ORAL RABIES VACCINATION: UNRESOLVED ISSUES AND DATA GAPS

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Abstract: Oral rabies vaccination (ORV) represents a potential wildlife management tool that may be applied to contain and perhaps eliminate specific rabies virus variants that persist in several terrestrial carnivore species in the U.S. Increasingly greater use of ORV in the U.S. since 1997 has sparked discussion within the wildlife profession regarding need, cost and effectiveness, as well as the potential for wildlife management and ecological impacts. We identify and present ORV-related issues and data gaps of concern to wildlife managers that should be addressed through research, rabies surveillance and population monitoring.

Key words: Procyon lotor, oral vaccine, rabies, raccoon, wildlife disease

INTRODUCTION

The ability to orally vaccinate wildlife against rabies was proven feasible in captive red foxes (Vulpes vulpes) in the U.S. in 1969 (Baer et al. 1971). Field application of this technology began in Europe in 1977 (Steck et al. 1982), targeting rabies in red foxes and continues to be applied in several European countries (Aubert et al. 1994, Stohr and Meslin 1996, Wandeler 2000, Zanoni et al. 2000). An ORV program was initiated in Ontario, Canada in 1989 (MacInnes, personal communication) continues with the goal of eliminating an arctic fox (Alopex lagopus) variant of rabies virus established in red foxes (MacInnes and LeBer 2000).

Experimental ORV programs began in the U.S. in the mid-1990's (Fearneyhough et al. 1998; Smith et al. 1999; Bigler, personal communication), after successful field safety and efficacy trials were conducted on Parramore Island, Virginia in 1990 (Hanlon et al. 1998), near Williamsport, Pennsylvania in 1991 (Hanlon and Rupprecht 1998), and Cape May, New Jersey from 1992 and 1993 (Roscoe et al. 1998). The more conservative pace in which ORV has been implemented in the U.S. has been discussed by Slate et al. (2002), and may be attributed to public health, regulatory/safety, economic, technological, and wildlife management issues.

The public health system in the U.S. is currently effective in keeping annual human mortality near zero (Rupprecht, personal communication). The medical system in the U.S., unlike that in Europe and Canada, is largely private or group insurance-based. Consequently, the monetary costs associated with rabies are diffuse and not as easily documented on a broad scale, masking the cumulative financial impact of wildlife rabies. Low annual human mortality in the U.S., due in
The process for vaccine licensure in the U.S. is arduous (VSTA 1985), as is the process for public involvement (NEPA 1969) to decide if ORV should be applied outside of controlled environments. Wildlife is a public resource, held in public trust and managed by state and federal agencies, making human dimensions related to wildlife management actions such as rabies control with ORV a critical programmatic consideration (Siemer and Brown 1994, Meltzer et al. 1997).

The relatively high cost of ORV (Uhaa et al. 1992, Meltzer 1996, Meltzer and Rupprecht 1998, Kemere et al. 2002) in relation to expected benefits must be weighed against competition for resources to address other public health diseases. In addition, given that human mortality approaches zero and that ORV would not directly lead to reduced annual deaths, benefit:cost ratios should be integrated with other less quantifiable criteria (e.g., stress, psychological trauma and fear associated with rabies) in the decision making process for wildlife rabies control.

The diversity (red and gray foxes [Urocyon cinereoargenteus], skunks—primarily the striped skunk [Mephitis mephitis], raccoon [Procyon lotor], and spillover of canine variant of rabies into coyotes [Canis latrans]), ecological complexity and distribution of terrestrial wildlife rabies reservoirs in the U.S. represents a daunting technical, logistical and ecological challenge to implementing effective programs over a broad geographical scale (Hanlon et al. 1999). Lack of a licensed vaccine to orally immunize skunks in the U.S. may confound the long-term rabies control objectives for the raccoon and red fox, given the increasing number of skunks infected with raccoon variant of the rabies virus in the eastern U.S. (Krebs et al. 2002, Guerra et al. 2003) and the persistence of arctic fox strain of rabies in skunks in southern Ontario (Maclnnes, personal communication).

ORV has been applied as a strategy in the U.S. to attempt to control specific terrestrial strains of rabies for over a decade. While progress has been made in implementing broader scale ORV programs that are supported by research, reservoir species monitoring and rabies surveillance (Slate et al. 2002), critical data gaps remain. We identify issues and data needs associated with this prospective technology of concern to wildlife managers that should be addressed.

BRIEF ORV CHRONOLOGY IN THE U.S.

Oral rabies vaccination has been conducted in the U.S. for over a decade. Field research trials that first focused on safety and efficacy with Vaccinia-Rabies Glycoprotein (V-RG) (Hanlon et al. 1998, Hanlon and Rupprecht 1998, Roscoe et al. 1998) during the early 1990’s led to licensing of Raboral V-RG®—currently the only licensed oral vaccine for use in wildlife in the U.S. The commercial availability of this licensed oral rabies vaccine and public support in turn facilitated the initiation of larger scale ORV projects (Hanlon and Rupprecht 1998) in Ohio (Smith et al. 1999), New York (Bigler, personal communication; Eidson, personal communication), Vermont (Bigler, personal communication), Maryland (Horman, personal communication), Massachusetts (Robbins et al. 1998), Florida (Olson et al. 2000) and Texas (Fearneyhough et al. 1998) that formed the basis for evaluation and refinement for future programs.
Figure 1. Trends in number of states, baits distributed and area orally vaccinated from 1995-2003.

In 1998, USDA, Wildlife Services (WS) received its first federal appropriation to help coordinate interstate cooperative ORV projects. By 2003, funding has increased to about 24 million, allowing for: nearly complete implementation of the containment barrier for raccoon rabies in the eastern U.S.; ORV of 60 miles into western Pennsylvania where raccoon rabies has been enzootic for over a decade; continued participation in a maintenance barrier for coyote rabies (canine strain) in south Texas; and restoration of a containment barrier for gray fox rabies in west-central Texas. In 2003, approximately 180,000 km$^2$ were orally vaccinated with over 10 million vaccine laden baits in 16 states to address strains of rabies unique to the raccoon and gray fox, as well as canine strain (spillover from canine strain along the south Texas-Mexico border) adapted to coyotes (Figure 1 and Figure 2).

The vision for the National ORV Program is to eliminate rabies in terrestrial carnivores. The immediate goals are to prevent specific strains of the rabies virus in the raccoon, gray fox (strain unique to Texas) and coyote from spreading to new, uninfected areas. The long range goal is to eliminate these strains. Rabies strain elimination is expected to be more challenging, in part, because specific rabies strains may have been established for long periods of time in some geographic areas (e.g., raccoon rabies was first described in 1947 in Florida [Bigler et al. 1973]).

ORV has been applied to create a “rabies free” status in some western European countries (World Health Organization 2002), nearly eliminate rabies in red foxes in southern Ontario (MacInnes, personal communication), and help eliminate rabies in coyotes in southern Texas (Fearneyhough et al. 1998; Sidwa, personal communication). However, achieving rabies strain elimination remains uncertain in the U.S., requiring broader scale ORV campaigns to be considered experimental, with a strong research underpinning. New research findings and tools will need to be integrated into contemporary ORV strategies so that they have the best chance to succeed in the long term.
DISCUSSION

WS formed a Rabies Management Team composed of WS operations and research personnel, other APHIS expertise, and external expertise from CDC, cooperating states, and universities. Furbearer biologists from the Northeast and Southeast Furbearer Technical Resources Committees, as well as a furbearer biologist representative from the Midwest Region, were invited to ensure access to state wildlife agency furbearer management expertise. Ten multidisciplinary focus teams were established from the Rabies Management Team to systematically focus on questions that would contribute to enhanced ORV effectiveness (Table 1). These teams meet annually and communicate routinely to provide guidance and recommendations on key issues of relevance to the national rabies control plan.

Issues and data gaps identified and discussed in this paper will be provided to one or more of the focus teams for further consideration and recommended action.
Potential Effects Of ORV

Raccoon conflicts/damage

The raccoon is designated as a “furbearer” in most states and is managed under state law. States set and administer regulated harvest seasons on raccoons (e.g., trapping and hunting). The raccoon, like other furbearers, has aesthetic, ecologic, utilization, recreational and other values (Kellert 1981, Sanderson 1987, The Northeast Furbearer Resource Technical Committee 2001). The raccoon is well adapted to exist in a wide spectrum of habitats and often occurs in higher densities in some suburban and suburban edge habitats (Riley et al. 1998). Its ability to prosper in residential and other developed settings often results in serious human-wildlife conflicts, property damage, and public health concerns. The raccoon may also cause damage to specific agricultural crops such as sweet corn.

Table 1. Ten interdisciplinary teams charged with evaluating critical subject areas integral to effective ORV and providing guidance to cooperative rabies control planning.

Baiting Support: Air and Ground
Baiting Strategies/GIS Planning
Communications Planning
Contingency Action Planning
Economic Analysis
NEPA Compliance
ORV Evaluation
Research Prioritization
Surveillance/Laboratory Support
Vaccine/Bait/Biomarker

Raccoons and disease

Raccoons are host to several diseases in addition to rabies (Davidson and Nettles 1997). Canine distemper is an important contagious disease in raccoons, which often produces neurological symptoms similar to rabies (Addison et al. 1987). Although humans are not at risk, distemper can be transmitted to unvaccinated dogs and domestic cats (Appel et al. 1974) by close contact with infected raccoons. Raccoon roundworm (Baylisascaris procyonis) may parasitize humans who accidentally ingest (larvated) eggs shed in raccoon feces. Visceral larval migrans may occur from raccoon roundworm and can be fatal humans (Davidson and Nettles 1997), underscoring public health concern regarding this parasitic disease in suburban environments (Roussere et al. 2003, Eberhard et al. 2003).

Effects of raccoons on other wildlife

As a predator, the raccoon impacts other species of wildlife. Sometimes these impacts affect management objectives of predated species. The raccoon has expanded its range to include the prairie pothole region of the U.S. and Canada, where it has become an important predator of waterfowl (Llewellyn and Webster 1960, Greenwood 1981). The raccoon may also be a significant source of predation on other nesting birds and reptiles, such as the Vermont endangered Eastern spiny softshell turtle (Apalone spinifera) (Parren 2003) and the Green Sea Turtle (Chelonia mydas) in Florida (Constantin, personal communication).

Wildlife biologists have suggested that the impact of raccoons on property, agriculture, public health and other wildlife needs to be studied in the context of ORV effects (i.e., does ORV exacerbate these effects in the short or long-term?). In addition, the potential effects of ORV on raccoon harvests by the public for pelts and food should be explored.

Prior to 1977, raccoon rabies was confined to the southeastern U.S., primarily Florida and Georgia (Bigler et al. 1973). From 1977 to mid-1983, a total of 1,608 raccoon rabies cases was reported from...
Washington, D.C. and West Virginia, Virginia, Maryland and Pennsylvania (Beck 1984). The most probable origin of this new epizootic was the translocation of raccoons from areas in the southeastern U.S., where raccoon rabies was enzootic, to the mid-Atlantic region that had not previously experienced raccoon strain of the rabies virus (Nettles et al. 1979). Monoclonal antibody analysis of rabies virus samples from the mid-Atlantic region revealed that this rabies virus variant was identical to the strain in raccoons in the Southeastern U.S. (Smith et al. 1984).

Raccoon rabies strain represents a new mortality factor as this variant of the virus spreads to previously unaffected portions of the raccoon’s range, except for the far southeastern portion of the U.S. where epizootics in raccoons began in 1950’s (McLean 1971). Expansion of the range for raccoon rabies raises several questions. How does rabies impact raccoon populations during the first epizootic episode and subsequent outbreaks? Is the level of rabies mortality predictable in first and subsequent epizootic waves and when the disease becomes enzootic? What is the relationship between rabies-induced mortality and the level of conflict, damage and predation attributed to raccoons locally or on a broader geographic scale? Is there a compensatory or additive mortality effect in areas where raccoon strain of the rabies virus and canine distemper occur sympatrically?

A clearer scientific understanding of the dynamics of wildlife diseases in relation to challenges facing wildlife management agencies is needed. Nevertheless, the best currently available information and analyses in progress should be helpful in framing retrospective and prospective research and analyses.

The first epizootic wave of raccoon rabies resulted in substantial laboratory testing of suspect animals in many states. In New York State alone, 11,896 animals were submitted to the state laboratory for rabies testing in 1993 after raccoon rabies had begun to spread along a broad front from southern part of the state. Of the raccoons submitted, 2,746 tested positive for raccoon strain of rabies through monoclonal antibody or nucleotide sequencing. In subsequent years, the New York Rabies Laboratory has never tested as many suspect animals as in the first epizootic wave of raccoon rabies; however, complacency and passive public health rabies surveillance creates a sampling bias that may confound the use of surveillance trends as a clear predictive index to rabies impacts on raccoon populations in New York and elsewhere. Nevertheless, retrospective analyses of rabies surveillance data may prove useful in enhancing our understanding of the potential impact of rabies on raccoon populations under pre, epizootic and post-epizootic conditions (Trimarchi, personal communication).

An analysis of WS national management information system data, during years when the mid-Atlantic epizootic spread northward, ranked the raccoon as the number one species (n>150,000) for which the program received requests for assistance to resolve conflicts (Slate et al. 1999). Most of the data input was from Maryland, New Hampshire and Vermont, states within the spread of raccoon rabies and with technical assistance hotlines. This data collection was not designed to characterize the extent of damage, public health impacts, or to field verify calls to determine their root cause. These data may circumstantially suggest that rabies mortality was insufficient to substantially dampened raccoon problems. However, the presence of raccoon rabies alone generates considerable anxiety among the public. Consequently, requests for assistance to WS
with raccoon conflicts may not be in direct proportion to raccoon densities (which may have been reduced by rabies) or the prevalence of rabies in raccoon populations.

Epizootiologic studies of canine distemper suggest that it is an important disease in raccoons and perhaps other carnivores (Budd 1970, Evans 1982, Hoff et al. 1974) and may cycle in response to raccoon density (Roscoe 1993). Roscoe (1993) indicated that the effects of canine distemper may diminish or become difficult to discern once rabies becomes established as a new disease in raccoons in New Jersey.

To better understand the dynamics of rabies and distemper, WS continues to collect serum samples to assess sero-conversion from ORV and to assess population levels of virus neutralizing antibodies to canine distemper. To date, WS has submitted over 5,000 raccoon serum samples taken for canine distemper testing from within or immediately adjacent to the current distribution of raccoon rabies. Serological analyses over time should provide indices of the potential effects of these viruses on raccoon populations.

**Current oral rabies vaccine limitations**

A concomitant increase in the number of skunks infected with raccoon variant of the rabies virus has raised concerns about an independent maintenance cycle for raccoon rabies in skunks (Guerra et al. 2003). The same may also be true for arctic fox strain (in red foxes) and skunks in southern Ontario (Nadin-Davis et al. 1999). Raboral V-RG®, the only licensed oral racabies vaccine in the U.S., is not efficacious in producing sufficient levels of population immunity in skunks at the current dose (≥10^{7.7} TCID\[tissue culture infected dose]\_50/ml) (Tolson et al. 1987). The national rabies control goals of strain containment and elimination may remain elusive until a strain independent oral vaccine (i.e., a vaccine that is effective in all wildlife reservoirs) is licensed for use in the U.S.

While all major reservoirs and vectors (domestic dog, domestic cat, bats, raccoon, skunks, coyote and bobcat) have been responsible for human deaths in the U.S. since 1990 (CDC 2003a), most of the 37 deaths have been confirmed bat variants of the rabies virus (CDC 2003b). There are several species of bats; some are commensal and live in houses and other dwellings. The prospect of effectively delivering oral vaccines in a coordinated fashion to eliminate bat rabies is remote at this time.

It has been speculated that terrestrial rabies strains in the U.S. may have been derived from transmission of bat rabies to carnivores and the subsequent species specific adaptive genomic changes in the rabies virus through passages among carnivores (Badrane and Tordo 2001). Documentation of skunk to skunk transmission of big brown bat rabies virus strains in the vicinity of Flagstaff, Arizona provides contemporaneous supporting evidence that terrestrial rabies could evolve from bat strains (Hughes et al. 2004). If true, evolution of new terrestrial variants of the rabies virus may be expected to occur from rabies virus transmitted by bats to terrestrial carnivores.

Wildlife biologists have expressed concern that rabies control goals may be unattainable and that bats are an important focus area given that they represent the most perplexing public health challenge.

The Rabies Management Team supported formation of a Special Vaccine Team to provide guidance on the development of new, strain independent oral rabies vaccines (i.e., immunogenic in all terrestrial reservoirs). The team has solicited and reviewed proposals for the development of prospective oral vaccines that should immunize all terrestrial rabies reservoir species. Funding has been
provided to explore canine adenovirus as a vector for the rabies glycoprotein gene. Research has been underway since 2000 in Ontario on a human adenovirus as a potential vector for the rabies glycoprotein gene (Yarosh et al. 1996). Other recombinant and non-recombinant vaccines also show promise that would be immunogenic in all terrestrial reservoir species (Dietzschold et al. 2003). Should one or more of these vaccines become licensed for use, contingency plans would ultimately be recommended to focally intervene with ORV to address reemergence of terrestrial rabies from bat sources of the rabies virus. Enhanced rabies surveillance would be central to the success of implementing such plans.

Education is an integral component of all forms of rabies control, including strategies involving ORV. However, the commensal nature of some bat species and the higher number of deaths attributed to bat rabies has elevated the need to initiate the bat rabies education campaigns that are in place in many states today to reduce the risk of exposure to bat rabies (CDC 2004). Other regional and national education efforts include a recently published pamphlet, “Bats and Rabies—A public health guide” produced by the Centers for Disease Control and Prevention (CDC), in collaboration with Bat Conservation. New York State Department of Health, Cornell University Extension and WS also recently released a state-of-the-art-video on bats and rabies. In addition, the Advisory Committee on Immunization Practices national recommendations have been modified to address potential and actual exposures to bat rabies (CDC 1999).

Economic and funding issues

Large scale ORV began with state funded programs in Texas in 1995 (Fearneyhough et al. 1998) and Ohio in 1997 (Smith et al. 1999). Incremental successes in Texas in pushing coyote rabies back to the Rio Grande (Fearneyhough et al. 1998) and in preventing the westward spread of raccoon rabies through Ohio were catalysts for increased federal funding and participation by WS. Federal funding is particularly critical for WS to provide expertise, resources and coordination among several eastern states with varying levels of rabies infrastructure and funding.

Wildlife biologists generally support funding for ORV, but are concerned that several economic and other related research questions remain unanswered. There is also concern about public perception of ORV as a broad scale control strategy and the potential cumulative effects of this technology.

ORV is costly. The costs are dominated by the unit price for bait/vaccine, currently either $1.00/coated sachet or $1.27/fishmeal polymer bait. Benefits are largely driven by the cost savings associated with reduced post-exposure prophylaxis (PEP). About 40,000 people annually receive PEP in the U.S. (Rupprecht, personal communication). The most recent estimate for the cost of PEP and indirect costs of receiving treatment is about $3,300 ($2,200 PEP and $1,100 indirect costs) (Shwiff et al. 2003). This cost does not take into account other indirect costs or the costs borne by municipal, county, state and federal agencies responsible for rabies control. The overall cost of living with all strains of rabies in the U.S. is placed conservatively at $300 million/year (Krebs et al. 1995).

Intervention with ORV to prevent raccoon rabies from spreading beyond its current distribution appears cost-beneficial based on the robust analysis conducted by Kemere et al. (2002). However, additional sophistication should be incorporated in future analyses, particularly in the form of
more realistic spatial scenarios for the spread of raccoon rabies in the absence of intervention. Also, rabies virus strain elimination represents a potentially different dynamic that requires thorough economic evaluation. Given that economics is a central issue to rabies control with ORV, WS is currently conducting or funding five economic analyses or related modeling studies to better characterize and understand the economic dynamics of rabies and rabies control.

CONCLUSIONS

ORV shows promise as a control method for specific rabies virus variants, but the task is daunting from a technical, logistical, financial and environmental perspective. Program evolution must be based on sound science. Several key issues and data gaps of concern to wildlife managers have been identified, including: how continued translocation of raccoons and other carnivores may impact control objectives, need for better characterization of damage caused by racabies reservoir species, effects racabies control may have on other important diseases, and need to better characterize costs of the major strains of rabies in relation to the benefits of ORV. This is by no means an exhaustive list. The Rabies Management Team’s challenge is to review and prioritize these issues and formulate strategies to address them within the myriad priorities associated with conducting racabies control on a broad geographic scale in the U.S.

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