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Animal Vaccines

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1 INTRODUCTION

Rabies in terrestrial animals, primarily carnivores, is caused by the classic genotype 1 rabies virus (RABV) (Nadin-Davis *et al.*, 2002; Wunner, 2002). Even though the widespread vaccination of domestic dogs has been the one most effective factor in the reduction of human rabies, the number of human deaths worldwide is greater than that of the combined deaths from polio, meningococcal meningitis, Japanese encephalitis, yellow fever, severe acute respiratory syndrome (SARS) and avian influenze (bird flu) (Wilde *et al.*, 2005). We have the 'tools' available to us in highly efficacious and safe animal and human vaccines. Multiple factors, discussed elsewhere in this book, can, however, prevent their use effectively in many areas of the world.

2 ANIMAL RABIES VACCINES

2.1 First generation of animal rabies vaccines

In his quest for a means to prevent rabies in humans, Louis Pasteur initiated research into animal rabies vaccine in France in the early 1880s (Bunn, 1991). Virus obtained from a rabid dog was first serially passed in rabbits by intracerebral inoculation at specified time intervals. Dogs were then vaccinated at various time intervals and challenged with rabies virus. Although this method produced acceptable results, Pasteur found that by serial intracerebral inoculation of monkeys with the dog origin virus, the incubation period increased while the virulence of the virus decreased. By using this regimen, Pasteur demonstrated that dogs vaccinated were resistant to subsequent challenge with virulent street (non-laboratory propagated) rabies virus.

In 1885, Pasteur attenuated, or weakened, the virus by desiccation (Bunn, 1991) to improve on the safety of these early attempts to produce a rabies vaccine. In a review by Friedberger and Frohner (1904), it was reported that Hogyes and Protopopoff and others conducted further studies to improve on the safety

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and efficacy of vaccines for dogs and to reduce the number of doses needed. In 1927, the First International Rabies Conference recommended that fixed virus for canine rabies vaccines be completely inactivated or attenuated so that they caused no disease in dogs vaccinated either subcutaneously (SC) or intramuscularly (IM) (Schoenig, 1930). For the next several decades, virtually all rabies nerve tissue origin (NTO) vaccines were inactivated with phenol using the method described by Semple (Bunn, 1991). The NTO vaccines currently in use for mass vaccination campaigns in Africa, Latin America and the Caribbean are primarily produced from rabies virus-infected suckling mouse brains or lamb brains. These vaccines have been shown to be effective in campaigns (WHO, 2004). However, NTO killed vaccines for dogs and other animals have often, in the past, resulted in post-vaccinal nervous system reactions that could result in the death of the vaccinated animals (Bunn, 1991). Better vaccines were needed.

Embryonated chicken eggs were used by Koprowski and Cox (1948) for serial passage of the Flury strain (a human rabies virus isolate). The virus was initially passed 136 times in 1-day-old chicks. Vaccine produced from the 40th to the 50th chicken embryo passage lost its viscerotropic properties but retained some neurotropic properties. This was designated as Flury low-egg passage (LEP). While effective in dogs, the vaccine occasionally caused rabies in young pups, cats and cattle (Bunn, 1991). To increase the safety of the vaccines in these species, Koprowski *et al.* (1954) increased the passages of the Flury strain in embryonated eggs until the virus was found to be non-pathogenic for dogs when inoculated intracerebrally following the 205th passage. This Flury high-egg passage (HEP) vaccine was declared safe for IM use in cats and cattle as well as puppies 3 months of age. However, since cases of vaccine-induced rabies occurred in cats administered IM with the Flury-HEP vaccine, it was later withdrawn from the market (Cabasso *et al.*, 1963; Dean and Guevin, 1963).

2.2 Parenteral modified live virus vaccines

The Flury and Kelev strains of the rabies virus are used to produce chick embryo origin (CEO) modified live virus (MLV) vaccines. Tissue culture (TC) vaccines, such as those derived with the Street Alabama Dufferin (SAD) strain, which was adapted to hamster kidney cells (Fenji, 1960) and the Evelyn-Rokitnicki-Abelseth (ERA) strain, are grown on porcine kidney cells (Abelseth, 1963) and are commonly used to produce MLV vaccines (Reculard, 1996). Several other MLV vaccines have been produced over the years. These MLV vaccines, especially those using the CEO, SAD and ERA strains are still used extensively in Asia and Africa and parts of Europe and have been adapted for oral immunization of carnivores, including domestic dogs and cats (Blancou and Meslin, 1996). The TC MLV vaccines produce fewer allergic reactions than the CEO vaccines. Potency tests for MLV vaccines for animal use consist of measuring the titer of infectious virus in a

sample from each filling lot (see Section 2.6.1). If the titer is as high as that proved efficacious in the species of animal for which the vaccine is intended, the vaccine is released for use (Sizaret, 1996).

Even though MLV vaccines have been trustworthy over the years, the use of inactivated (killed) cell culture vaccines is increasing in areas of the world where MLV vaccines are still in use. The WHO does not recommend MLV vaccines for parenteral use in animals (WHO, 2004) and no MLV rabies vaccines are currently licensed for use in the USA.

2.3 Oral modified live vaccines

The concept of oral rabies vaccines (ORV) was first proven to be successful in 1969 (Baer *et al.*, 1971). Using the SAD Berne strain of virus adapted from the ERA strain, several types of MLV ORV vaccines have been produced for use in baits for free-ranging animals that serve as vectors for the maintenance and transmission of the disease in wildlife species (Rupprecht *et al.*, 2004). ORV have been used extensively in Europe since 1977 and in Canada from 1989 with considerable success (Isara *et al.*, 1990; Aubert *et al.*, 1994). Unfortunately, the live-virus SAD vaccines contained some degree of residual pathogenicity for wild rodents (Artois *et al.*, 1992) and resulted in partially impaired immune responses in fox cubs <8 weeks old born from SAD B19-vaccinated vixens, resulting in insufficient protection against rabies (Muller *et al.*, 2001). Since the early to mid-1990s, the SAD strain used in vaccine has been replaced by the SAG-1 and SAG-2 (SAD-Avirulent-Gif) strains in the development of vaccines. The SAG-2 strain, the strain of choice, is a double mutant isolated from the SAD Berne strain after two successive selection steps utilizing anti-glycoprotein monoclonal antibodies. This strain is avirulent following intracerebral inoculation of immunocompetent mice and protects the mice against challenge with challenge virus standard (CVS) (Lafay *et al.*, 1994). The SAG-2 strain of rabies virus, packaged in chicken-head baits, has successfully protected captive African wild dogs against rabies challenge (Knobel *et al.*, 2003). In studies conducted at the Centers for Disease Control and Prevention in Atlanta, Georgia, USA, the SAG-2 vaccine produced no clinical illness in laboratory vaccinates (beagles) and residual SAG-2 virus was isolated from only one of 57 oral swabs from the dogs (Fekadu, *et al.*, 1996; Orciari *et al.*, 2001). No ORV derived from SAD/SAG origin vaccines are currently licensed for use in the USA (Compendium, 2006).

2.4 Oral live vaccinia-rabies virus glycoprotein recombinant vectored vaccine

A recombinant vaccinia virus expressing the rabies virus glycoprotein gene (V-RG) was developed by inserting the cDNA of the glycoprotein gene of the ERA strain

into the thymidine kinase gene of the Copenhagen strain of vaccinia virus. Initial studies of this new ORV were conducted to determine whether the V-RG recombinant virus vaccine satisfied the various criteria that had to be met for such a vaccine to be distributed in the wild (Kieny *et al.*, 1984; Wiktor *et al.*, 1984). Criteria included: the vaccine would be effective when delivered by an oral bait; the baits would be readily accepted by target species but would be rabies virus-free; the vaccine in the baits would have reasonably long-term genetic and thermal stability; the vaccine would be biologically contained in the host; oral exposure to baits with the vaccine would produce full protection against rabies virus challenge; that no non-target species would develop rabies if they ingested the baits; and that the baits were clearly identified and safe for contact with humans. In an extensive series of trials carried out in the USA and in France, these criteria were met and the vaccine was licensed in 1995 for raccoons to prevent spread of raccoon rabies (and later to prevent the spread of Mexican dog rabies to Texas coyotes along the south Texas border with Mexico) by the US Department of Agriculture (USDA) (Wiktor *et al.*, 1985; Rupprecht *et al.*, 1986; Brochier *et al.*, 1990, 1991, 1995; Desmettre *et al.*, 1990). The single licensed product is produced only by Merial, Inc., Athens, GA, USA as Raboral V-RG™ for use by governmental (State Public Health) agencies as an ORV for raccoons and coyotes.

In the USA, Raboral V-RG™ is currently delivered to raccoons and coyotes in an extended fishmeal polymer bait, which contains 150 mg of tetracycline hydrochloride as a bone biomarker and a plastic sachet containing 1.8 ml of the vaccine. An extruded poultry-based bait with identical vaccine content has been shown to be more effective for targeting gray foxes (Merial, Inc., Athens, GA, USA).

The successful use of the ORV to achieve containment or elimination of rabies in some terrestrial wildlife animals in the USA and Canada is indicated by the effective containment to near elimination of red fox rabies in southern Ontario (MacInnes *et al.*, 2001), canine rabies in south Texas (Fearneyhough *et al.*, 1998) and raccoon rabies in Ohio (Krebs *et al.*, 2005), southern Ontario (Rosatte *et al.*, 2001) and eastern New Brunswick (Slate *et al.*, 2005). In 2003, over 10 million baits were distributed in 15 states in the USA (Slate *et al.*, 2005). New and potentially more effective oral vectored vaccines and more effective baits, including a fishmeal coated sachet bait, are being developed for ORV (Slate *et al.*, 2005).

2.5 Parenteral live vaccinia-rabies virus glycoprotein recombinant vectored vaccine

A canarypox-rabies glycoprotein recombinant vaccine was developed and found to be as effective as other poxvirus-rabies glycoprotein recombinants (Taylor *et al.*, 1991, 1995). Live canarypox virus that expresses the rabies virus glycoprotein has been licensed in the USA as a parenteral monovalent vaccine for cats

and as a combination rabies vaccine for cats with feline panleukopenia virus, feline parvovirus and feline calicivirus vaccines included in the product. A combination canarypox-rabies vaccine with the whole-cell bacterin of *Neorickettsia risticii* included is also licensed for use in the prevention of Potomac fever in horses. These are the only rabies virus glycoprotein vaccines currently licensed in the USA (Compendium, 2006).

A recombinant adenovirus-vectored vaccine expressing rabies virus glycoprotein (Adrab.gp) was shown to be capable of inducing antibody immune responses in greyhound dogs immunized either subcutaneously or intramuscularly. The dogs had been previously vaccinated for rabies but had low or no rabies antibody titers (Tims *et al.*, 2000). This vaccine holds promise as a rabies virus vaccine for dogs.

2.6 Parenteral inactivated (killed) cell culture vaccines

The inactivated vaccines require that the rabies virus be produced in high concentrations. This is initially done by growing the virus strain (primarily CVS-11, Pittman-Moore (PM)-NIL 2 and Pasteur virus (PV)-BHK 21 strains) in the brain tissue of rabbits, baby hamster kidney (BHK) cells, suckling mouse brains (SMB), guinea pig brain cells, chick embryo cells (CEO), Vero cells or other substrates (Precausta and Soulebot, 1991; Reculard, 1996). Neonatal mice can be used as they lack the immunogenic (or allergenic) myelin that caused encephalomyelitis occasionally noted in animals vaccinated with earlier SMB NTO killed vaccines.

The production methods used for the TCO rabies vaccines have allowed less allergenic but more immunologic products (Greene and Rupprecht, 2006). Various methods, which are still valid, have been used to render the virus non-pathogenic or essentially inactivated (killed) as vaccines. These include, but are not limited to, beta propiolactone (BPL), UV light, and acetylethylamine as well as other amines. Phenol and formaldehyde are no longer recommended for virus inactivation (Reculard, 1996). The most commonly used inactivating agent is BPL. Once inactivated, adjuvants are added in order to increase the immune response to the antigen. The most common adjuvants are aluminum hydroxide, aluminum phosphate, saponin (in cattle vaccines) and, rarely, oil adjuvants (Precausta and Soulebot, 1991). Much of the information on cell lines, inactivating methods and adjuvants is proprietary and cannot be reported specifically for any one vaccine. The stability of these inactivated cell culture vaccines has allowed the rabies vaccine to be combined with other vaccines and bacterins such as canine distemper, canine adenovirus type 1, *Leptospira* and parvovirus for canines. For cats, the combination vaccines include feline panleukopenia-virus, feline parvovirus and feline calicivirus. A combined rabies and foot-and-mouth disease vaccine is available for cattle, sheep and goats (WHO, 2004). The potency and safety of the inactivated rabies vaccines have proven to be quite good.

2.6.1 The NIH test

In 1974, the National Institutes of Health (NIH) of the US Department of Health and Human Services (DHHS) adopted a mouse inoculation test to measure the potency of inactivated vaccines (Seligmann, 1973). This was necessitated because of the poor performance of the initial manufactured tissue culture origin vaccines (Bunn, 1991). Although a number of other tests to measure vaccine potency are used throughout the world, the NIH test is considered the 'gold standard' for measuring the ability of an inactivated vaccine to protect a mouse against virus challenge. The NIH test relies on challenge exposure of immunized mice to one virus strain (CVS), a strain thought to be derived from the original Pasteur isolate (Baer, 1997). This test has some inherent bias towards vaccine from the same virus strain origin when comparing vaccine efficacy across the variety of strains (i.e. SAD, Flury strain vaccines) used to prepare vaccines (Barth *et al.*, 1988), but this bias does not occur when non-Pasteur stain vaccines are tested for protective potential against wild virus strains (Baer, 1997; Wunderli *et al.*, 2003a). In addition, the NIH uses two doses of vaccine administered at a one-week interval by an intraperitoneal challenge two weeks later. This vaccination route is quite different from that used for routine administration of rabies vaccine. The second dose prevents an evaluation of the vaccine's primary immunologic potential and the challenge results in a disruption of the blood–brain barrier, allowing neutralizing antibodies in the serum to prevent infection. As a result of these limitations, the WHO has acknowledged that the NIH test needs some improvements or further suggesting that a new rabies potency test may be needed (WHO, 1992, 1994). Two recent reports have proposed an alternative method that avoids these shortcomings (Wunderli *et al.*, 2003a, 2003b).

2.6.2 Post-vaccinal complications

Due to the higher antigenic mass and the use of adjuvants, inactivated rabies vaccines have produced post-vaccinal local and systemic reactions. The most common non-neurologic reactions include soreness, lameness and regional lymphadenopathy in the injected limb. Fever and anaphylaxis have also been reported (Dreesen, 1999; Greene and Rupprecht, 2006). Focal vasculitis and granulomas have been seen 3–6 months after vaccination (Greene and Rupprecht, 2006). Post-vaccinal sarcomas may develop as a result of sustained inflammatory reactions at the site of the vaccination that involve the underlying dermas. Such post-vaccinal sarcomas are often aggressive and invasive, especially in cats, months to years following vaccination (Dubielzig *et al.*, 1993; Kass *et al.*, 1993; Greene and Rupprecht, 2006). A review of 239 cases of fibrosarcomas in cats following single vaccination showed that 37% of the cats with vaccination-site tumors had received rabies vaccine, 33% were administered a non-rabies combination vaccine and 30% received a feline leukemia vaccine (Hendrick *et al.*, 1994). It is not unusual

for palpable lesions to occur in cats administered killed vaccine subcutaneously (Schulze *et al.*, 1997). Adverse incidence rates for reactions to rabies vaccination in a retrospective study of 3587 ferrets was 1% when the rabies vaccine was given alone and 0.85% when given in combination with distemper vaccine. The most common adverse events were vomiting and diarrhea (Moore *et al.*, 2005). The new generation of vectored recombinant vaccines now appearing on the market, such as the avipoxvirus vaccine recently licensed for use for cats in the USA (a rabies glycoprotein, live canarypox vectored vaccine) appears to produce few, if any, allergic or neoplastic reactions (Greene and Dreesen, 1998; Greene and Rupprecht, 2006).

2.6.3 WHO Report

Animal rabies vaccines

The WHO's World Survey of Rabies reported that there are at least 23 countries or territories that reported producing animal rabies vaccines during 1999. For the production of animal rabies vaccines, 14 countries use cell culture, seven use neural tissue and six countries use embryonated eggs (WHO, 2002). Four countries produced more than one type of vaccine. Both MLV and inactivated vaccines are produced worldwide.

The 1998 WHO World Survey of Rabies reported that Brazil is the major producer of NTO rabies vaccines for animal use followed by Bangladesh, Romania, Tunisia and El Salvador (WHO, 2000). These five countries account for 99.8% of the 23.5 million doses of NTO vaccine, primarily SMB origin (Fuenzalida strain), reported produced for the year. This same 1998 survey reported that the USA produced approximately 54 million doses of TCO rabies vaccines, 84% of all TCO animal vaccines produced. Vietnam is reportedly the primary source of embryonated egg-origin animal vaccine, producing 88% of this vaccine produced worldwide. It should be noted here that Argentina, France, Germany, India and a number of other countries that presumably produce animal rabies vaccines did not contribute to the 1998 WHO report.

Latin America

During the 2-year period 1998–1999, the availability of rabies vaccines for dogs and cats in Latin America grew by 10.7% and the total doses of vaccine administered for these species rose by 3.1% (REDIPRA, 2001). Vaccine coverage increased from 2.2% in Brazil to 36.7% in the Southern Cone (Argentina, Chile, Paraguay, Uruguay). However, there was a 16.3% decline in the Andean Area (Bolivia, Columbia, Ecuador, Peru, Venezuela) and a 6.8% decline in Central America. This same report denotes that, in the Andean Area, 67% of the canine population was vaccinated, in the Southern Cone 14.7%, Brazil 85%, Central America 38%, Mexico 88% and Latin Caribbean 41%. The WHO recommends that 70% of dogs

in a population should be effectively immunized to prevent an epidemic of canine rabies (Coleman and Dye, 1996). There were 3600 laboratory confirmed canine rabies cases in all of Latin America during 1998 and 2500 during 1999. During the same periods, cattle accounted for 3298 and 3225 cases and other domestic animals accounted for 575 and 593 cases respectively.

2.6.4 USA

Vaccine types and licensing requirements

Many types of rabies vaccines are currently marketed in the USA for use in domestic animals. There are 12 inactivated monovalent rabies vaccines licensed for dogs and cats, two for ferrets, four for horses, four for cattle and five for sheep. Two inactivated vaccines are combined with other biologics for use in horses. In 2000, a new generation of vaccines was licensed for use in cats. These are the live canarypox-rabies virus glycoprotein recombinant vectored vaccines, either monovalent (one licensed vaccine) or in combination with feline panleukopenia virus, feline parvovirus and feline calicivirus vaccines (Compendium, 2006). A live vaccinia-rabies virus glycoprotein recombinant vectored vaccine is licensed for restricted use in wildlife raccoons and coyotes. As stated earlier, there are no MLV (attenuated) rabies vaccines licensed for use in the USA. All currently licensed killed rabies vaccines intended for use in carnivores must protect 22 of 25 or 26 of 30 (or a statistically equivalent number) animals from an IM challenge with a rabies virus for 90 days post challenge and 80% of controls must die from the challenge (Code of Federal Regulations, 2004). Alternative challenge requirements have been outlined when the test animals are of a species other than carnivores (Code of Federal Regulations, 2004). The US Department of Agriculture (USDA), Animal and Plant Health Inspection Service (APHIS), Center for Veterinary Biologics has jurisdiction over licensure of rabies vaccines in the USA.

Compendium of Animal Rabies Prevention and Control, 2006

The National Association of State Public Health Veterinarians (NASPHV) publishes annually the Compendium of Animal Rabies Prevention and Control (Compendium, 2006) in the *Journal of the American Veterinary Medical Association* each year. The annual Compendium is also available on the National Centers for Disease Control and Prevention (CDC) website (http://www.cdc.gov/mmwr/). This Compendium is a basis for animal rabies programs and the NASPHV issues it as recommendations. Some states (e.g. Georgia) and various cities and counties adopt the recommendations in the Compendium as regulations for animal rabies control and prevention.

The inactivated TCO vaccines should be used in animals at 3 months of age or older and then again one year later. This minimum age precludes maternal antibody blockage and recognizes the immature immune system's often poor response

(Greene and Dreesen, 1998). Depending on the vaccine, the animal species and, at times, local regulations, the animals should be vaccinated annually or triennially thereafter (Compendium, 2006). Depending on the vaccine type and the species, the vaccine is administered either IM or SC, while some vaccines can be administered either way. The minimum age for animal vaccination is 8 weeks of age for the licensed vectored vaccines. Regardless of the rabies vaccine type, only when the antibody response peaks, at approximately 28 days after primary vaccination, is the animal considered fully immunized, if vaccination has been administered in accordance with the manufacturer's recommendations.

From an epidemiologic viewpoint, the effectiveness of canine rabies prevention and control programs can be measured by comparing reports of rabies in dogs with reports of increases in cat rabies. This was apparent during the recent raccoon rabies epidemic in the Middle Atlantic and northeastern USA (Krebs *et al.*, 1997; Hanlon and Rupprecht, 1998). The increase in rabies cases in cats, while dog rabies cases remained substantially unchanged, reflects the vaccine status of the two populations as well as the number of feral animals in the two populations (Eng *et al.*, 1988; Petronek, 1998; Dreesen, 1999). Of 54 respondents in a survey of state and community health officials by Johnson and Walden (1996), 74% stated that canine rabies vaccination was required by state law while only 52% stated that cat vaccination was state law. The need for cat vaccination and feral population control cannot be overemphasized (Dreesen, 1999). Johnson and Walden's survey (1996) also noted that over-the-counter sales of rabies vaccines was permitted in 22 states and that, at that time, vaccination of wolf-hybrids was permitted in 14 states; however, in all but two of these 14 states the owner must sign a liability statement. Fourteen other states did not address the wolf-hybrid issue at all.

Ferrets and wolf-hybrids

In 1998, after extensive studies at the Centers for Disease Control and Prevention (Niezgoda *et al.*, 1997), a rabies vaccine for ferrets was approved by the USDA, APHIS. The ferret should be treated in a similar manner as a dog or cat in regard to vaccination and post-exposure management (Compendium, 2006).

Vaccination of wolf-hybrids with canine rabies vaccine is still a matter of considerable debate. In a meeting of taxonomists in 1996, it was concluded that rabies vaccines for dogs would *probably* protect wolves and their hybrids as they are genetically virtually indistinct from the domestic dog (Dreesen, 1999). At least one well-documented case of rabies has occurred in a properly vaccinated wolf-hybrid (Jay *et al.*, 1994). This animal was vaccinated with a 3-year vaccine at 4 months of age and received other vaccines and bacterins and an anthelminthic on the same day. Six months later the animal was found with a dead skunk in its mouth. Within 3 weeks the animal developed signs suggestive of rabies, was euthanized and rabies was confirmed in the laboratory. Currently,

there are no licensed rabies vaccines for wolf-hybrids and the 2006 Compendium states that wild animals and hybrids (offspring of wild animals crossbred to domestic animals) should not be kept as pets.

2.6.5 Post-exposure prophylaxis (PEP) for domestic animals

An animal can be considered to be immunized against rabies virus exposure approximately 28 days after the primary rabies vaccination, which is consistent with a peak antibody response (Compendium, 2006). Thus, an animal is considered immunized if the primary vaccination was administered at least 28 days previously and the follow-up vaccinations have been administered as recommended by the package insert and/or the Compendium (2006).

The NASPHV (Compendium, 2006) recommends that unvaccinated dogs, cats and ferrets exposed to a known or suspected rabid animal should be euthanized immediately. If not euthanized, the animal should be placed in strict quarantine for 6 months and vaccinated either upon entry into isolation or one month prior to release. Animals with expired vaccinations should be evaluated on a case-by-case basis. Currently, vaccinated dogs, cats and ferrets should be revaccinated immediately following exposure and kept under control and observation for 45 days. It has been shown that there is some evidence that the use of vaccine alone will not reliably prevent rabies from occurring in an unvaccinated domestic animal (Hanlon *et al.*, 2002). Vaccinated livestock exposed to rabies should be revaccinated and observed for 45 days (Compendium, 2006). If not previously vaccinated, food animals should be slaughtered within 7 days with disposal of tissues in the exposed area. If not slaughtered within this time period, the animal should be closely observed for 6 months.

As previously mentioned, the Compendium (2006) is issued as recommendations only. Some states do not strictly adhere to the recommendations. For example, the Texas Health and Safety Code originally followed the previously noted recommendations for animals exposed to rabies (Clark and Wilson, 1996). However, in 1988, the Code was amended; unvaccinated domestic animals exposed to a rabid animal were to be euthanized *or* vaccinated immediately after exposure, kept in isolation for 90 days and given booster vaccinations in the third and eighth week of isolation. This regimen was based loosely on recommendations for humans exposed to rabies virus. A retrospective study conducted by Clark and Wilson (1996) found that 99.7% of 713 unvaccinated animals did not develop rabies during the 1979–1987 period during which the recommendations of the NASPHV were followed. Two PEP failures did occur (0.3%). For the period 1988–1994, after the Texas Code was amended to allow PEP for unvaccinated animals exposed to rabies, 629 of 632 animals (99.5%) that received the PEP booster vaccinations did not die of rabies. There was no statistical difference between the two regimens under conditions followed in Texas. In a follow-up study for the years 1995–1998, Wilson and Clark (2001) found

only four of 830 (0.5%) domestic animals that received the PEP protocol, as recommended, during the previous 7-year period developed clinical rabies. They concluded that this is an effective PEP protocol and 'has been proven to be effective for the control of rabies in animals'. This alternative method of PEP for unvaccinated domestic animals exposed to rabies, as practiced in Texas, has not been endorsed in the Compendium (2006).

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