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Current Recommendations for the Prophylaxis and Treatment of Rabies†

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Abstract

Once onset of clinical rabies develops in an individual, death is inevitable. Thus, it is imperative that, for persons exposed or potentially exposed to rabies virus, prophylaxis must be instituted as soon as possible following the exposure.

Local wound management is an essential part of postexposure rabies prophylaxis. Exposed persons should receive a recommended series of a tissue culture or cell culture origin vaccine. The number of doses and route of vaccination differ in various regions of the world and are discussed in the text. The administration of a rabies immune globulin is generally recommended in conjunction with the first dose of the rabies vaccine. Nerve tissue origin vaccines, although used extensively in some parts of the world, are not recommended if cell or tissue culture vaccines are available. Decision trees are presented in the text to aid in determining if rabies vaccine is necessary following a known or presumed exposure to the virus, along with a table outlining the various rabies vaccines available in the World. Rabies pre-exposure immunisation is recommended for those individuals at risk of exposure to the virus. Pre-exposure prophylaxis consists of 3 doses of an approved rabies vaccine administered either intramuscularly or intradermally on days 0, 7, and 21 or 28 with periodic booster doses or titre determination depending on the level of risk of potential exposure to the virus.

† The opinions expressed in this article are those of the authors and may not represent those of the organisations to which they belong.

There is no treatment that is effective for preventing death due to rabies infection following the onset of clinical disease. Once introduced into the body, the virus may be sequestered in the muscle tissues for varying periods of time, quiescent, or perhaps undergoing local replication. Rabies virus is neurotropic, moving within the body primarily via axonal passage in the peripheral nervous system.[1] Efforts, therefore, must be directed towards preventing the virus from reaching the CNS where it results primarily in dysfunction of the respiratory centres and other essential functions and thus, invariably, death. Once the virus reaches nerve tissue within the outer sheaths of the peripheral nerves it is sequestered from the effects of the immune response, rendering vaccine treatment virtually ineffective. To prevent virus infection through centripetal movement to the CNS, primary wound management is necessary (see section 2.1) along with timely and proper administration of rabies vaccine and immunoglobulin.[2,3]

The decision to initiate postexposure prophylaxis should be made by medically qualified individuals. It is estimated that 90% of true rabies exposures occur in countries where medical intervention may be lacking, and that exposures often go unreported. The high cost, and the lack of readily available modern biologicals, are often the determining factors in postexposure treatments for rabies. Given these facts, the authors appreciate that some of the recommendations in this article may not be applicable in such situations.

Figures 1 through 4 included in this review are generic, and are primarily aimed at those in the US who may have need for such guidelines due to the relative infrequency of encounters with known and potentially rabid animals. These flowcharts will not fit all situations, but should be helpful in making decisions regarding human rabies treatment. In addition, a table listing World Health Organization (WHO) recommendations has also been included in this review.

Individuals at risk for frequent exposure to rabies should receive pre-exposure rabies vaccinations. Such people include, but are not limited to, animal control workers, veterinarians, animal biologists, animal rehabilitators, potholers (spelunkers) and those travelling in areas where rabies is endemic and antirabies drugs are unavailable or of poor quality.

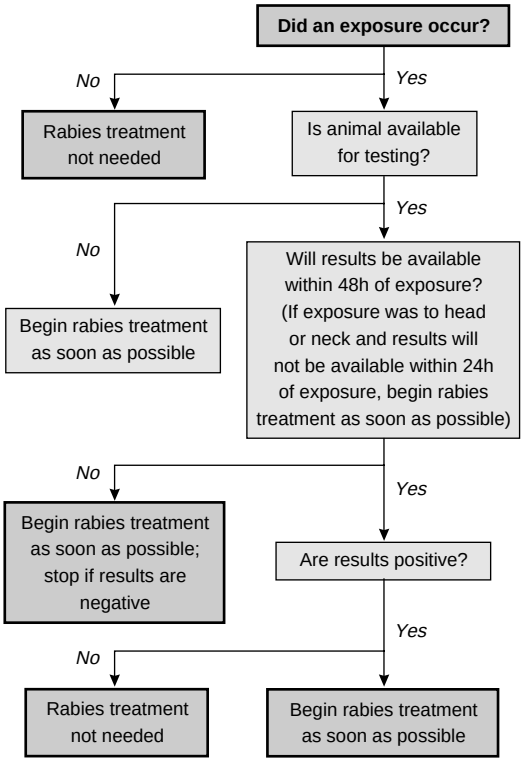

Fig. 1. High risk animals: decision tree for exposure to wild carnivores or bats; for bats, if there is uncertainty due to circumstances whether or not an exposure has occurred, assume that an exposure *has* occurred. Scheme is in general use in the US and may not apply elsewhere; please see table I for World Health Organization recommendations.

There are a number of different dosage regimens that have been shown to be effective for pre- and postexposure rabies immunisations.[4,5] The type of vaccine and the regimen used are often constrained by access to medical treatment, available funds to purchase the vaccine and immunoglobulins of choice, and prevailing local laws. The various regimens and vaccines presented in this article are those in most common use and approved or recommended by the US Public Health Service and/or the WHO.

1. Human Rabies Postexposure Prophylaxis (PEP)

1.1 Local Wound Treatment

Immediately wash the wound with soap and water and/or a viricidal agent, and irrigate the wound (or other potential entry point), as necessary, using a sterile solution, i.e. buffered saline. As medically necessary, apply an antibacterial compound to prevent secondary infections and provide antitetanus treatment. Debride the wound as required and thoroughly infiltrate the immediate area with rabies hyperimmune globulin (RIG). Suturing is not recommended unless unavoidable. If suturing is required, first infiltrate the wound thoroughly with RIG.[6-8]

1.2 Vaccination

1.2.1 US

The Advisory Committee on Immunisation Practices (ACIP) of the US Public Health Service recommends that human postexposure rabies prophylaxis for rabies-naïve (not previously vaccinated) individuals should consist of 5 doses of rabies vaccine administered intramuscularly (IM), 1 dose in the upper deltoid in adults or the anterior thigh in young children and infants, on each of days 0, 3, 7, 14 and 28, and a one-time administration of human RIG (HRIG), 20 IU/kg, upon the initiation of postexposure prophylaxis (PEP) on day 0.[3,9] In contrast to previous guidelines which suggested that up to 50% of HRIG was to be infiltrated in the wound(s), current recommendations are that as much HRIG as anatomically feasible should be infiltrated locally. Any remaining HRIG should then be administered in the gluteals.[9] It is critical that HRIG and vaccine are never drawn up in the same syringe, nor administered in the same anatomical site, as their effectiveness will be compromised due to the formation of antibody-antigen complexes.[10]

For previously immunised individuals, full PEP consists of 2 doses of rabies vaccine administered IM, one dose each on days 0 and 3; the administration of HRIG is contraindicated for preimmunised patients who either have received cell culture vaccines or have a demonstrated adequate titre (≥1 : 5) [complete neutralisation of the virus at a serum dilution of 1 : 5 on the rapid fluorescent focus inhibition test], and for those who have previously received PEP.[3]

In the US, a recent rising trend in human rabies cases has been attributed predominantly to bat-associated rabies virus variants. During retrospective investigations of human deaths attributed to rabies, the case histories often lack a definitive history of a bite from a bat, although encounters with bats have been reported in about 50% of the case investigations. Among the 21 human rabies deaths in the US from 1980 to 1997 associated with bat rabies variants, a bat bite was clearly identified in only one case. It is suspected that exposure to rabies from a bat may occur through a seemingly insignificant wound under conditions of somnolence or physical impairment, or during recreational or work-related activities. In response to this trend, current recommendations advise that when a bat is physically present and a bite cannot be reasonably excluded, and rabies cannot be ruled out through laboratory testing of the bat(s) in question, PEP should be considered (fig. 1).[10]

1.2.2 World Health Organization

The WHO Expert Committee on Rabies, 8th Report, 1992,[2] does not specifically recommend any one regimen for rabies PEP, stating that the vaccination schedule is dependent on the type and potency of the vaccine available. The following are the WHO approved regimens.[6,7]

The 5-dose 'Essen' regimen consists of one IM dose of vaccine given in the deltoids on days 0, 3, 7, 14 and 28 (or 30).

The 2-1-1 'Zagreb' regimen requires 2 doses on day 0 administered IM in the deltoid with a single dose on days 7 and 21. The advantage of this regimen is that it requires one less dose of vaccine and one less clinic visit.

The 2-site 'Thai Red Cross' intradermal (ID) regimen requires that one 0.1ml ID dose be administered at each of 2 sites, the forearm or upper arm, on days 0, 3 and 7, and one ID dose at one site on

days 30 and 90. ID doses should be administered only by staff trained in this technique. This regimen should not be used with an adjuvented tissue culture vaccine or with suckling mouse brain or sheep brain vaccines.

The 8-site 'Oxford' regimen consists of 8 ID doses, 0.1ml each, on day 0, at 4 sites on day 7, and at 1 site on days 28 and 90. Cell culture or avian tissue vaccines should only be used in this regimen. No adjuvented vaccine should be used.

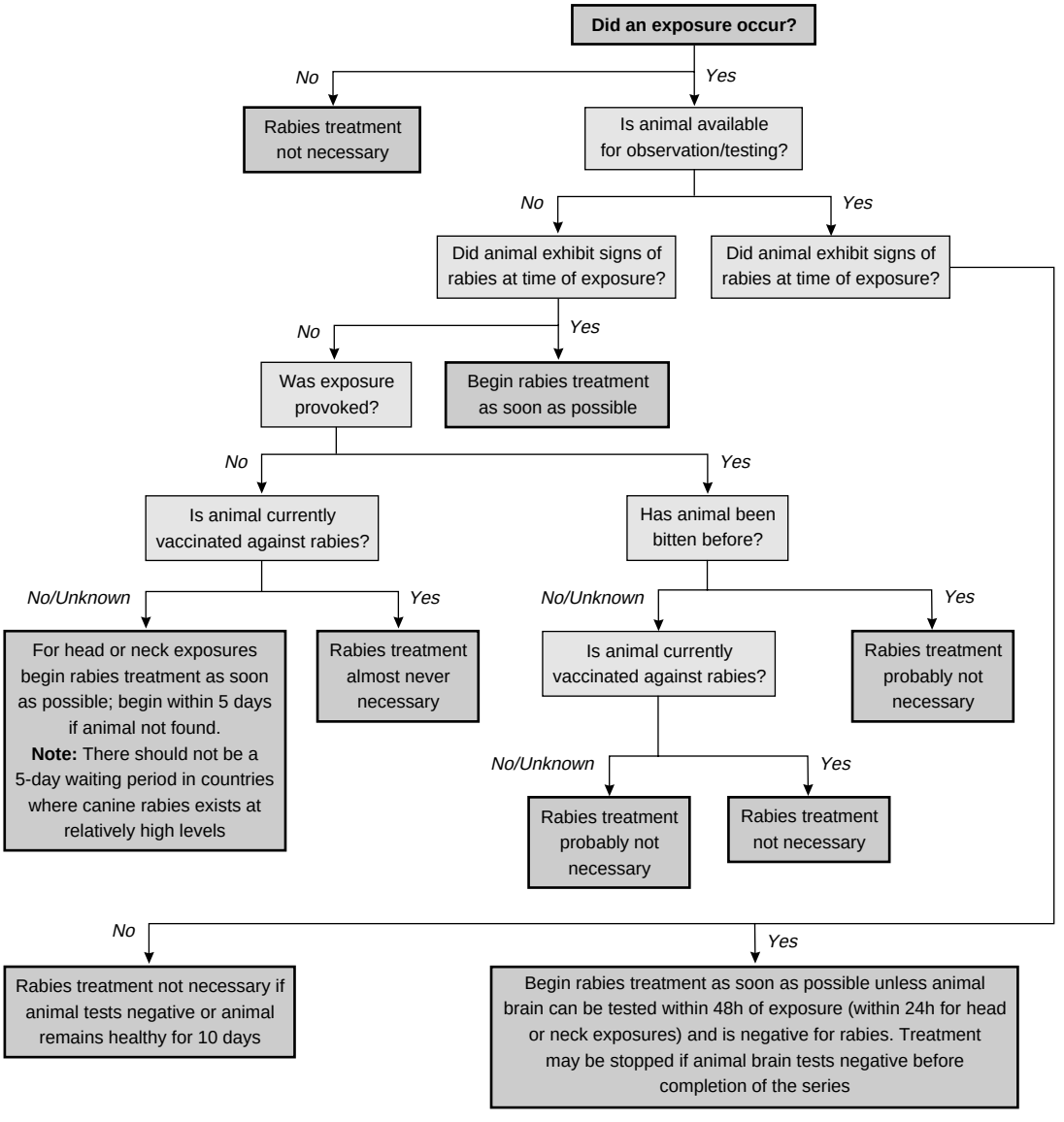

Fig. 2. Intermediate risk animals: decision tree for exposure to dogs, cats and ferrets. Scheme is in general use in the US and may not apply elsewhere; please see table I for World Health Organization recommendations.

It should be noted that with the Thai and Oxford regimens, the higher potency and purification of the cell culture and avian tissue vaccines produced on these substrates allows for ID injections.

The WHO recommends that RIG, either HRIG or purified equine RIG (pERIG) be given for all category III exposures, irrespective of the time between exposure and the initiation of PEP (table I).[2,6] The method and dose recommended is similar to that described above for the US; however, equine rabies immune globulin (ERIG) should be given at a dose of 40 IU/kg, rather than 20 IU/kg for HRIG.[2]

1.2.3 Nerve Tissue Vaccines

25% or more of all rabies vaccines manufactured worldwide are nerve tissue origin vaccines (NTOVs), produced typically in brain tissue of young sheep, goats or, preferably, suckling mice.[6,11] National authorities should recommend a regimen that has been shown to be effective. Due to residual amounts of encephalogenic substances in the final product, NTOVs are associated with higher rates of postvaccinal adverse events than the cell culture or avian tissue vaccines. This high rate of adverse reactions, along with relatively poor efficacy, far outweighs their one advantage, that of low cost.[12] NTOVs should be used only when there is no access to cell culture or avian tissue vaccines, or if the expense prohibits the use of such vaccines.

1.2.4 PEP: Comments

Once initiated, PEP regimens should be adhered to as closely as possible, as discussed above (sections 1.2.1 and 1.2.2), according to the vaccine used and the type of exposure. It is possible that alterations to the regimen may compromise overall PEP efficacy. Any interruption in the PEP vaccine schedule should be considered on a case-by-case basis. Generally, the regimen is simply resumed, as if no delay had occurred. If the delay has been significant or if the patient may be immunosuppressed, sequential monitoring of rabies titres may be appropriate, with the possible administration of additional vaccine on an *ad hoc* basis, as needed, in consultation with rabies experts. In no case should the entire series be reinitiated. The administration

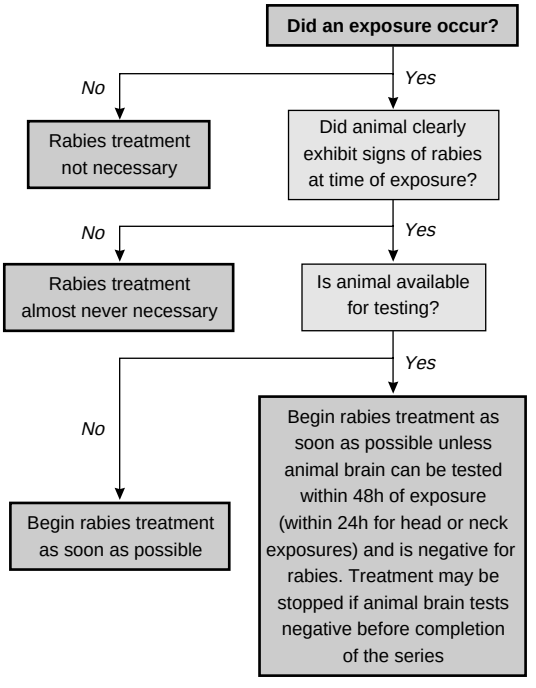

Fig. 3. Low risk animals: decision tree for exposure to livestock. Scheme is in general use in the US and may not apply elsewhere; please see table I for World Health Organization recommendations.

of additional HRIG, pERIG, ERIG, or repetition of the original dose is contraindicated. Treatment failures have been extremely rare with the proper and timely use of the modern avian tissue [i.e. purified duck embryo vaccine (DEV)] or cell culture vaccines.

Reliable access to sufficient stocks of HRIG may, at times, be problematic due to its human origin and consequent concerns about potential adventitious agents. For example, with the recent application of the nested polymerase chain reaction assay for the detection of hepatitis C in human origin products, access to HRIG for PEP was often delayed in the US. In such cases where the HRIG is not immediately available but is indicated (all PEP in the US; category III of the WHO guidelines, table I), the vaccination regimen should be initiated as soon as the treatment decision is made. The HRIG may be administered up to and including

day 7. It is most likely unnecessary on day 8 and later, or possibly contraindicated due to potential interference with active immunisation.[13] However, it is not uncommon for facial wounds to be infiltrated with RIG in countries where rabies is hyperendemic, regardless of the delay.

Although PEP should be initiated as soon as possible after a recognised exposure, it is never too late, unless clinical signs are already present. If a patient presents with a history of potential exposure that warrants treatment and a significant time delay may have occurred since the incident, full PEP should still be administered.

1.2.5 Vaccines for PEP

For worldwide use, there are 3 main types of rabies vaccines that are available: NTOVs, avian tissue vaccines (DEV) and cell culture vaccines (table II). The WHO recommends that rabies vaccines for human use should have a potency, as measured by the US National Institutes of Health test, of ≥2.5 IU/dose. The suckling mouse NTOV should have a potency of ≥1.3 IU/dose.[2,10] pERIG is employed extensively in some countries other than the US because it is a less expensive, but well tolerated and an effective alternative to HRIG, which is used exclusively in the US. However, it must be recognised that 1 to 6% of patients given ERIG develop serum sickness. It has been a practice to skin test patients before using ERIG,[10] but a recent review suggests that this is unnecessary as the skin test is not predictive of serum sickness and/or anaphylactic reactions arising from the use of modern purified or pepsin-enriched ERIG.[14]

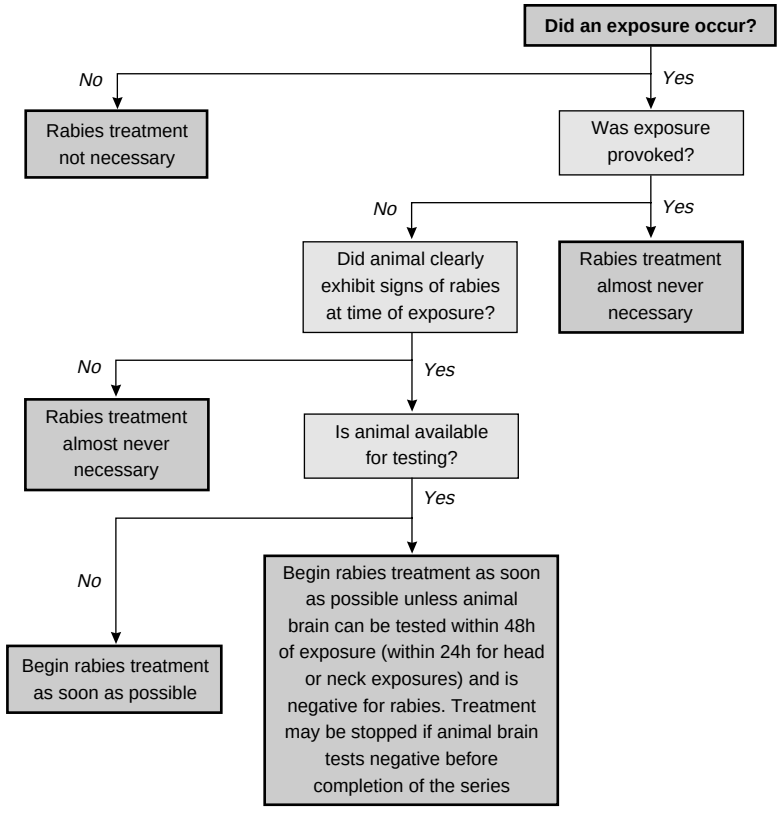

Fig. 4. Very low risk animals: decision tree for exposure to rodents and rabbits. Scheme is in general use in the US and may not apply elsewhere; please see table I for World Health Organization recommendations.

Table I. WHO guide for postexposure treatment[6]

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

a Exposure to rodents, rabbits and hares seldom, if ever, requires specific antirabies treatment.

b If an apparently healthy dog or cat in or from a low-risk area is placed under observation, it may be justified to delay specific treatment.

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

In the US, there are 3 (technically 4) human rabies vaccines licensed for use: 2 human diploid cell vaccines (HDCVs), a purified chick embryo cell vaccine (PCECV) and a rhesus monkey fetal lung cell vaccine (RLC) [table II]. There are 2 formulations of HRIG licensed for use. One incorporates a prolonged heat treatment step (58 to 60°C for 10 hours) in the manufacturing process for inactivation of potential adventitious agents. The other process consists of heating to 30°C for at least 6 hours followed by addition of a solvent and detergent for viral inactivation. Both formulations are considered to be well tolerated and efficacious.

2. Human Rabies Pre-Exposure Prophylaxis

2.1 Pre-Exposure Vaccination

Modern cell culture vaccines should be used whenever possible; purified DEV has also been shown to induce adequate antibody titres. Vaccine should be administered IM or ID in the upper deltoid on days 0, 7 and 28 in accordance with package instructions and licensure procedures.[2,3] According to the WHO, a few days' variation does not matter.[2,6]

Those at high risk due to potential occupational exposure in diagnostic, research or vaccine production laboratories should be preimmunised, with serological monitoring every 6 months; a booster dose should be given when the titre falls below 0.5 IU/ml (1 : 5 in the US). Other people at frequent or continuing risk (see section 1) should have a serum sample tested every year[2] (or every 2 years in the US[3]) and a booster administered when the titre falls below 0.5 IU/ml (or complete neutralisation at 1 : 5 in the US).

2.2 PEP for Those Previously Immunised

Local treatment of wounds should always be implemented immediately (see section 2.1). Two doses of an approved rabies vaccine should be administered IM in the upper deltoid, one each on days 0 and 3. No RIG is recommended, and in fact, this agent is contraindicated. In Thailand, more than 130 000 patients have received PEP using the 2-site Thai Red Cross ID regimen since 1987, using cell culture vaccines. Approximately 4000 of these have since been re-exposed and received 0.1ml ID doses of vaccine on days 0 and 3. No treatment failures have been reported.[15]

3. Conclusions

The WHO estimates that 40 000 to 60 000 people die each year due to infection from the rabies virus. Most of these deaths are the result of a bite from an infected dog. Current recommendations for

Table II. Human rabies vaccines in current use (after Wilde,[5] with permission)

Vaccine	Diluent volume (ml)	Country of origin	Virus strain
Human diploid cell (HDCV)	1.0	France	PM-strain
(HDCV-1D)	0.1	France	PM-strain
(HDCV)	1.0	Canada	Alabama-street
(HDCV)	1.0	Germany	PM-strain
(HDCV)	0.5	Switzerland	PM-strain
Purified chick embryo cell (PCEC)	1.0	Germany	Flury-LEP
	1.0	Japan	Flury-LEP
Purified vero cell (PVRV)	0.5	France	PM-strain
Purified duck embryo (PDEV)[a]	1.0	Switzerland	PM-strain
Rhesus lung cell (RLC, adjuvanted)	1.0	US	Kissling
Primary hamster kidney cell (PHKC, adjuvanted)	1.0	Russia	Vnukovo
	1.0	China	Beijing
Suckling mouse brain vaccine (SMB)[b]	2-5	Vietnam-South America	Several
Sheep brain vaccine (SV)[b]	2-5	India, Pakistan, Africa	Several

a PDEV contains a preservative and has been approved by the Swiss government for intradermal postexposure rabies treatment. It is currently being reformulated from 1.0 to 0.5ml of diluent.

b These vaccines are given subcutaneously as 8 to 17 daily injections, usually into the abdominal wall. They should be avoided whenever possible but must be used when one of the other products is not available and transporting the patient immediately to a higher level of care is not possible.

LEP = low egg passage ; **PM** = Pittman Moore.

persons exposed to rabies include immediate local wound therapy in conjunction with rabies vaccination, and often the use of the rabies immune globulin. Various regimens and vaccines are used depending on the region of the world. It is highly recommended by the WHO that only cell culture or tissue culture origin rabies vaccines be used; however, due to the relatively higher cost of these vaccines, nerve tissue origin vaccines are commonly used in many less developed countries. These latter vaccines often result in severe, life-threatening adverse reactions and are less effective in producing antibody response. The efficacy of the cell culture and tissue culture vaccines is well established. Rarely is there a report of a rabies death when exposed individuals receive these vaccines administered timely and properly. Such efficacy was noted in a study just completed (unpublished to date) in which volunteers (n = 160) received either 1 or 2 booster doses of a PCECV 1 year after a 3-dose pre-exposure vaccine series of either HDCV or PCECV. There was no significant difference ($p \leq 0.05$) in antibody response between the group receiving 1 dose and the group receiving 2 doses of the PCECV. Such results indicate that a cell culture vaccine such as PCECV can elicit excellent antibody response with a single dose in those previously immunised.

It is unfortunate that so many persons die needlessly from rabies when safe and efficacious vaccines are available to prevent the majority of such deaths. Greater effort must be made to make the cell culture and tissue culture rabies vaccines more readily available to those in need in the less developed countries of the world. Efforts are being directed at incorporating rabies pre-exposure immunisation in the childhood immunisation series in countries or cities where canine rabies is epidemic or highly endemic. Whether such programs will be successful or cost-effective is yet to be determined but this use of the new generation of safe and efficacious vaccines should be fully explored. Additionally, the possible use of the new DNA vaccines may hold promise for lowering the cost of rabies prophylaxis.

Rabies is an ancient disease; however, we are just now gaining significant knowledge in the pathogenesis, epidemiology and prevention of the disease to make the eradication of the disease in

humans in most, if not all, of the world a reality in the early decades of the next millennium.

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