Advanced Emergency Nursing Journal
Vol. 35, No. 2, pp. 110–119

APPLIED
PHARMACOLOGY

Column Editor: Kyle A. Weant, PharmD, BCPS

CE

Rabies Prophylaxis in the Emergency Department

Abby M. Bailey, PharmD, BCPS
Martina C. Holder, PharmD, BCPS
Stephanie N. Baker, PharmD, BCPS
Kyle A. Weant, PharmD, BCPS

ABSTRACT
The rabies virus is transmitted through exposure to infected saliva during either a bite or direct contact with mucosal tissues. Infection with this virus results in a progressive encephalitis, ultimately leading to coma, end-organ damage, and death. Because rabies-associated mortality is strikingly high, preventing viral transmission associated with an exposure is paramount. Fortunately, 2 available options exist for this purpose and include the rabies vaccine and the associated immunoglobulin. Patients presenting for consideration of rabies postexposure prophylaxis constitute a frequent complaint seen in the emergency department (ED) in most geographical areas. Management of these patients should be guided by an accurate and thorough discussion of the circumstances surrounding their exposure to attain maximum pharmacological benefit and avoid viral transmission. This article provides an overview of the practice recommendations surrounding rabies virus prophylaxis and their associated pharmacological characteristics in the ED. **Key words:** emergency department, immune globulin, postexposure, preexposure, prophylaxis, rabies virus, vaccination

FEW INFECTIOUS DISEASES are as devastating as that caused by the rabies virus (Warrell & Warrell, 2004). Fortunately, rabies is uncommon in developed nations secondary to various prevention programs (World Health Organization, 2012). What separates rabies from other infectious diseases is that it is essentially incurable if appropriate prophylactic measures are not taken following infection (Warrell & Warrell, 2004). Rabies is caused by a group of RNA viruses that cause acute, progressive encephalitis that results in more than 50,000 deaths annually worldwide. Although disease carries with it a high mortality rate, appropriate prophylactic measures initiated soon after exposure are almost universally effective. As a result, fewer than two deaths are reported each year in the United

Author Affiliations: *Department of Pharmacy Services, UK HealthCare (Drs Bailey, Holder, and Baker), and Department of Pharmacy Practice and Science, College of Pharmacy (Drs Bailey, Holder, and Baker), University of Kentucky, Lexington; and North Carolina Public Health Preparedness and Response, North Carolina Department of Health and Human Services, Raleigh (Dr Weant).*

Disclosure: *The authors report no conflicts of interest.*

Corresponding Author: *Kyle A. Weant, PharmD, BCPS, North Carolina Public Health Preparedness and Response, North Carolina Department of Health and Human Services, 100 East Six Forks Rd, Ste 150, Raleigh, NC 27699 (kaw9600@alumni.unc.edu).*

DOI: 10.1097/TME.0b013e31828f0b79

States, a staggering decline from historical levels (Centers for Disease Control and Prevention [CDC], 2008). This decrease in mortality through postexposure prophylaxis, although impressive, comes at the expense of a complex, lengthy, and costly process (Moran et al., 2000). The intent of this review is to discuss the relevant management issues associated with initial rabies exposure in the emergency department (ED), with a focused review of the available products for administration and their associated pharmacological characteristics.

BACKGROUND

An understanding of the method of transmission of the rabies virus is essential to ascertain the overall risk of acquisition for a patient who presents to the ED. The rabies virus is not viable outside of the host and is easily destroyed by environmental variables such as sunlight and heat (Leung, Davies, & Hon, 2007). Thus, it is necessary for exposure to occur through penetration of the skin by teeth or by direct transdermal or mucosal contact. Infected saliva following a bite is the most common route of viral transmission (Manning et al., 2008). The RNA viruses that cause rabies exist in multiple genotypes; however, all result in similar symptoms (Fooks, Brookes, Johnson, McElhinney, & Hutson, 2003; Hemachudha, Laothamatas, & Rupprecht, 2002; King, Meredith, & Thomson, 1994; Rupprecht & Gibbons, 2004). These viruses move through the peripheral nervous system, with their ultimate journey terminating in the central nervous system (CNS; Charlton, 1994). The virus then travels to other sites, such as the salivary glands, enabling transmission to other hosts.

Although all mammals have the ability to transmit the rabies virus, the primary reservoir worldwide is carnivorous mammals, with dogs accounting for the most human deaths each year (Fekadu, 1993; Krebs, Mandel, Swerdlow, & Rupprecht, 2005). However, canine vaccination and animal control programs have greatly reduced the cases of domestic animal rabies cases in the United States (Krebs et al., 2005; Schneider et al., 2007). As a result, wild animals, including raccoons, skunks, bats, and foxes, have become the most important, potential source of infection for both humans and domestic animals in the United States, accounting for 91.8% of the rabid animals reported in 2011 (Blanton, Dyer, McBrayer, & Rupprecht, 2012). Activities such as petting or handling an animal, or contact with blood or saliva on intact skin, do not constitute an exposure. Unprovoked animal attacks are far more likely than provoked attacks (i.e., bites sustained while attempting to feed or handle an apparently healthy animal) to indicate that an animal may be infected (Manning et al., 2008). Nonbite exposures have been documented in humans; however, they are exceedingly rare (Gibbons, 2002). Although no cases of human-to-human transmission have been documented as a result of occupational exposure, whenever caring for a patient who is possibly infected, standard barrier precautions are essential to minimize any risk of transmission that may exist.

Exposures involving bats provide a rather unique situation. The most common rabies virus variants responsible for human rabies in the United States are bat related, accounting for 87.5% of human rabies cases in the United States in the last decade (Blanton et al., 2012; Krebs et al., 2005). As such, all bat exposures require a thorough evaluation (Manning et al., 2008). It is entirely possible that a bite from a rabid bat may go unnoticed by the potential host and therefore postexposure prophylaxis is indicated even in the absence of a clear route of transmission. This includes situations in which persons were in the same room as a bat and who might be unaware that a bite, or direct contact, had occurred (CDC, 1999). Examples include a sleeping person awakening to find a bat in the room or a bat witnessed in the room with an unattended child, mentally disabled person, or intoxicated person. With any wild animal bite, postexposure prophylaxis should be considered if the animal is unavailable for testing.

The absence of symptoms does not constitute justification for delaying therapy or withholding treatment. The clinical presentation of this disease can occur with a wide variety of symptoms, beginning with a significant and variable incubation period, typically 1–3 months (Hemachudha et al., 2002; Rupprecht, Hanlon, & Hemachudha, 2002). This is secondary to the need for the virus to replicate in the muscle fibers following a bite prior to its movement into nerve tissue and subsequently entering the CNS (Hemachudha et al., 2002; Leung et al., 2007).

PRODUCTS AND ADMINISTRATION

Human Rabies Immune Globulin

Because of the delay in antibody production following the administration of the rabies vaccine, the administration of virus-neutralizing antibodies for immediate passive immunity is necessary for adequate postexposure prophylaxis (CDC, 1999). Two immune globulin formulations are available in the United States: HyperRAB S/D (Talecris Biotherapeutics, 2010) and Imogam Rabies-HT (Sanofi Pasteur, 2005). Following injection of these agents, antibodies present in the serum within 1 day and persist for close to 3 weeks (Sanofi Pasteur, 2005; Talecris Biotherapeutics, 2010).

Both human rabies immune globulin (HRIG) products are preservative-free immunoglobulin preparations obtained from human donors and should be used immediately following vial penetration. Both products should remain refrigerated and should not be frozen. To expedite flow through the ED in this often ambulatory population, ideally, these agents should be stored in automated dispensing cabinets of the ED, provided refrigeration is available. If it is dispensed from a central pharmacy, it is often cost-effective to dispense full vials rather than patient-specific doses, as it is unlikely that lost or unused doses can be reused, owing largely to the lack of preservatives and the infrequency of this presentation when compared with the expiration of the drug. The recommended dose for all age and weight groups of HRIG is 20 units/kg of total body weight. As the concentration of commercially available products is 150 units/ml and is available in 2- and 10-ml vials, rounding to the nearest vial size is recommended. The presence of ED pharmacists at the bedside and involved in protocol development will greatly assist in ensuring an evidence-based and cost-effective approach. The HRIG is indicated only for those who have not previously been vaccinated and should be administered concomitantly with the first dose of vaccine. Concomitant HRIG and vaccine administration has been demonstrated to be more effective than either used alone and is therefore the standard of care (Koprowski, Van Der Scheer, & Black, 1950). If there exists a bite wound or site of infection, as much of the dose of HRIG as is feasible should be injected around the wound (Sanofi Pasteur, 2005; Talecris Biotherapeutics, 2010). Any remaining dose should be administered intramuscularly in the deltoid, quadriceps, or anterolateral thigh. It is important that a location other than that used for vaccine inoculation is utilized to minimize the potential for interference (Rupprecht & Gibbons, 2004). Virus neutralization has been shown to be most effective when HRIG is injected directly around the wound, whereas only distant injection significantly increases the risk of viral infection (Dean, Baer, & Thompson, 1963). If no wound is visible, then the entire dose should be administered at sites other than that used by the vaccine. The administration of this dose may require multiple injections depending on the dose, ability to inject around the wound, and size of the patients' deltoid and quadriceps. Institutional standards should be followed regarding the maximum volume of intramuscular medication for specific sites.

Rabies vaccine and HRIG should never be mixed in the same syringe. Preparations of HRIG are not associated with the acquisition of disease (Rupprecht & Gibbons, 2004). It should be noted that these are blood products and therefore they may also carry with them the potential for the transmission of

viral diseases and Creutzfeldt-Jakob disease or contain antibodies to other agents and thus inhibit immune responses to noninactivated viral vaccines such as measles-mumps-rubella and varicella vaccines. These vaccines should be delayed for at least 3–4 months after postexposure prophylaxis to allow for the elimination of HRIG (Atkinson et al., 2002; Siber et al., 1993).

Vaccines

Rabies vaccines are inactivated vaccines that induce the production of virus-neutralizing antibodies within a few days and can last several years (Novartis, 2006; Sanofi Pasteur, 2012). Two rabies vaccines are licensed in the United States: human diploid cell vaccine (HDCV, Imovax Rabies) and purified chick embryo cell vaccine (PCECV, RabAvert; Manning et al., 2008). Similar to HRIG, both HDCV and PCECV are preservative free and therefore should be administered immediately after reconstitution (Novartis, 2006; Sanofi Pasteur, 2012). They both require refrigeration and should be protected from light as well.

Each 1-ml dose should be administered intramuscularly into the deltoid region. The vaccine may be injected into the anterolateral area of the thigh if necessary in young children and infants. Administration in the gluteal area is not recommended, as this may result in lower antibody titers and may damage the sciatic nerve (gluteus maximus site) (Fishbein, Sawyer, Reid-Sanden, & Weir, 1988). The vaccine should not be administered subcutaneously, intradermally, or intravascularly. The administration regimen for the rabies vaccines is discussed later, but a vaccination series is initiated and completed usually with one product. If needed, switching to another product may be considered if adverse effects prove intolerable (Briggs et al., 2000; CDC, 1999). Neither product is superior to the other, and the adverse effect profile is similar; however, PCECV should be avoided in patients with severe egg allergies. The available agents for human rabies prevention are outlined in Table 1.

Adverse effects

The use of both the vaccine and HRIG is associated with local injection site reactions such as pain, erythema, itching, and swelling and systemic reactions such as headache, nausea, abdominal pain, muscle aches, dizziness, and fever (Ajjan & Pilet, 1989; Arora, Moeller, & Froeschle, 2004; Sabchareon et al., 1999). Systemic hypersensitivity reactions are far less frequent, with most of these occurring 1–2 weeks after the injection of the vaccine (Bernard, Smith, Kader, & Moran, 1982; Boe & Nyland, 1980; Fishbein et al., 1993). No serious hypersensitivity reactions have been reported with the use of HRIG.

It is recommended that the rabies vaccination series not be interrupted or discontinued because of local and mild adverse reactions. Attempts should be made to alleviate reactions through the use of anti-inflammatory agents, antihistamines, and antipyretics (Manning et al., 2008). In situations where serious systemic hypersensitivity reactions occur, it is necessary to carefully consider a patient's risk for acquiring rabies before discontinuing the vaccination series.

In a patient with a history of hypersensitivity to the rabies vaccine who presents for revaccination following a possible infection, medication pretreatment with agents such as anti-inflammatory agents, antihistamines, and antipyretics should be considered on the basis of the success of such agents used during the prior hypersensitivity reaction. Because of a high risk of an anaphylactic reaction in this population, epinephrine should be on-hand during vaccine administration and subsequent monitoring (Kroger, Atkinson, Marcuse, & Pickering, 2006). About half of immediate hypersensitivity reactions occur on the first day of vaccination, with the remainder occurring 6–14 days later.

Table 1. Available agents in the United States for human rabies prevention

Product	How supplied	Dose	Route	Indication	Common adverse events	Administration
Vaccine RabAvert (Chiron Behring) Imovax (Aventis Pasteur)	One vial of freeze-dried vaccine (single dose) One vial of sterile diluent for reconstitution (1 ml)	1 ml	Intramuscular	Preexposure or postexposure prophylaxis	Injection site reactions (i.e., erythema, itching, and swelling), systemic reactions (i.e., headache, nausea, abdominal pain, muscle aches, dizziness, and fever) Rarely, hypersensitvity reactions in those with severe egg allergies may occur (RabAvert)	Administer into deltoid region May administer into anterolateral thigh if necessary Administer in opposite and distant site from the location for HRIG administration
HRIG HyperRAB S/D (Grifols Therapeutics) Imogam Rabies-HT (Aventis Pasteur)	150 units/ml Available in vials of 2 or 10 ml	20 units/kg[a]	Local[b]	Postexposure prophylaxis only	Injection site reactions (i.e., erythema, itching, and swelling), systemic reactions (i.e., headache, nausea, abdominal pain, muscle aches, dizziness, and fever)	Delay administration of live vaccines for 3–4 months Inject HRIG into a location other than that used for vaccine inoculation Limit intramuscular sites of injection to 5–10 ml if necessary after infiltration around the wound

Note. HRIG = human rabies immune globulin.

[a]HRIG is dosed on actual body weight, with no adjustments for extremes in age or body weight.

[b]As much of the product as is anatomically feasible is infiltrated into and around the wound; the remainder is administered intramuscularly, in the deltoid or quadriceps.

PROPHYLAXIS

Preexposure

Although patients are unlikely to present to an ED to receive preexposure prophylaxis, it is important for the practitioner to be cognizant of its use in order to provide appropriate care to those who have received it and had a potential exposure. Preexposure prophylaxis helps provide protection for those who may be at a high and/or continuous risk of contracting the virus, and it provides protection to those persons who are at a risk for an unrecognized exposure to rabies (Manning et al., 2008). For these individuals, preexposure vaccination eliminates the need for HRIG and decreases the total number of vaccine doses following exposure. Those qualifying for preexposure prophylaxis should receive three 1-ml injections for postexposure prophylaxis. One injection per day should be given on Days 0, 7, and 21 (or 28), with Day 0 being the day of first injection (Manning et al., 2008).

The persons who are at high and continuous risk for infection include veterinarians and their staff, animal handlers, rabies researchers, and certain laboratory workers. In addition, some international travelers are candidates for preexposure vaccination if they are likely to come in contact with animals in areas where rabies is prevalent and immediate access to appropriate medical care might be limited. Routine preexposure prophylaxis for the general U.S. population or travelers to areas where rabies is not prevalent is not recommended (Fishbein & Arcangeli, 1987; LeGuerrier, Pilon, Deshaies, & Allard, 1996). To further delineate those at higher risk, the reader is directed to guidelines related to travel that are available from the CDC (www.cdc.gov/travel/diseases/rabies.htm) or local and state health departments.

Although the assessment of rabies virus–neutralizing antibody levels can indicate the immune status of a patient to rabies, its correlation with infection susceptibility is unclear (Manning et al., 2008). Current recommendations suggest that rabies virus–neutralizing antibody levels be measured periodically on the basis of an individual's risk for exposure and that booster doses be administered only when indicated (Manning et al., 2008). Attempting to ascertain the rabies virus–neutralizing antibody titer for decision making about postexposure prophylaxis is inappropriate, as it will delay care and not change the recommendations for treatment.

Postexposure

Patients presenting to the ED for potential postexposure prophylaxis constitute the most common presentation related to the rabies virus. Postexposure prophylaxis in a previously unvaccinated patient includes wound care, infiltration of rabies immune globulin, and vaccine administration (CDC, 1999; World Health Organization, 2005). Although the administration of postexposure prophylaxis is not a medical emergency, appropriate prophylaxis should not be delayed for unnecessary reasons. Practitioners should always err on the side of treatment in uncertain situations (Bernard et al., 1982; Dreesen, Bernard, Parker, Deutsch, & Brown, 1986). Any bite wound should be cleansed thoroughly, a process that has been shown to be effective in reducing the risk of transmission (Dean et al., 1963; Kaplan, Cohen, Koprowski, Dean, & Ferrigan, 1962). The use of virucidal antiseptics (i.e., povidone-iodine and ethanol) and topical antibiotics has been suggested for initial wound treatment as well. The closure of bite or scratch wounds should be avoided if possible; yet, this should be determined on a case-by-case basis (McDermid et al., 2008).

The administration of both HRIG and rabies vaccine is recommended for previously unvaccinated persons following the determination of a possible rabies exposure regardless of the interval between exposure and initiation of prophylaxis. The HRIG is administered only once to provide immediate coverage until the patient responds to the vaccine by producing his or her own antibodies (Cabasso, Loofbourow, Roby, & Anuskiewicz, 1971; Manning et al., 2008).

If HRIG is not administered at the outset, it can be administered up to, and including Day 7, of the prophylaxis series (Khawplod et al., 1996). After this time period, antibody response to the vaccine is presumed to have occurred and the administration of HRIG may negatively impact antibody production.

An individual who has received preexposure prophylaxis and is exposed to rabies should receive two intramuscular doses of the vaccine, one immediately and one 3 days later. The administration of HRIG is unnecessary and should not be used (Fishbein et al., 1986). Patients who have not been previously vaccinated should receive immunoglobulin in addition to the full standard course of four vaccine doses over 14 days (Rupprecht et al., 2010). This recommendation is updated from the previous CDC recommendations for a five-dose regimen published in 2008. It should be noted that all versions of rabies vaccine package inserts might not reflect this update. The first dose of vaccine should be administered as soon as possible after exposure. This is considered Day 0 of the postexposure prophylaxis series, and the remaining doses should be administered on Days 3, 7, and 14 (Manning et al., 2008; Rupprecht & Gibbons, 2004). An exception includes exposures involving patients who are immunosuppressed, as they should receive a five-dose series of the vaccine on Days 0, 3, 7, 14, and 28. Additional information regarding the provision of postexposure prophylaxis in all populations can be obtained both from the CDC (http://www.cdc.gov/rabies/) and from state and local health departments.

Subsequent doses should ideally be obtained at a location other than the ED, such as a local health department, infectious diseases clinic, or primary care office, if possible. Adherence to the complex series of vaccinations can provide a substantial challenge for the general public, from both a time and cost perspective. For minor deviations from the immunization schedule, vaccination can be resumed where it was left off and the same interval be maintained between doses (Rupprecht & Gibbons, 2004). When substantial deviations from the schedule occur, immune status should be assessed by performing serologic testing 7–14 days after administration of the final dose in the series (Manning et al., 2008). Adequate and redundant forms of documentation are strongly encouraged because of the complexity of prophylaxis in this setting. Communication with outside practitioners is also essential to ensure that potential medication errors are minimized.

Some domestic species are low risk, and thus if a healthy dog or cat bites a human, the animal may be observed for 10 days to ascertain the presence or absence of the virus (Jenkins et al., 2004). If the animal remains healthy, the patient does not need postexposure prophylaxis and can discontinue postexposure prophylaxis if it was previously initiated (Manning et al., 2008). If the animal develops symptoms consistent with viral infection and the infection is confirmed within 24–48 hours after the animal is euthanized, there remains adequate time to initiate prophylaxis. If potentially infected animals are brought to the ED with the patient, it is important to keep them out of the ED if at all possible and contact animal control immediately.

Despite all versions of the vaccine and HRIG being labeled as pregnancy Category C drugs, as a result of the high mortality risk associated with untreated rabies and the fact that studies have indicated no increased incidence of abortion, premature births, or fetal abnormalities associated with rabies vaccination, pregnancy is not considered a contraindication to postexposure prophylaxis (Chutivongse, Wilde, Benjavongkulchai, Chomchey, & Punthawong, 1995). As with any medication used in pregnancy, the risks and benefits should always be considered on a case-by-case basis. Preexposure prophylaxis may be indicated during pregnancy if the risk of acquiring rabies outweighs the risk of any adverse fetal effects.

The costs associated with rabies prophylaxis can be substantial. The Advisory Committee on Immunization Practices estimates the cost of one dose of HRIG to be up to U.S.

$1,434 and the cost of each dose of vaccine to be up to U.S. $679 (Manning et al., 2008). These costs are in addition to general medical care charges. Therefore, judicious and appropriate use of both the immunoglobulin and vaccine is imperative to assist in controlling health care costs.

CONCLUSION

Rabies is transmitted primarily through infected saliva contained in the bite of an infected mammal and almost uniformly results in encephalitis leading to death. Although the major reservoirs worldwide are dogs, in the United States, the majority of naturally acquired human cases have been from bats. Appropriate preexposure and postexposure prophylaxis is almost completely effective and is therefore of the utmost importance. Even though guidelines have not always been implemented correctly, no failures in prophylaxis have been documented since current biologics have been licensed. The majority of deaths in the United States occur in humans unaware of they have been bitten and who therefore did not obtain postexposure prophylaxis. Postexposure prophylaxis should be instituted liberally when exposure is suspected, and it is warranted regardless of the interval between exposure and presentation. Delays in initiating prophylaxis are associated with treatment failure, and the length of delay that renders postexposure prophylaxis ineffective is unclear. It is critical that all ED practitioners be familiar with the appropriate evaluation of patients presenting with a possible rabies exposure and ensure that expeditious and appropriate prophylaxis is provided to help prevent the development of this lethal disease.

REFERENCES

Ajjan, N., & Pilet, C. (1989). Comparative study of the safety and protective value, in preexposure use, of rabies vaccine cultivated on human diploid cells (HDCV) and of the new vaccine grown on Vero cells. *Vaccine*, *7*(2), 125–128.

Arora, A., Moeller, L., & Froeschle, J. (2004). Safety and immunogenicity of a new chromatographically purified rabies vaccine in comparison to the human diploid cell vaccine. *Journal of Travel Medicine*, *11*(4), 195–199.

Atkinson, W. L., Pickering, L. K., Schwartz, B., Weniger, B. G., Iskander, J. K., & Watson, J. C. (2002). General recommendations on immunization. Recommendations of the Advisory Committee on Immunization Practices (ACIP) and the American Academy of Family Physicians (AAFP). *Morbidity and Mortality Weekly Report Recommendations and Report*, *51*(RR-2), 1–35.

Bernard, K. W., Smith, P. W., Kader, F. J., & Moran, M. J. (1982). Neuroparalytic illness and human diploid cell rabies vaccine. *JAMA*, *248*(23), 3136–3138.

Blanton, J. D., Dyer, J., McBrayer, J., & Rupprecht, C. E. (2012). Rabies surveillance in the United States during 2011. *Journal of the American Veterinarian Medical Association*, *241*(6), 712–722.

Boe, E., & Nyland, H. (1980). Guillain-Barre syndrome after vaccination with human diploid cell rabies vaccine. *Scandinavian Journal of Infectious Diseases*, *12*(3), 231–232.

Briggs, D. J., Dreesen, D. W., Nicolay, U., Chin, J. E., Davis, R., Gordon, C., . . . Banzhoff, A. (2000). Purified chick embryo cell culture rabies vaccine: Interchangeability with human diploid cell culture rabies vaccine and comparison of one versus two-dose postexposure booster regimen for previously immunized persons. *Vaccine*, *19*(9–10), 1055–1060.

Cabasso, V. J., Loofbourow, J. C., Roby, R. E., & Anuskiewicz, W. (1971). Rabies immune globulin of human origin: Preparation and dosage determination in nonexposed volunteer subjects. *Bulletin of the World Health Organization*, *45*(3), 303–315.

Centers for Disease Control and Prevention. (1999). Human rabies prevention—United States, 1999. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morbidity and Mortality Weekly Report Recommendations and Report*, *48*(RR-1), 1–21.

Centers for Disease Control and Prevention. (2008). *Rabies—2008*. Retrieved from http://www.cdc.gov/rabies/location/usa/index.html

Charlton, K. M. (1994). The pathogenesis of rabies and other lyssaviral infections: Recent studies. *Current Topics in Microbiology and Immunology*, *187*, 95–119.

Chutivongse, S., Wilde, H., Benjavongkulchai, M., Chomchey, P., & Punthawong, S. (1995). Postexposure rabies vaccination during pregnancy: Effect on 202 women and their infants. *Clinical Infectious Diseases*, *20*(4), 818–820.

Dean, D. J., Baer, G. M., & Thompson, W. R. (1963). Studies on the local treatment of rabies-infected wounds. *Bulletin of the World Health Organization*, *28*(4), 477–486.

Dreesen, D. W., Bernard, K. W., Parker, R. A., Deutsch, A. J., & Brown, J. (1986). Immune complex-like disease in 23 persons following a booster dose of rabies human diploid cell vaccine. *Vaccine*, *4*(1), 45–49.

Fekadu, M. (1993). Canine rabies. *Onderstepoort Journal of Veterinary Research*, *60*(4), 421–427.

Fishbein, D. B., & Arcangeli, S. (1987). Rabies prevention in primary care. A four-step approach. *Postgraduate Medicine*, *82*(3), 83–90, 93–85.

Fishbein, D. B., Bernard, K. W., Miller, K. D., Van der Vlugt, T., Gains, C. E., Bell, J. T., . . . Horman, J. T. (1986). The early kinetics of the neutralizing antibody response after booster immunizations with human diploid cell rabies vaccine. *American Journal of Tropical Medicine and Hygiene*, *35*(3), 663–670.

Fishbein, D. B., Sawyer, L. A., Reid-Sanden, F. L., & Weir, E. H. (1988). Administration of human diploid-cell rabies vaccine in the gluteal area. *The New England Journal of Medicine*, *318*(2), 124–125.

Fishbein, D. B., Yenne, K. M., Dreesen, D. W., Teplis, C. F., Mehta, N., & Briggs, D. J. (1993). Risk factors for systemic hypersensitivity reactions after booster vaccinations with human diploid cell rabies vaccine: A nationwide prospective study. *Vaccine*, *11*(14), 1390–1394.

Fooks, A. R., Brookes, S. M., Johnson, N., McElhinney, L. M., & Hutson, A. M. (2003). European bat lyssaviruses: An emerging zoonosis. *Epidemiology and Infection*, *131*(3), 1029–1039.

Gibbons, R. V. (2002). Cryptogenic rabies, bats, and the question of aerosol transmission. *Annals of Emergency Medicine*, *39*(5), 528–536.

Hemachudha, T., Laothamatas, J., & Rupprecht, C. E. (2002). Human rabies: A disease of complex neuropathogenetic mechanisms and diagnostic challenges. *Lancet Neurology*, *1*(2), 101–109.

Jenkins, S. R., Auslander, M., Conti, L., Leslie, M. J., Sorhage, F. E., & Sun, B. (2004). Compendium of Animal Rabies Prevention and Control, 2004. *Journal of the American Veterinarian Medical Association*, *224*(2), 216–222.

Kaplan, M. M., Cohen, D., Koprowski, H., Dean, D., & Ferrigan, L. (1962). Studies on the local treatment of wounds for the prevention of rabies. *Bulletin of the World Health Organization*, *26*, 765–775.

Khawplod, P., Wilde, H., Chomchey, P., Benjavongkulchai, M., Yenmuang, W., Chaiyabutr, N., . . . Sitprija, V. (1996). What is an acceptable delay in rabies immune globulin administration when vaccine alone had been given previously? *Vaccine*, *14*(5), 389–391.

King, A. A., Meredith, C. D., & Thomson, G. R. (1994). The biology of southern African lyssavirus variants. *Current Topics in Microbiology and Immunology*, *187*, 267–295.

Koprowski, H., Van Der Scheer, J., & Black, J. (1950). Use of hyperimmune anti-rabies serum concentrates in experimental rabies. *American Journal of Medicine*, *8*(4), 412–420.

Krebs, J. W., Mandel, E. J., Swerdlow, D. L., & Rupprecht, C. E. (2005). Rabies surveillance in the United States during 2004. *Journal of the American Veterinarian Medical Association*, *227*(12), 1912–1925.

Kroger, A. T., Atkinson, W. L., Marcuse, E. K., & Pickering, L. K. (2006). General recommendations on immunization: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *Morbidity and Mortality Weekly Report Recommendations and Report*, *55*(RR-15), 1–48.

LeGuerrier, P., Pilon, P. A., Deshaies, D., & Allard, R. (1996). Preexposure rabies prophylaxis for the international traveller: A decision analysis. *Vaccine*, *14*(2), 167–176.

Leung, A. K., Davies, H. D., & Hon, K. L. (2007). Rabies: Epidemiology, pathogenesis, and prophylaxis. *Advances in Therapy*, *24*(6), 1340–1347.

Manning, S. E., Rupprecht, C. E., Fishbein, D., Hanlon, C. A., Lumlertdacha, B., Guerra, M., . . . Hull, H. F. (2008). Human rabies prevention—United States, 2008: Recommendations of the Advisory Committee on Immunization Practices. *Morbidity and Mortality Weekly Report Recommendations and Report*, *57*(RR-3), 1–28.

McDermid, R. C., Saxinger, L., Lee, B., Johnstone, J., Gibney, R. T., Johnson, M., . . . Bagshaw, S. M. (2008). Human rabies encephalitis following bat exposure: Failure of therapeutic coma. *Canadian Medical Association Journal*, *178*(5), 557–561.

Moran, G. J., Talan, D. A., Mower, W., Newdow, M., Ong, S., Nakase, J. Y., . . . Childs, J. E. (2000). Appropriateness of rabies postexposure prophylaxis treatment for animal exposures. Emergency ID Net Study Group. *JAMA*, *284*(8), 1001–1007.

Novartis. (2006). RabAvert rabies vaccine [Package insert]. Emeryville, CA: Novartis Vaccines and Diagnostics Inc.

Rupprecht, C. E., Briggs, D., Brown, C. M., Franka, R., Katz, S. L., Kerr, H. D., . . . Cieslak, P. R. (2010). Use of a reduced (4-dose) vaccine schedule for postexposure prophylaxis to prevent human rabies: Recommendations of the advisory committee on immunization practices. *Morbidity and Mortality Weekly Report Recommendations and Report*, *59*(RR-2), 1–9.

Rupprecht, C. E., & Gibbons, R. V. (2004). Clinical practice. Prophylaxis against rabies. *The New England Journal of Medicine*, *351*(25), 2626–2635.

Rupprecht, C. E., Hanlon, C. A., & Hemachudha, T. (2002). Rabies re-examined. *Lancet Infectious Diseases*, *2*(6), 327–343.

Sabchareon, A., Lang, J., Attanath, P., Sirivichayakul, C., Pengsaa, K., Le Mener, V., . . . Riffard, P. (1999). A new Vero cell rabies vaccine: Results of a

comparative trial with human diploid cell rabies vaccine in children. *Clinical Infectious Diseases*, *29*(1), 141–149.

Sanofi Pasteur. (2005). Imogam Rabies-HT [Package insert]. Swiftwater, PA: Sanofi Pasteur Inc.

Sanofi Pasteur. (2012). Imovax rabies vaccine [Package insert]. Swiftwater, PA: Sanofi Pasteur Inc.

Schneider, M. C., Belotto, A., Ade, M. P., Hendrickx, S., Leanes, L. F., Rodrigues, M. J., . . . Correa, E. (2007). Current status of human rabies transmitted by dogs in Latin America. *Cad Saude Publica*, *23*(9), 2049–2063.

Siber, G. R., Werner, B. G., Halsey, N. A., Reid, R., Almeido-Hill, J., Garrett, S. C., . . . Santosham, M. (1993). Interference of immune globulin with measles and rubella immunization. *Journal of Pediatrics*, *122*(2), 204–211.

Talecris Biotherapeutics. (2010). HyperRAB S/D [Package insert]. Research Triangle Park, NC: Talecris Biotherapeutics Inc.

Warrell, M. J., & Warrell, D. A. (2004). Rabies and other lyssavirus diseases. *Lancet*, *363*(9413), 959–969.

World Health Organization. (2005). Expert consultation on rabies. *World Health Organization Technical Report Series*, *931*, 1–88, back cover.

World Health Organization. (2012). *Rabies fact sheet*. Retrieved from http://www.who.int/mediacentre/factsheets/fs099/en/