STANDARD OPERATING PROCEDURES
Rabies Protection Program

1. SCOPE

Rabies is a viral infection of the central nervous system. It is typically transmitted by the introduction of saliva or neural tissue from an infected animal into open cuts or wounds or via percutaneous exposure (i.e. scratches, punctures or bites). An effective rabies virus vaccination is available and is offered free of charge to employees who have potential exposure to rabies virus in their work at Boston University or Boston Medical Center. This Standard Operating Procedure (SOP) establishes a system of information and safeguards that should be followed at Boston University when working with the rabies virus or animals known to carry rabies in the research environment.

2. PROCEDURE

2.1 AGENT

Rabies virus (genus *Lyssavirus*, family *Rhabdoviridae*)
Rabies is an acute, fatal, incurable infectious disease that is caused by an RNA virus.

2.2 LABORATORY AND RESEARCH HAZARD

The typical route of transmission in the research environment involves virus-laden saliva or neural tissue from an infected animal introduced via a bite, scratch, or break in the skin or mucous membrane. Two documented cases of laboratory transmission have involved aerosol transmission in work with attenuated strains of rabies virus. Although an instance of possible airborne transmission was reported in a cave in Texas in 1956, this was not definitively confirmed. It occurred after exposure to caves inhabited by several million bats, of which a small percentage were infected with rabies. One researcher had chronic skin lesions on his neck, unrelated to contact with bats, and may have been exposed in this way. Another worker, who had visited the cave in which airborne transmission was postulated had blood on his face after one of the cave visits, but could not remember being bitten by a bat. Later experiments to test for airborne exposure were inconclusive (Messenger et al., 2003). Two cases of rabies have been attributed to airborne exposures in laboratories, and two cases of rabies have been attributed to probable airborne exposures in a cave in Texas occupied by bats.

The viral agent may be present in all tissues of infected animals, with highest titers present in the central nervous system tissue, salivary glands, and saliva. Accidental parenteral inoculation, cuts, or sticks with contaminated laboratory equipment, bites by infected animals, and exposure of mucous membranes or broken skin to infectious tissue or fluids are the most likely source of exposure for laboratory and animal care personnel. Infectious aerosols have not been a demonstrated hazard to personnel working with clinical material, conducting diagnostic examinations, or in field situations.

Types of Exposures:

Rabies is transmitted only when the virus is introduced into open cuts or wounds in skin or onto mucous membranes. If there has been no exposure (as described in this section), post-exposure

treatment is not necessary. The likelihood of rabies infection varies with the nature and extent of exposure. Two categories of exposure (bite and non-bite) should be considered.

The risk of rabies after a bite by a rabid animal (5-80%) to an exposed individual is about 50 times the risk after a scratch (0.1-1.0%). The risk of rabies after contamination of minor wounds with infected saliva is very low (<1%). The risk after bites depends on the severity of the bite (80% after multiple bites by rabid wolves) and the site of exposure. The risk of rabies after bites on the lower extremities (5%) or bites on upper extremities (25%) is markedly less that the risk after a bite to the head (60%). All of these risk estimates are in the absence of post-exposure prophylaxis and are largely based on 19th century historical records.

Bite

Any penetration of the skin by teeth constitutes a bite exposure. All bites, regardless of location, represent a potential risk of rabies transmission. Bites by some animals, such as bats, can inflict minor injury and thus be undetected. Bites to the face and hands carry the highest risk, but the site of the bite should not influence the decision to begin treatment.

Strains of bat rabies have been documented in Massachusetts since 1961, and infected bats have been identified throughout the state. Since 1920, 92% of the 26 domestically acquired rabies cases in humans in the U.S. have involved bat rabies. Of those infected with bat rabies, a history of exposure to a bat was not documented in 88% of cases. This finding suggests that even limited contact with bats may be associated with transmission. Bat bites may be less severe, and therefore more difficult to recognize that bites from larger animals. Post-exposure prophylaxis should be given in a situation where a bat is physically present and a bite, or any other exposure/contact, cannot be ruled out. Bats captured following a human exposure should never be released. Bats captured should undergo testing for rabies.

Nonbite

Nonbite exposures from terrestrial animals rarely cause rabies. Occasional reports of transmission by nonbite exposures suggest that such exposures constitute sufficient reason to consider postexposure prophylaxis. The nonbite exposures of highest risk appear to be among persons exposed to large amounts of aerosolized rabies virus and surgical recipients of corneas transplanted from patients who died of rabies.

The contamination of open wounds abrasions, mucous membranes, or theoretically, scratches with saliva or other potentially infectious materials (such as neural tissue) also constitutes a non-bite exposure. If the material containing the virus is dry, the virus can be considered noninfectious. Other contact by itself such as petting a rabid animal or contact with the blood, urine, or feces (e.g., guano) of a rabid animal does not in itself constitute an exposure and is not an indication for post-exposure prophylaxis. Although occasional reports of transmission by non-bite exposure suggest that such exposures may constitute sufficient reason to initiate post-exposure prophylaxis under some circumstances, non-bite exposures rarely cause rabies. Because the rabies virus is inactivated by desiccation and ultraviolet light irradiation, in general, if the material containing the virus is dry, the virus can be considered noninfectious.

Situations with little or no risk include petting a rabid animal or coming into contact with an animal's blood, urine, feces, or skunk spray and do not require prophylaxis, unless the animal is a bat, because bat bites may be less severe and go unrecognized. If these body parts or secretions are mixed with saliva, the exposure should be evaluated accordingly.

Human-to-Human

Ten cases of human-to-human transmission of rabies have been reported. Eight occurred in recipients of transplanted corneas in Thailand, India, the United States, Iran and France. Stringent guidelines for acceptance of donor corneas have reduced this risk. In addition to corneal transplants, two cases of human-to-human transmission, one from a bite and one from kissing occurred in Ethiopia. Stringent guidelines for acceptance of donor corneas have been implemented to reduce risk. Routine delivery of health care to a patient with rabies is not an indication for postexposure prophylaxis unless exposure to mucous membranes or non-intact skin to potentially infectious body fluids has occurred. Adherence to standards will minimize the risk of airborne exposure.

EVALUATING EXPOSURES TO WILD AND DOMESTIC ANIMALS

Decisions to give post exposure prophylaxis after humans post-exposure prophylaxis after a human has been exposed to a potentially rabid animal should be based on the following: (1) whether the animal is high-risk or a low-risk animal, (2) the health of the animal, i.e., whether it is exhibiting signs consistent with rabies, (3) the availability of the exposing animal for testing or if it is a domestic animal (dog, cat, ferret) or livestock (cattle, horse or sheep), for quarantine, (5) type of exposure, and (6) knowledge of the epidemiology of rabies in the area. Now that raccoon and bat rabies are found throughout Massachusetts, all of Massachusetts is considered endemic for animal rabies, and exposure should be evaluated with this in mind.

Animal with rabies can appear aggressive ("furious rabies") or normal or meek ('dumb rabies"). Common signs of rabies include neurological signs such as paralysis and ataxia, and hypersalivation. Rabies can be shed in saliva for days before signs of rabies appear. Therefore, the behavior of the animal, is **NOT** a reliable indicator of whether or not the human exposed, is at risk.

Animal Rabies Epidemiology and Evaluation of Involved Species

Bats

Rabid bats have been documented in the 49 continental states, and bats are increasingly implicated as important wildlife reservoirs for variants of rabies virus transmitted to humans. Recent epidemiologic data suggest that transmission of rabies virus can occur from minor, seemingly unimportant, or unrecognized bites from bats. The limited injury inflicted by a bat bite (in contrast to lesions caused by terrestrial carnivores) and an often-inaccurate recall of the exact exposure history might limit the ability of health-care providers to determine the risk of rabies resulting from an encounter with a bat. *Human and domestic animal contact with bats should be minimized, and bats should never be handled by untrained and unvaccinated persons or be kept as pets.*

In all instances of potential human exposures involving bats, the bat in question should be safely collected, if possible, and submitted for rabies diagnosis. Rabies postexposure prophylaxis is recommended for all persons with bite, scratch, or mucous membrane exposure to a bat, unless the bat is available for testing and is negative for evidence of rabies. *Postexposure prophylaxis might be appropriate even if a bite, scratch, or mucous membrane exposure is not apparent when there is reasonable probability that such exposure might have occurred.*

On the basis of the available but sometimes conflicting information from the 21 bat-associated cases of human rabies reported since 1980, in 1-2 cases, a bite was reported; in 10-12 cases, apparent contact occurred but no bite was detected; and in 7-10 cases, no exposure to bats was reported, but an undetected or unreported bat bite remains the most plausible hypothesis. Clustering of bat-associated human cases within the same household has never been reported. Consequently, postexposure prophylaxis should be considered when direct contact between a human and a bat has occurred, unless the exposed person can be certain a bite, scratch, or mucous membrane exposure did not occur. In instances in which a bat is found indoors and there is no history of bat-human

contact, the likely effectiveness of postexposure prophylaxis must be balanced against the low risk such exposures appear to present. In this setting, postexposure prophylaxis can be considered for persons who were in the same room as the bat and who might be unaware that a bite or direct contact had occurred (e.g., a sleeping person awakens to find a bat in the room or an adult witnesses a bat in the room with a previously unattended child, mentally disabled person, or intoxicated person) and rabies cannot be ruled out by testing the bat. Postexposure prophylaxis would not be warranted for other household members.

Wild Terrestrial Carnivores
Raccoons, skunks, foxes, and coyotes are the terrestrial animals most often infected with rabies. All bites by such wildlife must be considered possible exposures to the rabies virus. Postexposure prophylaxis should be initiated as soon as possible after patients are exposed to wildlife unless the animal has already been tested and shown not to be rabid. If postexposure prophylaxis has been initiated and subsequent immunofluorescence testing shows that the exposing animal was not rabid, postexposure prophylaxis can be discontinued.

Signs of rabies among wildlife cannot be interpreted reliably; therefore, any such animal that exposes a person should be euthanized at once (without unnecessary damage to the head) and the brain should be submitted for rabies testing. If the results of testing are negative by immunofluorescence, the saliva can be assumed to contain no virus, and the person bitten does not require postexposure prophylaxis.

Other Wild Animals
Small rodents (e.g., squirrels, hamsters, guinea pigs, gerbils, chipmunks, rats, and mice) and lagomorphs (including rabbits and hares) are almost never found to be infected with rabies and have not been known to transmit rabies to humans. From 1990 through 1996, in areas of the country where raccoon rabies was enzootic, woodchucks accounted for 93% of the 371 cases of rabies among rodents reported to CDC. In all cases involving rodents, the state or local health department should be consulted before a decision is made to initiate antirabies postexposure prophylaxis.

The offspring of wild animals crossbred to domestic dogs and cats (wild animal hybrids) are considered wild animals by the National Association of State and Public Health Veterinarians (NASPHV) and the Council of State and Territorial Epidemiologists (CSTE). Because the period of rabies virus shedding in these animals is unknown, these animals should be euthanized and tested rather than confined and observed when they bite humans. Wild animals and wild animal hybrids should not be kept as pets. Animals maintained in United States Department of Agriculture-licensed research facilities or accredited zoological parks should be evaluated on a case-by-case basis.

Domestic Dogs, Cats, and Ferrets
The likelihood of rabies in a domestic animal varies by region; hence, the need for postexposure prophylaxis also varies. In the continental United States, rabies among dogs is reported most commonly along the United States-Mexico border and sporadically in areas of the United States with enzootic wildlife rabies. During most of the 1990s, more cats than dogs were reported rabid in the United States. The majority of these cases were associated with the epizootic of rabies among raccoons in the eastern United States. The large number of rabies-infected cats might be attributed to fewer cat vaccination laws, fewer leash laws, and the roaming habits of cats. In many developing countries, dogs are the major vector of rabies; exposures to dogs in such countries represent an increased risk of rabies transmission.

On the basis of new information regarding rabies pathogenesis and viral shedding patterns in ferrets, ferrets are now considered in this category with dogs and cats rather than as wild terrestrial

carnivores. A healthy domestic dog, cat, or ferret that bites a person may be confined and observed for 10 days. Any illness in the animal during confinement or before release should be evaluated by a veterinarian and reported immediately to the local public health department. If signs suggestive of rabies develop, the animal should be euthanized and its head removed and shipped, under refrigeration, for examination by a qualified laboratory. If the biting animal is stray or unwanted, it should either be observed for 10 days or be euthanized immediately and submitted for rabies examination.

Circumstances of Biting Incident and Vaccination Status of Exposing Animal
An unprovoked attack by an animal is more likely than a provoked attack to indicate that the animal is rabid. Bites inflicted on a person attempting to feed or handle an apparently healthy animal should generally be regarded as provoked. A currently vaccinated dog, cat, or ferret is unlikely to become infected with rabies.

2.3 LABORATORY RESEARCH PRECAUTIONS

Biosafety Level 2 (BSL 2) practices and facilities are recommended for all activities *utilizing known or potentially infectious material*. BSL 2 practices include: limited access, biohazard warning signs, sharps precautions, biosafety manual defining waste decontamination or medical surveillance policies. BSL 2 facilities Immunization is recommended for all individuals prior to working with rabies virus or with infected animals, or engaging in diagnostic, production, or research activities with rabies virus. Immunization is also recommended for all individuals entering or working in the same room where rabies virus or infected animals are used. While it is not always feasible to open the skull or remove the brain of an infected animal within a biosafety cabinet, it is pertinent to wear heavy protective gloves to avoid cuts and scratches, and face shields to protect the eyes nose and mouth from exposure to infectious droplets or tissue fragments. Primary containment and personal precautions, as described for BSL 3 may be indicated for activities with high potential for droplet or aerosol production, and for activities involving production quantities for concentrations of infectious materials. Animal Biosafety Level (ABSL) 2 applies to live animals with potential rabies exposure. See attachment 5, at end of this document for BSL and attachment 6 for ABSL level requirements.

2.4 EMPLOYEES AT RISK

Naturally or experimentally infected laboratory animals, their saliva, and their tissues are potential sources of infection to laboratory and animal care personnel. Such personnel are also at risk of acquiring rabies infection from working with the rabies virus, from direct contact with quarantined animals potentially infected with rabies, from exposure to potentially infected animal tissues, and from work involving the capture or destruction of potentially infected wild animals. This includes researchers who are capturing animals for ecological studies that have low incidence of rabies.

RISK ASSESSMENT (see Attachment 4)

2.4.1 Continuous Risk Category

2.4.1.1 Nature of Risk – Virus present continuously, often in high concentrations. Specific exposures likely to go unrecognized. Bite, non-bite, or aerosol exposure.

2.4.1.1 Typical Populations – Rabies research laboratory workers and rabies biological production workers. This category includes all individuals involved in experiments using rabies virus and all animal care staff handling animals that have been infected with the rabies virus.

2.4.2 **Frequent Risk Category**

2.4.2.1 Nature of Exposure – Exposure is usually episodic, with source recognized, but exposure also might be unrecognized. Bite, non-bite or aerosol exposure.

2.4.2.2 Typical Populations – Rabies diagnostic lab workers, spelunkers, veterinarians and animal-control and wildlife workers in areas with rabies rates. Veterinarians and staff, and animal-control and wildlife workers in rabies-enzootic areas. Potential exposure due to the manipulation of wild animal species known to harbor rabies virus, including but not limited to bats, dogs, cats, ferrets, and wild terrestrial carnivores. Staff that handle wild or quarantined cats, dogs, ferrets or other wild species known to harbor rabies virus are included. Includes wild species that are known to harbor rabies virus and that will not be identified as such by quarantine.

2.4.3 **Infrequent Exposure Category**

2.4.3.1 Nature of Exposure – Exposure nearly always episodic with source recognized: bite, or non-bite exposure.

2.4.3.2 Typical Populations – Veterinarians and animal-control and wildlife workers in areas of low rabies rates. Veterinary students. Travelers visiting areas where rabies is known to be enzootic and immediate care is unavailable. This category includes veterinarians and animal care staff who will only handle purpose-bred or post-quarantine wild animals that have not been infected with the rabies virus. Rodents including squirrels, hamsters, guinea pigs, gerbils, chipmunks, rats, mice, hares, rabbits that are rarely infected with the rabies virus have not been known to transmit rabies to man.

2.4.4 **Rare Exposure Category**

2.4.4.1 Nature of Exposure – Exposure always episodic with source recognized. Bite or non-bite. exposure.

2.4.4.2 Typical Populations – U.S. population at large, includes persons in rabies-epizootic areas.

2.5 PRE-EXPOSURE PROPHYLAXIS

Purpose: The purpose of pre-exposure vaccination is to simplify post-exposure prophylaxis in those at risk of exposure and should be considered for a number of at risk groups. Anyone who has received pre-exposure prophylaxis with rabies vaccine and who is later bitten or exposed MUST also receive post-exposure prophylaxis.

Safety: All anti-rabies products licensed in the U.S. are safe and effective and cannot cause rabies. Pre-exposure vaccination of immunosuppressed persons is not recommended.

Continuous Risk Category

2.5.1.1 These individuals are required to undergo a primary course of vaccination with serologic levels of rabies antibodies monitored every six months. Vaccination requires three doses of human diploid cell vaccine (1.0 ml HDCV) given intramuscularly in the deltoid. Vaccine is given on days 0, 7 and 21 or 28.

2.5.1.2 Thereafter, persons in the continuous risk category will undergo serological testing for rabies antibody using the rapid fluorescent focus inhibition test (RFFIT) every six months. Booster doses of vaccine are administered if antibody titer is below a serum titer corresponding to complete neutralization at a 1:5 serum dilution.

2.5.2 **Frequent Risk Category**

2.5.2.1 Individuals in the frequent risk category are required to undergo a primary course of vaccination with the human diploid cell vaccine (1.0 ml HDCV) given intramuscularly in the deltoid. Vaccine is given on days 0, 7 and 21 or 28. Thereafter, persons in the frequent risk category will undergo serological for rabies antibody using the rapid fluorescent focus inhibition test (RFFIT) every two years. Booster doses of vaccine are administered if serum titer is below complete neutralization at a 1:5 serum dilution.

2.5.3 **Infrequent Risk Category**

2.5.3.1 Animal users as defined in the infrequent risk category are ***offered*** rabies vaccination as the primary course as listed above.

2.5.3.2 It is not recommended that those in the infrequent risk category have serologic testing or booster vaccination.

2.5.4 **Rare Risk Category – No vaccination necessary.**

2.6 **POST EXPOSURE PROPHYLAXIS (see Attachment 1 (PDF), Attachment 2 (PDF), and Attachment 3 (PDF).**

FIRST AID: The exposed individual should immediately cleanse the wound with soap and water and a viricidal agent, such as a povidone-iodine solution. Exposed mucous membranes should be irrigated with potable water for 15 minutes. Tetanus-diphtheria booster should be given if greater than 5 years since last dose of tetanus. Prophylactic antibiotics should be administered as indicated. Suturing must be evaluated by weighing cosmetic factors against the risk of bacterial infection.

2.6.1 The individual should report the exposure to their supervisor and to the appropriate occupational health clinic. For international travel contact International SOS at 1-800-523-6586 (24 hours a day) ask to speak to the nurse. *Please make arrangements before travel*.

2.6.1.1 The occupational health clinic for the Charles River Campus is at 930 Commonwealth Avenue, West (entrance on Pleasant Street), Monday through Friday 9:00 am – 4:00 pm. At Boston University Medical Campus, the Boston Medical Center Occupational & Environmental Medicine Department is located at 732 Harrison Avenue in the Preston Family Building on the 5th Floor, Monday through Friday 7:00 am – 4:00 pm. Persons sustaining rabies exposures occurring outside these times should proceed to the Boston Medical Center Emergency Department at 88 East Newton Street for clinical evaluation and treatment.

2.6.1.2 Rabies exposures occurring on the job but outside of the Boston University Campus should be treated emergently at the nearest hospital emergency room. Call International SOS at 1-800-523-6586, 24 hours a day service to locate appropriate facilities *in advance* of travel if travel is international.

2.6.2 After wound cleansing, a **previously vaccinated** individual should be injected

intramuscularly with 1.0 ml of HDCV on Day 0. An additional 1.0 ml intramuscular injection of HDCV should be given on day 3 post-exposure.

2.6.3 After wound cleansing, an **unvaccinated** individual should receive a dose of **human rabies immunoglobulin HRIG (20 IU per kilogram body weight)**. If anatomically feasible, the full dose should be infiltrated around the wound. Any remaining volume should be administered intramuscularly at an anatomical site distant from the site of subsequent vaccine administration. In addition, intramuscular injections in the deltoid area of **1.0 ml HDCV are to be administered at the time of exposure (day 0) and post exposure on days 3, 7, 14 and 28.**

Off-schedule Post-Exposure Prophylaxis: During the first 2 weeks if an individual misses and of the doses, adjust the schedule so that t individual receives 4 doses in the first 14 post exposure days. The fifth dose can be given at 28 days post exposure. If an individual misses any doses in the second 2 weeks consult the manufacturer and adjust the schedule accordingly. The fifth dose can be given at 28 days or more days following the initiation of post-exposure prophylaxis. Do not give live-virus vaccines for 4 months following the administration of HRIG.

Post-exposure Prophylaxis Reporting and Consultations: The initiation of rabies prophylaxis must be reported the Massachusetts Department of Public Health (105 CMR 140). In the City of Boston, providers are requested to report to the Boston Public Health Commission. Appropriate forms can be obtained form the Division of Epidemiology and Immunization at (617) 983-6900. The Division of Epidemiology is also available for consultation about exposures: at the above number on weekdays and at (617) 983-6200 on evenings/weekends for emergencies.

Reporting Exposures: In order to facilitate animal control effort (quarantine and euthanasia) all animal bites should be reported as follows:

- Report animal bites to humans to the local board of health or their designated local officials.
- Also report animal bites or other exposures to the appropriate agencies as follows:

1. For human exposures to domestic animals other than ferrets: Bureau of Animal Health, Department of Food and Agriculture at (617) 626-1794.
2. For human exposures to ferrets: Division of Fisheries and Wildlife, Department of Fisheries, Wildlife and Environmental Law Enforcement at (617) 727-3151.

TREATMENT OF WOUNDS AND IMMUNIZATIONS

The essential components of rabies postexposure prophylaxis are wound treatment and, for previously unvaccinated persons, the administration of both RIG and vaccine. Persons who have been bitten by animals suspected or proven to be rabid should begin postexposure prophylaxis immediately. Incubation periods of greater than 1 year have been reported in humans. Thus, when a documented or likely exposure has occurred, postexposure prophylaxis is indicated regardless of the length of the delay, provided the clinical signs of rabies are not present.

In 1977, the World Health Organization recommended a regimen of RIG and six doses of HDCV over a 90-day period. This recommendation was based on studies in Germany and Iran. When used this way, the vaccine was found to be safe and effective in protecting persons bitten by animals proven to be rabid and induced an excellent

antibody response in all recipients. Studies conducted in the United States by CDC have documented that a regimen of one dose of RIG and five doses of HDCV over a 28-day period was safe and induced an excellent antibody response in all recipients. Clinical trials with RVA and PCEC have demonstrated immunogenicity equivalent to that of HDCV.

Treatment of Wounds
Immediate and thorough washing of all bite wounds and scratches with soap and water and a virucidal agent, such as povidone-iodine solution irrigation, are important measures for preventing rabies. In studies of animals, thorough wound cleansing alone without other postexposure prophylaxis has been shown to reduce markedly the likelihood of rabies. Tetanus prophylaxis and measures to control bacterial infection also should be administered as indicated. The decision to suture large wounds should take into account cosmetic factors and the potential for bacterial infections. Prophylactic antibiotics should be administered as indicated.

Immunization
Postexposure antirabies vaccination should always include administration of both passive antibody and vaccine, with the exception of persons who have previously received complete vaccination regimens (preexposure or postexposure) with a cell culture vaccine or persons who have been vaccinated with other types of vaccines and have had documented rabies antibody titers. These persons should receive only vaccine (see Postexposure Therapy for Previously Vaccinated Persons). The combination of RIG and vaccine is recommended for both bite and non-bite exposures (see Rationale for Treatment), regardless of the interval between exposure and initiation of treatment.

Human Rabies Immune Globulin Use
HRIG is administered only once (i.e., at the beginning of antirabies prophylaxis) to previously unvaccinated persons to provide immediate antibodies until the patient responds to HDCV, RVA, or PCEC by actively producing antibodies. If HRIG was not administered when vaccination was begun, it can be administered through the seventh day after the administration of the first dose of vaccine. Beyond the seventh day, HRIG is not indicated since an antibody response to cell culture vaccine is presumed to have occurred. Because HRIG can partially suppress active production of antibody, no more than the recommended dose should be administered. The recommended dose of human HRIG is 20 IU/kg body weight. This formula is applicable to all age groups, including children. If anatomically feasible, the full dose of HRIG should be thoroughly infiltrated in the area around and into the wounds. Any remaining volume should be injected intramuscularly at a site distant from vaccine administration. This change in the recommendations for HRIG administration is based on reports of rare failures of postexposure prophylaxis when smaller amounts of HRIG were infiltrated at the exposure sites. HRIG should never be administered in the same syringe or in the same anatomical site as vaccine.

Vaccine Use
All rabies vaccine used in the United States are killed cell culture-derived vaccines. Human Diploid cell vaccine (HCDV), grown in human fiberblasts, is inactivated with beta-propriolactone and ultra-filtration and contains neomycine. It is effective if given with HRIG promptly following exposure. The dose is 1cc (2.5 IU) IM, regardless of age and weight. Adults and children should receive HDCV in the deltoid area and infants in the anterolateral thigh.

Rabies Vaccine Adsorbed (RVA) is another rabies vaccine licensed in the U.S. It is manufactured and distributed by BioPort Corporation. At the present time, BioPort is not manufacturing or distributing RVA. RVA is produced from virus grown in fetal rhesus lung diploid cells concentrated by absorption or aluminum phosphate. RVA is administered IM as described for HDCV.

A purified chick embryo cell (PCEC) vaccine is another vaccine licensed in the U. S. It became available in the U.S. in the fall of 1997. It is manufactured and distributed by Chiron Corporation. It is prepared from fixed rabies virus strain Flury LEP grown in primary cultures of chicken fibroblasts. The virus is inactivated with beta-proprionolactone and further processed by zonal centrifugation in a sucrose density gradient. It is formulated for IM

administration only. PCEC is available in a single-dose vial containing lyophilized vaccine that is reconstituted in the vial with the accompanying diluent, to a final volume of 1.0 ml just before administration.

Three rabies vaccines are currently available in the United States (Table 1); any one of the three can be administered in conjunction with RIG at the beginning of postexposure therapy. A regimen of five 1-mL doses of HDCV, RVA, or PCEC should be administered intramuscularly. The first dose of the five-dose course should be administered as soon as possible after exposure. Additional doses should be administered on days 3, 7, 14, and 28 after the first vaccination. For adults, the vaccination should always be administered IM in the deltoid area. For children, the anterolateral aspect of the thigh is also acceptable. The gluteal area should never be used for HDCV, RVA, or PCEC injections because administration of HDCV in this area results in lower neutralizing antibody titers.

TABLE 1. Rabies biologics -- United States, 1999

Human rabies vaccine	Product name	Manufacturer
Human diploid cell vaccine (HFCV) Intramuscular Intradermal	 Imovax Rabies Imovax Rabies I.D.	Pasteur-Merrieux Serum et Vaccins, Connaught Laboratories, Inc. Phone: (800) VACCINE (822-2463)
Rabies vaccine adsorbed (RVA) Intramuscular	Rabies Vaccine Adsorbed (RVA)	BioPort Corporation Phone: (517) 335-8120 Technical Questions: (517) 327-1500
Purified chick embryo cell vaccine (PCEC) Intramuscular	RabAvert	Chiron Corporation Phone: CHIRON (800) 244-7668
Rabies immune globulin (RIG)	Imogam Rabies-HT	Pasteur-Merrieux Serum et Vaccines, Connaught Laboratories, Inc. Phone: (800) VACCINE (822-2463)

Treatment Outside the United States

U.S. citizens who are exposed to rabies while traveling outside the United States in countries where rabies is enzootic might sometimes receive postexposure therapy with regimens or biologics that are not used in the United States (See Table 6 below). This information is provided to familiarize physicians with some of the regimens used more widely abroad. The regimens described in the references in this report have not been submitted for approval by the FDA for use in the United States. If postexposure prophylaxis is begun outside the United States using one of these regimens or biologics of nerve tissue origin, it might be necessary to provide additional therapy when the patient reaches the United States. State or local health departments should be contacted for specific advice in such cases. If titers are obtained, specimens collected 2-4 weeks after preexposure or postexposure prophylaxis should completely neutralize challenge virus at a 1:5 serum dilution by the RFFIT.

Purified equine rabies immune globulin (ERIG) has been used effectively in developing countries where RIG might not have been available. The incidence of adverse reactions has been low (0.8%-6.0%), and most of those that occurred were minor. In addition, unpurified antirabies serum of equine origin might still be used in some countries where neither RIG nor ERIG are available. The use of this antirabies serum is associated with higher rates of serious adverse reactions, including anaphylaxis.

Although no postexposure vaccine failures have occurred in the United States since cell culture vaccines have been routinely used, failures have occurred abroad when some deviation was made from the recommended postexposure treatment protocol or when less than the currently recommended amount of antirabies sera was administered. Specifically, patients who contracted rabies after postexposure prophylaxis did not have their wounds cleansed with soap and water, did not receive their rabies vaccine injections in the deltoid area (i.e., vaccine was administered in the gluteal area), or did not receive RIG around the wound site.

Vaccines and Immune Globulins Used in Other Countries

Many developing countries use inactivated nerve tissue vaccines made from the brains of adult animals or suckling mice. Nerve tissue vaccine (NTV) is reported to induce neuroparalytic reactions among approximately 1 per 200 to 1 per 2,000 persons vaccinated; suckling mouse brain vaccine (SMBV) causes reactions in approximately 1 per 8,000 persons vaccinated. The vaccines HDCV, PCEC, PDEV, and purified vero cell rabies vaccine (PVRV) (See Table 6. below) are cell culture-derived and not of nerve tissue origin. In addition, unpurified antirabies serum of equine origin might still be used in some countries where neither RIG nor ERIG are available. The use of this antirabies serum is associated with higher rates of serious adverse reactions, including anaphylaxis.

Table 6. Cell culture rabies vaccined widely available outside the United States

Purified chick embryo cell vaccine (PCEC)	Rabipur
Purified verocell rabies vaccine (PVRV)	Verorab
	Imovax-Rabies vero
	TRC Verorab
Human diploid cell vaccine (HDCV)	Rabivac
Puirfied duck embryo vaccine (PDEV)	Lyssavac

VACCINATION AND SEROLOGIC TESTING

Serologic Response Shortly After Vaccination
All persons tested during several CDC studies 2-4 weeks after completion of preexposure and postexposure rabies prophylaxis in accordance with ACIP guidelines have demonstrated an antibody response to rabies. Therefore, serum samples from patients completing preexposure or postexposure prophylaxis do not need to be tested to document seroconversion unless the person is immunosuppressed (see Precautions and Contraindications). If titers are obtained, specimens collected 2-4 weeks after preexposure or postexposure prophylaxis should completely neutralize challenge virus at a 1:5 serum dilution by the RFFIT. In animal studies, neutralizing antibody titers have been shown to be imperfect markers of protection. Antibody titers will vary with time since the last vaccination. Differences among laboratories that test blood samples also can influence the results.

Cell culture vaccines have been used effectively with RIG or ERIG worldwide to treat persons bitten by various rabid animals. Worldwide, the World Health Organization estimates that 10-12 million persons are started on postexposure therapy annually. An estimated 16,000-39,000 persons in the United States receive a full postexposure course with HDCV each year. When postexposure prophylaxis has been properly administered, no treatment failures have occurred in the United States.

Serologic Response and Preexposure Booster Doses of Vaccine
Although antibody levels do not define a person's immune status, they are a marker of continuing immune response. To ensure the continuity of an immune response, titers should be checked periodically, with booster doses administered as needed. Two years after primary preexposure vaccination, a 1:5 serum dilution will neutralize challenge virus completely (by the RFFIT) among 93%-98% of persons who received the three-dose preexposure series intramuscularly and 83%-95% of persons who received the three-dose series intradermally. If the titer falls below the minimum acceptable antibody level, a preexposure booster dose of vaccine is recommended for a person at continuous or frequent risk for exposure to rabies (See Attachment 4 PDF). The following guidelines are recommended for determining when serum testing should be performed after primary preexposure vaccination:

A person in the continuous-risk category (See Attachment 4 PDF) should have a serum sample tested for rabies antibody every 6 months.
A person in the frequent-risk category (See Attachment 4 PDF) should have a serum sample tested for rabies antibody every 2 years.
State or local health departments can provide the names and addresses of laboratories performing rabies serologic testing.

ADVERSE REACTIONS HDCV, RVA, and PCEC

Reactions after vaccination with HDCV, RVA, and PCEC are less serious and less common than with previously available vaccines. In previous studies with HDCV, local reactions (e.g., pain, erythema, and swelling or itching at the injection site) have been reported among 30%-74% of recipients. Systemic reactions (e.g., headache, nausea, abdominal pain, muscle aches, and dizziness) have been reported among 5%-40% of recipients. Three cases of neurologic illness resembling Guillain-Barre syndrome that resolved without sequelae in 12 weeks have been reported. In addition, other central and peripheral nervous system disorders have been temporally associated with HDCV vaccine, but a causal relationship has not been established in these rare reports.

An immune complex-like reaction occurred among approximately 6% of persons who received booster doses of HDCV 2-21 days after administration of the booster dose. The patients developed generalized urticaria, sometimes accompanied by arthralgia, arthritis, angioedema, nausea, vomiting, fever, and malaise. In no cases have these reactions been life threatening. This reaction occurred less frequently among persons receiving primary vaccination. The reactions have been associated with the presence of betapropiolactone-altered human albumin in the HDCV and the development of immunoglobulin E (IgE) antibodies to this allergen.

Human Rabies Immune Globulin
Local pain and low-grade fever might follow receipt of HRIG. Although not reported specifically for HRIG, angioneurotic edema, nephrotic syndrome, and anaphylaxis have been reported after injection of immune globulin (IG), a product similar in biochemical composition but without antirabies activity. These reactions occur so rarely that a causal relationship between IG and these reactions has not been established.

Both formulations of RIG, BayRabTM and Imogam Rabies-HT, undergo multiple viral clearance procedures during preparation. There is no evidence that any viruses have ever been transmitted by commercially available HRIG in the United States.

Management of Adverse Reactions
Once initiated, rabies prophylaxis should not be interrupted or discontinued because of local or mild systemic adverse reactions to rabies vaccine. Usually, such reactions can be successfully managed with antiinflammatory and antipyretic agents, such as ibuprofen or acetaminophen. When a person with a history of serious hypersensitivity to rabies vaccine must be revaccinated, antihistamines can be administered. Epinephrine should be readily available to counteract anaphylactic reactions, and the person should be observed carefully immediately after vaccination.

Although serious systemic, anaphylactic, or neuroparalytic reactions are rare during and after the administration of rabies vaccines, such reactions pose a serious dilemma for the patient and the attending physician. A patient's risk of acquiring rabies must be carefully considered before deciding to discontinue vaccination. Advice and assistance on the management of serious adverse reactions for persons receiving rabies vaccines may be sought from the state health department or CDC.

All serious systemic, neuroparalytic, or anaphylactic reactions should be reported to the Vaccine Adverse Event Reporting System (VAERS) via a 24-hour toll-free telephone number ({800} 822-7967).

PRECAUTIONS AND CONTRAINDICATIONS

Immunosuppression
Corticosteroids, other immunosuppressive agents, antimalarials, and immunosuppressive illnesses can interfere with the development of active immunity after vaccination. For persons with immunosuppression, preexposure prophylaxis should be administered with the awareness that the immune response might be inadequate (see Primary or Preexposure Vaccination). Patients who are immunosuppressed by disease or medications should postpone preexposure vaccinations and consider avoiding activities for which rabies preexposure prophylaxis is indicated. When this course is not possible, immunosuppressed persons who are at risk for rabies should be vaccinated by the IM route and their antibody titers checked. Failure to seroconvert after the third dose should be managed in consultation with appropriate public health officials (see Preexposure Vaccination and Serologic Testing).

Immunosuppressive agents should not be administered during postexposure therapy unless essential for the treatment of other conditions. When postexposure prophylaxis is administered to an immunosuppressed person, it is especially important that a serum sample be tested for rabies antibody to ensure that an acceptable antibody response has developed.

Pregnancy
Because of the potential consequences of inadequately treated rabies exposure, and because there is no indication that fetal abnormalities have been associated with rabies vaccination, pregnancy is not considered a contraindication to postexposure prophylaxis. If the risk of exposure to rabies is substantial, preexposure prophylaxis might also be indicated during pregnancy.

Allergies
Persons who have a history of serious hypersensitivity to rabies vaccine should be revaccinated with caution (see Management of Adverse Reactions)

3. IMPLEMENTATION

3.1 Completion of a vaccination series for the rabies virus and documentation of current and adequate immunity to rabies virus is required for all individuals entering spaces or rooms in which rabies infected animals are present, and for all individuals whose job duties include anticipated contact with wild animals known to carry the rabies virus.

3.2 All principal investigators using the rabies virus must enroll all personnel manipulating the rabies virus in this Rabies Protection Program. Those individuals with potential exposure to animals which are rabies infected or which belong to species known to carry rabies virus are offered rabies protection upon enrollment in the Boston University Animal Exposure Surveillance Program. It is the responsibility of the PI and the individual to contact the Occupational Health Program to obtain services when potential exposure to rabies is anticipated and to maintain their currency with the medical evaluation of their titer status as defined above. See section 3.5 below for international medical travel arrangements.

3.3 Biosafety Level 2 practices, containment equipment and facilities are required for all activities involving the use or manipulation of rabies virus or rabies infected animals (ABSL-2).

3.4 All laboratories utilizing rabies virus and all ABSL-2 animal housing areas utilizing rabies virus are inspected by the Department of Environmental Health and Safety to verify appropriate containment and work practices. Additional primary containment, personnel precautions and personal protective equipment, such as those described for Biosafety Level 3, may be indicated for activities with a high potential for droplet and aerosol production and for activities involving production quantities or high concentrations of the rabies virus.

3.5 Travel to foreign countries with potential exposure to rabies including field biology work or bat research must include identification of health care facilities and an understanding or the requirements to access medical resources in the location or nearest resources for post-exposure treatment and other medical issues that may occur. These arrangements must be identified prior to arrival. Contact **International SOS at 1-800-523-6586 if calling from the U.S.** (More details to this arrangement need to be worked out to cover post-docs or other individuals who are not students or employees). Contact International SOS by calling collect 215-245-4707 when you are outside the U.S. Boston University has a policy with this organization. Ask to speak with the nurse. Please identify a source for post-exposure prophylaxis and care for other medical issues. This is a 24-hour a day program.

3.6 The Boston University Rabies Protection Program is designed to reflect full compliance with the recommendations of the Advisory Committee on Immunization Practices (ACIP) in the document Human Rabies Prevention, published by the Centers of Disease Control in the Morbidity and Mortality Weekly Report on January 8, 1999 (Volume 48, No. RR-1). See References for this document by clinking on link listed at end of this document.

See References for Information on Biosafety Levels and Animal Biosafety Levels, and Personal Protective Equipment.

Boston University

Human Diploid-Cell Rabies Vaccine

I understand that due to my occupational exposure to potentially infectious material and/or animals, I may be at risk of getting a rabies infection. The purpose of the Human Diploid-Cell Rabies vaccine (HDCV) is to provide immunity to the rabies virus. The vaccination series consists of three (3) injections. The injections are given on days 0, 7 and 21 or 28.

For persons at continuous risk of rabies exposure (i.e. persons working with rabies virus in research environment) a blood sample will be tested for rabies antibody titers every 6 months. If the serum titer is not adequate, a booster injection of HDCV vaccine will be required. For those who are frequently exposed to the rabies virus (i.e. veterinarians and staff handling wild animal species known to harbor rabies) a blood sample will be tested for rabies antibody titers every 2 years and a booster injection of HDCV vaccine will be given if necessary. Employees in these two groups are **required** to undergo vaccination, which is offered free of charge at Employee Health Services.

Veterinarians and staff who handle purpose-bred or post-quarantine wild animals that have not been infected with rabies virus, or staff that handle animals not known to harbor rabies virus are offered rabies vaccination. Any individual in these categories who elects to be vaccinated is not required to have antibody titers or booster vaccination.

The vaccine has the potential to produce certain side effects including but not limited to the following: injection site soreness, redness, or itching; headache, fatigue or dizziness; nausea, vomiting, abdominal pain; arthralgias (aching joints), fever and malaise. The incidence of serious side effects from the vaccine is less than one percent (1%), whereas the outcome after a rabies infection causing encephalomyelitis (swelling and inflammation of the brain and spinal cord) is *always* fatal. Pre-exposure vaccination of immunosuppressed persons is not recommended.

Name: _____ SSN/ID: _____

Boston University

Consent for Rabies Vaccination

The risks and benefits of receiving the Human Diploid-cell Rabies Vaccine (HDCV) and the risks of acquiring rabies from an occupational exposure have been explained to me. I acknowledge that no guarantees have been made to me regarding the effectiveness of the vaccine or the absence of adverse reactions to the vaccine. I voluntarily give my consent to receive the HDCV vaccine.

_____ _____
Signature Date

Human Diploid-Cell Rabies Vaccine (HDCV) DECLINATION

I understand that due to my occupational exposure to potentially infectious materials and/or animals, I may be at risk of acquiring rabies infection. I have been given the opportunity to be vaccinated with HDCV vaccine at no charge to myself. However, I decline the HDCV vaccination at this time. I understand that by declining this vaccine, I will be excluded from those projects that involve working with the rabies virus, or from tasks, which are included in the Continuous Risk Category or the Frequent Risk Category. I further understand that if I sustain a potential exposure to rabies that I must seek immediate medical care even if I have been vaccinated to receive post-exposure treatment.

_____ _____
Signature Date

PRIOR Human Diploid-Cell Rabies Vaccine (HDCV)
(Complete if applicable; documentation must be provided)

I have previously received the rabies vaccination in _____(*indicate year received*)

By _____(*indicate doctor/clinic*).

_____ _____
Signature Date

FOR CLINIC USE ONLY		
Date Administered		
Vaccine Manufacturer		
Lot Number		
Expiration Date		
Injection Site		
Signature		Date

References:

Attachment 1. Guide To Rabies Post–Exposure Evaluation and Management
PDF

Attachment 2. Management of Human Exposure to Suspected Rabid Animals
PDF

Attachment 3. Rabies Post-Exposure Prophylaxis Schedule
PDF

Attachment 4. Rabies Pre–Exposure Prophylaxis Guide
PDF

Attachment 5. Biosafety in Microbiological and Biomedical Laboratories, 4th Edition
Laboratory Biosafety Levels


"Laboratory Biosafety Levels"


"BSL Table III"

Section III, Table 1. Summary of Recommended Biosafety Levels for Infectious Agents
http://www.cdc.gov/od/ohs/biosfty/bmbl4/bmbl4s3t.htm

Attachment 6. Biosafety in Microbiological and Biomedical Laboratories, 4th Edition
Vertebrate Animal Biosafety Level Criteria


"Vertebrate Animal Biosafety Level Criter


"Animal Vertebrate BSL Table IV"

Section IV, Table 1. Summary of Biosafety Levels for Activities in Which Experimentally or Naturally Infected Vertebrate Animals Are Used
http://www.cdc.gov/od/ohs/biosfty/bmbl4/bmbl4s4t.htm

BMBL: Agents Summary Statements- Viral Agents: Rabies Virus
Biosafety in Microbiological and Biomedical Laboratories 4th Edition pp 167–168. 5/99
http://www.cdc.gov/od/ohs/biosfty/bmbl4/bmbl4toc.htm pp 170-171.

Human Rabies Prevention - United States, 1999 Recommendations of the Advisory Committee on Immunization Practices (ACIP) html

http://www.cdc.gov/mmwr/PDF/rr/rr4801.pdf

Public Health Fact Sheet on Rabies (PDF) / MS Word version

Rabies and Bats, FAQ for Physicians

Prevention of Rabies in Humans (PDF)

Hanlon, CA, Rupprecht CE, Health Precautions for Bat Workers
(In-press with permission) See page 5-6 for discussion on personal protective equipment.

"Health Precautions
for Bat Workers"

Messenger, S.L., C.E. Rupprecht, and J.S. Smith. 2003. Bats, emerging virus infections, and the rabies paradigm. Pp. 622-679. In: Bat Ecology (T.H. Kunz and M.B. Fenton, eds.). University of Chicago Press, Chicago.

Management of Rabies in Humans
http://www.cdc.gov/ncidod/dvrd/rabies/professional/publications/miscellaneous/management.pdf

Additional Information on Rabies from The Commonwealth of Massachusetts Department of Public Health

I. Rabies Control Plan Massachusetts 2003
http://www.state.ma.us/dph/cdc/epii/rabies/controlplan/rabiescp.htm

Cover Page, Index and List of Attachments
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Chapter 1. General Information
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Chapter 2. Human Exposure 2003
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Chapter 3. Domestic Animal; Issues
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Chapter 4. Wild Animal Issues
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Chapter 5. Cape Cod Oral Rabies Vaccination Program
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Attachment 1. Guide To Rabies Post–Exposure Evaluation and Management
PDF

Attachment 2. Management of Human Exposure to Suspected Rabid Animals
PDF

Attachment 3. Rabies Post-Exposure Prophylaxis Schedule
PDF

Attachment 4. Rabies Pre-Exposure Prophylaxis Guide
PDF

Attachment 5. Advisory Committee on Immunization Practices Statement on Rabies Prevention and CDC Rabies Website link.
PDF

Attachment 6. Recommendation for Petting Zoos, Petting Farms, Animal Fairs, and Other Events and Exhibits where Contact Between the Public and Animals is Permitted
PDF

Attachment 7. Notice of Possible Exposure to Rabies and Quarantine Order
PDF Sample Notice of Possible Exposure to Rabies and Quarantine Order
PDF Definitions
PDF Sample Order of Quarantine

Attachment 8. Rabies Protocol: Management of Dogs and Cats Exposed to Wildlife
PDF

Attachment 9. Rabies Protocol: Management of Dogs and Cats Exposed to Other Domestic Animals
PDF

Attachment 10. Rabies Protocol: Management of Dogs and Cats Which Expose Humans
PDF

Attachment 11. MDPH, SLI, Virology Laboratory's Guidelines for Submission of Specimens for Rabies Testing
PDF

Attachment 12. Useful Rabies Contact Information- Telephone Numbers and Web Resources (Vaccine Contacts/Emergency Information)
PDF

Attachment 13. Compendium of Animal Rabies Prevention and Control
PDF

II. Commonwealth of Massachusetts Department of Public Health Rabies Website

Massachusetts Department of Public Health Rabies Information
http://www.state.ma.us/dph/cdc/epii/rabies/rabies.htm

General Information on Rabies

- Public Health Fact Sheet on Rabies (PDF) / MS Word version
- Bats and Rabies, A Public Health Guide – Centers for Disease Control (PDF) / MS Word version
- Risk of Rabies Associated with Different Animals
- Other Agencies Involved in Rabies Control
- Rabies Pathogenesis and 10–Day Animal Quarantine
  Two-sided Card (PDF 172k)

Four-sided Card (PDF 209k)

- A Summary of Rabies in Massachusetts, 1992-2002 (PDF 107k) / MS Word Version
  This document summarizes the number of animals submitted and tested for rabies in Massachusetts by species, year, month and county for a 10 year period.

Recommendations

- Animal Exposure Protocol for Camps

Information for Local Boards of Health

- 2003 Rabies Control Plan for Cities and Towns

Information for Healthcare Providers

- Management of Human Exposure to Suspect Rabid Animals (PDF) / MS Word version
- Prevention of Rabies in Humans (PDF)
- Rabies and Bats, FAQ for Physicians
- Recommendations for Pre-Exposure Prophylaxis / (PDF version 86k)
- Rabies Post-Exposure Prophylaxis Schedule

Information for Veterinarians and Animal Control Officers

- Management of Dogs and Cats Exposed to Wildlife
- Management of Dogs and Cats Exposed to Other Domestic Animals
- Management of Dogs and Cats Which Bite Humans
- Massachusetts Rabies Immunization Program for Dogs, Cats, and Ferrets

Related Links

- Massachusetts Division of Fisheries, Wildlife, and Environmental Law Enforcement
- Massachusetts Department of Food and Agriculture, Bureau of Animal Health
- US Department of Agriculture, Wildlife Services
- Centers for Disease Control Rabies Homepage
- Centers for Disease Control Rabies Kids' Website