture or embryonated eggs.

7.1.2 Nerve tissue vaccines

Nerve tissue vaccines induce more severe adverse reactions and are less immunogenic than CCEEVs. WHO strongly recommends discontinuation of the production and use of nerve tissue vaccines and their replacement by CCEEVs. Nerve tissue vaccines are now produced for human use only in Algeria, Argentina, Bolivia and Ethiopia.

The Consultation again strongly recommends that production and administration of vaccines based on animal central nervous systems, including suckling mouse brain, be discontinued and replaced by CCEEVs. A four-step strategy for replacing nervous tissue vaccine by modern rabies vaccines produced on cell culture or embryonated eggs has been prepared (*4*) and is attached as *Annex 4* to this report.

7.2 WHO prequalification of human rabies vaccines

Vaccines supplied through United Nations agencies should be prequalified by WHO. Prequalification ensures the quality, safety and efficacy of vaccines and their suitability for use in national immunization programmes in low- and middle-income countries. Prequalification is an established procedure, initiated voluntarily by vaccine manufacturers, for initial and continuous evaluation by WHO of nationally licensed vaccines. After initial prequalification, products are reassessed at regular intervals to ensure continuing quality.

A vaccine must be licensed in its country of manufacture as a prerequisite to prequalification. The vaccine characteristics must be suitable for use in national immunization programmes with regard to potency, thermostability, presentation, labelling and cold chain volume. The producer must also meet international standards of quality and good manufacturing practice. Prequalification involves a review of the production process and quality control procedures, testing the consistency of lots, a WHO audit of the manufacturing facilities with observers from the responsible national regulatory authority, assurance of continued acceptability and reassessment at regular intervals. Continued compliance is monitored. Three rabies vaccines are prequalified for intramuscular use: purified Vero cell rabies vaccine, purified chick embryo cell vaccine and purified duck embryo vaccine. A list of WHO prequalified vaccines is available online (https://extranet.who.int/gavi/PQ_Web/).

The Consultation encourages rabies vaccine manufacturers to enter the WHO prequalification process and Member States to purchase WHO prequalified vaccines.

7.3 Requirements for human rabies vaccines

7.3.1 Potency requirements, tests and standards

The minimal acceptable potency of CCEEVs is 2.5 IU per intramuscular dose, as determined in the mouse protection potency test (5). Work is under way on alternative assays based on serum neutralization (6, 7–9) and assays based on fewer animals (10), peripheral challenge (11) and others (12). The efficacy of these alternative tests should be established in multicentre studies conducted by WHO collaborating centres, national regulatory authorities and control laboratories, in collaboration with manufacturers.

There is currently no evidence that the recommendation of a potency of 2.5 IU per intramuscular dose and a volume of 0.1 mL per intradermal dose (corresponding to a potency of ≥ 0.25 IU per dose) (see *sections 9.3.3* and *9.3.4*) should be revised. Standards for vaccines and immunoglobulins can be found at: http://www.nibsc.org/search.aspx?cx=004532883405257870201:nbpiibbtndm&cof=FORID%3A10&ie=UTF-8&q=rabies&sa=Search&filter=0.

The international standard for rabies vaccine is used in standardizing the mouse protection test and in vitro assays for G protein content. In 2008, a candidate vaccine was calibrated against the fifth international standard in a collaborative study and became the sixth international standard for rabies vaccine. When used in mouse protection tests, this standard contains 8 IU per ampoule, i.e. 8 IU/mL, when reconstituted in 1 mL of distilled water. Other units are used in in vitro assays, such as enzyme immunoassays and single radial immunodiffusion tests, to determine the RABV G protein antigen content (*13*).

7.3.2 Characterization and evaluation of rabies vaccines

More than a dozen species or genotypes of *Lyssavirus* have been described as causative agents of rabies (see *section 3*). Lyssavirus genomes vary considerably, RABV being by far the most common causative virus for human rabies and the only virus used to date in vaccines. Current vaccines may not protect against lyssaviruses other than those in phylogroup I (see *section 3*). The virus strains used in vaccines should be carefully selected, and the antigenic identity of the virus strains and the identity and purity of the cell lines used for production should be evaluated periodically. Comprehensive genetic characterization by full genome sequencing of vaccine virus strains is recommended.

General principles for nonclinical and clinical evaluation of inactivated rabies vaccines have been published by WHO (*3*). Preclinical testing is a prerequisite for the initiation of clinical trials in humans and includes immunogenicity studies (proof of concept) and safety testing in animals. Clinical development of rabies vaccines should include evaluation of their use for PrEP and PEP, with various vaccination schedules and routes of administration, the onset, extent and duration of protection and the requirement for and timing of booster vaccination. Clinical trials should adhere to the principles described in WHO guidelines for good clinical practice (*14*) and to those for the design, conduct and analysis of vaccine clinical trials, described in WHO guidelines for clinical evaluation of vaccines (*3*). All clinical trials should be approved by the relevant national regulatory authority.

7.4 Routes of vaccine administration

Current rabies vaccines are produced as individual doses for intramuscular injection. CCEEVs reconstituted with 0.5 or 1 mL of diluent in one intramuscular dose vial with a potency of $\geq$ 2.5 IU per dose can be used for both PrEP and PEP.

The cost of cell culture-based vaccines for intramuscular administration limits their widespread use in many areas where rabies is present. WHO promotes the use of intradermal administration of these vaccines as a safe, immunogenic and cost- and dose-sparing alternative to intramuscular administration. Only one or two vials of vaccine are required to complete a full course of PEP by the

intradermal route, thereby reducing the volume used and the direct cost of vaccine by 60–80% in comparison with standard intramuscular injection (*15*). There is no evidence that vaccines administered intradermally are more potent than those recommended for intramuscular administration (*16*). Intradermal vaccination results in an equivalent immune response at a lower dose, thus sparing vaccine in PrEP and PEP. Appropriate training should be given to ensure full intradermal instillation of the vaccine and to avoid accidental subcutaneous injection. Both routes induce rapid recall responses upon booster immunization.

Once opened, vials should be stored at +2 ºC to a maximum of + 8 ºC for no longer than 6–8 h. Rather than discarding vaccine after this time, any remaining vaccine in a vial could be used for PrEP, particularly for professionals active in animal disease control or for staff at health facilities who regularly attend to clinical rabies patients (see *section 8.2*). Scheduling follow-up PrEP visits for patients within similar periods may help to minimize wastage. Nevertheless, intradermal administration remains cost–effective in all cases for both PrEP and PEP (*15*).

Vaccine manufacturers should provide clinical evidence that new products are also immunogenic, effective and safe when given intradermally and include suitability for intradermal vaccination on the product label. The administration should adhere to WHO guidance for all routes specified and to standards approved by national health authorities. In particular, the vaccine should be compared with a vaccine of known immunogenicity, efficacy and safety, be tested serologically with a FAVN test (see *section 5*) and the results published in an international, peer-reviewed journal.

In countries in which intradermal administration is an approved route for PrEP or PEP, manufacturers of vaccines proven to be safe and effective when given by this route should register their product for intradermal use and state in the product insert that their vaccine can be used intradermally. Countries are encouraged to make national regulatory amendments to allow cost-saving intradermal administration of rabies vaccines.

7.5   Adverse events after active immunization

In general, CCEEVs are safe and well tolerated. Adverse events may occur, however, depending in part on the purity of the inactivated RABV, which may vary among batches (*17*). In 35–45% of vaccinated people, minor, transient erythema, pain or swelling occurs at the site of injection, particularly after intradermal administration of a booster. Mild systemic adverse events, such as transient fever, headache, dizziness and gastrointestinal symptoms, have been observed in 5–15% of vaccinated people. Serious adverse events are rare; they include Guillen-Barré syndrome and allergic reactions (*18*).

True vaccine failures are extremely rare when high-quality CCEEVs are used in conjunction with prompt, proper wound care, adherence to the cold chain and compliance with vaccination schedules. Delay in seeking treatment, improper wound care, unnoticed wounds, direct nerve inoculation and lack of patient compliance with vaccination schedules, among other factors (e.g. vaccine and cold chain quality), may, however, contribute to treatment failure and subsequent death (*19*). Treatment failure and death have also been reported after use of non-WHO prequalified vaccines and vaccines that do not have their stated efficacy (i.e. "fake" vaccines).

7.6   Duration of immunity

CCEEVs establish immunological memory that is assumed to persist for the life of the individual, even after titres of neutralizing antibodies decrease or are no longer measurable. Clinical data confirm that vaccinated people respond to booster immunization within 7 days (*20–22*), even if the initial course of PrEP or PEP was administered decades previously and regardless of the route of priming or booster immunization (intramuscular or intradermal) and the presence or absence of detectable titres of RABV-specific antibodies at the time of the booster. In addition, published data indicate that periodic booster doses of vaccine are not required after primary rabies vaccination (*23*), except as an additional precaution for people whose occupation puts them at continual or frequent risk of exposure (see *section 8.2*). Nevertheless, all vaccinated individuals subsequently exposed to rabies, according to the WHO definition of exposure, should receive an abbreviated course of PEP, as specified in *section 8*.

7.7   Failure of rabies vaccine and of full post-exposure prophylaxis

Failure of PEP, that is, when a patient dies despite having received the correct protocol in a timely manner, are extremely rare among the estimated 20 million people who receive PEP each year. The few PEP failures that have been reported all occurred in developing countries and almost all involved one or more deviations from the WHO-recommended prophylaxis protocol (*19*). The main deviations from the recommended protocol that lead to death are: delay in seeking rabies prophylaxis; lack of or improper administration of rabies immunoglobulin (e.g. failure to inject all bite sites); lack of or improper primary wound care; and/or poor-quality rabies vaccine (*24*).

7.8   Rabies immunoglobulins

People with category III exposure who have not received at least two doses of PrEP or PEP and severely immunocompromised people with category II exposure (e.g. AIDS patients or transplant recipients) should receive

both an effective rabies vaccine and rabies immunoglobulin (*25, 26*). Rabies immunoglobulins should preferably be administered into and around the wound site to neutralize the RABV still present therein (see *section 8.4*).

Three classes of biological product are available for passive immunization: human rabies immunoglobulin, equine rabies immunoglobulin and highly purified F(ab´)2 fragments produced from equine immunoglobulin (*27*). Patients with open wounds from suspected or proven rabid animals should receive passive immunization as specified in *section 8*. *Annex 5* gives an overview of currently available rabies immunoglobulin products and their producers.

Rabies immunoglobulin should be given with the first dose of vaccine into and around the wound site. Scrupulous wound cleaning and deep irrigation, with application of a potent antiseptic agent, and timely administration of the first CCEEV dose are key factors in increasing survival where RIG is unavailable and should be performed immediately when the patient presents. Human immunoglobulin should be given at a maximum dose of 20 IU/kg of body weight and equine immunoglobulin at 40 IU/kg of body weight. Equine immunoglobulin is considerably less expensive than the human product, and most of the new equine preparations are potent, highly purified and safe, with few adverse events. Serum sickness can occur 1 week after administration of highly purified equine rabies immunoglobulin in < 1–3% of recipients. The risk for anaphylactic reaction is low (1/150 000), and the reaction is generally treatable.

Skin tests are not recommended before administration of equine RIG, as such tests poorly predict severe adverse events and their results should not be the basis for not giving equine immunoglobulin if it is needed. Equine immunoglobulin should be administered under conditions that would allow management of an anaphylactic reaction.

RIGs are in short supply throughout the world. New technology may lead to use of mAbs in PEP. WHO has recommended use of mAb "cocktails" containing at least two antibodies against RABV, as alternatives for RIGs in PEP (*28*). Several human mAbs have been tested against rabies. The first (a single mAb) was recently licensed by the Serum Institute of India (*29*). Studies so far show the equivalence of its performance to human RIG. The availability of this mAb could fill critical public health gaps. As it is made by recombinant technology, it will be less prone to problems such as availability, safety and purity. It should be recommended for use in public health programmes, depending on the epidemiological and geographical setting, with monitoring of its safety and efficacy (clinical outcomes) during post-marketing use.

The second international standard preparation of human immunoglobulin is held and distributed on request by the WHO International Laboratory for Biological Standards at the National Institute for Biological Standards and Control, Potters Bar, Hertfordshire, United Kingdom (*13*). The current WHO reference serum for standardization contains 30 IU per ampoule.

7.9 References

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8.   Prevention of human rabies

Rabies is almost always fatal, but it can be prevented by vaccination before and/or after suspected or proven exposure to the virus. The composition and use of rabies vaccines and immunoglobulins used for prophylaxis should comply with WHO recommendations for production and control and for immunogenicity and safety when given by either the intramuscular or the intradermal route (*section 7* and *8.3.4*).

8.1   General considerations

PrEP is strongly recommended for people who are at high risk of exposure to RABV and other lyssaviruses because of their professional or other activities and, in special cases, because of their residence in a remote area. In travel medicine, PrEP is recommended only for people travelling to remote areas where timely access to adequate PEP cannot be guaranteed or if the individual is at high risk of contact with wild animals, particularly bats (see *section 8.7*).

After exposure to RABV, PEP, i.e. prompt use of rabies vaccine with proper wound washing and management and simultaneous administration of RIG, when indicated, is almost 100% effective in preventing rabies, even if the exposure was severe. When exposure is to an animal that is suspected, probably or confirmed to be rabid (see *section 11*) or when there is doubt about the factors that led to the exposure, PEP should be initiated and medical advice sought, if available.

Vaccines can be administered intradermally or intramuscularly. Rabies vaccines labelled for intramuscular use can be used safely via the intradermal route, even if this constitutes off-label use. For intradermal administration, the recommended sites include the deltoids, lateral thighs or suprascapular areas that drain into regional lymph glands (see *annexes 6* and *7*). For intramuscular administration, the vaccine should be injected into the deltoid muscle for adults and children aged ≥ 2 years; for children aged < 2 years, the anterolateral thigh is recommended (see *Annex 7*). Rabies vaccine should not be administered in the gluteal area, as induction of an adequate immune response is less reliable. The site is selected on the basis of the degree of privacy that can be provided and sociocultural acceptance.

One intradermal dose is 0.1 mL of vaccine, and one intramuscular dose is an entire vial of vaccine, irrespective of the vial size. Day 0 is the date of administration of the first dose. As far as possible, vaccination schedules should be completed in the stipulated time; however, there is no need to restart the series if the doses are not given on the exact schedule, as variations of a few days are unlikely to affect the response to vaccination. Rabies vaccines and RIG can be used during pregnancy and lactation.

8.2 Pre-exposure prophylaxis

PrEP is recommended for individuals who are at high risk of exposure to rabies or to bat lyssavirus because of their occupation, travel (see *section 8.8*) or residence in an endemic setting with limited access to timely, adequate PEP. PrEP obviates administration of RIG after a bite. Vaccine-induced immunological memory is probably life-long if PEP is given after exposure. Published data indicate that periodic booster doses of vaccine are not required after primary rabies vaccination, except as an additional precaution for people whose occupation puts them at continual or frequent risk of exposure (see *section 8.2.1*).

Table 6 provides an overview of WHO-recommended PrEP regimens. To save cost, intradermal PrEP should be given to enough individuals in the same session so that opened vials are used within 6–8 h. There is evidence to support single-day priming vaccination for healthy people aged 5–47 years, by either a two-site intradermal or a one-dose intramuscular vaccination on day 0 (*6–9*). The single day pre-exposure vaccination should be considered only when time does not permit the two-visit PrEP and before travel to areas with ready access to rabies vaccines in the event of exposure; the second dose should be administered upon return or as soon as possible. In case of exposure before the second dose, a full PEP should be administered. There is no evidence that single-day priming is adequate for inducing long-term immunity (> 1 year).

Table 6
WHO-recommended and alternative pre-exposure prophylactic regimens

PrEP regimen	Duration of course	Number of injection sites per clinic visit (days 0, 3, 7, 14, 21–28)	References
WHO-recommended intradermal regimen			
Two visits	7 days	2-0-2-0-0	*1–4*
WHO-recommended intramuscular regimen			
Two visits	7 days	1-0-1-0-0	*5*
PrEP under specific circumstances			
Single visit, intradermal	1 day	2-0-0-0-0	*6–9*
Single visit, intramuscular	1 day	1-0-0-0-0	*6–9*

Generally, no effective immune response is to be expected in the first 7 days after the first vaccine dose. Therefore, people exposed to rabies during those days should receive a full course of PEP, including RIG (for category III exposure). People who discontinued a PEP series after administrations of at least two doses of vaccine should be considered to be vaccinated before exposure.

8.2.1 Recommendations for occupational and programmatic PrEP administration

The risk of infection with RABV depends on the nature of the exposure, the epidemiological setting and the accessibility of biologicals for PEP. PrEP is indicated for individuals who are at risk of occupational exposure, particularly animal health care workers; medical professionals who regularly provide care to people with rabies can consider PrEP. Individuals who work in laboratories with high concentrations of live RABV or lyssavirus should be tested for antibodies every 1–2 years to monitor the levels in order to ensure adequate immune response in case of a detected, unnoticed exposure and to apply risk mitigating measures. The laboratory supervisor or the employer is responsible for assessing the relative risk of exposure and for undertaking extra monitoring of the immunity of laboratory workers. Serological testing and booster vaccination are recommended only if the risk of exposure to RABV continues. If serological testing is not available, a routine booster vaccination before assignment to an at-risk work position might be considered; however, periodic booster injections are recommended as an added precaution only for people whose occupation places them at continual or frequent risk of exposure; antibody monitoring, if available, is preferred. Professionals who are not at continual risk of exposure, such as certain veterinarians and animal health officers, should undergo serological monitoring every 2 years. As vaccine-induced immunity persists in most cases for decades, booster vaccination would be recommended only if RABV neutralizing antibody titres fall to < 0.5 IU/mL.

PrEP for entire populations is not cost–effective in most settings and is therefore not recommended; however, widescale PrEP should be considered in remote settings with limited access to PEP if the annual dog bite incidence is > 5% or if exposure to vampire bats is prevalent. The decision should be based on strong epidemiological evidence and the local context. PrEP should not divert attention from essential mass dog vaccination campaigns to control the disease at its source (see *section 9*).

Booster doses of rabies vaccines are not necessary for people living in or travelling to high-risk areas who have received a primary series of PrEP or PEP.

8.2.2 PrEP for immunocompromised people

People with documented immunodeficiency should be evaluated individually. Immunodeficient patients should receive an intradermal or intramuscular PrEP

regimen as shown in *Table 6*, plus a third administration of vaccine on days 21–28. Immunodeficient patients who are clinically monitored and well managed, such as HIV-infected people receiving antiretroviral therapy, are considered not to be immunocompromised and have been shown to respond to rabies and other vaccines in the same way as healthy individuals (*10*). In the event of exposure, a complete PEP course, including RIG, is recommended.

8.3   Post-exposure prophylaxis

People with WHO category II or III exposures (see *section 8.3.1* and *Annex 8*) should receive PEP without delay as an emergency procedure. PEP consists of the following steps.

- All bite wounds and scratches should be attended to as soon as possible after exposure; thorough washing and flushing of the wound for approximately 15 min with soap and copious amounts of water is required. When available, a viricidal topical preparation should be applied to the wound. Application of local remedies is strongly discouraged.

- RIG should be administered for category III exposures. Wounds that require suturing should be sutured loosely and only after RIG infiltration into the wound, in addition to proper wound care and tetanus boosters, if applicable.

- A series of potent, effective rabies vaccines that meet WHO recommendations (see *section 8.3.4)* should be administered promptly after exposure.

8.3.1   Evaluation of suspected exposure to RABV

Categories of exposure and PEP (see also *Annex 8*)

In countries or areas enzootic for rabies, exposure to suspected, probably or confirmed rabid domestic or wild animals is categorized as follows:

- category I: touching or feeding an animal or licks on intact skin: no exposure; PEP not indicated;

- category II: nibbling of uncovered skin, minor scratches or abrasions without bleeding: exposure; PEP indicated with vaccine; to be treated as category III if exposure was to a bat; and

- category III: single or multiple transdermal bites or scratches, contamination of mucous membranes with saliva from licks, licks on broken skin, exposure due to direct contact with bats: severe exposure; PEP indicated with vaccine and RIG.

For categories II and III exposures, thorough local wound treatment (see *section 8.3.1*) is of paramount importance. The incubation period of the majority of cases is 2–3 months, while 2–3% of cases have had an incubation period > 1 year, with an exceptional case of 8 years (*11, 12*).

Therefore, when the supply of biologics is limited, it may be reserved for suspected and probable exposure within the past 12 months. In the case of exposure to an animal confirmed to be rabid, rabies vaccine should be provided regardless of the time since exposure, even if the exposure is reported years afterwards.

Risk assessment of potential exposure to RABV

Bites, licks, and scratches, particularly from dogs, are extremely common, and the reported annual bite incidence is 0.1–5% globally (*13–15*). Even in settings endemic for dog-mediated rabies, most exposure to domestic animals is not to rabid animals (*16*), although the proportion varies by setting and is underreported. The rates of exposure to RABV among people who seek medical care may be influenced by cultural health-seeking behaviour, rabies surveillance capacity and local epidemiology; national rabies programmes should consider routine evaluation of rabies surveillance systems to improve understanding of the risk for rabies from biting animals. Determination of whether exposure to RABV has occurred should include consideration of factors such as:

- the epidemiology of rabies in the country;

- the severity of exposure (see *section 8.3.1*);

- the species and clinical features of the animal (see definitions of animal rabies in *section 11*);

- the vaccination status of the animal (dogs and cats);

- the animal's availability for observation (dogs and cats); and

- the results of laboratory testing.

When possible, the risk presented by the animal should be assessed by trained personnel familiar with the clinical signs of rabies in animals (*Table 7*). Programmes with such integrated response mechanisms after reported exposure to animal rabies are referred to as "integrated bite case management" programmes (see *section 11*). They can improve the detection of individuals exposed to RABV, increase adherence to vaccination recommendations and reduce unnecessary administration of vaccine or RIG (*16, 17*). The risk that wildlife acting unusually have rabies may be high and should be evaluated with regard to suspected exposure in the context of the local epidemiology (*18*).

Table 7
Matrix for determining the risk for exposure to RABV, by type of exposure and the characteristics of the dog[1]

Exposure consideration	Probability of death based on level of exposure	Information collected at time of bite							Quarantine or testing	
		Dog symptomatic	Dog dead at follow-up	Dog bite was not provoked	Stray dog	Dog bite multiple people	Dog not vaccinated	Dog healthy and available for quarantine	Dog healthy 10 days post-bite	Tested negative
Bite to head/neck	45.0%	High	High	High	High	High	High	Low	No risk	No risk
Multiple severe bite wounds	27.5%	High	High	High	High	Moderate	Moderate	Low	No risk	No risk
Bites to young children	27.5%	High	High	High	High	Moderate	Moderate	Low	No risk	No risk
Bites to extremities	5.0%	High	Moderate	Moderate	Moderate	Moderate	Low	Low	No risk	No risk
Minor bites (no break in skin)	1.0%	Moderate	Moderate	Moderate	Moderate	Moderate	Low	Low	No risk	No risk
Probability the dog has rabies		62.2%	39.7%	15.0%	13.9%	10.6%	4.7%	0.08%	0.0%	0.0%

Source: reference 19, with permission

[1] Risk estimated as the product of the probability that the dog had rabies and the probability that, if it was rabid, the severity of exposure would result in death

In addition to the criteria listed above, PEP may be indicated to alleviate the psychological burden of fear of rabies in animal-bite victims and their relatives. Animals to which humans were exposed that are not available for assessment or observation should be suspected of having rabies, and PEP should be instituted immediately. Exposure of the face or neck and exposure of young children may result in a shorter incubation period, and PEP should be administered immediately if the animal is considered likely to have rabies. People exposed to animals that conform to the definitions of animals suspected, probably or confirmed to be rabid should initiate PEP immediately. When possible, animals that conform to the definition of a suspected or probable case should be killed humanely and the body tested for rabies. If the laboratory tests are negative, PEP can be discontinued. People who have received at least two doses (intradermal or intramuscular) of a cell culture vaccine on an appropriate schedule before discontinuation should be considered as having received PrEP (see *section 8.2*).

Generally, dogs, cats and domestic ferrets that are available for assessment, are deemed healthy by a trained professional and can be observed for 10 days represent a very low risk (*20*). If the animal does not conform to the definition of a suspected case and is available for observation, the wound should be thoroughly washed and the patient counselled on prevention of rabies, but PEP may be delayed during the observation period. If the animal dies, escapes or shows symptoms consistent with rabies during the observation period, PEP should be instituted immediately. PEP should be delayed only when an advanced surveillance programme is in place, in which trained professionals can assess animal rabies in a timely manner and there is reliable laboratory capacity (*Table 8*).

When an animal has been identified as suspected, probably or confirmed to have rabies (see *section 11*), a retrospective risk assessment should be conducted immediately to identify everyone who may have been exposed to the same animal, and they should be given PEP. Dogs, cats and domestic ferrets should be considered infectious for the 10 days before onset of clinical signs and throughout their clinical illness (*21, 22*). The infectious periods of other animals are not well characterized, and a more conservative 14-day clinical investigation is recommended. A retrospective assessment should be conducted when a human rabies case is identified, and PEP should be administered to people who were exposed to the animal responsible for the human case, even months later.

Table 8
Recommendations for rabies PEP on the basis of surveillance capacity

Rabies surveillance programme	Programme description	When to initiate PEP	When to discontinue PEP
No routine surveillance	No trained professionals capable of assessing animals for rabies No laboratory capacity for timely testing of samples	Initiate PEP immediately	Do not discontinue PEP, unless a trained professional has confirmed that the animal is healthy 10 days after the bite
Limited surveillance	Trained professionals capable of assessing animals for rabies are available in some communities. Laboratory capacity exists, but testing and reporting may be delayed.	Initiate PEP immediately	Do not discontinue PEP, unless tests at a qualified laboratory give negative results. *or* A trained professional has confirmed that the animal is healthy 10 days after the bite.
Advanced surveillance (i.e. integrated bite case management)	Trained professionals capable of assessing animals for rabies are consistently and reliably available in the community in which the exposure occurred. Laboratory capacity exists and can reliably test samples and report results within several days of the bite.	Initiate PEP immediately for bites to the head, neck, other highly innervated sites, multiple or deep wounds and for bites to children.[a] When the animal is available and determined by a trained professional to present a low risk, PEP may be delayed.	Do not discontinue PEP, unless tests at a qualified laboratory give negative results. *or* A trained professional has confirmed that the animal is healthy 10 days after the bite.

[a]   Because of their small stature and higher risk of severe exposure, children should recive PEP immediately.

PEP is generally not required for people who sustain animal bites, scratches and other contacts (except for contacts with bats) in an area free of terrestrial rabies, confirmed by adequate rabies surveillance; however, the decision should be based on a risk assessment conducted by a medical professional knowledgeable in the local epidemiology of rabies.

The recommendations given here are a general guide; they can be adapted to each situation and setting, for instance when a reliable history of exposure cannot be obtained such as from an infant and in areas where rabies is enzootic

and follow-up observation of the biting animal and/or laboratory testing are not readily available.

8.3.2   Atypical routes of exposure

Human-to-human transmission of rabies has not been confirmed, except in the case of transplants and a single case of probable perinatal transmission (*23, 24*). Therefore, a decision to provide PEP for people who have been exposed to people with rabies should take into consideration the low risk and should not jeopardize the supplies of vaccine or RIG for people with category II or III exposure to animals with suspected rabies (*23*). RABV can, however, be found in saliva, tears and nervous tissues of people with rabies, which represents a theoretical route of transmission. If category II or III exposure to infectious materials occurred during the infectious period, exposed people should be treated accordingly. Contact investigations should be conducted with medical professionals and other people who may have had close contact with the case. Examples of potential routes of human-to-human exposure include biting and mucosal exposure to infectious materials during medical procedures, kissing or intimate touching. No information is available on the risk of rabies transmission through breastfeeding, but pathobiology and epidemiology indicate that there is no relevant public health risk.

Human rabies cases due to exposure to RABV other than through a bite are extremely rare. Rabies can, however, be transmitted by ingestion of experimentally infected animals; however, no human cases resulting from consumption of raw meat from a rabid animal have been documented (*25, 26*). It is not advisable to consume the meat from a rabid animal, particularly if it is raw. PEP should be considered for people who have a category II or III exposure (see *section 8.3.1*) due to processing of meat from a rabid animal.

Infectious RABV has not been isolated from the milk of rabid cows, and no human rabies cases have been attributed to consumption of raw milk. Although drinking raw milk from a rabid animal is not advised, there is no evidence that this results in exposure to RABV, and PEP is not advised. Milk that has been pasteurized presents no risk for RABV transmission.

Bites of wild animals, particularly monkeys, are normal when people feed them or handle their food and when the animal is threatened, cornered or trapped. These situations should be avoided to reduce unnecessary use of PEP. Rabies is very uncommon in rodents (*27*), and no human rabies cases due to bites by rodents have been reported.

Rarely, rabies can be contracted by inhalation of virus-containing aerosols in laboratories in which materials that contain highly concentrated live RABV is handled or in caves with a high density of rabies-infected bats (*28*). Wild carnivore species and bats (*Carnivora* and *Chiroptera*) present a higher risk for rabies transmission than other wildlife, as they are the reservoirs of RABV (*18*).

8.3.3 Local treatment of wounds

Prompt local treatment of all bite wounds and scratches is an important step in PEP. The recommended first-aid procedures include immediate, thorough flushing and washing of all wounds with soap and water and application of povidone iodine or another substance with virucidal activity. If soap or a virucidal agent is not available, the wound(s) should be thoroughly and extensively washed with water. Eyes and mucosa should be thoroughly rinsed with water. People who live in areas endemic for rabies should be taught simple local wound treatment and warned not to use procedures that may further contaminate or enlarge the wound.

A bleeding wound at any site indicates potentially severe exposure and should be infiltrated with either equine or human RIG. Most severe bite wounds are best treated by a daily dressing, followed by secondary suturing when necessary. If suturing after wound cleansing cannot be avoided, the wound(s) should first be thoroughly infiltrated with human or equine RIG and suturing delayed for several hours to allow diffusion of the immunoglobulin through the tissues before minimal sutures are done. Secondary sutures are less likely to become infected and present better cosmetic results if done under optimal conditions. An infected bite wound is not a contraindication to injection of RIG (*29*). Bites on the tips of the fingers or toes, ear lobes, nasal area or external genitalia can be safely injected with RIG, provided excessive pressure is avoided, as this can cause compression syndromes (*30*). Other treatment, such as administration of antibiotics and tetanus prophylaxis, should be given as appropriate for potentially contaminated wounds.

8.3.4 WHO-recommended PEP regimens

As clinical care settings and preferences in countries vary, WHO recommendations list preferred PEP regimens and alternatives, all of which have been assessed for immunogenicity, clinical outcome, feasibility and cost-effectiveness (*Table 9*). WHO recognizes the equivalent clinical effectiveness of the intradermal route, and intradermal administration of PEP is the preferred, most cost–effective route in clinics in which several new bite patients are seen per week. Rabies vaccines labelled for intramuscular use can be used safely via the intradermal route, even if this constitutes off-label use.

For adults, vaccine should always be administered in the deltoid area of the arm; for young children (aged < 2 years), the anterolateral area of the thigh is recommended (see *Annex 7*). One intradermal dose corresponds to 0.1 mL of vaccine and one intramuscular dose is an entire vial of vaccine, irrespective of the vial size. Health care personnel should be careful not to inject less than the full 0.1 mL intradermal dose due to the dead space in the syringe or needle mount (insulin syringes may be used). Day 0 is the date of administration of

the first dose of vaccine. RABV vaccines and RIG can be used during pregnancy and lactation, and life-saving PEP should never be withheld from pregnant or lactating women; any of the WHO-recommended PEP regimens can be used.

Table 9

WHO-recommended and alternative pre-exposure prophylactic regimens

PrEP regimen	Duration of course	No. of injection sites per clinic visit (days 0, 3, 7, 14, 21–28)	References
WHO-recommended intradermal regimen			
1 week, two sites	7 days	2-2-2-0-0	[a]
WHO-recommended intramuscular regimen			
2 weeks	14–28 days	1-1-1-1-0	*31*
3 weeks	21 days	2-0-1-0-1	*32*
Alternative immunogenic intradermal regimens			
1 month, two sites	≤ 28 days	2-2-2-0-2	*33*
1 month, simplified four sites	≤ 28 days	4-0-2-0-1	*34, 35*
1 week, four sites	7 days	4-4-4-0-0	*36–38*

[a] Tarantola et al. Intradermal rabies post-exposure prophylaxis can be abridged with no measurable impact on clinical outcome in Cambodia, 2003–2014 (manuscript in preparation).

Evidence from an observational study suggests that changes in the rabies vaccine product and/or the route of administration should be allowed in unavoidable circumstances to ensure completion of a PEP schedule (*39*). PEP need not be restarted, and the schedule of the new administration route should be adopted.

8.3.5 Rabies PEP for immunocompromised individuals

Many circumstances lead to immunosuppression and different immunoregulatory pathways to compromised immune response. In most settings, it is not possible to determine the source or severity of immunosuppression when patients consult for PEP. If the condition is well managed, however, such

as for HIV patients who are under treatment and monitored, individuals will probably respond to vaccine in the same way as people who are not severely immunocompromised or are healthy, as observed in studies conducted for routine vaccines (*10*).

Clinical experience suggests that, whenever possible, the best PEP options available (the most immunogenic regimen, high-quality vaccines and RIG) should be used, regardless of the route of vaccine administration. Meticulous, very thorough wound-cleaning as first aid to bite victims is of utmost importance in immunocompromised patients. When feasible, the RABV neutralizing antibody response should be determined 2–4 weeks after vaccination to assess whether an additional dose of vaccine is required. If possible, an infectious disease specialist or the patients' treating clinician with expert knowledge or the patient's disease history should be consulted. The wide variation in the causes of a compromised immune system and the limited information available indicate the need for targeted studies.

8.3.6 Rabies PEP for previously immunized people

For exposed or re-exposed patients who can document previous complete PrEP or PEP and people who discontinued a PEP series after at least two doses of rabies vaccine, the following apply:

- no RIG indicated;

- intradermal administration of PEP:

    - one-site intradermal vaccine administration on days 0 and 3;

    - four-site intradermal vaccine administration on day 0 only;

- one-site intramuscular administration of an entire vaccine vial on days 0 and 3.

People who cannot document previous PEP equivalent to PrEP or complete PrEP should receive a full PEP, including RIG if indicated.

8.4 Use of rabies immunoglobulins for passive immunization

The role of RIG in passive immunization is to provide neutralizing antibodies at the site of exposure before patients start producing their own antibodies as a result of vaccination. Therefore, RIG should be administered to all patients with a category III exposure when supplies are available, except those who received PrEP, as described in *section 8.2*. When access to RIG cannot be guaranteed for all people with a category III exposure, it may be used sparingly and prioritized for those at greatest risk, with consideration of additional high-

risk factors (see *section 8.3.1*). Vaccine should be administered regardless of the availability of RIG.

RIG is administered only once, preferably at or as soon as possible after initiation of post-exposure vaccination. It is not indicated beyond the seventh day after the first dose of rabies vaccine, regardless of whether the doses were received on days 3 and 7, because an active antibody response to the rabies vaccine has already started, and this would represent a waste of RIG. The maximum dose of human RIG is 20 IU/kg of body weight, while that of equine immunoglobulin and F(ab')2 products is 40 IU/kg of body weight.

The entire immunoglobulin dose, or as much as anatomically possible (but avoiding possible compartment syndrome), should be infiltrated carefully into or as close as possible to the wound(s) or exposure sites. Evidence suggests that injecting the remaining RIG volume intramuscularly at a distance from the wound provides no or little additional protection against rabies as compared with infiltration of the wound alone (*40–43*). If, however, there is a high likelihood that there are additional small wounds (e.g. if a child does not report all wounds), exposure was to bats or exposure was other than through a bite, injection of the remaining RIG volume intramuscularly as close as possible to the presumed exposure site, to the degree that is anatomically feasible, is indicated. The same applies for mucosal exposure with no wound, and rinsing with RIG can be considered. In the case of suspected exposure to RABV in an aerosols, an intramuscular injection of RIG is nevertheless recommended.

Use of the same syringe or mixing rabies vaccine and RIG are not advised. For severe and multiple wounds, which require more immunoglobulin than the maximum dose, the product may be diluted with sterile normal saline to a volume sufficient for effective, safe infiltration of all wounds.

A mAb product was licenced in 2017 in India and is currently being used there in clinical settings. Depending on the geographical and epidemiological context, use of mAbs is encouraged as an alternative to RIG. WHO recommends that a registry be maintained to monitor the clinical use and outcomes of mAb products for rabies PEP.

8.5 Contraindications and precautions to be taken in post-exposure prophylaxis

There are no contraindications to PEP. PEP can be safely given to infants, pregnant women and immunocompromised individuals, including children with HIV/AIDS. It should be given as indicated by the nature of the exposure in a setting in which the staff are adequately trained in its administration and in the management of possible adverse reactions, as for any other vaccination.

As for all vaccinations, recipients should be kept under medical supervision for at least 15–20 min after vaccination. A previous severe reaction

to any component of a rabies vaccine is a contraindication for use of the same vaccine for PrEP or PEP, and the vaccine product should be changed.

8.6   Supply limitations

Governments and responsible agencies should enact regulations to ensure that all people with suspected, probable or confirmed exposure to rabies have timely access to adequate PEP administered by competent staff, including in the private sector. Intradermal administration should be included in the recommendations of all countries. When possible, cost–effectiveness should be studied to determine the best methods of access to rabies vaccines and biologicals (*44–47*).

In settings where there is no regular access to vaccines and RIGs or the supply is insufficient to meet demand, it might be necessary to consider diverting the supplies to people with high-risk exposure. If a limited amount of RIG is available, it should be prioritized for exposed patients on the basis of the following criteria:

- multiple bites;

- deep wounds;

- bites to highly innervated parts of the body, such as the head, neck and hands;

- severe immunodeficiency;

- bites from an animal with confirmed or probable rabies; and

- a bite, scratch or exposure of mucous membranes from a bat.

Restricting RIG or vaccine to people with high-risk exposure to rabies may endanger those with lower-risk exposure and should be considered carefully before being implemented. Assessment of the risk associated with animals with suspected rabies, as described in *section 8.3.1*, can reduce unnecessary use of rabies biologicals and should be considered when the RIG and/or vaccine supply cannot meet demand.

8.7   Travel to rabies-affected countries and areas and indications for pre-exposure prophylaxis

Assessment of the individual risk of exposure to RABV is recommended for travellers, which should take into consideration: the remoteness of the destination, the prevailing rabies epidemiology and the cumulative duration of the stay in endemic setting(s). PrEP should be considered for travellers who will

have extensive outdoor activities in remote rural areas and where timely access to adequate PEP is not guaranteed. PrEP should also be considered for people who regularly participate in activities such as caving that are likely to lead to direct contact with bats. Travellers to rabies-affected countries and areas should be aware of the risk of rabies and the need to seek PEP if they are exposed.

Travellers to rabies-affected countries and areas should avoid contact with free-roaming animals, especially dogs, cats and monkeys, and with free-roaming and captive wild animals. For people who visit caves inhabited by bats, casual exposure to cave air is not a concern, but cavers should be warned not to handle bats. Physical contact with bats should be followed by PEP (see *section 8.3.1*).

Fig. 4 shows four categories of countries and areas, from no risk to low, moderate and high risk of circulation of RABV and other lyssaviruses. The categorization is based on the major animal host or transmitter and lyssavirus species involved (for a map of the endemicity of dog-mediated rabies see *section 2*) and the availability of reliable, laboratory-based surveillance data on the reservoir species. Access to proper medical care and the availability of rabies vaccines and immunoglobulins were also taken into consideration.

Figure 4
Countries and areas classified as no, low, medium and high risk of circulation of RABV and other lyssaviruses
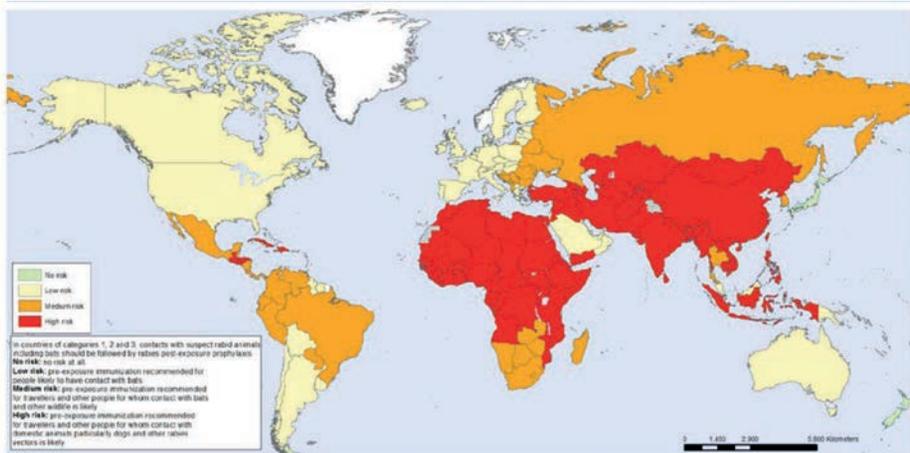
In both no- and low-risk areas, proper medical care, rabies vaccine and immunoglobulins are accessible in a timely manner, and reliable laboratory-based surveillance data are available. In medium- and high-risk areas, access to proper medical care, rabies vaccines and immunoglobulins depends on the local setting and are not accessible in a timely manner throughout; partial laboratory-based surveillance data are available but may not cover all reservoir species or geographical settings in the country.

Suggested certificates for pre- and post-exposure vaccination against rabies are shown in *Annex 9.*

8.8   Education to prevent bites

Programmes to prevent dog bites are conducted in order to reduce the risk of rabies, save the costs of PEP and wound care, eliminate the trauma of dog bites and restore healthy dog–human relationships. Meta-analyses indicate that education programmes to prevent bites are moderately successful in affecting children's behaviour (*48, 49*), although the quality of the evidence is low. Currently, there is no direct evidence that such programmes affect dog-bite rates. Human behaviour towards dogs is the result of a complex interaction between knowledge, emotion and experience (*19, 50*), and education to prevent dog bites is most effective when it involves live dogs. The complexity of such education means that the programmes are likely to require more time and resources than education on other aspects of rabies.

Careful consideration should be given to the costs and benefits of the components of a holistic rabies education programme. It is recommended that knowledge, attitude and practice surveys be conducted to determine each stage of an education programmes on rabies. Depending on the setting, bite prevention may also include education on conduct in areas where rabies is circulating in wildlife, with particular emphasis on not touching or handling bats.

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9.   Prevention and control of rabies in dogs

As more than 95% of human rabies cases are transmitted by dogs, the control and elimination of rabies in dogs prevent rabies at its source. Dog-mediated rabies has been eliminated in North America, western Europe, Japan and parts of Asia and South America; however, it is still widespread, in over 100 countries and territories, predominantly in the developing world (see *section 2*).

9.1   Case definition of animal rabies

The clinical signs of rabies in animals vary widely. A case is clinically defined as that in an animal that presents with any of the following signs:

- hypersalivation

- paralysis

- lethargy

- unprovoked abnormal aggression (e.g. biting two or more people or animals and/or inanimate objects)

- abnormal vocalization

- diurnal activity of nocturnal species.

Cases of animal rabies are classified as:

- suspected: a case that is compatible with a clinical case definition of animal rabies;

- probable: a suspected case with a reliable history of contact with a suspected, probably or confirmed rabid animal and/or an animal with suspected rabies that is killed, died or disappeared within 4–5 days of illness being observed;

- confirmed: a suspected or probable case that is confirmed in a laboratory; and

- not a case: a suspected or probable case that is ruled out by laboratory tests or epidemiological investigation (i.e. appropriate quarantine period of eligible animals).

Laboratory confirmation should be performed with a standard diagnostic test defined by WHO or OIE (see *section 5*) (*1*). If other diagnostic tests are used, confirmation of the results with an internationally recognized secondary test may be required (particularly for negative results), depending on the sensitivity and

specificity of the initial tests. Accurate diagnosis of rabies in animals is especially important when human exposure to the suspected animal has been reported.

9.2   Methods for controlling dog rabies

As rabies control programmes involve multiple agencies and sectors, including those of animal and public health, they require a "one health" approach, with effective intersectoral cooperation. Mass parenteral canine vaccination campaigns with vaccines manufactured according to international standards are the mainstay of dog-mediated rabies control (*1–4*). To achieve control and eventual elimination of rabies, campaigns must be conducted recurrently (usually annually) with a vaccination coverage of at least 70% (*5, 6*), which should be sufficient to maintain the required level of herd immunity in the susceptible population despite dog population turnover (births, deaths, animal movement) in the period between campaigns. The coverage should be evaluated routinely, with appropriate epidemiological counselling to ensure that the goals are met in all target areas. It is of utmost importance that rabies vaccination programmes are flexible enough to allow timely, adequate responses to changes in epidemiological conditions.

Greater community awareness, engagement and mobilization can improve the turn-out for vaccination campaigns, their cost–effectiveness and sustainability and the surveillance and management of rabies cases. When dogs cannot be handled by their owners or when no single owner claims responsibility for vaccination, professional dog handlers can catch and restrain dogs humanely for vaccination after suitable training to ensure they can catch dogs efficiently, reliably and humanely; inexpert handling can injure both handlers and dogs and may make future vaccination more difficult. As handlers are likely to have a higher rate of dog-bite injuries, pre-exposure vaccination is highly recommended (see *section 8.2*).

Oral rabies vaccination (ORV) of dogs may improve coverage in situations in which dogs cannot be restrained or caught and should be used as a complementary measure to improve overall vaccination coverage in dog rabies control programmes (see *section 9.2.3*).

Directors of vaccination programmes should take into account the local ecology of the dog population, including whether they are owned and confined, owned and roaming, owned by the community or ownerless. This information ensures that the method maximizes access to dogs and is adapted to the sociocultural context. Free-roaming dogs play a key role in the transmission of rabies and must be included in vaccination campaigns.

Mass dog vaccination has repeatedly been shown to be effective for controlling dog-mediated rabies, whereas removal of dogs does not decrease dog density or control rabies in the long run. Mass culling of dogs should therefore not

be a part of a rabies control strategy: it is ineffective and may be counterproductive to vaccination programmes, particularly when they target free-roaming dogs. For more information on humane dog population management, see Chapter 7.7 of the OIE *Manual of diagnostic tests and vaccines for terrestrial animals*: "Stray dog population management" (*7*).

Euthanasia of a dog suspected of being rabid prevents further transmission to humans and animals and prevents further suffering of the dog (see *section 9.1* for a case definition of animal rabies). If the clinical diagnosis of rabies is unclear, the dog can be quarantined and observed; however, if the signs progress, humane euthanasia should be performed (*7*).

9.2.1   Main components of a dog rabies control programme

The elements to be included in a dog rabies control programme are listed below.

- Establish a national strategy, focal points and committees to prepare, implement and monitor long-term plans for rabies elimination based on understanding of the local epidemiology, education and awareness campaigns, mass dog vaccination and provision of PEP or PrEP to populations at risk (see *section 8*).

- Enhance intersectoral cooperation among veterinary services, public health and wildlife management to design evidence-based approaches to the elimination of human and animal rabies.

- Support integration of rabies control activities into all levels of the health service, and align them with other public health or animal disease control programmes. Integrated delivery of rabies control measures may have wider benefits in terms of strengthening health and veterinary service delivery, particularly in remote areas and neglected communities, improving intersectoral collaboration and building community trust.

- Stimulate cooperation with the pharmaceutical industry and institutions for the provision of vaccines, both human and veterinary, and technical cooperation to ensure correct storage, prompt delivery and appropriate administration of high-quality vaccines.

- Seek funding from bilateral, multilateral, public and private agencies and other donors in the framework of technical cooperation or humanitarian aid.

- Conduct campaigns and education programmes to increase awareness of the benefits of responsible dog ownership, basic care of bites from animals with suspected rabies and avoiding exposure to animals.

- Strengthen surveillance and diagnostic capacity to include rapid diagnostic tests and rabies notification systems.

- Institute effective cross-border collaboration for rabies control and elimination.

9.2.2   Strategic planning and management of dog vaccination campaigns

Vaccination campaigns should be strategically planned and well managed, with adequate resources. The "rabies blueprint" prepared by the Partners for Rabies Prevention provides guidance on planning and implementing parenteral dog vaccination campaigns (http://caninerabiesblueprint.org/) (*8*). Another tool that could be used for strategic planning and allocation of funding is the "Planning aid for the control of dog-mediated human rabies deaths based on dog vaccination" (*9*).

Studies of dog ecology

In planning a vaccination campaign, the dog population should be estimated and dog-keeping practices ascertained to calculate the resources required and the appropriate methods for accessing dogs for vaccination (*8*). The dog population can be estimated from the human:dog ratio; however, this ratio varies widely, and poor human census data may reduce the accuracy of estimates of the dog population. Furthermore, low reporting and variable patterns of dog ownership in urban areas make it difficult to estimate dog populations accurately. Other methods for estimating dog populations include surveys and capture–mark–recapture approaches, which cover the free-roaming population. Details of these methods are given in the "canine rabies blueprint". Such surveys are often usefully combined with post-vaccination surveys to evaluate vaccination coverage, and population estimates can be revised for future campaigns (*10, 11*). Information from dog registries can be useful, but, as these do not include unregistered or ownerless dogs, use of this source alone will result in underestimation of the total dog population.

Vaccination and immunization coverage

Low or patchy vaccination coverage of dogs, missing even a small proportion of communities, may facilitate the persistence of rabies and jeopardize the prospects of elimination, even if the average coverage of the region is high.

Vaccination is most effective when carried out over contiguous areas with comprehensive coverage rather than many small, separate areas (*12*).

Reactive vaccination in an outbreak is not recommended as an alternative to regular (e.g. annual), systematic, proactive vaccination campaigns, unless greater surveillance shows that the incidence has been reduced to low levels in a few remaining foci. Reactive strategies take longer to control rabies and are less likely to be successful than systematic vaccination in an entire area. The required immunization coverage can be achieved if the vaccination programme includes well-designed educational campaigns, intersectoral and interdisciplinary cooperation, community participation, local commitment to planning and execution, the availability of high-quality vaccine, media support and effective general coordination and supervision of activities by the appropriate authorities.

Implementing and monitoring dog vaccination campaigns

During mass vaccination campaigns, all dogs should be vaccinated, including newborn puppies, regardless of weight, state of health or prior vaccination. Although the aim should be to vaccinate as many dogs as possible, herd immunity is achieved by vaccinating at least 70% of the rabies-susceptible dog population.

One reason for low vaccination coverage is that puppies, which often comprise a large proportion of the population, are not vaccinated (*13*), mainly because it is not recommended by the vaccine manufacturer or by national guidelines. Studies in South Africa, Tunisia and the United Republic of Tanzania indicate, however, that young pups (< 3 months of age) mount an effective immune response when given a high-quality vaccine, with no adverse effects. Owners and vaccination teams should therefore be aware that puppies, including newborns, should also be vaccinated to ensure adequate population coverage, even though this may represent off-label use.

Four basic approaches have been described to access dogs for vaccination campaigns: house-to-house visits, fixed vaccination posts in well-recognized sites in a community, temporary vaccination posts set up by mobile teams and mobile "street vaccination" teams. Posts are usually sufficiently attended only when they are located fewer than 500 m or about a 10-min walk away. The choice of approach should be decided at local level, as it depends on the sociocultural context of the community. A combination of approaches may be used.

Administration of rabies vaccine can be linked with other health interventions (e.g. deworming, neutering and other vaccination programmes), which might provide additional health benefits for the dog and provide an incentive for engagement of both owners and veterinary practitioners in vaccination campaigns (*14*).

Timing of campaigns

Rabies vaccination campaigns are generally conducted annually, but more frequent campaigns may be necessary in areas in which the incidence of rabies in dogs and/or population turnover is high or the programme has not yet achieved its desired outcome. Intensive vaccination campaigns lasting less than 1 month have been effective in rabies control in Latin America, Asia and Africa. Campaigns should, however, reach at least 70% of the dog population, and coverage should not be compromised in the pursuit of speed. Campaigns might be organized on weekends or during school time or holidays to improve turn-out, as children often bring their dogs for vaccination.

Monitoring vaccination campaigns

Registration and permanent identification of vaccinated dogs is recommended; however, research is still required to identify methods of identification that are cost–effective, safe, quick and simple to apply in the field and well accepted by both dogs and owners. Lack of resources or capacity to permanently identify dogs should not preclude implementation of a vaccination campaign. The use of coloured tags, paint or spray marks or plastic collars as temporary marking has proven to be useful in identifying vaccinated dogs and can motivate owners to take their dogs for vaccination. Temporary or permanent identification of vaccinated dogs is necessary for evaluating the vaccination coverage rate and for differentiating unvaccinated dogs for follow-up vaccination.

Routine serological monitoring in the context of mass dog vaccination campaigns, including ORV campaigns, can be expensive and is not necessary if:

- a high-quality vaccine manufactured according to international standards has been used;

- vaccination teams have been trained and have used a proper injection technique, dog handling and vaccine vial management; and

- the cold chain has been maintained throughout.

If repeated annual vaccination campaigns that reach the targeted coverage do not result in a decrease in the number of animal rabies cases, one or more of the above elements may not have been complied with, or the estimate used to calculate dog vaccination coverage is not accurate. Well-designed serological and other studies (e.g. vaccine potency, cold chain monitoring) may then be warranted to determine post-vaccination antibody responses. Serological testing should be carried out during the period of peak antibody response, at or around 28 days post-vaccination, as rapidly declining antibody titres can make interpretation of serological results difficult if sampling is carried out longer after vaccination.

Properly validated ELISAs can be used as an alternative to seroneutralization assays (see *section 5*).

Cost–effectiveness of dog vaccination

Dog vaccination in combination with PEP is more cost–effective in preventing human deaths from rabies than PEP alone (*15–17*). The demand for PEP does not, however, invariably decrease with a decrease in the incidence of dog rabies.

A study in Chad on the effect of a contributuion of dog owners to the costs of dog registration or vaccination campaigns showed that fee-based vaccination campaigns increased the cost per dog vaccinated and lowered the vaccination coverage of dog populations as compared with free vaccination campaigns (*18*). In the Philippines, the willingness of residents to pay an average of US$ 1.67 for dog vaccination and US$ 0.70 for dog registration depended on socioeconomic and demographic factors such as age, income, number of dogs owned and municipality of residence (*19*). These factors should therefore be considered before introducing such fees. If a paid contribution jeopardizes vaccination, the intervention (registration, marking, vaccination, certificate delivery) should be provided free of charge and the cost balanced against the public health benefits of rabies control.

Vaccines to be used

Vaccines are susceptible to changes in temperature, including freezing, and care must be taken to ensure that the cold chain is maintained within an acceptable temperature range (2–8 °C). Vaccines that induce immunity for a minimum duration of 2 years should be used in annual campaigns to revaccinate all dogs.

Revaccination has no adverse effects. Although annual booster vaccination of dogs may not be necessary if they have received a vaccine that induces long-term immunity and more selective vaccination could potentially save costs, turning people and their dogs away at vaccination points could send out a confusing message. Further, in many campaigns, the direct cost of revaccination is likely to be lower than the fixed costs of the campaign.

Vaccination of puppies < 3 months of age with high-quality, inactivated rabies vaccine has been shown to result in effective seroconversion (*20*). All dogs, including puppies < 3 months of age, should be included in vaccination campaigns in endemic regions.

Where vaccination certificates are issued, pre-printed certificates may increase efficiency. As maternal antibody may interfere with vaccination, puppies should receive a vaccination certificate only after they have received a booster dose.

Vaccines available

Veterinary vaccines have been developed for use against rabies in domestic mammals and wildlife. They are either inactivated (killed), modified-live or recombinant products. Whatever the method for vaccine production, the quality of the source material and standards (e.g. virus master seed, specific pathogen-free eggs, cell seed) should be clearly documented, particularly with regard to sterility, safety and potency.

Rabies vaccines for animals should be approved by the competent State authorities and comply with national requirements for vaccines. If there are no adequate national regulations for veterinary biologicals with regard to potency, sterility, safety and efficacy, reference should be made to the relevant international standards. For further information on veterinary vaccines available for rabies in dogs and wildlife, including potency requirements, see Chapter 2.1.17, Rabies (infection with rabies virus), of the OIE *Manual of diagnostic tests and vaccines for terrestrial animals* (*1*).

Nerve tissue vaccines induce more severe adverse reactions and are less immunogenic than modern cell culture vaccines. WHO and OIE strongly recommend discontinuation of the production and use of nerve tissue vaccines and their replacement by modern cell culture vaccines. The use of modified live-virus vaccines produced from egg- or cell culture-adapted strains for parenteral vaccination of dogs is also discouraged. Vaccination should be undertaken with inactivated vaccines (with or without adjuvant).

Safety considerations

All members of a vaccination team who handle dogs should receive PrEP before the campaign. Adequate PEP should be available for people who are exposed during the campaign.

In the event of accidental exposure to modified live RABV vaccines, medical assistance should be sought and PEP considered. The potential risk to animals, humans and the environment of recombinant vaccines, such as those containing live pox or adenovirus vectors, should be assessed, and methods for mitigation or treatment, particularly in humans, should be identified before field use.

For detailed information on the minimal requirements for animal rabies vaccine safety, see Chapter 2.1.17, Rabies (infection with rabies virus), of the OIE *Manual of diagnostic tests and vaccines for terrestrial animals* (*1*).

9.2.3   Oral vaccination campaigns

ORV has been successfully used to control the disease in certain wildlife reservoir species (*21*). ORV of dogs is a complementary measure that can be used

to increase vaccination coverage in mass parenteral dog vaccination campaigns, e.g. in contexts where reaching 70% vaccination coverage is compromised by the presence of free-roaming dog populations. Countries should assess the suitability and necessity for both parenteral vaccination and ORV in their rabies control strategy. *Annex 10* gives an overview of currently available ORV products.

Target populations

Only semi-restricted and unrestricted dogs (and owned, fully restricted dogs that cannot be handled) that cannot be vaccinated parenterally under normal conditions should be considered for ORV. It is likely that these dogs will be identified only after mass parenteral vaccination campaigns have been attempted. ORV may help to improve vaccination coverage in these hard-to-reach dog subpopulations.

Methods of distribution

ORV has been used to vaccinate dogs in relatively small field trials (*22–25*). To limit the possibility of contact of non-target species (including humans) with vaccine and bait, the "hand-out" model has been used, in which baits are presented directly to dogs (owned or unowned) on the street. Oral vaccine baiting can be implemented simultaneously with door-to-door or central point parenteral campaigns, e.g. for aggressive dogs and those that are difficult to handle. ORV should always be conducted by trained vaccinators.

Efficacy

Parenteral vaccination must remain the primary method of immunization. It has been shown repeatedly to result in a robust immune response in > 95% of dogs that are vaccinated appropriately. Parenteral vaccines are injected directly into subcutaneous or muscle tissue, nearly guaranteeing that the vaccine will be recognized by a competent host immune system. Oral vaccination of dogs cannot be guaranteed to achieve such high seroconversion rates because of several important issues in delivery and immunology. Oral vaccines require that a dog is attracted to the bait, chews it and breaks the sachet or blister and that the vaccine is deposited in the correct amount onto the oral mucosa. Furthermore, oral vaccines are modified live or recombinant constructs and must replicate in the host in order to induce an immune response. For these reasons, parenteral vaccination with inactivated vaccines is the preferred choice for accessible dogs; the utility of ORV for semi-restricted, non-restricted and unapproachable dog subpopulations can nevertheless be clearly beneficial (*25*).

Safety

Oral rabies vaccines licensed according to international standards are considered to be safe; however, safety should always be thoroughly assessed before ORV in the field. In Haiti, assessment of the safety of a modified-live RABV oral vaccine showed that the probability of a human death due to contact with the oral rabies vaccine was 0 per 1 billion baits distributed by the hand-out method, and the probability of a human death due to a dog bite was 0.3 per 1 billion baits distributed by the hand-out method (assuming PEP was not given to any exposed person). In Tunisia, no exposure to the vaccine bait occurred when baits were distributed door to door (equivalent to the hand-out method), whereas a 1.4% rate of contact was observed with "transect line" distribution (*26*).

It is the responsibility of countries to study the opportunity of introducing ORV into their rabies control strategy. If an oral vaccine includes a genetically modified organism, the legal implications of its release into the environment should be considered. WHO recommends that ORV be used in pilot studies to evaluate its feasibility and efficacy before widescale application. Researchers and project designers should assess the product, identify potential hazards and evaluate the risks associated with its introduction into the environment.

Guiding principles for investigating and conducting ORV are described in Chapter 2.1.17, Rabies (infection with rabies virus), of the OIE *Manual of diagnostic tests and vaccines for terrestrial animals* (*1*). Countries that are considering use of ORV of dogs should ensure the safety of the viral construct on the target and non-target species, including humans (*25*). As shown in Europe and the USA with regard to rabies vaccination of wildlife, selection of safe, effective oral rabies vaccine constructs and appropriate contingency plans for non-target exposure to the vaccine can make the human risk nearly negligible (*27*). Particular attention should be paid to safety in lower-income communities where ORV may be administered in areas of high human population density, the prevalence of immunodeficiency is higher, access to medical care may be less reliable and the literacy rate may be low so that people cannot read warning labels.

After a vaccine and baiting system has been selected and before positioning of vaccine baits in the environment, sufficient information should be provided to the public so that, in general, public support and cooperation are elicited. The information should include the potential risks associated with the vaccine and the assistance that will be available if contact with humans or other non-target occurs.

Setting up surveillance systems to detect human contact with vaccine and/or bait and establishing rules for documentation and follow-up of cases of human exposure to the vaccine are of utmost importance. In the event of accidental exposure to modified live RABV vaccine, medical assistance should

be sought and PEP considered (see *section 8*). Both exposure by direct contact with the vaccine and exposure to animals that were vaccinated recently (i.e. one to several hours previously) should be reported. There is no evidence that oral rabies vaccines are actively excreted in saliva, but, because of the presence of liquid vaccine in the oral cavity after consumption, contact with dogs that have just been given oral vaccine should be avoided or minimized for at least 1 h and preferably longer (*25*). Surveillance programmes should be capable of detecting rabid dogs in the area of ORV, and all positive samples should be characterized molecularly to ensure that the vaccine did not revert to a state of virulence.

International organizations, particularly WHO and OIE (including their networks of reference centres), collaborate with governments in assessing the risks associated with the use and application in the field of each type of product (modified live vaccine, recombinant vaccine and other constructs) for target and non-target species; identifying the efficacy and safety requirements for each type of product; and defining the criteria for distribution in the field. The main criteria for assessing use of oral rabies vaccines in dogs are:

- the origin (manufacturer);

- vaccine type: modified live virus, recombinant live virus or other construct;

- safety in the target animal(s);

- safety in non-target animals;

- safety in non-human primates;

- development of humoral immunity in the vaccinated primary target animal;

- results of virulent challenge protection studies;

- bait contact rates for a bait distribution method;

- bait matrix attractiveness to confined and free-roaming dogs;

- thermostability of the bait matrix under field conditions and forecast;

- excretion of viable RABV into the environment (saliva and faecal samples);

- cost–benefit;

- current licensure of the product in any country and/or currently recommended by an international public and/or animal health body for field use;

- community support for oral vaccination of dogs against rabies;

- possibility of post-vaccination monitoring for people potentially exposed directly to the vaccine or as a result of contact with recently vaccinated dogs; and

- access to PEP for humans exposed or potentially exposed to the vaccine (PEP adapted to the vaccine construct, which may include agents other than lyssaviruses).

Full details of relevant procedures, tests and protocols should be obtained from relevant national regulatory authorities and/or relevant international guidelines (OIE, WHO, *European Pharmacopeia,* US Code of Federal Regulations).

Licensure

Preferably, countries in which ORV is used will license the product for use in dogs; however, many countries affected by dog-mediated rabies lack the regulatory bodies to license biological products and rely on other countries to obtain licensure. This creates a global dilemma, in that countries (and vaccine manufacturers) that can license vaccine products are usually not affected by dog-mediated rabies and have no incentive to license these oral products for use in dogs.

Manufacturers are encouraged to license ORV products for dogs, according to international standards, to assist regulatory authorities in endemic countries in expeditiously approving ORVs for use in their rabies programmes. Countries in which use of ORV is being considered and that have the capacity to license products should prioritize the evaluation and licensure of ORV products before widescale field use. When licensure is not available, countries should consider off-label use of ORV products that have been licensed for species other than dogs, provided adequate studies of safety and efficacy have been conducted.

9.3   International movement of animals

International movement of animals is of significance for human public health as it can facilitate the introduction, emergence or re-emergence of rabies in new countries or areas. Regulations for importing domestic, captive wild and wild mammals from rabies-free countries or from countries that are considered to be infected with rabies should comply with OIE international standards, including presentation of a valid international veterinary certificate (*28*). For

further information on international movement of animals, refer to Chapter 8.14 of the OIE *Terrestrial Animal Health Code* (*29*).

9.4   Humane dog population management

Dog populations are managed humanely mainly by responsible dog ownership and provision of sterilization services and basic dog health care (*7*). The objective of dog population management in the context of dog-mediated rabies control is to improve and maintain vaccination coverage and reduce risky dog behaviour. Reducing the population size is not an effective means of reducing the number of rabies cases, although it may have other benefits (e.g. with regard to dog welfare or nuisance behaviour) (*30*). Management of dog populations may therefore be beneficial in dog-mediated rabies control.

Humane dog population management is an effective strategy for reducing dog population turnover and creating a healthy, sustainable population. As the status and composition of dog populations varies from country to country, no one intervention will work in all situations. Authorities should work with people who know the local dog population in order to understand ownership, demographics and the attitude of the local community towards dogs. This information can form the basis for a tailored package of tools for long-term, sustainable management (*8, 31*). For further information on humane dog population, see Chapter 7.7 of the OIE Terrestrial Animal Health Code (*7*).

9.5   Vaccination versus sterilization

Priority should be given to dog vaccination, as it is the most effective means of reducing dog-mediated rabies (*32*). A publicly available stochastic model allows comparison of the effects of various budget allocations to sterilization and vaccination, in terms of cost and predicted human deaths, which can be accessed at: https://bioecon.shinyapps.io/CanineRabiesWebApp/. Sterilization of dogs should be pursued when:

- funds and time for sterilization are from a different source from that for vaccinations;

- high vaccination coverage has already been achieved, and surplus funds are available; and

- the cost of both sterilization and vaccination is low.

Sterilization might also be considered in rare ecological circumstances, such as when it might markedly prolong the longevity of the dogs, when there is no demand or desire for additional dogs and it can be done inexpensively.

Countries are encouraged first and foremost to invest in widescale vaccination campaigns.

9.6   National programmes for dog rabies control: lessons from the field

Since formally pledging to eliminate human deaths from dog-mediated rabies in 1983, Latin American countries have decreased the number of cases by over 90%, with a similar decrease in human deaths (*4*). This has been achieved predominately by mass vaccination of over 50 million dogs annually, with concurrent appropriate treatment of people at risk of rabies (PrEP or PEP) and epidemiological surveillance. The success of vaccination campaigns in Latin America was due to the central coordinating role of the public health sector and the involvement of communities in rabies control (*33*).

Programmes for testing proof of concept in KwaZulu–Natal (South Africa) and the Visayas (Philippines) have also reduced the number of human rabies cases by mass dog vaccination and extended access to PEP. In KwaZulu–Natal, the number of cases was significantly reduced by annual dog vaccination campaigns, and the number of dog-mediated rabies cases was reduced by > 80%. The project is now being extended throughout southern Africa, with renewed support and momentum. The regional programme for rabies elimination in the Visayas is part of the national rabies programme, which is implemented jointly by the departments of agriculture, health and education and involves dog vaccination campaigns in the Western, Eastern and Central Visayas and Bohol (*3*). Intensive education campaigns were conducted to engage the community, increase dog vaccination and responsible pet ownership and improve surveillance, diagnostic capability and access to PEP. Within 6 years of the start of control activities in the Visayas, the number of human cases approximately halved, and two provinces, five island municipalities and five smaller islands have been declared rabies free (*34*).

In 2010, Bangladesh initiated a national strategy to eliminate rabies by 2020, by intersectoral collaboration of health and livestock ministries and local governments. The strategy includes advocacy, communication and social mobilization, dog-bite management, mass dog vaccination and dog population management. Dog vaccination has been scaled up from one municipality in 2011 to 64 municipalities and city corporations. A snowball technique of capacity-building for dog catchers and vaccinators has resulted in training of several thousand expert dog catchers, which is essential in a country in which 83% of dogs roam freely. The programme achieved a minimum population coverage of 70% within 1 week through local campaigns and reduced unplanned dog killing in municipalities. Three vaccination rounds are planned by 2020 to cover an estimated 1.6 million dogs. With this strategy, the number of human

rabies cases decreased from over 2000 annually before 2011 to fewer than 200 as communicated to WHO for 2016 (*35, 36*).

In N'Djaména, Chad, mass dog vaccination campaigns conducted in 2012 and 2013 reached 70% coverage, resulting in a decrease in the annual dog rabies incidence from 0.7/1000 in 2012 to 0.07/1000 in 2014 (*37*). After the campaigns, no dog rabies cases were reported in N'Djaména for over 9 months (January–October 2014). A deterministic transmission model fitted to demographic and epidemiological data suggested that rabies transmission in dogs has been interrupted by the vaccination campaigns (*9*). In 2015 and 2016, rabies cases were reported in the periphery of the town and then in the town centre, indicating that reintroduction into areas of previous dog vaccination is a continuous threat and that mass interventions must be coordinated at a higher regional scale for a sustainable effect. Geographical boundaries such as rivers serve as short-term barriers; however, dog movement is strongly driven by human movement, and rabies may be propagated by human transport of dogs across natural barriers and over larger distances.

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10. Prevention and control of rabies in wild animals

Rabies is a viral zoonosis associated with many species of *Carnivora* and *Chiroptera*, which are the primary hosts of RABV. Only Chiroptera species are the primary hosts of almost all other lyssaviruses (see *section 3*). With progress in molecular approaches to the identification and phylogeny of virus variants, understanding of lyssavirus epidemiology has improved significantly.

10.1 Epidemiology and ecology of rabies in carnivore species

Table 10 gives an overview of the epidemiology and ecology of rabies in carnivore species. It reflects documented cases of rabies transmission; undocumented transmission of rabies by other carnivore species remains possible.

Table 10
Epidemiology and ecology of rabies in carnivore species

Country or region	Species in which rabies is documented	Note (reference)
Africa	Domestic dog	Primary hosts of RABV (*1*) Frequent RABV spillover threatens endangered wild African canids such as the Ethiopian wolf (*C. simensis*) and African wild dogs (*Lycaon pictus*) (*2–4*)
Southern Africa	Jackal (*Canis adustus* and *C. mesomelas*)	Sustained transmission of canid RABV variant (*5*)
Advanced surveillance (i.e. integrated bite case management)	Bat-eared fox (*Otocyon megalotis*)	Sustained transmission of canid RABV variant (*6*)
	Mongoose (Herpestidae family)	Sustained transmission of RABV variant (*7*)
Namibia	Kudu (*Tragelaphus strepsiceros*)	Canid RABV cause of significant mortality (*8*) Direct kudu–kudu oral transmission suspected
Continental Asia	Red fox (*Vulpes vulpes*)	Found in forest–steppe and steppe zones
Russian far east, northern China and Korean Peninsula	Raccoon dog (*Nyctereutes procyonoides*)	(*9*)

Country or region	Species in which rabies is documented	Note (reference)
Southern China and Taiwan	Ferret badger (*Melogale moschata*)	Considered primary host for human rabies May be sole reservoir host in Taiwan (*10*)
Israel, West Bank, Gaza Strip and Turkey	Red fox (*V. vulpes*)	Sustained RABV spillover from dogs led to recent emergence in Turkey (*11*)
Islamic Republic of Iran, Oman, Saudi Arabia and Yemen	Red fox (*V. vulpes*) Golden jackal (*C. aureus*)	Increasing numbers of cases reported (*12*)
Other countries in Middle East and Asia	Red fox (*V. vulpes*)	Limited phylogenetic evidence suggests that wildlife do not represent an independent transmission cycle in regions where dog rabies is endemic (*13*).
Europe	Red fox (*V. vulpes*)	Northern, western and central Europe free (*14, 15*) Prevalent in eastern and south-eastern Europe
	Raccoon dog (*N. procyonoides*)	Second most frequently reported infected species Presumed to act as another primary wildlife host (*16*) No predominant adapted variant identified
North America	Many primary RABV hosts and overlapping geographical ranges, which poses a challenge to animal rabies control. Each wild species maintains at least one predominant host-adapted RABV but may be infected with other RABV variants. Spillover to other wild and domestic animals is frequent in all areas.	
	Red fox (*V. vulpes*)	Oral vaccination important for control
	Grey fox (*Urocyon cinereoargenteus*)	Primary host, particularly in southwest USA Eliminated in Texas by oral vaccination
	Coyote (*Canis latrans*)	
Eastern Canadian border, USA	Raccoon (*Procyon lotor*)	Primary host (*17*)

Country or region	Species in which rabies is documented	Note (reference)
Polar regions	Arctic fox (*V. lagopus*)	Primary host (*17*) Maintains host-adapted RABV variants of Arctic lineage Arctic-like RABV also found in central and South-East Asia (*18, 19*)
Central plains, California	Striped skunk (*Mephitis mephitis*)	Primary host (*20*)
Mexico	Skunk (*Spilogale* spp.) Coati (*Nasua nasua*)	Primary host
South America	Marmoset (*Callithrix jacchus*) Crab-eating fox (*Cerdocyon thous*) Kinkajou (*Potus flavus*) Coati	Distinct viruses detected in several species (*21–23*) Wildlife surveillance insufficient to make major epidemiological inferences Further information available at http://www.paho.org/panaftosa
Caribbean islands, including Cuba, Dominican Republic, Grenada, Haiti and Puerto Rico	Indian mongoose (*Herpestes auropunctatus*)	Primary host

10.2   Epidemiology and ecology of rabies in bats

Lyssaviruses have been detected in bats throughout the world, although different species are present in different regions (*Table 11*) (see also *Table 3* in *section 3*). Bats have been identified as vectors for all *Lyssavirus* species except Mokola virus and Ikoma lyssavirus (see *section 3*), for which the true primary host are yet to be identified. This observation strongly suggests that bats are true primary hosts for lyssaviruses.

Bats have several traits that are different from those of carnivore rabies hosts, such as small size, long life, low intrinsic population growth rates and a variety of well-defined ecological niches. Consequently, the properties of the lyssaviruses adapted to bats are assumed to be different from those that cause rabies in carnivores. The factors involved in maintenance of lyssaviruses in bats are still poorly understood. Little is known about lyssaviruses that have been isolated only once.

Table 11
Epidemiology and ecology of lyssaviruses in bats

Lyssavirus	Species in which lyssavirus is documented	Note (reference)
Rabies virus	Haematophagous bats, including Common vampire bat (*Desmodus rotundus*) Insectivorous bats, including Silver-haired bat (*Lasionycteris noctivagans*) Big brown bat (*Eptesicus fuscus*) Free-tailed bat (*Tadarida brasiliensis*) Eastern tri-coloured bat (*Perimyotis subflavus*) Mouse-eared bats (*Myotis* spp.)	Distinct variants Frequent spillover to terrestrial animals Major cause of human rabies (*24*)
Lagos bat virus	Eidolon helvum (Nigeria) *Epomophorus* spp. (South Africa) Other bat spp. (Central African Republic, Senegal and South Africa) *Nycteris gambiensis* (Gambia)	No human cases reported to date Infrequent spillover to mammals reported (*25*) Surveillance and virus characterization probably insufficient
Duvenhage virus	*Miniopterus* spp. (South Africa)	First isolated from a person in 1970 in Transvaal, South Africa Human cases of rabies due to Duvenhage lyssavirus were reported twice in South Africa (*6*) and once in The Netherlands (contracted in Kenya) (*1*)
Shimoni bat virus	Commerson leaf-nosed bat (*Hipposideros commersoni*) (Kenya)	First detected in 2009 (*26*)
Australian bat lyssavirus	Frugivorous megabat spp.: *Pteropidae poliocephalus* *P. alecto* *P. scapulatus* *P. conspicillatus* Yellow-bellied sheath-tailed bat (*Saccolaimus flaviventris*)	First detected in 1996 Three confirmed human deaths, in 1996, 1998 and 2013 Spillover to horses detected (*20*)

Lyssavirus	Species in which lyssavirus is documented	Note (reference)
European bat lyssavirus-1	Serotine bats (*Eptesicus serotinus*)	Sporadic cases of rabies diagnosed in bats Surveillance in Europe remains heterogeneous (*27*) Three autochthonous human rabies fatalities confirmed: two in the Russian Federation (1977, 1985) and one in Finland (1985) (*28*)
European bat lyssavirus-2	Myotis bats (*M. dasycneme* and *M. daubentonii*)	One autochthonous human rabies fatality confirmed in Scotland (2002) (*28*)
West Caucasian bat virus	Common bent-wing bat (*Miniopterus schreibersii*)	Isolated in the Russian Federation (2002) (*29*)
Bokeloh bat lyssavirus	Natterer's bat (*Myotis nattererii*)	Isolated in Germany (2010) and France (2012) Antigenically and genetically close to European bat lyssavirus-2 and Khujand virus (*30*)
Lleida bat lyssavirus	*Miniopterus schreibersi*	Isolated on the Iberian Peninsula (2012) (*31*)
Aravan virus	Lesser mouse-eared bat (*Myotis blythi*)	Isolated in an apparently healthy bat in Kyrgyzstan (1991)
Khujand virus	Whiskered bat (*Myotis mystacinus*)	Isolated in Tajikistan (2001) (*32*)
Irkut virus	Tube-nosed bats (*Murina* spp.)	Classified as a lyssavirus in 2002 One human rabies case reported in far-eastern Russian Federation (2007) (*29*)
Gannoruwa bat lyssavirus	Indian flying foxes (*Pteropus medius*)	Isolated once in Sri Lanka (2014) (*33*)

10.2.1 Rabies in insectivorous bats in the Americas

To date, all bat lyssaviruses in the Americas have been categorized as RABV. Since the elimination of dog-mediated rabies in North America, most autochthonous case fatalities in humans are caused by bat-associated RABV (*23*). Many genetically and antigenically distinct variants of RABV circulate in numerous species of insectivorous bats, several within a single species, and the geographical distribution of variants overlaps. There appears to be an inverse correlation between cross-species transmission and phylogenetic distance among insectivorous bat species (*34*). Spillover to terrestrial animals is observed frequently.

10.2.2 Vampire bat rabies

Vampire bat-mediated rabies is a major public health problem in the subtropical and tropical areas of the Americas, from Mexico to Argentina. An RABV variant related to the other American bat viruses is maintained in haematophagous bats, mainly by different subpopulations of the common vampire bat (*Desmodus rotundus*) (see *Table 11*) (*34*), and is transmitted frequently to domestic animals and humans. During the past decade, the incidence of human infection with RABV spread by *D. rotundus* increased considerably in South America, especially in remote areas of the Amazon rainforest, where these bats commonly feed on humans (*35*). Vampire bat-transmitted bovine rabies also has a significant economic effect on the livestock industry.

10.3 Rabies in rodents

Testing of tens of thousands of wild and synanthropic rodents in areas endemic for rabies across the world has revealed only exceptional instances of dead-end spillover of RABV infection. This indicates that rodents are not primary hosts and do not play a role in the transmission or maintenance of rabies. PEP is not indicated after a rodent bite (see *section 8.3.2*).

10.4 Wildlife species of special concern

Frequent spillover of RABV from more abundant primary hosts (such as domestic dogs) is considered to contribute to possible extinction for several of the world's most highly endangered carnivore species. Thus, rabies is a threat to conservation after outbreaks in highly endangered populations of Ethiopian wolves (*Canis simensis*) in the Bale Mountains National Park, in African wild dogs (*Lycaon pictus*) in eastern and southern Africa and in the Blanford's fox (*Vulpes cana*) in Israel. Elimination of dog-mediated rabies would reduce the threat of disease and the risk of extinction of these endangered populations.

Rabies has been recorded in wolves (*Canis lupus*) everywhere in the northern hemisphere where rabies occurs in wildlife; however, wolves become rabid only due to spillover infection and do not play a major role in rabies transmission. Although wolves are susceptible and readily succumb to the disease, they cannot sustain circulation of RABV independently of other wildlife, as wolf population densities and dynamics do not support epizootics and the highly territorial nature of wolves prevents ready spread of the disease from one pack to another. Once a pack member is infected, however, the disease can decimate the pack because of wolves' highly social nature, with regular contact among the animals. The genetic make-up of RABV isolated from wolves is identical to that found in more abundant carnivore primary hosts in their vicinity (either domestic dogs or wild species). Although wolves are not a true primary reservoir,

wolves and most other carnivores (e.g. foxes, coyotes) can transmit RABV to other naive, susceptible hosts. Because they migrate over long distances, wolves that are incubating RABV are believed to reintroduce wildlife rabies into freed areas.

10.5 Elimination of rabies in wild carnivores

10.5.1 Reduction of animal populations

Past strategies for elimination of wildlife rabies included reducing primary host density by culling, on the basis of the rationale that rabies transmission is density-dependent, disease incidence increasing proportionally with host density. Rabies transmission in wildlife may, however, be less dependent on density than was previously assumed; therefore, reducing host population density is unlikely to be effective in controlling or eliminating the disease (*36*). This conclusion is borne out by observations that widescale culling campaigns to reduce wild carnivore populations have failed to eliminate the disease (*37*). Reducing the primary host density is therefore not recommended as a means of controlling rabies in wildlife for humane, economic and ecological reasons.

10.5.2 Immunization

Mass vaccination is a more effective control method than culling and is efficient for reducing disease incidence in all primary wildlife host species. The method emerged independently in Europe and North America, and the ORV strategy originally developed for foxes in the late 1970s has been used to eliminate fox rabies in large parts of northern, western and central Europe, Canada and the USA. Its success was due to the development of effective, safe vaccines, machine-made baits that are attractive to a variety of species, automated, computer-supported aerial bait distribution, adequate vaccination strategies and strong political commitment (*17*).

An ORV strategy that works for one wild carnivore primary host species will not necessarily work for others. While adapted fox ORV strategies have been used quite successfully for other primary wildlife hosts, including coyotes, grey foxes and raccoon dogs, they require optimization for raccoons, for example (*38*). Other strategies are also needed for other primary wildlife hosts, such as mongooses and skunks.

As ORV programmes are designed to eliminate wildlife rabies from a defined area or to prevent spread of the disease by creating an immunological barrier (containment, *cordon sanitaire*), they must result in sufficient herd immunity to reduce transmission (i.e. the effective reproductive rate of the disease falls below 1) in the target primary wild host. The level of herd immunity

required depends on the transmission dynamics of the disease in particular target species and populations and on local conditions.

ORVs used in the field must fulfil the requirements of OIE and WHO as well as national or international regulatory authorities for biological products, i.e. immunogenicity, efficacy, safety and stability, and be licensed or registered (see *section 9.2.3*). Baits should be designed for each target wild animal species to ensure that the vaccine is released onto a susceptible target tissue (oropharyngeal mucosa or tonsils) to elicit an immune response. The bait casing should fulfil three functions: carry the attractant for the target species, contain a biomarkers used in baits (e.g. tetracycline) for assessment of bait uptake by the target population and protect the vaccine blister, capsule or sachet from ultraviolet light to ensure the stability of the virus titre. Specific requirements for bait casings are laid down in relevant standards (*39*). The bait must be thermostable in order to guarantee its palatability and the stability of the vaccine strain titre. It should be tested before marketing authorization at various temperatures under various field conditions of landscape, temperature and humidity (*39*). Vaccine baits distributed from the air should not break when they fall onto the ground. Warning labels should be printed on the blister or bait matrix.

If oral rabies vaccine baits of proven efficacy, stability and bait-casing attractiveness are used, bait uptake and herd immunity in the target population depend on other factors, such as the baiting method, adequate spatial distribution of baits, timing and frequency of ORV campaigns and the abundance of bait competitors.

10.5.3 Planning, implementing and evaluating ORV programmes for wildlife

Oral rabies vaccine has become the essential tool for preventing geographical spread and for controlling and eliminating rabies when the primary host is wildlife. An epidemiological assessment of the prevailing rabies situation based on results from reliable surveillance and laboratory studies of rabies cases in target and non-target species (wild and domestic) is the foundation of ORV programme planning. The basic requirements for planning, implementing and evaluating widescale vaccination campaigns or field trials are available online: https://rabiesblueprint.org/. ORV programmes should include a cost–benefit analysis for public health.

Planning
Strong political commitment is a prerequisite for any ORV programme to ensure its legal framework, planning, organization and evaluation, and an inclusive national rabies committee should be constituted. An effective ORV programme is based on a comprehensive plan that outlines the benefits, the objectives, roles (the agencies to be involved), responsibilities and chains of command as well as

infrastructure (laboratory requirements and equipment, cold chain), time frame of the programme, estimated costs and funding. The plan should also include information on the areas to be covered in consecutive years, taking into account the patterns of movement of wildlife populations, geographical characteristics, the rabies situation in neighbouring countries, the vaccination strategy (timing, mode of bait distribution, bait density, flight line distance), safety considerations and surveillance and monitoring of campaigns. The size of the target population should be estimated, with baseline levels of the biomarker (if applicable) in the target species before implementation of the programme.

As a long-term, widescale approach is the most effective, the programme should be sustainable in the long term, with adequate financial, administrative and logistic support. ORV campaigns should continue for at least 2 years after the last confirmed case of rabies. WHO can provide the necessary expertise upon request.

Implementation

Adequate infrastructure and logistics should be available to guarantee optimal bait distribution (airports, aircraft, storage facility for baits, personnel) and eventual coverage over wide areas. The timing of ORV campaigns and the pattern of distribution of vaccine baits should be based on the biology and habitat of the target species and landscape features. ORV campaigns are usually conducted twice a year, in spring and in autumn, in temperate climate zones (Europe) or once a year in regions with a lower density of target species (North America) and subtropical climate zones (Mediterranean Basin). Bait is delivered mainly from fixed-wing aircraft or helicopters (*38*). Manual distribution should complement aerial distribution or may be the only way to distribute baits in densely populated or settled areas.

Before vaccine bait is distributed, local meetings should be organized by the national rabies committee for all stakeholders, including hunters, trappers, wildlife service staff, forest officers, physicians, veterinarians and local authorities, to discuss the programme in detail and agree on the responsibilities of each. Press releases to inform the public should be issued, with information on the area to be covered by the programme, the timing of campaigns and appropriate measures to be taken in case of accidental exposure to the vaccine.

Appropriate storage, transport conditions and cold-chain requirements should be strictly adhered to during handling and delivery of vaccine baits in the field. In Europe, for example, the optimal pattern for the distribution of vaccine bait is parallel flight lines approximately 500 m apart, although the flight line distances may be adapted according to the population density of the target species and landscape features. A global positioning system (GPS) and digital recording of flight routes and the coordinates of bait drops may be used during aerial distribution.

Adequate laboratory facilities and trained personnel should be available to conduct the recommended standard tests for routine diagnosis of rabies (see *section 5*) and for monitoring campaigns by detecting biomarkers, serology, virus titration and characterization of RABV isolates. Quality assurance systems should be in place.

Evaluation

The responsible authorities and personnel should be sensitized to the importance of adequate surveillance and monitoring of ORV campaigns. This includes sampling of specimens, timely reporting of rabies cases, database management, timely epidemiological data analysis and interpretation of results to monitor the progress of the vaccination campaign. Regular dissemination of information to stakeholders, including competent authorities, is crucial. Specialists should be assigned to investigate the prevailing and changing epidemiological situation in both humans and animals, evaluate the campaign and report regularly to the responsible authorities. National meetings should be held with all stakeholders to discuss the progress of the programme and any adaptation of the strategy that might be required for future campaigns.

Surveillance and monitoring of the effectiveness of vaccination are important for assessing and adjusting vaccination campaigns. The incidence of rabies is the main indicator of the performance of any ORV programme and for certifying freedom from disease. A risk-based sampling scheme should be used, in which "indicator animals" that are ill, suspected of being rabid, have abnormal behaviour, are found dead or were involved in human exposure are examined. The number of animals should be sufficient to demonstrate a statistically acceptable degree of certainty (*40*). Surveillance should generally be conducted before, during and after distribution of vaccine, not only in the vaccination areas but also in neighbouring areas, particularly those free of rabies, in order to detect spread of the epizootic or re-infection as early as possible to ensure a swift response and countermeasures. RABV isolated from animals in the vaccination area should be characterized.

The efficacy of ORV programmes with respect to bait uptake, seroprevalence and characterization of RABV isolates is measured by adequate sampling of hunted or trapped animals of the target species. In the USA, for example, the programme consists of pre- and post-bait serology and targeted (e.g. "roadkill" and reports of "nuisance" animals) public health surveillance. Reference zones for monitoring ORV campaigns should be selected in the vaccination area, in which a statistically sufficient, homogeneously distributed sample can be guaranteed in order to test for the presence of tetracycline (used in baits) and serological markers in the target species.

Basic denominators, e.g. species, dates of finding and submission, location (latitude and longitude), age, sex, results of laboratory investigations (fluorescent antibody or cell culture isolation test, virus characterization, biomarker detection, serology) should be collected for all animals for epidemiological analyses, including temporal and spatial patterns. To eliminate rabies in wildlife, "progressive control pathways" and procedures for international certification of rabies-free status should be established.

International cooperation

International cooperation and coordination in planning, implementing and evaluating ORV programmes ensure success and cost–effectiveness. Contact should be made with neighbouring countries in deciding on a policy and should be maintained until the disease is eliminated. Regular multilateral meetings with representatives of the public health and veterinary authorities of neighbouring regions and countries ensure coordination of activities along common borders and transparency. Involvement of WHO collaborating centres, OIE reference laboratories and other international organizations is recommended. Presentation of the results of ORV programmes at international conferences helps maintain awareness and commitment to rabies elimination.

Other options

Strategic trapping of wild carnivores and releasing them after parenteral vaccination (trap–vaccinate–release) has been used with apparent success in some areas of North America, primarily for skunks and raccoons (*39*).

10.6   Control of rabies in bats

Eliminating the disease in bats is challenged by the lack of effective vaccines against many of the lyssaviruses and lack of effective delivery systems for bat vaccination. Therefore, elimination of bat rabies not feasible. The public health risk associated with bat rabies (except that transmitted by vampire bats) is lower than that associated with rabies in carnivores, although the consequences of infection are also severe.

Chiroptera play an important role in global ecology, such as in seed dispersal and pollination of many valuable plants, thereby restoring cleared or damaged rainforests and ensuring the production of fruit that support local economies and diverse animal populations. Furthermore, many of the more than 1300 bat species consume vast amounts of insects, including some of the most damaging agricultural pests. Therefore, any method for indiscriminate destruction of bats should be excluded, especially as nonhaematophagous bats are protected in most countries.

Education of the public is the key to preventing bat-transmitted human rabies. This should include basic information on avoiding potentially infectious contact with bats, seeking proper medical attention after exposure and preventing bats from establishing colonies in "sensitive" buildings such as hospitals and schools.

Vampire bat-transmitted bovine rabies can be controlled by vaccinating cattle and by other sanitary measures, such as identifying, monitoring and georeferencing natural and artificial shelters of haematophagous bats. In national sanitary legislation in many Latin America countries, the approach to controlling vampire bat-transmitted rabies is to control the population of the primary host species, which has been successful in preventing rabies in cattle populations. Current strategies should be reviewed and updated, with studies to promote innovation in the control of haematophagous bats. As for other potential exposure to rabies, prompt PEP is recommended in cases of human exposure to vampire bats. Given the high exposure of some remote populations to vampire bat rabies, preventive vaccination of populations living in highly enzootic areas with limited access to anti-rabies biologicals should be considered.

10.7   Other public health measures

The general public should be better advised to avoid direct contact with wildlife in general and with animals that are behaving abnormally and are sick in particular. Anyone bitten by a wild or domestic animal, particularly in areas where wildlife rabies is endemic, should seek medical attention (see *section 8.3*). In countries that have been declared free of terrestrial rabies, it is important that the public be aware that anyone potentially exposed to bat rabies should receive prompt PEP. Translocation of wildlife for any purpose except conservation should be banned or strongly discouraged.

10.8   References

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11.   Surveillance of rabies

Effective control and elimination of a disease require effective surveillance. Public health surveillance consists of continuous, systematic collection, analysis, interpretation and dissemination of information on health events (*1, 2*). Its aim may be to demonstrate the presence and distribution of the disease in humans and animals as part of control, improve awareness of the situation or, ultimately, document the absence of disease (*3*). According to this definition, surveillance is always linked to specific control activities and immediate response and is therefore distinct from monitoring. Monitoring is conducted intermittently and consists of analysis of routine processes within a surveillance system or intervention. In rabies control, monitoring may include cross-sectional measurements of animal populations and vaccination coverage, observation of marks applied to dogs during mass parenteral vaccination or bait uptake after oral vaccination campaigns (*4*). Less systematic monitoring may include cross-sectional measurements of animal populations and vaccination coverage in certain activities. Further details of monitoring in ORV programmes and enhanced surveillance of wildlife are given in section 10. The capacity to detect, assess, notify and report on health events is a critical component of the International Health Regulations (2005) (*5*) and a principle of high-quality veterinary services.

11.1 Surveillance systems

The design and implementation of a surveillance system should be customized to stated public health objectives or interventions (*6, 7*). With respect to rabies, the interventions should be adapted to the epidemiology of the disease and capacity in the areas of study. During the endemic phase, if there is no systematic rabies control, the main objective should be to determine the disease burden in humans and animals spatiotemporally and in populations at risk. In practice, surveillance at this stage may be passive, as cases are likely to be detected even if fewer humans or animals are evaluated, because of the high incidence of disease. Other than the diagnostic tests for animals involved in human exposure, those described in *section 5* and in Chapter 2.1.17 of the OIE *Manual of diagnostic tests and vaccines for terrestrial animals* (*8*) may be used to supplement "gold-standard" diagnostics, such as direct fluorescent antibody and direct rapid immunohistochemical tests, to increase the case detection rate when resources or logistics might otherwise make confirmatory testing impossible (*9*). The objectives of surveillance should be adapted as rabies control programmes are established in an area. In addition to continued passive public health surveillance, targeted, active monitoring is necessary to verify animal vaccination and other interventions. Use of more sensitive, gold-standard diagnostic tests and ensuring the proficiency of the staff who conduct the tests become increasingly important as control is extended. The quality of surveillance data is directly related to its use to inform management decisions about interventions. As control activities reduce the number of human rabies cases to zero (validation) and eventually result in elimination of rabies in the targeted animals (verification), additional surveillance will be necessary, as discussed in *section 12*.

Regardless of the state of rabies control, the probability of detecting rabies during surveillance is a function of its incidence, the level of awareness and vigilance and also appropriate infrastructure and logistics to collect and transport samples to confirm rabies. To promote awareness and vigilance and to ensure that rabies is recognized as a priority, human and animal rabies must be notifiable nationally. Standard case definitions (*Tables 12* and *13*) should be disseminated widely by national health and veterinary services. Surveillance data should be reported through appropriate channels according to published protocols to facilitate timely data-sharing and analysis, when possible through existing national electronic surveillance or health management information systems for infectious disease reporting.

Table 12
Animal case definitions and corresponding surveillance activity

Case	Definition	Surveillance activity
Suspected	A case that is compatible with a clinical case definition of animal rabies Clinical case definition: An animal that presents with any of the following signs (*10, 14*) ▪ hypersalivation, ▪ paralysis, ▪ lethargy, ▪ unprovoked abnormal aggression (biting two or more people or animals and/or inanimate objects), ▪ abnormal vocalization and ▪ diurnal activity of nocturnal species	Notify appropriate local authorities of a suspected rabid animal. Collect the primary history of an animal if available (ownership status, vaccination status, previous exposure, date of onset of signs) (see *Annex 2*). Collect central nervous system samples for laboratory diagnosis, if available.
Probable	A suspected case plus a reliable history of contact with a suspected, probably or confirmed rabid animal and/or An animal with suspected rabies that is killed, died or disappears within 4–5 days of observation of illness	Systematically record secondary information, and link to primary history. Notify the appropriate authorities according to national protocols.
Confirmed	A suspected or probable animal case confirmed in a laboratory[a]	Notify the appropriate authorities for follow-up of any human or animal exposure. Systematically record laboratory diagnosis, and link with case record.
Not a case	A suspected or probable case that is ruled out by laboratory tests or epidemiological investigation (i.e. appropriate quarantine period in eligible animals).	Notify the appropriate authorities for follow-up of any human or animal exposure. Systematically record laboratory diagnosis, and link with primary history.

[a] Laboratory confirmation should be performed with a standard diagnostic test, as defined by WHO (see *section 5*) or the OIE manual (*8*). If other diagnostic tests are used, depending on their sensitivity and specificity, confirmation with a validated secondary test may be required, particularly in the case of negative results.

Table 13
Human case definitions and corresponding surveillance activity

Case	Definition	Surveillance activity
Suspected	A case that is compatible with the clinical case definition: a person presenting with an acute neurological syndrome (i.e. encephalitis) dominated by forms of hyperactivity (furious rabies) or a paralytic syndrome (paralytic rabies) that progresses towards coma and death, usually due to cardiac or respiratory failure, typically within 7–10 days of the first sign if no intensive care is instituted. The syndrome may include any of the following signs: aerophobia, hydrophobia, paraesthesia or localized pain, dysphagia, localized weakness, nausea or vomiting.	Notify the appropriate local authorities according to national protocols. Collect appropriate samples from the patient according to national protocols. Conduct a verbal autopsy to collect a case history for the patient for further characterization (*Annex 11*).
Probable	A suspected case plus a reliable history of contact with a suspected, probably or confirmed rabid animal (see *Table 12*).	Identify contacts of the patient and/or animal involved for follow-up.
Confirmed	A suspected or probable case that is confirmed in a laboratory.[a]	Systematically record the laboratory diagnosis and link with verbal autopsy information. Notify the appropriate authorities of a confirmed human rabies case according to national protocols.

[a]   Ante-mortem diagnosis of human rabies depends on the samples collected and the diagnostic tests available (see *section 5*).

The minimum epidemiological indicators to be provided by rabies surveillance are information on the annual incidence of the disease in both humans and animals and the incidence of PEP (as a proxy for suspected and confirmed exposure to rabies) (*Table 14*). Measures of incidence are essential in

rabies control and prevention to ensure appropriate management of cases and outbreaks, to monitor trends, to evaluate the effectiveness of interventions and to estimate the burden of disease. Measurement of rabies-specific antibodies is not recommended for routine rabies surveillance.

Table 14
Monitoring use of human rabies post-exposure prophylaxis

	Exposure or PEP category	Surveillance activity
Suspected exposure	Person presenting for health care with a history of a bite, scratch or contact with infectious material from a suspected, probably or confirmed rabid animal (see *Table 12*).	Assess risk (see *section 8*) according to national protocols to determine whether additional investigation is required.
PEP received	PEP has been recommended for the person with suspected exposure. and The person has received at least one dose of rabies vaccine and/or rabies immunoglobulin.	The appropriate authorities notified according to national standard protocol. As indicated by protocols, investigation of exposure to identify the suspected rabid animal and whether other people or animals were exposed. Systematic recording of information from the investigation. Systematic recording of information on the patient receiving PEP, including basic demographics and the date biologicals were received, until completed or lost to follow-up.
PEP not received	A person with suspected exposure who has been recommended for PEP and A person who did not receive rabies vaccine or rabies immunoglobulin	When indicated, initiate investigation of suspected exposure in order to document why PEP was not initiated and to identify suspected rabid animals and further exposure. Appropriate authorities notified according to the national standard protocol.

Optimal surveillance will target all cases of suspected human and animal rabies. Case definitions should facilitate systematic recognition of suspected cases and further categorization of cases on the basis of clinical, epidemiological and diagnostic features. Surveillance protocols should specify the activities required for each case classification (e.g. suspected case is identified, local health authorities notified, primary data collection started). Surveillance and case management

protocols should be circulated to the relevant people and officials in the reporting structure. Diagnostic confirmation is the gold standard for human and animal cases, although clinical cases may also be confirmed by verbal autopsy (*Annex 11*) for human cases and by evaluating dogs according to the case definitions (*Table 12*) and on the investigation form (*Annex 12*).

Active surveillance of healthy animals to which human exposure has not been reported rarely returns valuable surveillance data, because large numbers of animals must be tested to identify a single rabies case. When the large number of negative animals is aggregated into passive surveillance data, the proportion of cases observed among animals at higher risk (e.g. involved in human exposures, "roadkill") may be diluted, suggesting a lower overall risk of exposure to rabies if not interpreted correctly. Animal health professionals (e.g. private and public veterinarians, veterinary paraprofessionals, animal control officers and game wardens) are those most likely to see a clinically rabid animal in a professional setting. They are also most likely to be engaged in animal rabies surveillance at community level, where cases are first identified. They should be aware of the clinical signs in a suspected case, methods for sample collection and the process for reporting.

All components typically intersect when a person has been bitten by a suspected rabid animal. "Integrated bite case management" involves conducting investigations of suspected rabid animals and sharing information with both animal and human health investigators for appropriate risk assessments (*section 8*). Such programmes are resource intensive but ultimately help to prevent human deaths from rabies by active identification of suspected exposure (particularly in areas endemic for dog-mediated rabies) and can improve the overall quality of surveillance (*10, 12*). Bites should trigger immediate triage, including determining the vaccination status of the biting animal and follow-up if rabies is suspected, such as by observing the animal (10 days for cats and dogs) or testing post mortem. Furthermore, a timely response by medical and veterinary staff in the field ensures appropriate management and follow-up of cases and improves case detection rates; it can also motivate field and hospital staff to continue reporting cases. The response should include prompt feedback on reports and diagnostic test results, advice on management of cases and rabies control measures to be taken. In countries where rabies control programmes are well established, integrated bite case management may ensure more targeted use of PEP on the basis of risk assessments and diagnostic input, thus reducing administration of PEP for low-risk exposure.

In addition to routine reporting, epidemiological analysis of surveillance data allows estimation of trends and spatial dynamics; understanding of trends by species (including humans) is the foundation for any intervention programme. Such analyses should be done routinely (e.g. monthly) and more detailed reports at least annually. The basic trends should be estimated for the numbers of investigations and cases (for human PEP, rabid humans and rabid animals, see *Tables 12–14*). Maps of surveillance data should be drawn to identify the distribution of cases. When possible, both cases and non-cases reported to the surveillance system should be mapped in order to identify any gaps in surveillance coverage that might be responsible for a lack of observed cases. More detailed reports should include control activities and their impact on the rabies burden.

The surveillance system should also be monitored and evaluated routinely to determine whether the surveillance objectives are being achieved and to improve the overall system (*1, 5*). Routine monitoring may include assessment of the timeliness and completeness of monthly reporting. Action should be taken when deficiencies are identified to ensure that annual results can be analysed promptly and accurately. Surveillance systems should periodically be evaluated more extensively (e.g. every few years or if the objectives change) to ensure that they are operating efficiently and delivering high-quality data that are useful for public health interventions. Guidelines for evaluating a public health surveillance system have been published (*1*).

In all situations and particularly in areas in which elimination is the aim, routine characterization of virus isolates from human and animal cases is encouraged in order to identify the sources of infection and their geographical origin (*13*). Surveillance of humans and animals should be maintained even after elimination, with viral characterization to document importation of rabies or unrecognized domestic circulation of rabies (*3*).

11.2   Global reporting

Timely notification of animal rabies cases to the OIE through the World Animal Health Information System (www.oie.int/wahid) is a legal obligation of OIE members (*3*). For transparency and to allow comparison and aggregation of global data for advocacy, national data should be shared with other regional and global reporting systems, such as the WHO Global Health Observatory (http://www.who.int/gho/neglected_diseases/rabies/en/), the WHO District Health Information Software system (version 2; DHIS2) and other regional databases, such as the Rabies Bulletin Europe (http://www.who-rabies-bulletin.

org/); the Regional Information System for Epidemiological Surveillance of Rabies (SIRVERA; sirvera.panaftosa.org.br/index.php) and the System of Epidemiological Inormation on Rabies (SIEPI) in Latin America; and the Rabies epidemiological bulletin of the Pan-African Rabies Control Network (PARACON) in Africa (paracon.rabiesalliance.org/bulletin/).

A template has been prepared for recording minimum data for indicators (*Annex 13*). It can be completed online by downloading it at: http://www.who.int/rabies/advancing_global_rabies_data_collection/en/. It is part of an integrated platform for surveillance and control of neglected tropical diseases (based on DHIS2) to facilitate integration of disease-specific surveillance activities into a more efficient, sustainable health information system. Many programmes of the Neglected Tropical Diseases and other WHO departments, including on tuberculosis, HIV/AIDS, malaria, health information systems and information management and technology, collaborate to build in-house capacity and support integration. At global level, the system will act as a data warehouse for good-quality data and permit the identification and analysis of trends and monitoring and evaluation of all programmes at a single site. The platform will also contribute to validation or verification of elimination goals (see *section 12*). Publicly available data will continue to be displayed on the Global Health Observatory. When possible, the operators of these global and regional reporting systems should collaborate to improve interoperability among the systems in order to reduce redundant data requests and entries by national authorities.

11.3   References

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12.   Reaching zero human deaths from rabies

With a global target of zero human deaths due to dog-mediated rabies by 2030, worldwide, harmonized processes are required to acknowledge and measure country progress towards this goal (*1*). The processes must allow for differing states of advancement, i.e. some countries have yet to reach zero human rabies deaths (see validation, below), while others have, or are close to, interrupting rabies disease transmission.

Fig. 5 is based on country data and shows rabies elimination (in terms of canine and human rabies cases) in a continuum of five phases, from endemicity, to elimination, to maintaining freedom from disease. "Endemic" indicates the number of confirmed rabies cases per month in an endemic country with limited control measures in place. "Control" indicates a steep decrease in rabies incidence after mass interventions. "Zero Human Deaths" shows interruption of dog–human rabies transmission and no human deaths. "Elimination" shows interruption of rabies transmission and no canine cases. "Maintenance" refers to continuing freedom from disease, e.g. by preventing incursion and/or re-emergence of canine or human rabies.

Figure 5

Progression of countries from endemic rabies to elimination of dog-mediated rabies by implementation of sustained mass dog vaccination programmes
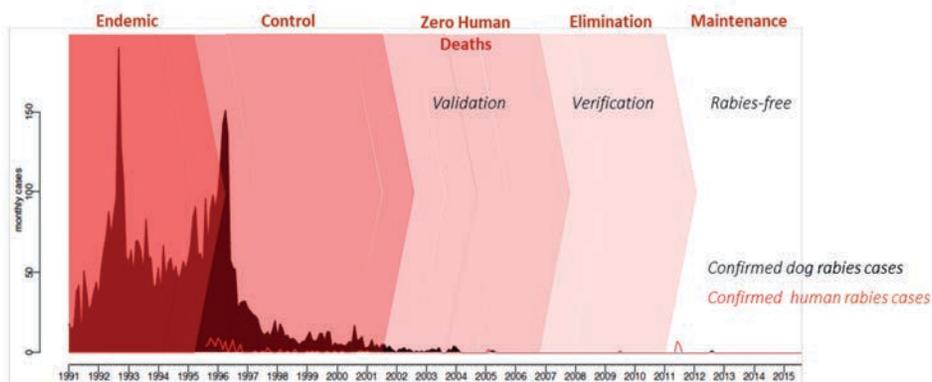
This aim of this section is to define activities that allow countries to:

- Validate elimination of rabies as a public health problem, i.e. reaching zero human rabies deaths, defined as the absence of a human death from dog-mediated rabies for at least 24 months in a country that is operating and continues to maintain adequate surveillance for rabies and demonstrates an effective rabies control programme in human and animal populations. The occurrence of cases caused by rabies variants other than canine rabies should not preclude validation of reaching zero human rabies deaths or verification of interrupting rabies transmission. Validation of reaching zero human rabies deaths will be conducted by WHO in a desk review of evidence (see *section 12.3* and *Annex 14*).

- Verify elimination of dog-mediated rabies, i.e. interrupting rabies transmission, defined as the absence of dog-mediated rabies cases for a period of at least 24 months in the presence of high-quality surveillance according to international standards. The proposed procedures for verification of the interruption of rabies disease transmission are being discussed with the international organizations involved (see *section 12.4* and *Annex 14*).

- Be declared rabies-free, which follows from verification, and recognizes countries or areas that are free of both dog rabies and terrestrial rabies. The aim of these definitions is to assist public health authorities in assessing the risk for contracting rabies after contact with animals. They differ from the current OIE definition of rabies-free countries for the purpose of animal movement (*2*).

A country or area that is free of dog rabies is one in which:

- No case of indigenously acquired infection due to dog-mediated RABV has been confirmed in humans, dogs or cats or any other animal species at any time during the previous 24 months.

- Any autochthonous positive case was shown by molecular characterization and epidemiological investigation to be a spillover from wildlife. If an imported case in carnivores is confirmed, the status of the country or area shall not be affected if molecular characterization confirms the non-indigenous source of the virus, and epidemiological tracing backwards and forwards reveals no evidence of secondary dog infections.

A country or area that is free of terrestrial rabies is one in which:

- No case of indigenously acquired infection due to dog-mediated RABV or wild carnivore RABV has been confirmed in humans or any domestic or wild animal species (excluding bats) at any time during the previous 24 months.

- Any autochthonous positive case was shown by molecular characterization and epidemiological investigation to be a spillover from bats (both bat rabies variants and bat lyssaviruses).

If an imported case is confirmed, the status of the country or area shall not be affected if a risk assessment and/or molecular characterization confirms the nonindigenous source of the virus and epidemiological tracing backwards and forwards reveals no evidence of secondary infections in any wild or domestic carnivore. Laboratory-confirmed infection in some wild animals (e.g. mongooses) should be considered an indicator of the presence and circulation of rabies.

12.1   Core elements of validation, verification and rabies-freedom

Measures to validate rabies freedom must be underpinned by robust evidence and data that can be assessed independently, as premature cessation of control could result in resurgence of the disease, with major public health, economic and political ramifications. The core requirements for validation, verification and rabies-freedom are as follows.

- Rabies in all animal species and humans is notifiable.

- Continuous, effective surveillance is in operation and meets WHO and OIE standards for surveillance and diagnostic testing (see *sections 5* and *11*).

- Adequate, targeted sampling is performed among the main susceptible domestic and wild animal species throughout the country.

- A national rabies control strategy (with mass dog vaccination and access to human PEP) has been effective in controlling rabies.

- Measures to prevent importation of rabies-infected animals are in place (see *section 9.3*).

Sections *12.2* and *12.3* provide more detailed summaries of the proposed processes for validation and verification, respectively.

Regional platforms for data collection ensure consistency among regions and sufficiency for both validation and verification, e.g. *European rabies bulletin, the Rabies epidemiological bulletin* of the Pan-African Rabies Control Network (PARACON) and the Regional Information System for Epidemiological Surveillance of Rabies in Latin America. Timely notification to OIE through the World Animal Health Information System and, when appropriate, to regional platforms for data collection is required. These platforms should support submission of data on essential indicators for validation and verification and also provide a valuable repository of dossiers containing information for other countries and regions.

The objective of all countries in endemic regions is to reach zero human rabies deaths and, ultimately, to interrupt dog-mediated rabies transmission nationally and then regionally. As in the model for poliomyelitis, annual regional meetings could be held to review rabies-free documentation submitted by national programme coordinators or relevant OIE delegates after 2 years without detection of a case under enhanced surveillance, leading to regional verification of interrupting rabies disease transmission.

12.2   Validation of zero human deaths from rabies

Indicator: Absence of human deaths from rabies for 24 months

For a country to be recognized internationally as having eliminated rabies as a public health problem, with zero human deaths over 24 months, rabies must be notifiable in humans and animals, and the country must provide evidence of:

- an effective national rabies control and elimination strategy;

- a decrease in the number of dog rabies cases due to implementation of the national rabies control and elimination strategy; and

- a decrease in the number of human deaths from rabies due to im-plementation of the national rabies control and elimination strategy.

If a country has verified interruption of transmission of dog-mediated rabies (see below), it will be considered also to have validated elimination of rabies as a public health problem.

Annex 14 presents a draft template for the proposed documentation required to validate reaching zero human deaths from rabies.

12.3   Verification of interruption of rabies transmission

The following is proposed as a means of verifying the interruption of rabies transmission; however, the requirements for verification remain under discussion.

Indicator: Absence of dog-mediated rabies cases for 24 months

For a country to be recognized internationally as having eliminated dog-mediated rabies, rabies must be notifiable in humans and animals, the country should be able to document the absence of dog-mediated rabies cases (i.e. the absence of animal cases due to a canine RABV variant) for at least 24 months and provide evidence:

- of a post-elimination strategy or contingency plan that covers access to dog vaccine and PEP, procedures for surveillance and epidemiological investigation of any introduction of rabies from other countries or regions;

- that the decrease in the number of cases of dog-mediated animal rabies to zero is due to implementation of the national rabies elimination strategy; and

- maintenance of zero dog-mediated human rabies cases.

Given the time required for verification, countries are recommended to first self-declare freedom from dog-mediated rabies, according to OIE procedures (*3*). The documentation required for an OIE self-declaration will subsequently be taken into consideration and reviewed to verify that rabies transmission has been interrupted. *Annex 14* shows a template of the proposed dossier required to verify interruption of rabies disease transmission.

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13. Global and regional activities on rabies

Since rabies was identified as a tripartite (WHO, FAO and OIE) priority in 2011, the disease has become a model for a coordinated "one health" approach between the human and the animal health sectors (*1, 2*). This commitment was renewed in 2017, with the launch of an updated tripartite concept note (*3*). In 2015, WHO and OIE, in collaboration with FAO and the Global Alliance for Rabies Control (GARC), organized a global rabies conference in Geneva, bringing together partners and stakeholders in veterinary and human health, government and the private sector (*4*), and launched the *Global framework for the elimination of dog-mediated human rabies*, outlining the commitment and actions required to achieve a common goal of zero human rabies deaths by 2030, worldwide (*5*). Many partners contribute to the prevention, control and elimination of human and animal rabies at global, regional and national levels, including the Association of South-East Asian Nations (ASEAN), the South Asian Association for Regional Cooperation, Humane Society International, Mission Rabies, Vets Beyond Borders, World Animal Protection and the Bill & Melinda Gates Foundation. They aid in preparing global standards and policies, resource mobilization, regional coordination and direct support of national programmes.

13.1 WHO global and regional activities

13.1.1 WHO headquarters

WHO sets global norms and standards, engages partners and stakeholders and supports countries in the control and elimination of rabies. Since 2002, WHO has maintained a website that provides information on rabies in humans and animals, awareness materials and a selection of WHO reports and peer-reviewed articles (http://www.who.int/rabies/en/).

WHO facilitates data collection on human rabies cases around the world and is working with OIE to harmonize country, regional and global reporting systems for animal (through the World Animal Health Information System) and human rabies (through WHO). Data have been used to generate maps of global rabies distribution (*6*), which are also published on the Global Health Observatory (http://www.who.int/gho/neglected_diseases/rabies/en/), so that they can be shared among stakeholders and sectors.

Between 2009 and 2015, WHO managed a rabies elimination pilot programmes funded by the Bill & Melinda Gates Foundation in KwaZulu–Natal, South Africa, south-eastern United Republic of Tanzania and the Visayas archipelago in the Philippines (*7*). The success of these projects in reducing the numbers of cases of canine and human rabies provides proof of concept that

rabies elimination is feasible in various country contexts. Lessons learnt from the projects are now being used in international initiatives to catalyse rabies control (*8*).

Since the launch of the Global framework, WHO has been working with partners to prepare a global strategic plan to end human deaths from dog-mediated rabies by 2030. This includes a country-centric approach, with international partners (WHO, FAO, OIE and GARC) to support, empower and catalyse national entities to control and eliminate rabies.

In 2017, WHO revised its *Position on rabies vaccine and rabies immunoglobulins*, which was endorsed by the Strategic Advisory Group of Experts on Immunization. The updated document provides more feasible programme recommendations to improve access to affordable rabies biologicals, especially for underserved populations. The PEP and PrEP regimens and guidance for the prudent use of vaccine and RIG have also been updated. It has been estimated that using the updated intradermal PEP regimen would allow almost 500 additional patients to be treated for every 1000 vials of rabies vaccine, an increase over the numbers treated with traditional intramuscular regimens such as the Essen.

WHO is building the evidence base for inclusion of human rabies vaccine in the 2018 Vaccine Investment Strategy of Gavi, the Vaccine Alliance. If successful, this would ensure subsidized access to human rabies vaccine in low- and middle-income, Gavi-eligible countries. In 2013, Gavi invested in evaluating the operational feasibility, public health impact and cost of improving access to rabies PEP in low-income settings in Africa and Asia. Studies were conducted in over 20 countries to characterize PEP distribution and delivery systems, the demand for rabies vaccine and how vaccine needs can be forecast. The studies clarified the availability, accessibility and cost of PEP and RIG, by country and in urban and rural areas, indicating the causes and risk factors for:

- the limited availability and supply of PEP in some countries,

- underreporting of rabies cases,

- lack of regular monitoring of PEP use and

- patients not seeking or not completing PEP.

Stock-outs were frequent, due to either low budget allocation for rabies biologicals at central level, ineffective use of PEP at treatment centres and/or lack of accurate vaccine forecasting. In all the countries, the projects triggered additional activities, such as updating of the national rabies strategy or guidelines and improving rabies reporting and surveillance systems.

13.1.2 WHO regional offices

South-East Asia

The WHO Regional Office for South-East Asia has been proactive in preparing standards and guidelines, issuing recommendations and providing technical support to Member States for the prevention and control of human and animal rabies in the Region. It advocates use of cost–effective intradermal vaccination to improve the availability and affordability of modern rabies vaccines and phasing out of the production and use of nerve tissue vaccine. Nerve tissue vaccines have now been abandoned in Bangladesh, Cambodia, India, the Lao People's Democratic Republic, Myanmar, Nepal, Pakistan and Viet Nam. In Bangladesh, India and Sri Lanka, practical training was conducted for medical and veterinary laboratory professionals in the use of DRIT and direct fluorescent antibody tests for rabies diagnosis.

The aim of the ASEAN regional elimination strategy is to eliminate human rabies in the Region by 2020 by progressive control of dog rabies and human prophylaxis in rabies-endemic countries and maintaining the status of rabies-free areas (*9, 10*). WHO is working with the ASEAN Secretariat, member countries, FAO and OIE to provide technical support for the development and implementation of the strategy.

The WHO Regional Office for South-East Asia is also working with the Secretariat of the South Asian Association for Regional Cooperation and member countries to advocate for regionally coordinated rabies control activities in South Asia. A workshop on prevention and control of rabies in the Region, held in Colombo, Sri Lanka, in 2015, recommended strengthening of rabies surveillance, laboratory networks, dog vaccination campaigns and humane dog population management (*11*).

Americas

In 1983, the Veterinary Public Health unit of the Pan American Health Organization (PAHO)/WHO Regional Office for the Americas began an official programme for elimination of dog-mediated human rabies in the Americas. The initial objective was to eliminate rabies from the principal cities of Latin America. In 1992, the objective was extended to include elimination of dog-mediated human rabies in small conglomerates and rural areas. Since its inception, the programme has resulted in a decrease by more than 90% in the numbers of human and canine rabies cases in the Americas.

The programme made surveillance a priority and improved access to human prophylaxis, mass dog vaccination and good governance. The Regional Information System for Epidemiologic Surveillance of Rabies in the Americas (http://sirvera.panaftosa.org.br/) issues reports on human and animal rabies on the basis of official data entered by health and agriculture ministries in Member

States. Data from 1970 onwards are available for consultation on-line. From the PAHO revolving fund, PAHO Member States can procure high-quality, life-saving human rabies vaccines and immunoglobulin for prophylaxis. In 2015, procuration of canine rabies vaccine was included in the revolving fund for national rabies programmes for use in dog mass vaccination campaigns.

Every 2 years, a meeting is convened of the Directors of National Programs for the Prevention and Control of Rabies (REDIPRA) in the Americas to discuss and update the epidemiological situation and strategies for the prevention and control of rabies. The conclusions and recommendations of REDIPRA are submitted for their consideration and endorsement to ministers of health and agriculture during high-level inter-American ministerial meetings on health and agriculture, organized by PAHO's department of Veterinary Public Health. In 2016, during the 59th Directing Council of PAHO, Resolution CD55. R9 was approved, which includes the *Plan of action for the elimination of neglected infectious diseases and post-elimination actions for 2016–2022* and promotes elimination of dog-mediated human rabies in all remaining areas of the Americas by 2022 or earlier (*12*).

13.1.3 WHO network of collaborating centres on rabies

A network of WHO collaborating centres on rabies support WHO activities at country, intercountry, regional, interregional and global levels (http://apps.who.int/whocc/List.aspx?tor=rabies&). The collaborating centres strengthen the institutional capacity of Member States by providing information, services, research and training for rabies-related activities, including diagnosis, surveillance, research, monitoring and evaluation of human and animal rabies elimination programmes.

Collaborating centres are officially designated by WHO on the basis of a jointly agreed work plan, usually for 4 years, which is renewable after annual evaluation of their performance by WHO. The work plan depends on the expertise or specificity of the centre but usually covers:

- collection, collation and dissemination of information on rabies;

- standardization of rabies diagnostic reagents and prophylactic and therapeutic substances, as well as methods and procedures for their application;

- design and application of appropriate techniques;

- provision of reference substances and other services;

- participation in collaborative research under the Organization's leadership;

- training, including research training; and

- coordination of activities carried out by several institutions.

There are 14 designated WHO collaborating centres for reference research on rabies. Four are in Asia, five in Europe and five in the Americas (*Annex 15*).

13.2   Examples of activities by partners

The three major international organizations involved in rabies (WHO, FAO and OIE) and GARC, as well as nongovernmental organizations, animal welfare organizations and other public and private stakeholders are united to reduce the global burden of rabies.

13.2.1 Global activities

Food and Agriculture Organization of the United Nations (FAO)

FAO contributes to rabies control by raising awareness and providing policy advice and technical support for animal rabies control. It is supporting the establishment of animal health clubs in schools in Sierra Leone and has a special interest in the impact of rabies on livestock production (*13*). As part of the stepwise approach towards rabies elimination, FAO has organized global stakeholder consultations on rabies prevention in Africa, the Caucasus and Asia to assist countries in identifying their needs with regard to rabies control (*14*).

At country level, FAO has sent missions of its Emergency Management Centre–Animal Health to control rabies outbreaks in Bali, Indonesia, and Viet Nam. In Bali, this led to integrated bite case management, with improved communication between the human and animal health sectors and team training to ensure successful capture and vaccination of street dogs that are difficult to handle (*15*). FAO strengthens diagnostic capacity through the Institute for Experimental Zooprophylaxis in Venice, Italy (the FAO reference centre for rabies) and the Network of West African Rabies Laboratories (RESOLAB) and by conducting proficiency testing in laboratories in southern Africa.

FAO is also involved in dog population management and, with World Animal Protection, conducted training on dog catching, handling and vaccination after a rabies outbreak in the Republic of the Congo (*16*). In 2013, rabies was listed as a priority in the FAO *Global framework for the progressive control of transboundary animal diseases* (*17*).

World Organisation for Animal Health (OIE)

The OIE is an intergovernmental organization that issues science-based standards, guidelines and recommendations for the improvement of animal health and welfare while promoting strong veterinary services worldwide.

Internationally agreed diagnostic laboratory methods and requirements for the production and control of animal rabies vaccines and other biological products are published in the OIE *Manual of diagnostic tests and vaccines for terrestrial animals* (*18*). The OIE Terrestrial animal health code (*19*) lists measures adopted internationally for the control of rabies in animals and for control of the stray dog population, which includes promotion of responsible dog ownership.

The World Animal Health Information System (www.oie.int/wahid) is a global online web-based notification system that supports OIE Member Countries in reporting animal rabies. The "performance of veterinary services pathway", a laboratory twinning programme and the network of reference laboratories and collaborating centres provide policy advice, strategy design and technical assistance for the diagnosis, control and elimination of rabies in animals and aid countries in strengthening their veterinary services, laboratories, surveillance and reporting.

At the 2016 OIE World Assembly of the Delegates, Member Countries agreed to maintain the efforts to foster political will and long-term social commitment towards rabies elimination (*20*). They requested the OIE and interested parties to sustain their commitment to the elimination of dog-mediated human rabies by 2030 as a priority in the public interest.

Global Alliance for Rabies Control (GARC), Partners for Rabies Prevention and World Rabies Day

GARC is the foremost registered charity dedicated specifically to reducing the global burden of rabies. Its mission is to eliminate human deaths from rabies and to relieve the burden of rabies in animals, especially dogs (www.rabiesalliance.org/).

GARC was instrumental in establishing the Partners for Rabies Prevention (*21*), an informal group that comprises the main international agencies with an interest in rabies, including WHO, FAO, OIE, WHO and OIE rabies collaborating centres and reference laboratories, nongovernmental organizations for animal welfare, networks of rabies experts and representatives of industry. The Partners for Rabies Prevention have initiated studies and projects for control activities and advocacy for rabies elimination, including: a reassessment of the global burden of dog-mediated rabies (*22*), a global survey of rabies notifiability (*23*) and the *Blueprint for rabies prevention and control* (*24*), which includes the stepwise approach to rabies elimination (*25*).

GARC's World Rabies Day campaign (rabiesalliance.org/world-rabies-day/) was initiated in 2006 to raise awareness and mobilize resources for prevention of human rabies and control of animal rabies. During the past 10 years, the campaign has held 1717 registered events in 116 countries, with activities ranging from awareness campaigns to dog walks to professional training seminars, which

have resulted in announcements of improvements to rabies control policies by governments (*26*).

More recently, GARC has organized several certificate courses to build capacity in rabies control, which are freely available from the GARC educational platform (https://rabiesalliance.org/ capacity-building/gep). The courses include a rabies educator certificate (to train community educators), an animal handling and vaccination certificate (for animal health technicians and dog vaccination staff), a community caregivers certificate (for community volunteers) and a community health care certificate (for health care professionals).

Mission Rabies

Mission Rabies is an international nongovernmental organization that implements rabies elimination programmes in endemic regions. Flagship projects are based in the Indian state of Goa, Ranchi city in Jharkhand and the southern region of Malawi through partnership with local governments. The campaigns include mass dog vaccination, rabies education, community awareness and surveillance of dog-mediated rabies. A unique smartphone app based on geospatial technology has been developed to improve epidemiological assessment of control strategies and direct teams to remote areas. To date, over 800 000 data entries have been made on the platform in Asia, Africa and Europe. In 2016, a total of 213 423 dogs were vaccinated, 540 000 children were taught about rabies, and 64 rabid dogs tested positive for rabies. The Malawi campaign is based on a combination of central and door-to-door vaccination, while in the campaigns in India a net catch–vaccinate–release and door-to-door approaches are used. In Goa, financial support for the campaign is provided by the Government of Goa, and FAT testing facilities have been established in the Government diagnostic investigation unit to provide timely testing and reporting of rabies cases. Since an increase in rabies control in 2014, the number of reported human deaths from rabies has fallen from 17 in 2014, to 5 in 2015 and 1 in 2016. Pilot campaigns have also been undertaken in Sri Lanka, Uganda and the United Republic of Tanzania through partner organizations to support effective field protocols for wider application.

World Animal Protection

World Animal Protection is an international nongovernmental organization committed to ending cruelty to animals; it has particular expertise in managing free-roaming dogs in communities around the world. The organization works with governments and international bodies, including WHO, OIE, FAO and GARC, other nongovernmental organizations and local communities to ensure that dog populations are managed humanely (www.worldanimalprotection.org).

World Animal Protection advocates a "one health" approach to managing

dog populations and for effective, ethical, sustainable interventions to create harmonious coexistence between dogs and people (*27*). The aim of their "Red collar" campaign in 2011–2016 was to end inhumane culling of dogs in response to rabies in Bangladesh, China, Indonesia, the Philippines and the United Republic of Tanzania (Zanzibar). In Africa, World Animal Protection is working with the Government of Kenya to pilot test their national rabies elimination strategy and with Sierra Leone in development of their national rabies elimination and dog population management strategy. It works in partnership with GARC in rabies elimination in several other African countries through PARACON and is also working in Brazil, China and Costa Rica to develop a "one health" dog population management approach.

13.2.2 Regional networks

Africa
PARACON was founded in 2015 to strengthen the capacity of a network of rabies experts in Africa. It resulted from the merging of the Southern and Eastern African Rabies Group and the African Rabies Expert Bureau and included African countries that were not previously associated with either organization. Through workshops held through PARACON and similar regional networks, GARC and international partners use tools such as the "rabies blueprint" and the stepwise approach to rabies elimination to support countries in progressing towards elimination of dog-mediated rabies (*28*). The new PARACON *Epidemiological bulletin* will improve the collection and visibility of surveillance and other data necessary to monitor the progress of control (*29*).

Americas
In Latin America, the REDIPRA is held every 2 years to review strategies for rabies control, make recommendations for countries and coordinate the regional response. The 15th REDIPRA, held in Brazil in 2015, urged surveillance of the last sites of dog-mediated rabies (*30*). In 2015, a subgroup was created for Bolivia, Chile, Colombia, Ecuador, Peru and Venezuela, coordinated by PANAFTOSA–PAHO, the Andean Health Organization and the Amazon Cooperation Treaty Organization. An international conference on rabies in the Americas (http://www.rabiesintheamericas.org/) is organized annually to review and discuss rabies research and control in the region. The meeting has an international committee consisting of members from Brazil, Canada, Mexico and the USA.

Asia
WHO, FAO and OIE have established a functional coordination mechanism for intersectoral collaboration to prevent and control zoonoses

in the Asia–Pacific, supported by the European Commission-funded "highly pathogenic emerging diseases" project, established in 2010 (*31*). A tripartite workshop has since been organized to operationalize the "one health" concept in Member countries.

WHO, the Institut Pasteur and the University of Lausanne organized the first international training course on rabies surveillance and control for Asian countries in Phnom Penh, Cambodia, in October 2015 to establish networks of local champions in seven countries. The course was first held in Senegal in 2013 and was conducted in Cambodia in 2015 and in Cameroon in 2016. The next course will be organized in Tehran, Islamic Republic of Iran, in October 2017 for countries in the Middle East and Central Asia.

Europe

The WHO Rabies bulletin Europe was created in 1977 and is hosted by the WHO Collaborating Centre for Rabies Surveillance and Research at the Friedrich-Loeffler Institute in Germany. The database is used in more than 40 European countries to report confirmed rabies cases in humans and in wild and domestic animal species every 3 months. Aggregated country and surveillance data maps are freely available online (www.who-rabies-bulletin.org/). Human rabies cases and the epidemiology of rabies are also presented in *Eurosurveillance*, a peer-reviewed scientific journal published by the European Centre for Disease Prevention and Control (http://www.eurosurveillance.org/)

The European Union rabies subgroup of the task force on the eradication of animal diseases comprises private and governmental experts. Its task is to assess and provide recommendations on co-financed ORV campaigns in European member states and neighbouring non-member countries. The reports are publicly available online (http://ec.europa.eu/food/animals/animal-diseases_en).

Since 2008, the European Union Reference Laboratory for Rabies in Nancy, France, has organized annual meetings of European national rabies laboratories to standardize diagnostic techniques.

Middle and Near East

The Middle East and eastern Europe rabies expert bureau is an inter-regional network established in 2010. It is composed of representatives of countries in Central Asia, Europe, the Middle East and North Africa that are enzootic for rabies, who work to improve rabies control and prevention at local, regional and global levels. The members met for the third time in 2015 in Lyon, France, to review the current rabies situation in the network and to discuss use of the "one health" approach against rabies (*32*).

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14.   Research

The areas for future research are means for limiting the impact of rabies on individuals and populations and evidence and new tools to improve prevention and management strategies, including improved delivery of interventions for humans and animals. The areas identified as priorities for future research are listed below.

14.1   Improve programmatic delivery of rabies interventions

Better methods for delivering interventions in current programmes for both human and animal rabies are needed. In operational research, well-designed protocols, rigorous statistical standards and unbiased sampling are essential. In the evaluation of interventions, appropriate comparison groups should be included, when possible. Research should include:

- Innovation and development of new vaccines in collaboration with manufacturers to optimize cost–effectiveness, delivery in the community, easy storage, thermostability and shelf-life, while maintaining vaccine safety and efficacy.

- Innovative, cost–effective methods for delivering rabies biologicals to remote populations with limited or no access to health care. The methods being considered include training of health care staff in intradermal administration of rabies vaccines, innovation in the controlled temperature chain, research to facilitate administration of rabies vaccines (e.g. subcutaneously), coordinated use of existing cold chains and decentralization of animal-bite treatment clinics.

- Proof-of-concept studies on the impact of bite prevention education in reducing the number of dog bites and the potential exposure of people to rabies.

- Refinement of the current recommendations to achieve vaccination of 70% of the dog population to interrupt rabies transmission. These should indicate whether targeted vaccination of dogs at risk in high-transmission areas should be a priority.

- Applied research on integration of dog rabies control into other human and animal health programmes.

14.2 Improve the quality and availability of data on rabies

Accurate data on the disease burden and risk are essential for setting regional, national and subnational priorities for rabies prevention and control. Research is required to improve diagnostic and surveillance capability, particularly in low-resource, endemic settings. The priorities include:

- Evaluation of novel methods for improving surveillance in endemic settings, such as proof-of-concept studies of the role of integrated bite case management (*1*), verbal autopsy, testing of encephalitic patients (*2*) and new technology to improve rabies case detection and reporting.

- Innovation in strategies to enhance uptake of decentralized, field-based rabies diagnostics and evaluation of their impact on the effectiveness (i.e. sensitivity, representiveness and timeliness) of surveillance, for example by optimizing methods for collecting and preparing diagnostic samples in the field or at the bedside or by developing and validating a sensitive, specific ante-mortem test suitable for use in the field or at points of care.

- Robust, sustainable data capture platforms to facilitate the flow of data from the field to central health services and regional and global repositories. This would improve estimates of the global, regional and country burdens of rabies. Modelling could be used to obtain estimates if there are gaps in the available data.

- International standards for rabies diagnosis, including for molecular techniques, and means for quality control of rabies diagnostic testing to ensure reliable results.

- Methods to quantify the strength of rabies surveillance systems that could be used in conjunction with processes to validate and verify the attainment of zero human rabies deaths (see *section 12*). This might include better understanding of the processes responsible for the maintenance and elimination of rabies in certain geographical locations and viral characterization to infer linkages among infections and establish the origin of transmission.

14.3 Evidence and new tools to improve the prevention and management of rabies

New tools can simplify programme delivery, improve diagnostic capacity and make PEP and RIG more affordable. With regard to rabies biologicals, research should be done to obtain robust clinical data on the immunological outcomes of accelerated PEP and PrEP schedules and on alternatives to RIG, such as mAbs. The priorities include:

- Further research on the cost–effectiveness, feasibility and potential of novel tools for vaccine delivery, such as needle-free jet injection, microneedle injection systems and topical patches.

- Use of novel immunocontraceptive products to improve management of animal populations and to combine surgical or non-surgical sterilization with parenteral or oral rabies vaccination (*3*). These should be tested in dogs that can be closely monitored to determine humaneness, long-term effect at population level, feasibility and cost–effectiveness.

- Protocols for data and sample size to prove the non-inferiority of new PEP and PrEP regimens, which would also be important for establishing regulation of rabies biologicals and other novel products such as mAbs.

- Recommendations for immunization of individuals with repeated exposure, optimal spacing of PEP and the number of boosters over a lifetime. Better understanding of the factors that determine seroconversion and clinical outcomes in immunocompromised individuals would be helpful.

- Vaccines that protect against other lyssavirus strains (i.e. phylogroup II and III lyssaviruses) could be investigated as multivalent vaccines, and further studies should be conducted on the activation and protection induced by novel vaccine carriers and adjuvants when used for PEP. Characterization of new lyssavirus species should indicate whether commercially available rabies biologicals are likely to be protective.

- Studies on intravenous administration of RIG (particularly for non-bite exposures) and the levels of antibody required for passive immunization and their duration (particularly for mAbs).

▪ Development and validation of effective therapeutics for PEP and/ or antiviral therapy for the treatment of clinically rabid patients (see *section 6*). Novel therapies should be validated only in well-resourced reference centres with trained teams experienced (or under expert guidance) in managing rabies patients, with ethically accepted protocols, after discussions with the family and a collegial decision and after other life-threatening but curable illnesses (differential diagnoses to rabies encephalitis) have been ruled out.

The Consultation emphasized the importance of programme-directed research to overcome current challenges in rabies control, which will catalyse efforts to reach the global goal of zero human rabies deaths by 2030, worldwide. Beyond that goal, research should be conducted on interruption of rabies transmission, monitoring of rabies-free status and broadening the research agenda to include lyssaviruses other than rabies. These research priorities may be biased, as the survey was open only to the participants of the meeting. Overall, research should improve public health outcomes for populations at risk of rabies.

14.4   References

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15.   Concluding remarks

Dr Rungrueng Kitphati (Director, Thailand Department of Disease Control) closed the meeting by thanking the participants, the organizers, the media and Chulalongkorn University on behalf of the Thai Ministry of Public Health. Dr Bernadette Abela-Ridder thanked Chulalongkorn University and the organizers, working groups and participants for their contributions, input and advocacy.

Dr Gowri Yale, Mission Rabies, shared a success story from Goa, a small Indian state with a population of approximately 2.4 million and an estimated 150 000 dogs. Since 2013, the project has vaccinated 50 000 dogs annually and has provided an education team to build awareness of rabies in schools and communities and a hotline to signal rabid dogs for removal. Human deaths from rabies per year in Goa decreased from 24 to 5, and no cases have been reported thus far in 2017. This compelling example adds to the body evidence that rabies elimination is feasible with existing tools. Sustained commitment, collaboration and support to implement control measures remain the key to reaching zero human rabies deaths by 2030, worldwide.

16.   Acknowledgements

Annexes

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Annex 2.   Record form for cases of possible exposure to rabies

Case no.:   Date: Time:

Patient details

Name: Age: Sex:

Address:

Telephone (home and mobile):

Telephone (work):

GP and Tel:

Details of exposure

Country and town: Date of exposure:

Date of travel:

Nature of exposure: bite/lick/saliva/scratch/other (to specify):

Site of exposure:

Was the skin broken?   Yes/No   Did the wound/s bleed?   Yes/No

Number of wounds:

Depth of bite(s):   Superficial/deep   WHO category of exposure: I / II / III:

Details of animal

Type of animal: wild/domestic   Species:

Bite: provoked/unprovoked: (details):

Is the animal's owner/home known?   Yes/No

Were efforts made to trace the animal?   Yes/No

When was the animal last seen alive?

Animal's vaccination status, if known:

Details of treatment

Rabies vaccination history of the patient:

Did s/he previously receive at least two doses of intramuscular/intradermal rabies vaccination, either as pre-exposure or post-exposure prophylaxis? Yes/No

Details (day/ date/ vaccine name / batch no):

Did s/he previously receive rabies immunoglobulin? Yes/No

Details (date / type (eRIG/hRIG/mAb) / location / volume):

Other information:

Contact on-call virologist/physician for advice with above information.

If unavailable, contact:

Was anti-rabies post-exposure prophylaxis given previously?   Yes/No

Which rabies vaccine was given?

Details (day/date etc.):

Was rabies immunoglobulin given?   Yes/No

Locally/systemically: Other information

Contact on-call virologist/physician for advice with above information

If unavailable, contact:

Recommended treatment

Thorough wound washing with water/ soap/ antiviral agent.

Rabies immunoglobulin:

Human rabies immunoglobulin, max dose 20 IU/kg body weight

Equine rabies immunoglobulin, max dose 40 IU/kg body weight

Injection site:

Patient weight (kg):   Volume recommended (IU and mL):

Post-exposure course arranged?   Yes/No

- ▪ Rabies vaccination (recommended for WHO category II and III exposures):
- – Three-day, two-site intradermal: days 0 and 3 (2 sites)
- – Three-day, one-site intramuscular: days 0 and 3 (1 site)
- – One-day, four-site intradermal: day 0 (4 sites)

- ▪ Standard course for non-previously immunized people*:
- – One-week, two-site intradermal: (2 sites) days 0, 3 and 7
- – Two-week, one-site intramuscular: (1 site) days 0, 3, 7, and between days 14 to 28
- – Three-week intramuscular: days 0 (2 sites), 7 (one site), and 21 (one site)
- – Other (specify)

* People are considered previously vaccinated for rabies if they received at least two doses of intramuscular/intradermal rabies vaccination, either as pre-exposure or post-exposure prophylaxis.

General practitioner informed via letter/e-mail/phone/SMS text? Yes/No

Name, telephone and signature of completing physician:

Annex 3. Human rabies vaccines and producers worldwide, as of August 2017

Vaccine	Brand	Producer	Country	Cell line	WHO prequalified	Type
PVRV	N/A	Butantan Institute	Brazil	Vero cells	No	Liquid
HDCV	Chengdu Kanghua	Chengdu Kanghua	China	Human diploid cells	No	Lyophilized
PVRV	SPEEDA	Liaoning Chengda Co.	China	Vero cells	No	Lyophilized
PVRV	N/A	Changchun Changsheng Life Sciences Ltd.	China	Vero cells	No	Lyophilized
PVRV	N/A	Guangzhou Nuocheng Biological Products Co.	China	Vero cells	No	Lyophilized
PVRV	N/A	Ningbo RongAn Biological Pharmaceutical Co.	China	Vero cells	No	Lyophilized
PVRV	N/A	Jilin Maifeng Biological Pharmaceutical Co.	China	Hamster kidney cells	No	Liquid
PPHKCV	N/A	Zhongke Biological Pharmaceutical Co.	China	Hamster kidney cells	No	Liquid
PPHKCV	N/A	Henan Yuanda Biological Pharmaceutical Co	China	Vero cells	No	Liquid
PIKA, inactivated, with TLR3-based adjuvant		Yisheng Biopharma Inc.	China	Vero cells	No	?
PVRV	Verorab	Sanofi Pasteur	France	Vero cells	Yes	Lyophilized

Vaccine	Brand	Producer	Country	Cell line	WHO prequali-fied	Type
HDCV	Imovax	Sanofi Pasteur	France	Human diploid cells	No	Lyophilized
PCECV	Rabavert	GSK	Germany	Chick embryo cells	Yes	Lyophilized
PCECV	Rabipur	GSK	India	Chick embryo cells	Yes	Lyophilized
HDCV	Rabivax	Serum Institute of India	France	Human diploid cells	No	Liquid
PDEV	Lyssavac-N /Vaxirab	Zydus-Cadila	India	Duck embryo cells	Production stopped	Lyophilized
PCECV	Vaxirab-N	Zydus-Cadila	India	Chick embryo cells	No, successor of Vaxirab	Lyophilized
PVRV	Indirab	Bharat Biotech	India	Vero cells	No	Lyophilized
PVRV	Abhayrab	Indian Immunologicals	India	Vero cells	No	Lyophilized
BHKV	Kokav Vaccination	Tarasevich Institute	Russian Federation	Hamster kidney cells	No	?
NTV	?	Pasteur Institute Algiers	Algeria	Mouse brain	No	Liquid?
NTV	?	?	Argentina	Sheep brain?	No	Liquid?
NTV	?	?	Bolivia	Mouse brain	No	Liquid?
NTV	?	Ethiopian Public Health Institute	Ethiopia	Sheep brain?	No	Liquid?

BHKV, baby hamster kidney cell vaccine; HDCV, human diploid cell vaccine; N/A, not available; NTV, nerve tissue vaccine; PCECV, purified chick embryo cell vaccine; PDEV, purified duck embryo cell vaccine; PPHKCV, purified primary hamster kidney cell vaccine; PVRV, purified Vero cell vaccine

Annex 4. Four steps for replacing nerve tissue vaccine by modern rabies vaccines produced on cell culture or embryonated eggs

Countries that are still producing or using neural tissue-based vaccines should follow this four-step strategy to replace nerve tissue vaccines by modern vaccines.

Step 1: Relevant national authorities, usually under the leadership of national health authorities, should make the final decision to change from nerve tissue vaccines to modern vaccines. After reviewing the safety, immunogenicity and efficacy of modern vaccines, the authorities should evaluate the local conditions and assess the feasibility and cost of replacing nerve tissue vaccine. Consideration should be given to the use of the cost-saving intradermal regimens for rabies pre- and post-exposure prophylaxis.

Step 2: National guidelines should be formulated that give clear instructions on use of modern vaccines for pre- and post-exposure prophylaxis, including indications for their use and routes of administration; similarly, guidance should be given for use of rabies immunoglobulin and other products. The guidelines should be drawn up by technically competent experts on the basis of the recommendations in reports of the WHO Expert Advisory Group on Rabies, other WHO advisory groups, up-to-date scientific literature, the experience of international and national experts and observations. They should be disseminated to all centres that provide pre- and post-exposure prophylaxis. The guidelines must be based on clear policies concerning, e.g. vaccine subsidy (if any) and handling leftover vaccine, and should be regularly updated.

Step 3: Rabies centres should receive a constant supply of safe, effective, WHO-recommended rabies vaccines and immunoglobulin from a central office. Once the decision is made to stop nerve tissue vaccine production and use, the procurement of modern vaccines should start, to avoid any gap in provision of treatment when the nerve tissue vaccine supplies run out. Coordination with regulatory bodies for registration of new rabies biologicals and for post-marketing surveillance of new rabies vaccines and rabies immunoglobulin is also important.

Step 4: A network of specialized bite centres should be set up, in which the staff are trained in giving pre- and post-exposure prophylaxis and managing adverse reactions; adequate quantities of rabies biologicals at these centres must be ensured. A referral system should be established to maximize the benefit of the intradermal regimen and to reduce the amount of leftover vaccine. A quality assurance system should be instituted, with standards that are followed by all centres. Provincial and municipal governments should be involved in establishing new centres, ensuring a sustainable supply of rabies vaccines, immunoglobulin and other supplies and guaranteeing reporting, investigation of human rabies cases and monitoring of the rabies programme.

Annex 5. Rabies immunoglobulin (RIG) products and producers worldwide, as of August 2017

Category	Product name or brand name	Formula-tion	Vial size	Company	Country
eRIG	Anti-rabies serum	N/A	N/A	Butantan Institute	Brazil
eRIG	CARIG (enzyme refine)	300 IU/mL	4 mL	Cadila Pharma	India
eRIG	Rabix-IG	200 IU/mL	5 mL	Incepta Pharmacueticals	India
eRIG	Abhay-RIG	300 IU/mL	5 mL	Indian Immunological	India
eRIG	Anti-rabies serum	300 IU/mL	5 mL	Haffkine	India
eRIG	EquiRab	300 IU/mL	5 mL	Bharat Serums and Vaccines	India
eRIG	Pars	200 IU/mL	5 mL	Newgen (Cadila Pharmaceuticals Ltd)	India
eRIG	Anti-rabies serum	300 IU/mL	5 mL	Serum Institute of India	India
eRIG	Anti-rabies serum	300 IU/mL	5 mL	Central Research Institute Kasauli HP	India
eRIG	Plasmarab	300 IU/mL	5 mL	Premium Serums	India
eRIG	TRCS eRIG	200 IU/mL	5 mL	Queen Saovabha Memorial Institute	Thailand
hRIG	Human rabies immunoglobulin	100 IU/mL	2 or 5 mL	Hualan Biological Bacterin Co.	China
hRIG	Human rabies immunoglobulin	100 IU/mL	1, 2 or 5 mL	Sichuan Yuanda Shuyang Pharmaceutical Co. Ltd	China
hRIG	Human rabies immunoglobulin	100, 200 or 500 IU/vial	N/A	China National Biotec Group (Sinopharm subsidiary)	China
hRIG	Human rabies immunoglobulin	200 IU/vial	2 mL	China Biologic Product, Inc.	China
hRIG	Imogram Rabies-HT	150 IU/mL	2 or 10 mL	Sanofi Pasteur	France

Category	Product name or brand name	Formula-tion	Vial size	Company	Country
hRIG	Pars	150 IU/mL	2 mL	Newgen (Cadila Pharmaceuticals Ltd)	India
hRIG	Berirab-P	150 IU/mL	2 or 5 mL	Bharat Serums and Vaccines	India
hRIG	Rabglob	150 IU/mL	2 or 5 mL	Bharat Biotech International Ltd	India
hRIG	KamRAB/ KedRAB	150 IU/mL	2 or 10 mL	Kamada Ltd	Israel
hRIG	Human rabies immunoglobulin	150 IU/mL	500 IU	Bio Products Laboratory Limited	United Kingdom
hRIG	HyperRAB S/D	150 IU/mL	2 or 10 mL	Grifols USA	USA
hRIG	Rabigam	150 IU/mL	2 mL	National Bioproducts	South Africa
RmAb	Rabishield	40 or 100 IU/mL	2.5 mL	Serum Institute of India	India

Annex 6.   Technique for intradermal administration of rabies vaccine and precautions to be taken

The intradermal route is safe, immunogenic and more cost–effective than the standard intramuscular route and is therefore recommended, especially when vaccine and financial resources are in limited supply. Rabies vaccines labelled for intramuscular use can be used safely via the intradermal route, even if this constitutes off-label use.

Intradermal administration can be used for immunocompromised individuals or individuals receiving chloroquine, hydroxychloroquine drugs or long-term corticosteroid or other immunosuppressive therapy.

As the volume of an intradermal vaccine dose is smaller than that of an intramuscular dose, the intradermal route is especially suitable for treating many patients at the same centre, i.e. within the recommended period of 6 h after reconstitution of the vaccine. As currently available rabies vaccines do not contain preservatives, they must be refrigerated after reconstitution and must be discarded after 6 h.

Preliminary steps before administering rabies vaccine intradermally:

Before administering rabies vaccine intradermally:

- All staff must be adequately trained in the intradermal injection technique.

- If the vaccine is given as part of post-exposure prophylaxis, additional steps should be followed; i.e. the wound must be washed and, if applicable, the appropriate dose of rabies immunoglobulin administered.

- An appropriate 1.0-mL syringe (insulin or tuberculin syringe) and a short, fine hypodermic needle should be used. More costs are saved if a fixed-needle syringe is used, as the void volume is reduced.

- The intradermal schedule should be selected. WHO recommends the 1-week, two-site intradermal regimen (2-2-2-0-0) for post-exposure prophylaxis (see *section 8.3.3*).

Administering rabies vaccine intradermally
Step 1

Aseptically reconstitute the vaccine immediately before administration with the appropriate volume of diluent provided by the manufacturer. Do not use a different diluent or a different amount of diluent.

Draw enough vaccine into the syringe to inject a single patient, using appropriate sterile precautions. Carefully remove any air bubbles.

Disinfect the injection site with antiseptic, then stretch the surface of the skin and insert the tip of the needle (bevelled edge facing upwards) into the upper layer of the skin (dermis), ensuring that the needle and syringe are almost parallel to the skin surface.

Step 2

BBegin injecting the vaccine. If the needle is in the correct position, there is considerable resistance.

A raised papule, which looks like orange peel, will appear immediately, measuring 6-8 mm in diameter.

If the vaccine is injected easily, or if the papule does not appear, it has been given subcutaneously, i.e. too deeply. In such cases, the correct injection should be repeated.

Step 3

Once all doses of 0.1 mL of vaccine have been injected into the same patient, discard the needle and the syringe.

Reconstituted vaccine can be used for more than one patient; however, a sterile syringe and needle must be used to draw up vaccine for each patient.

The reconstituted vaccine must be stored in a refrigerator at 2-8 °C and used within 6 h.

Annex 7. Sites for intramuscular and intradermal administration of human rabies vaccine

Intramuscular and intradermal human rabies vaccine administration

Deltoid muscles for adults and children

Do NOT inject in the gluteal region

Anterolateral thigh for infants and small children

REMINDER

Bite wounds:

15 minutes

Wash immediately for 15 minutes, with soap, water and disinfectant

Annex 8. Recommended post-exposure prophylaxis according to type of exposure

Category of exposure	Type of exposure to a domestic or wild animal suspected or confirmed to be rabid or animal unavailable for testing	Recommended post-exposure prophylaxis
I	Touching or feeding animals, licks on intact skin (no exposure)	None, if reliable case history is available[a]
I I	Nibbling of uncovered skin Minor scratches or abrasions without bleeding (exposure)	Administer vaccine immediately Stop treatment if animal remains healthy throughout an observation period of 10 days[b] or is proven to be negative for rabies by a reliable laboratory using appropriate diagnostic techniques. Treat as category III if bat exposure involved.
I I I	Single or multiple transdermal[c] bites or scratches, contamination of mucous membrane or broken skin with saliva from animal licks, exposures due to direct contact with bats (severe exposure).	Administer rabies vaccine immediately, and rabies immunoglobulin, preferably as soon as possible after initiation of post-exposure prophylaxis. Rabies immunoglobulin can be injected up to 7 days after administration of first vaccine dose. Stop treatment if animal remains healthy throughout an observation period of 10 days or is proven to be negative for rabies by a reliable laboratory using appropriate diagnostic techniques.

[a] If an apparently healthy dog or cat in or from a low-risk area is placed under observation, treatment may be delayed.

[b] This observation period applies only to dogs and cats. Except for threatened or endangered species, other domestic and wild animals suspected of being rabid should be euthanized and their tissues examined for the presence of rabies antigen by appropriate laboratory techniques.

[c] Bites especially on the head, neck, face, hands and genitals are category III exposures because of the rich innervation of these areas.

Annex 9.   Suggested rabies vaccination certificates for humans

The vaccination certificate below is provided as a model. Certificates should be kept carefully by the vaccinated person with his or her personal health documents. Blank certificates should be supplied by the manufacturer of the vaccines.

Certificate of pre- or post-exposure rabies vaccination

Name:

Date of birth: Sex:

Address:

Telephone no.:

For pre-exposure prophylaxis, see 2.1.

Post-exposure prophylaxis

Date of exposure: WHO category of exposure: I / II / III

Biting animal: healthy/sick   Animal vaccinated for rabies: Yes / No

RABV neutralizing antibody titre/ method:

Observations after 10 days (when relevant):

Treatment details

1. Wound washed with water/soap/antiviral agent: Yes / No

    Rabies immunoglobulin

Date of treatment: Clinic / hospital name:

Place:

Type of rabies immunoglobulin: human/equine/mAb

Name of rabies immunoglobulin:

Manufacturer (batch no. / expiry date):

Patient weight: Dose (IU):

Total volume infiltrated into and around wound (mL):

2. Rabies vaccination for pre- or post-exposure prophylaxis

2.1 Pre-exposure vaccination regimens:

- One week, two-site intradermal: days 0 and 7

- One week, one-site intramuscular: days 0 and 7

2.2 Modified post-exposure vaccination regimen (for people immunized previously*):

- Three-day, two-site intradermal: days 0 and 3
- Three-day, one-site intramuscular: days 0 and 3
- Single-day, four-site intradermal: day 0

2.3 Post-exposure vaccination regimen (for people not previously immunized*):

- One-week, two-site intradermal: days 0, 3 and 7
- Two-week, one-site intramuscular: days 0, 3, 7 and between days 14–28
- Three-week intramuscular: days 0 (2 sites), 7 (one site) and 21 (one site)
- Other (specify)

* People who have received at least two sessions of intramuscular or intradermal rabies vaccination, as either pre- or post-exposure prophylaxis, are considered previously immunized against rabies.

Pre- or post-exposure prophylaxis vaccination record

Date of vaccination	Day 0	Day 3	Day 7	Day 14	Day 21	Day 28
Date of vaccination						
Vaccination centre/Place						
Vaccine type/name						
Manufacturer (batch no.)/ Expiry date						
Dose (mL)						
Route (intradermal or intramuscular)						
Site of vaccination						
Adverse event, if any						
RABV neutralizing antibody titre, if done/ method						
Signature of physician						

General remarks (if any):

Annex 10. Currently available oral rabies vaccine products

Vaccine strain	Product name or brand name	Formulation	Vial size	Company	Country
SPBN-GASGAS	IDT Biologika	RABV	3rd	Reverse genetics with site-directed mutagenesis	Licensed for wildlife
ERA G333	Prokov	RABV	3rd	Reverse genetics with site-directed mutagenesis	Licensed for wildlife
SAG2*	Virbac	RABV	2nd	Monoclonal selection mutant	Licensed for wildlife
SAD B19	IDT Biologika	RABV	1st	Serial (passaged in vivo/in vitro)	Licensed for wildlife
SAD Bern	Bioveta	RABV	1st	Serial (passaged in vivo/ in vitro)	Licensed for wildlife
RB-97	FGBI "ARRAIH"	RABV	1st	Serial (passaged in vivo/ in vitro)	Licensed for wildlife
VRC-RZ2	No information	RABV	1st	Serial (passaged in vivo/ in vitro)	No information
KMIEV-94	No information	RABV	1st	Serial (passaged in vivo/ in vitro)	No information
V-RG*	Merial	Vaccinia virus		Recombinant, expressing rabies glycoprotein	Licensed for wildlife
AdRG1.3	Artemis Technologies	Adenovirus		Recombinant, expressing rabies glycoprotein	Licensed for wildlife

Annex 11. Verbal autopsy questionnaire

Suspected rabies

Name of interviewer: _____ Date of interview: – – / – – / – – – –

Name of deceased: _____

State/Province:_____City/Locality: _____

Street: _____

GPS coordinate: _____ / _____

I. Information about respondent

1.1 Name of main respondent _____

1.2 Contact information

State/Province:_____ City/Locality: _____

Street: _____

GPS coordinate: _____ / _____

1.3 Age of main respondent _____ (in years)

1.4 To the main respondent:

What was your relationship to [deceased's name]?

- Parent
- Spouse
- Sibling
- Child
- Son-in-law or daughter-in-law
- Parent-in-law
- Friend or neighbour
- Community leader
- Health care worker (facility name): _____
- Other (specify)_____

II. Information about patient

2. Demographics

2.1 Country of origin of deceased: _____

2.2 Ethnic group (optional) _____

2.3 Nationality (optional) _____

2.4 Sex _____

2.5 Age (years) _____ Unknown

2.5.1 For infants, record the most appropriate: Month(s) _____Week(s) _____ Days _____

2.6 Occupation _____

2.7 Level of education

- ▪ Illiterate
- ▪ Below primary
- ▪ Primary or middle
- ▪ Secondary or high
- ▪ College graduate
- ▪ Postgraduate
- ▪ Professional degree
- ▪ Other (specify) _____
- ▪ Unknown

III. Exposure (during previous 12 months)

3.1 Did any family pets or livestock die during the 12 months before the patient's illness?

- ▪ Yes (Date of death: – – / – – / – – – –)
- ▪ No
- ▪ Unknown

3.2 Did [deceased's name] have any contact with animals (bite, scratch, lick) within the 12 months before the illness that led to death?

- ▪ No
- ▪ Yes
- ▪ Unknown

3.3 If yes, please describe the animal contact events

	Animal 1	Animal 2	Animal 3
3.3.1 On what date did [deceased] have contact with this animal?	– – / – – / – – – –	– – / – – / – – – –	– – / – – / – – – –
3.3.2 What type of animal?	– Dog – Cat – Bat – Livestock – Other: _____	– Dog – Cat – Bat – Livestock – Other: _____	– Dog – Cat – Bat – Livestock – Other: _____
3.3.3 Was the animal owned?	– Owned by deceased – Owned by community – Not owned – Wild – Unknown	– Owned by deceased – Owned by community – Not owned – Wild – Unknown	– Owned by deceased – Owned by community – Not owned – Wild – Unknown
3.3.4 Did the animal have any signs of disease (Describe)?	☐Yes ☐No ☐Unknown – Aggression – Paralysis – Biting – Hypersalivation – Lethargy – Other:	☐Yes ☐No ☐Unknown – Aggression – Paralysis – Biting – Hypersalivation – Lethargy – Other:	☐Yes ☐No ☐Unknown – Aggression – Paralysis – Biting – Hypersalivation – Lethargy – Other:
3.3.5 Is the animal alive today? (If no, estimate date of death?)	☐Yes ☐No ☐Unknown – – / – – / – – – –	☐Yes ☐No ☐Unknown – – / – – / – – – –	☐Yes ☐No ☐Unknown – – / – – / – – – –
3.3.6 Was the animal observed for at least 10 days after the exposure?	– Yes, alive after 10 days – Yes, died during observation – No – Unknown	– Yes, alive after 10 days – Yes, died during observation – No – Unknown	– Yes, alive after 10 days – Yes, died during observation – No – Unknown
3.3.7 Was the animal tested for rabies?	– Yes, rabies positive – Yes, rabies negative – No – Unknown	– Yes, rabies positive – Yes, rabies negative – No – Unknown	– Yes, rabies positive – Yes, rabies negative – No – Unknown

	Animal 1	**Animal 2**	**Animal 3**
3.3.8 Was the deceased bitten by this animal?	☐Yes ☐No ☐Unknown *Location of bite:* – Head – Trunk – Upper limb – Hands – Lower limb – Genitalia – Other:	☐Yes ☐No ☐Unknown *Location of bite:* – Head – Trunk – Upper limb – Hands – Lower limb – Genitalia – Other:	☐Yes ☐No ☐Unknown *Location of bite:* – Head – Trunk – Upper limb – Hands – Lower limb – Genitalia – Other:
3.3.9 Did the deceased have other contact with the animal (i.e. licked, scratched)?	– Scratch – Saliva contact with open wound or mucous membrane – Neural tissue contact with open wound or mucous membrane – Other:	– Scratch – Saliva contact with open wound or mucous membrane – Neural tissue contact with open wound or mucous membrane – Other:	– Scratch – Saliva contact with open wound or mucous membrane – Neural tissue contact with open wound or mucous membrane – Other:
3.3.10 What treatment did the patient recieve for this contact?	– Washed the wound – Sought medical care – Received rabies vaccination	– Washed the wound – Sought medical care – Received rabies vaccination	– Washed the wound – Sought medical care – Received rabies vaccination

Notes:

4. Rabies treatment

4.1 Did [deceased's name] receive treatment for any of the animal exposures above?

- Yes
- No
- Don't know

4.2 Was any of this treatment received at home?

- Wound washing
- Over the counter medications
- Traditional medicines
- Other: _____
- None
- Unknown

4.3 Where did [deceased's name] go for medical care for any of the exposures listed above?

	Traditional healer	Medical practitioner	Other: _____
Facility name			
Facility location			
Date(s) visited	1: – – / – – / – – – – 2: – – / – – / – – – – 3: – – / – – / – – – –	1: – – / – – / – – – – 2: – – / – – / – – – – 3: – – / – – / – – – –	1: – – / – – / – – – – 2: – – / – – / – – – – 3: – – / – – / – – – –
	– Antibiotics – Tetanus – Wound washing – Rabies post-exposure prophylaxis or treatment – Traditional medicine – Other (specify)	– Antibiotics – Tetanus – Wound washing – Rabies post-exposure prophylaxis or treatment – Traditional medicine – Other (specify)	– Antibiotics – Tetanus – Wound washing – Rabies post-exposure prophylaxis or treatment – Traditional medicine – Other (specify)

4.4 If the patient received rabies vaccination, please record the type of vaccine and dates received:

- Nerve tissue vaccine
  - No. of injections _____
  - Date started: – – / – – / – – – –
  - Vaccination series completed? _____Yes _____No _____Donít know
  - If yes, date completed: – – / – – / – – – –
- Nerve tissue vaccine
  - Cell culture vaccine
  - No. of injections _____
  - Date started: – – / – – / – – – –

CCV	RIG	Vaccine 1	Vaccine 2	Vaccine 3	Vaccine 4	Vaccine 5
Dose received?	– Yes – No – Unknown	– Yes – No – Unknown	– Yes – No – Unknown	– Yes – No – Unknown	– Yes – No – Unknown	– Yes – No – Unknown
Date received?						

4.5 Had the patient ever been vaccinated against rabies prior to this exposure?

- Yes: Year of vaccination: – – / – – / – – – –
- No
- Unknown

5. Signs and symptoms

5.1 Time to symptom onset and death

Interviewer: I am going to ask you some questions about [deceased's name's] activities during the 3 months before the illness began and during the illness.

5.1.1 When did the illness that led to death begin?

Day – – Month – – Year – – – – Unknown

5.1.2 If you donít remember the exact date, approximately how long ago did the illness begin?

Day – – Month – – Year – – – – Unknown

5.1.3 How many days after illness did [deceased's name] die?

Number (estimate if needed): _____

5.2 During the illness did [deceased's name] seek medical assistance?

- Yes: (Date): – – / – – / – – – –
- No
- Unknown

5.3 During the illness was [deceased's name] admitted to a hospital?

- Yes: (Date): – – / – – / – – – –
- No
- Unknown

5.4 Characteristics of illness that led to death

5.5 Was any relevant diagnostic testing performed?

Disease	Test performed	Date	Result	Comment
Encephalitis	Lumbar puncture Blood count		WBC count:	
Rabies	DFA or DRIT			
Mosquito-borne encephalitis				
Herpes simplex virus				
Zoster encephalitis				
Enterovirus				
Measles virus				
Bacterial meningitis				
Malaria				
Toxoplasmosis				

5.6 Date of death

5.6.1   What was the date of [deceased's name] death? Day – – /Month – – /Year – – – –

5.6.2   Where did [deceased's name] die?

- Home
- Hospital (specify)_____
- Other health facility (specify) _____
- Other (specify)_____

5.6.3   Did anyone else in the community develop an illness similar to [deceased's name] within the past 12 months? (If "Yes", collect contact information for other suspected cases to initiate verbal autopsy of additional cases.)

- Yes
- No
- Unknown

If yes, please describe:

6. Postmortem information

6.1 Postmortem report available (if any):

- Yes
- No
- Unknown

6.2 Death certificate available?

- Yes
- No
- Unknown

6.3 Did [deceased's name] have any evidence of recent wounds?

- Yes
- No
- Unknown

6.4 Did [deceased's name] have any evidence of healed wounds?

- Yes

- No
- Unknown

Contact investigation

Collect the names and contact information for any family, community members or hospital workers who had contact with the suspected rabies case in the 14 days before symptom onset until death.

Collect the names and contact information for any people who had contact with the animal suspected of transmitting rabies to the case.

Risk assessments should be conducted with these people to rule out potential exposure.

Information to guide enumerators in deciding on the likelihood of human rabies

Human *exposure* to rabies

Possible exposure: A person who had close contact (usually a bite or scratch) with a rabies-susceptible animal in (or originating from) a rabies-infected area (question 3.2).

Probable exposure: A person who had close contact (usually a bite or scratch) with an animal displaying clinical signs consistent with rabies at time of the exposure or within 10 days following exposure in a rabies-infected area (questions 3.3.4, 3.3.5, 3.3.6).

Confirmed exposure: A person who has had close contact (usually a bite or scratch) with a laboratory-confirmed rabid animal (question 3.3.7).

Human clinical case definition:

A person with fever (question 5.4.3); AND two or more clinical signs compatible with rabies (questions 5.4.5, 5.4.6, 5.4.7, 5.4.8, 5.4.9, 5.4.10, 5.4.11, 5.4.12, 5.4.14, 5.4.15, 5.4.16, 5.4.17); AND no previous vaccination for rabies (questions 4.4 and 4.5); AND death within 21 days of symptom onset (question 5.1.3); AND no other laboratory findings consistent with an alternative diagnosis (question 5.5).

OR

A person whose health care record contains a diagnosis of rabies (question 5.5).

OR

A person whose death certificate lists rabies as a cause of death or a significant condition contributing to death (questions 6.1 and 6.2).

Classification of human rabies

Not a case: Does not meet the clinical definition
Suspected: A case that is compatible with the human clinical case definition
Probable: A suspected case with probable or confirmed exposure to rabies
Confirmed: A suspected or probable case that is confirmed in a laboratory

Determination of case category

Names of Investigator(s), signatures of local informants and designation

1. _____ _____

2. _____ _____

3. _____ _____

4. _____ _____

Additional enclosures (description) as evidence of rabies

1. _____ (Pages_____)

2. _____ (Pages_____)
3. _____ (Pages_____)
4. _____ (Pages_____)

Annex 12. Animal bite investigation form

Date of notification: _ _/ _ _ / _ _ _ _ Name: _____
Animal ID: |__|__| |__|__| |__||__|

NOTIFICATION

1. Reported from: ☐ Surveillance unit_____

> Medical contact's name: _____
> Telephone number: _____
> Patient's name: _____
> Age: _____
> Telephone number: _____

☐ Health department: _____
☐ Hospital: _____

   ☐ Veterinary agent: _____
   ☐ Veterinarian
   ☐ Public

2. Reason for report:
☐ Human exposure (bite or scratch)   ☐ Sick animal   ☐ Hit by car
☐ Other _____

3. Type of animal: ☐ Dog   ☐ Cat   ☐ Goat   ☐ Pig   ☐ Mongoose
☐ Other _____

4. Was this animal: ☐ Owned   ☐ Stray   ☐ Unknown

5. Location of animal exposure: District_____
Commune _____ Street_____
Notes:

INVESTIGATION

6. Date of investigation: _ _/ _ _ / _ _ _ _

7. Type of investigation? ☐ Owner telephone consultation ☐ In-person investigation

8. How many people were bitten by the animal? _____ How many people were scratched by the animal? _____

9. How many people started rabies vaccine? _____How many people did you refer for medical treatment? _____

10. What other animals were bitten by this animal? How many?
☐ Dog _____ ☐ Cat _____ ☐ Goat _____ ☐ Other _____

11. Was the animal located? ☐ Yes ☐ Alive ☐ Escaped capture
☐ Dead, killed by owner ☐ Dead, killed by public

☐ Dead, killed by car ☐ Dead, natural causes ☐ Dead, unknown causes

No ☐ Not found ☐ Dead, killed by owner ☐ Dead, killed by public
  ☐ Dead, killed by car ☐ Dead, natural causes ☐ Dead, unknown causes

12. Where was animal located? Department/Commune_____
GPS coordinate: _____ / _____

13. What is the animal's age?
☐ Puppy ☐ Junior ☐ Adult ☐ Senior ☐ Unknown

14. What is the animal's sex? ☐ Male ☐ Female

15. Has the animal been vaccinated for rabies?
☐ Yes, year: _____ ☐ Not vaccinated ☐ Unknown

Notes:

ASSESSMENT

16. Signs of disease: ☐ Aggression ☐ Biting ☐ Hypersalivation ☐ Paralysed ☐ Lethargy ☐ Unknown ☐ Other (specify) _____
 	
17. Rabies assessment:
☐ Healthy   ☐ Sick, signs of rabies   ☐ Sick, not rabies   ☐ Dead
☐ Other (specify) _____
 	
18. Assessment decision:
☐ Quarantine   ☐ Euthanize   ☐ Dead   ☐ Other _____
 	
        ☐ Euthanised ☐ Natural causes ☐ Other _____
        ☐ Killed by owner ☐ Killed by community
 	
19. Quarantine results: ☐ Healthy after 14 days
 	
20. Was the animal submitted for testing?   ☐ Yes, date: _____   ☐ No
 	
Notes:
Day 5 follow-up:
Day 10 follow-up:

LAB
21. Date specimen received at laboratory: _____ 22. Lab ID Number: _____ 23. Date tested: _____ 24. Test results: ☐ Positive   ☐ Negative   ☐ Inconclusive

☐ Hospital notified, date: _ _/ _ _ / _ _ _ _

☐ Health department notified, date: _ _/ _ _ / _ _ _ _

Annex 13. WHO data collection template

Country
Country subdivision (if applicable):
Focal point (ministry of health, other; please indicate):

Year	Human rabies	Bite cases				Post-exposure prophylaxis		Animal rabies				Remarks
	Human rabies	No. of dog bites			No. of bites by other animals[b]	Post-exposure prophylaxis		Rabies cases		Dog population		
	No. of cases[a]	Category II	Category III	Category unknown	No. of bites by other animals[b]	No. of people received PEP	No. of people received RIG additional to PEP	No. of cases in dogs	No. of cases in other animals[b]	No. of dogs in country	No. of dogs vaccinated	
2016												
2015												
2014												
2013												
2012												
Source[c]												

PEP, post-exposure prophylaxis; RIG, rabies immunoglobulin

[a] Should include both confirmed by laboratory and diagnosed on clinical grounds

[b] Other mammals only; please indicate species in remarks column.

[c] Please indicate data source for every indicator (e.g. ministry of health, national statistics office, national health report or estimate)

Annex 14. Template dossier for validation and verification

This template dossier was designed to help managers of national rabies programmes prepare a dossier with supporting evidence for presentation to WHO, requesting validation that rabies has been eliminated as a public health problem and/or requesting verification that dog-mediated rabies has been eliminated. The information presented in the dossier will help reviewers to understand the achievements of the programme by providing both epidemiological evidence and the broader context.

<div align="center">

(Country)

Date of submission:

Date of review:

</div>

1. Background

A country previously endemic for rabies may apply for accreditation as having eliminated rabies as a public health problem (validation) if it has not had a human death from dog-mediated rabies for at least 2 years (24 months), is operating and continues to maintain an adequate surveillance and reporting system for rabies and demonstrates effective implementation of a rabies control programme in human and animal populations.

A country may apply for accreditation as having eliminated dog-mediated rabies (verification) if it, in addition to meeting the criteria for validation described above, is operating and continues to maintain an enhanced surveillance and reporting system for rabies and demonstrates an effective strategy for maintaining freedom from dog-mediated rabies.

1.1 General documentation (optional)

Adequate documentation is necessary to provide the essential data for validation and verification. It is preferable that these data and subsequent documentation be standardized among countries within a region.

For *both validation and verification*, provide an overview of:

    a. Demographic and economic features of the country

    b. Overview of the health care system in the country

    c. Overview of the animal health system in the country

    d. Information about past rabies epidemiology in the country, including interventions before enforcement of the current national rabies programme

For *verification*, also provide an overview of:

    a. Procedures for provision of post-exposure prophylaxis

    b. Procedures for clinical and laboratory diagnosis of human and animal cases

    c. If completed, evidence of zero human rabies deaths (e.g. documentation submitted for validation)

2. Rabies programme overview (required)

For *validation*, describe in narrative form:

    a. Evidence of a national rabies control programme, including:

        i. Regulatory framework relevant to rabies, including rabies notification

        ii. National rabies control strategy, including implementation, responsibilities by sector, structure and year established

        iii. Data collection and management system

    b. Evidence that control activities are in place, including:

        i. Availability and provision of PEP in the country

        ii. Campaigns on rabies awareness and dog-bite prevention

        iii. Overview of dog vaccination campaigns

        iv. Information on dog population management measures in place, including movement regulations

        v. OIE endorsement[1] of an official control programme for dog-mediated rabies, if successfully sought

For *verification*, describe in narrative form:

    a. For formerly endemic countries, evidence that mass dog vaccination programmes controlled rabies i.e.:

        i. Overview of dog vaccination campaigns over at least 5 years, including ongoing mass dog vaccination programmes in at-risk areas or other evidence of successful control of canine rabies

        ii. Estimated dog population size, methods for coverage and population estimates

    b. Information on dog population management measures in place Evidence that the national control programme has controlled rabies

        iii. A decrease in the occurrence of rabies over at least 5 years for countries with a recent history of endemic rabies

---

[1] OIE endorsement processes for dog-mediated rabies control programmes are being prepared and are expected to come into effect in 2019.

iv. OIE self-declaration of freedom from rabies if successfully sought (http://www.oie.int/index.php?id=169&L=0&htmfile=chapitre_selfdeclaration.htm) (optional)

3. Implementation of national rabies control and prevention strategy

3.1 Evidence of control activities (required)

For *both validation and verification*, describe in narrative form:

- Availability and provision of PEP in the country, including:
  - type of vaccine and RIG available and their distribution mechanisms sub-nationally
  - number and proportion of animal bite treatment or primary health care centres with capacity for PEP (provision of vaccine only versus vaccine and RIG)
  - standard operating procedures for PEP administration
  - number of vaccine and RIG doses administered per year
  - proportion of PEP courses administered by intramuscular or intradermal regimens
  - PEP payment systems

- Number and geographical coverage of campaigns on rabies awareness and dog-bite prevention
- Dog vaccination campaigns during the past 5 years, including:
  - number of dogs vaccinated per year and by appropriate administrative sub-division
  - vaccination coverage by year and by appropriate administrative subdivision
  - estimated dog population in the country
  - target animal populations for vaccination
  - type of vaccine used
  - source of vaccine
  - current vaccine stocks

- Dog population management, including regulations on dog movement.

For *verification,* also describe:

- The method by which dog vaccination coverage and population sizes were estimated over a minimum of 5 years.
- Emergency preparedness and response plan to be implemented in case of introduction or re-emergence of dog-mediated rabies.

3.2 Rabies surveillance (required)

For *both validation and verification*, describe:

a. Evidence that adequate rabies surveillance is in place to detect rabies deaths if they were to occur, including:

   i. National notification of both human and animal rabies cases

   ii. Capability to diagnose rabies cases with WHO-/OIE-recommended standard diagnostic tests

   iii. Evidence of sample submissions from all parts of endemic and adjacent (rabies-free) areas of the country, including maps showing positive and negative test results to assess coverage and possible gaps in surveillance

   iv. The number of suspected or probable human rabies cases or probable rabies exposures that have been investigated each year and the nature of the investigation (including clinical and laboratory diagnosis, verbal autopsy, community surveys, trace-back investigations)

   v. Incidence of cases of acute encephalitis syndrome (AES)[2] per 100 000 people per year and description of the surveillance system for detection, reporting and investigation of cases of human AES from all areas of the country; OR

   vi. If AES data are not available, or are not exhaustive, demonstration of a surveillance system able to detect, report and investigate suspect cases of human rabies from all areas of the country

   vii. Rabies surveillance for animals in line with the OIE Terrestrial animal health code (Chapter 1.4: http://www.oie.int/index.php?id=169&L=0&htmfile= chapitre_surveillance_general.htm), including:

     – Number of rabies cases in dogs and other animals (clinical and laboratory-confirmed)

     – Number of dog and other suspected rabid animal bite incidents in humans and animals per year

---

[2] AES is clinically defined as a syndrome in a person of any age, at any time of year involving acute onset of fever and at least one of: (a) change in mental status (including symptoms such as confusion, disorientation, coma or inability to talk); (b) new onset of seizures (excluding simple febrile seizures). Other early clinical findings may include increased irritability, somnolence or abnormal behaviour greater than that seen with usual febrile illness. The incidence of AES will be evaluated with reference to expected levels.

- Number of routine epidemiological investigations on suspected or probable rabies cases in dogs, including procedures for rapid collection and transport of samples from suspected cases to a laboratory for diagnosis
- Sampling strategy used
- Methods for monitoring dog vaccination coverage

For *verification*, also describe:

b. Evidence that enhanced dog rabies surveillance has been in place for at least 24 months after the last detected rabies case, including:

i. Risk assessment of probable exposures presenting to health facilities
- Numbers of probable exposures reported (and PEP courses initiated)
- Number of alerts on and early detections of any imported cases

ii. Epidemiological investigations of probable exposures undertaken rapidly (< 14 days from clinical presentation) and the outcome of the investigation, including:
- Numbers of probably rabid animals reported
- Sample collection and testing of all dead or killed suspected rabid animals. It is expected that samples can be recovered from ~50% of suspected animals. All animals that did not survive the 10-day observation period should be tested.
- In the event of a confirmed human or animal rabies case, molecular characterization of the virus isolate to identify whether the case was due to infection with a wildlife variant, a bat lyssavirus or a non-indigenous infection (if available).

3.3 Procedures to maintain validation and/or verification (required)

For both *validation and verification*, describe in narrative form:

a. Plans for post-validation and/or post-verification rabies surveillance, including:
i. Procedures and evidence of continued surveillance to ensure early detection of any imported case and the appropriate treatment of people exposed to non-canine rabies variants or lyssaviruses or bitten while travelling
b. Plans for continued provision of human post-exposure prophylaxis
c. Cross-border plan to prevent reintroduction of rabies from neighbouring countries

For *verification*, also describe:

    a. OIE self-declaration of country free from infection with dog-mediated RABV (see Chapter 1.6 of the OIE Terrestrial animal health code: http://www.oie.int/index.php?id=169&L=0&htmfile=chapitre_selfdeclaration.htm).

    b. Evidence that a contingency plan is in place to effectively respond to an introduction

        i.   Animal movement regulations

        ii. Regular risk assessments

           – Of incursions from other countries/regions

           – Of other circulating wildlife rabies variants/ lyssaviruses

        iii. Outbreak response strategy, including evidence of continued access to dog vaccines and PEP in the event of an outbreak

4. Resources and partnerships (optional)

For *both validation and verification*, provide:

    a. Briefly describe the human resources employed to implement the programme

    b. Estimate internal and external financial resources used for the programme over time

    c. Sustainable resource mobilization strategy for the post-validation/verification phase

5. Special issues (optional)

For *both validation and verification*, provide the following:

    a. Descriptions of any special circumstances that have affected the programme. These could include, but are not limited to:

        i.   Stability or security issues in the country; and/or

        ii. Re-introduction from other rabies-endemic countries.

    b. Descriptions of any specific efforts to investigate rabies cases and/or intervention coverage in difficult-to-reach populations (e.g., nomadic peoples, internally displaced persons, or refugees).

6. Bibliography (required)

Insert a bibliography of all data sources used to develop this dossier, including:

- Ministry of health records
- Records from veterinary services
- Published papers (scientific, policy, etc.)
- Academic theses and dissertations

Copies of unpublished documents may be requested by WHO.

7. Abbreviations (required)

Insert a list of all abbreviations used in the dossier, with their definitions.

Annex 15. WHO collaborating centres on rabies, neurovirology, viral zoonoses and zoonoses control

WHO Collaborating Centre for Reference and Research on Rabies, Institut Pasteur, 28 rue du Docteur Roux, 75724 Paris, France
Head, Dr Hervé Bourhy; e-mail: herve.bourhy@pasteur.fr

WHO Collaborating Centre on Research and Management on Zoonoses Control, Laboratory of Rabies and Wild Animals of Nancy, Agricultural and Veterinary Technopole, PO 40009, 54220 Malzéville, France
Head, Dr Florence Cliquet; e-mail: florence.cliquet@anses.fr

WHO Collaborating Centre for the Characterization of Rabies and Rabies-related Viruses, Animal Health and Veterinary Laboratories Agency, Weybridge, Surrey KT15 3NB, United Kingdom
Head, Dr Anthony Fooks; e-mail: tony.fooks@apha.gsi.gov.uk

WHO Collaborating Centre for Rabies Surveillance and Research, Friedrich-Loeffler Institut, Federal Research Institute for Animal Health, Sudufer 10, 17493 Greifswald-Insel Reims, Germany
Head, Dr Thomas Müller; e-mail: thomas.mueller@fli.bund.de

WHO Collaborating Centre for Traveller's Health, University of Zurich, Hirschengraben 84, 8001 Zurich, Switzerland
Head, Dr Christoph Hatz, e-mail: christoph.hatz@unibas.ch

WHO Collaborating Centre for Control and Epidemiology of Rabies in Carnivores, Canadian Food Inspection Agency, 3851 Fallowfield Road, ON, Canada
Head, Dr Christine Fehlner-Gardiner; e-mail: Christine.Fehlner-Gardiner@inspection.gc.ca

WHO Collaborating Centre for Neurovirology, Thomas Jefferson University, 233 South 10th Street, Philadelphia, PA 19107, USA
Head, Dr Matthias Schnell; e-mail: matthias.schnell@jefferson.edu

WHO Collaborating Centre for Reference and Research on Rabies, Wistar Institute, 3601 Spruce Street, Philadelphia, PA 19104, USA
Head, Dr Hildegund Ertl; e-mail: ertl@wistar.upenn.edu

WHO Collaborating Centre for Reference and Research on Rabies, Centers for Disease Control and Prevention, 1600 Clifton Road, Atlanta, GA 30333, USA
Head, Dr Jesse Blanton; e-mail: asi5@cdc.gov

WHO Collaborating Centre in Rabies, Institut Pasteur of São Paulo, Av. Paulista, 393, São Paulo, Brazil
Head, Dr Lucianna Gomes / Dr Juliana Galera Castilho; e-mail pasteur@pasteur.saude.sp.gov.br / jgcastilho@pasteur.saude.sp.gov.br

WHO Collaborating Centre for Rabies Epidemiology, Division of Zoonosis, National Centre for Disease Control, 22-Sham Nath, Delhi 110054, India
Head, Dr Mala Chabra; e-mail: malachhabra@yahoo.co.in

WHO Collaborating Centre for Reference and Research in Rabies, Department of Neurovirology, National Institute of Mental Health and Neurosciences, PO Box 2900, 560029 Bangalore, India
Head, Professor V. Ravi / Dr Reeta Mani; e-mail: virusravi@gmail.com/ drreeta@gmail.com

WHO Collaborating Centre for Research on Rabies Pathogenesis and Prevention, Queen Saovabha Memorial Institute, Thai Red Cross Society, 1871 Rama IV Road, 10330 Bangkok, Thailand
Head, Professor Visith Sitprija; e-mail: sitprija@yahoo.com; and Dr Pakmanee Narumol; e-mail: npakmanee@yahoo.com

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Since the launch of the Global framework to eliminate human rabies transmitted by dogs by 2030 in 2015, WHO has worked with the Food and Agriculture Organization of the United Nations, the World Organisation for Animal Health, the Global Alliance for Rabies Control and other stakeholders and partners to prepare a global strategic plan. This includes a country-centric approach to support, empower and catalyse national entities to control and eliminate rabies.

In this context, WHO convened its network of collaborating centres on rabies, specialized institutions, members of the WHO Expert Advisory Panel on Rabies, rabies experts and partners to review strategic and technical guidance on rabies to support implementation of country and regional programmes.

This report provides updated guidance based on evidence and programmatic experience on the multiple facets of rabies prevention, control and elimination. Key updates include: (i) surveillance strategies, including cross-sectoral linking of systems and suitable diagnostics; (ii) the latest recommendations on human and animal immunization; (iii) palliative care in low-resource settings; (iv) risk assessment to guide management of bite victims; and (v) a proposed process for validation and verification of countries reaching zero human deaths from rabies.

The meeting supported the recommendations endorsed by the WHO Strategic Advisory Group of Experts on Immunization in October 2017 to improve access to affordable rabies biologicals, especially for underserved populations, and increase programmatic feasibility in line with the objectives of universal health coverage.

The collaborative mechanisms required to prevent rabies are a model for collaboration on One Health at every level and among multiple stakeholders and are a recipe for success.

Rabies is a vaccine-preventable disease. The provision of support to countries will end the pain and suffering due to rabies that burdens people, especially children. Investing in rabies control and elimination strengthens health systems, improves equity and access to health care and contributes to sustainable development. Investment in rabies elimination is not only for elimination of this fatal but preventable disease but also for building capacity in the world's most neglected regions.

This report, requested by countries, provides hands-on guidance to drive progress towards rabies elimination.

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