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# Oral Rabies Vaccination: A National Perspective on Program Development and Implementation

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**Abstract** Persistence of unique rabies virus variants in a diverse array of terrestrial carnivores and insectivorous bats makes rabies control in the U.S. a complex task. The public health system in the U.S. is effective in keeping human deaths near zero each year in the face of enzootic wildlife rabies, but the annual cost of coexistence with the disease is high, exceeding \$300 million. In addition, each year tens of thousands of people are impacted by anxiety, fear, and trauma associated with potential or actual rabies exposure to themselves and their domestic animals. Exclusion, proper storage and disposal of garbage, and removal of problem animals are often effective alternatives to address wildlife rabies threats at specific sites; however, oral rabies vaccination (ORV) is the only currently available technique that shows promise for wildlife rabies control on a broad geographic and species scale. In this paper, we discuss progress toward using ORV to contain specific terrestrial rabies virus variants in the U.S. and planning towards coordinated national efforts to explore the elimination of terrestrial variants of rabies virus in the U.S.

**Key Words:** baiting, disease, rabies, public health, oral rabies vaccination, bat rabies, fox rabies, skunk rabies, raccoon rabies, coyote rabies

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## INTRODUCTION

Rabies is one of the oldest recorded infectious diseases. It is an acute, fatal encephalitis caused by a virus that is almost always transmitted by the bite of a rabid animal. Worldwide, rabies is estimated to cause 50,000 to 70,000 human deaths annually (Meslin et al. 1994). However, human rabies deaths in the U.S. and other developed countries annually approach zero as the result of effective, integrated public health programs that rely on public health education, rabies surveillance, case investigation, efficient and accurate laboratory diagnosis, pet vaccination programs, and safe and effective post-exposure prophylaxis.

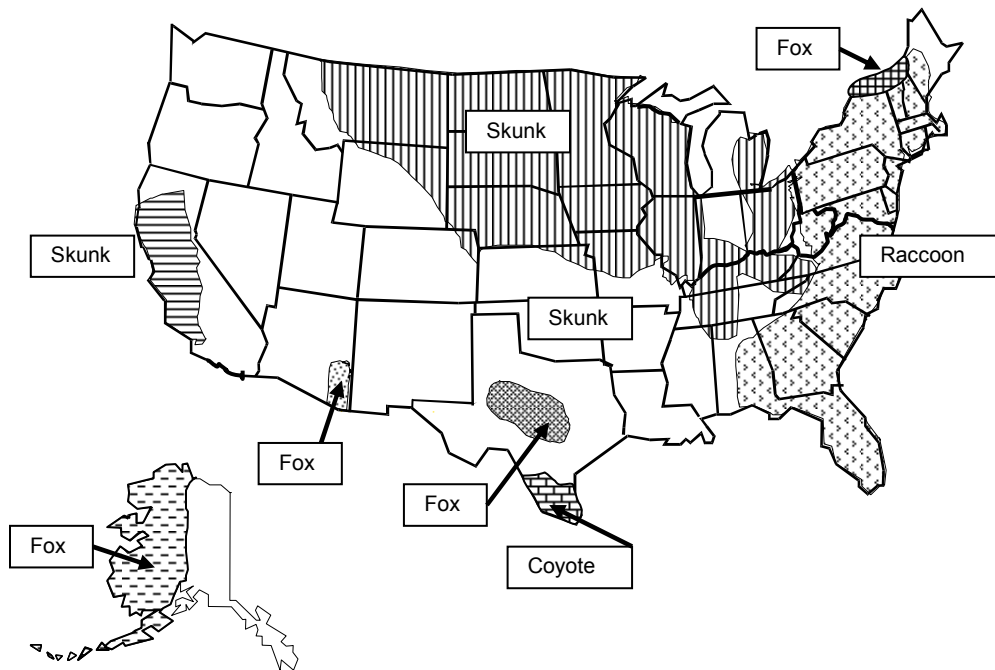
During the early 1960s, wild mammals emerged as the most frequently reported animals infected with rabies in the U.S., replacing the domestic dog as the dominant reservoirs for the virus (Krebs et al. 2001). For the past decade or more, wildlife—primarily terrestrial carnivores and insectivorous bats—have accounted for at least 90 % of all animal rabies cases reported in the U.S. and Puerto Rico. The persistence of rabies virus among diverse carnivore and bat species greatly confounds rabies control.

In spite of a public health strategy that is effective in preventing human rabies deaths in the U.S., the financial cost of coexistence with wildlife rabies is high, exceeding \$300 million annually (Fishbein and Robinson 1993).

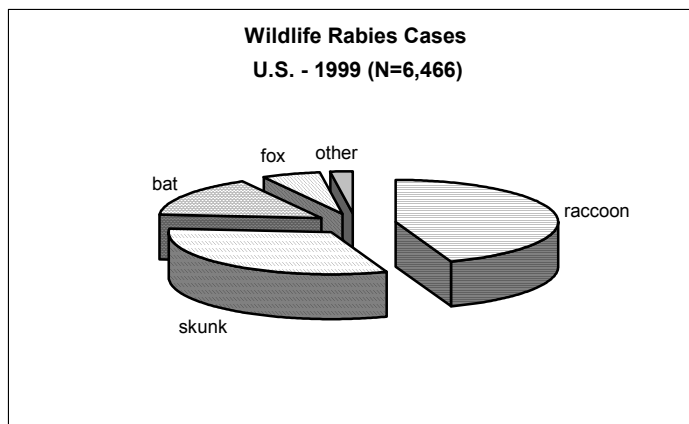
Anxiety, fear, and trauma are examples of less easily quantifiable impacts to humans associated with rabies threats to people and their pets and livestock (Meltzer and Rupprecht 1998 a, b; McQuiston et al. 2001).

Rabies viruses occur in the wild as unique variants adapted to specific species or geographic areas occupied by a reservoir species (Smith et al. 1992) (Figure 1). The most frequently reported species with rabies in the U.S. are the raccoon (*Procyon lotor*) and skunk (primarily striped skunks, *Mephitis mephitis*) (Figure 2). Insectivorous bats (*Chiroptera* spp.); arctic fox (*Alopex lagopus*), red fox (*Vulpes vulpes*), and gray fox (*Urocyon cinereoargenteus*); and coyote (*Canis latrans*) are also important reservoirs for the virus, as is the small Indian mongoose (*Herpestes auro punctatus*) in Puerto Rico (Krebs et al. 2000). Although “spillover” of the virus has been reported in several mammalian taxa, including rodents and deer (Childs et al. 1997, Krebs et al. 2001), additional reservoir species have not been documented (Smith 1996).

Many challenges to contemporary rabies control programs underscore the need for collaboration among multiple disciplines. These include: varying ecological, behavioral, and biological attributes of diverse wildlife rabies reservoirs; the effective application of oral vaccines; environmental compliance; conducting meaningful research to address existing data gaps; and



**Figure 1. Distribution of terrestrial reservoirs of rabies in the United States (adapted from CDC map in Krebs et al. 2000).**



**Figure 2. Frequency of rabies in important wildlife reservoirs during 1999 in the U.S. (adapted from CDC, Krebs et al. 2000).**

economic accountability. Cooperation among federal, state, county, and municipal agencies with differing missions and perspectives in turn place increased emphasis on the need for sound communication and coordination among partners. The limitation associated with only a single licensed oral vaccine (Hanlon and Rupprecht 1998) and the spectrum of public attitudes toward wildlife and rabies control with ORV (Siemer and Brown 1994, Meltzer et al. 1997) also contribute to the challenge of wildlife rabies control on a large scale.

Hanlon et al. (1999) discussed the potential applicability of passive wildlife rabies surveillance,

habitat modification, population suppression (local and broad scale), contraception, trap-vaccinate-release, and oral vaccination as rabies control alternatives. While each approach may have applicability independently or when integrated into a strategy, our discussion will focus on ORV during the past decade with the objective of providing an update of activities, accomplishments, and planning directed toward control of specific terrestrial rabies virus variants in the U.S.

#### **ORV MECHANISM AND STRATEGIES**

The mechanisms for oral vaccine to immunize

individual animals essentially involve replication of the virus in the animal's mouth (Wandeler 1991). Once the immune system is sensitized, immunocompetent individuals produce rabies virus neutralizing antibodies, which are an effective means of protection against productive infection (Orciari et al. 2001, Lambot et al. 2001).

At the wildlife population level, ORV programs are designed to achieve sufficient population (herd) immunity to meet rabies control goals. Goals may include preventing spread of specific rabies virus variants to new geographic areas, reducing the number of positive cases in defined enzootic areas, or eliminating specific variants from some or all of their existing range.

Elimination represents an ideal goal for some rabies virus variants, with success depending on a myriad of factors. Key factors include: 1) access to safe, effective and inexpensive vaccines; 2) availability of attractive, target-specific baits; 3) sufficiently sensitive surveillance to delineate epizootic rabies fronts, as well as to identify rabies foci in enzootic areas requiring timely treatment; 4) favorable geographic features, such as mountains and large bodies of water to help spatially frame ORV strategies; 5) dependable and adequate funding to guard against administrative failures; and 6) adequate documentation and confidence in the anticipated financial and social benefits to be derived from specific ORV programs.

Prior to the development and application of monoclonal antibodies in the late 1970s (Wiktor and Kopowski 1978), rabies was thought to occur as a single undifferentiated virus strain. Use of monoclonal antibodies has led to the identification of unique rabies virus variants adapted to "cycle" within specific wildlife species (Smith 1989). This enhanced understanding of the dynamics of wildlife rabies has in turn led to application of ORV strategies that can be focused on the species that act as reservoirs for specific virus variants.

## **ORV HISTORY**

### **Late 1960s to 1994**

The concept of ORV was conceived at the Centers for Disease Control and Prevention (CDC) and proven to be feasible in the red fox (Baer et al. 1971). Switzerland was the first country to use oral vaccine in the field in an attempt to control rabies in red foxes (Steck et al. 1982). Since that time, research has led to the development and implementation of ORV programs in several Western European countries (Aubert et al. 1994, Stohr and Meslin 1996). ORV programs using either attenuated rabies vaccines or the recombinant Raboral V-RG<sup>®</sup> have resulted in several European countries being designated free of rabies (Wandeler 2000, Zanoni et al. 2000).

In North America, the Province of Ontario, Canada expanded research during the mid-1970s to evaluate the prospect of using ORV to eliminate rabies that became established in red foxes in the southern part of the Province during the late 1950s (MacInnes and LeBer

2000). Since 1989, the Ontario Ministry of Natural Resources has aerially distributed about 12 million baits containing an attenuated rabies virus (ERA vaccine) that has reduced rabies in foxes by more than 97% (MacInnes, pers. com.).

Although the ability to vaccinate wildlife orally against rabies was conceived and first tested under captive conditions in the U.S., field application of this technology has progressed at a more conservative pace than in Europe and Canada. The slower pace at which ORV has been embraced in the U.S. may be attributed in part to several factors, including a medical system in which the monetary costs associated with rabies are often not well documented and diffuse, masking the cumulative financial impact of wildlife rabies. Although post-exposure prophylaxis is relatively expensive at about \$2,000 (Krebs et al. 1998), access to effective vaccines to protect humans who may be exposed, often en masse (Noah et al. 1996), and minimize the number of rabies-related deaths may create ambivalence toward the need for ORV. Philosophical opposition to oral vaccination as a prospective wildlife management method for any purpose, let alone to achieve improved public health and long-term financial savings, likely also has had an effect on use of ORV in the U.S. The relatively high costs of ORV in the face of competition for resources has influenced budgetary support for programs. Finally, uncertainty of long-term technical success remains a concern that can only be removed by the favorable outcome of current ORV projects. In spite of a more metered enthusiasm for ORV in the U.S., the success of early field safety and efficacy trials with V-RG in Virginia (Hanlon et al. 1998), Pennsylvania (Hanlon and Rupprecht 1998) and New Jersey (Roscoe et al. 1998) during the late 1980s and early 1990s, supported the licensing of Raboral V-RG<sup>®</sup>—the only licensed oral vaccine for use in wildlife in the U.S. The commercial availability of this vaccine and support for limited programs in turn facilitated the initiation of ORV projects (Hanlon and Rupprecht 1998) in Ohio (Smith et al. 1999), New York (Bigler, pers. comm.; Eidson, pers. comm.), Vermont (Bigler, pers. comm.), Maryland (Horman, pers. comm.), Massachusetts (Robbins et al. 1998), Florida (Olson et al. 2000) and Texas (Fearneyhough et al. 1998) that are the building blocks for scientific evaluation and refinement for future programs.

### **1994 to 2001**

The ORV initiatives that followed the inaugural field trials in Virginia, Pennsylvania, and New Jersey were undertaken by state or county governments or universities, with limited technical and financial support provided either by CDC or USDA APHIS Wildlife Services (WS), or a combination from both federal sources. With mounting U.S. Congressional support in 1997, WS received a federal appropriation in FY 1998 to participate in cooperative ORV in Texas, Ohio, Vermont, and New York (Table 1). WS used these resources to

help meet the needs for each cooperative program, including contracting for air services to distribute baits, assistance with hand and aerial bait distribution, purchase of baits, and providing wildlife management expertise in sampling wildlife for post-vaccination evaluation.

To better ensure strategic ORV planning that would lead to greater program stability and effectiveness, WS formed a Rabies Management Team in 1997 composed of WS operations and research personnel (National Wildlife Research Center—NWRC), other APHIS expertise, and external expertise from CDC, cooperating states, and universities. The team was designed to bring together a coalition of expertise from multiple disciplines to establish short- and long-term program goals, strategically plan to meet those goals, and prioritize research to systematically address questions that would contribute to enhanced ORV effectiveness. The Rabies Management Team meets annually and communicates via conference calls and email throughout the year on key issues.

In 1999, as a result of confirmed index cases of raccoon rabies in southern Ontario (Rosatte et al. 2001), the threat of raccoon rabies moving south and west around the Ohio vaccination barrier, and reduced state funding for the gray fox ORV project in Texas (Figure 3), WS formulated a funding strategy based on input from cooperators to secure additional resources through the regular appropriations process as well as from emergency sources (Commodity Credit Corporation [CCC] and APHIS Contingency Fund). The distribution and spread of raccoon variant of rabies, in particular, necessitated this action given that states could not succeed independently in meeting regional and national rabies control goals. Clearly, long-term success of ORV would require increased federal support and leadership to bring multiple states together in a coordinated strategy.

**Table 1. Recent USDA APHIS Wildlife Services funding history for rabies control.**

| Federal fiscal year | Funding level (\$ millions) | Geographic area specified              |
|---------------------|-----------------------------|--|
| 1998                | 1.3                         | NY, OH, TX, VT                         |
| 1999                | 1.8 <sup>1</sup>            | NY, OH, TX, VT                         |
| 2000                | 1.7 <sup>2</sup>            | NY, OH, TX, VT                         |
| 2001                | 7.1 <sup>3</sup>            | NY, OH, VT, WV, eastern states, TX     |
| 2002                | 18.3 <sup>4</sup>           | NY, OH, VT, WV, eastern states, TX, WY |
| 2003                | 25.5 <sup>5</sup>           | NY, OH, VT, WV, eastern states, TX, WY |

<sup>1</sup> includes \$225,000 from the APHIS Contingency

<sup>2</sup> includes \$65,000 of APHIS funds

<sup>3</sup> Includes \$4.1 million in Commodity Credit Corporation funds

<sup>4</sup> Includes \$6.5 million in Commodity Credit Corporation funds

<sup>5</sup> Based on projection from the President's Budget Proposal of \$13.7 million increase

The following recommended course of action was pursued by WS in response to feedback from five stakeholder meetings held from December 1999 – May 2000: 1) expand vaccination zones along the Canadian border with New York and Vermont, and to vaccinate for the first time the upper Connecticut River Valley between Vermont and New Hampshire to contain raccoon variant from extending its range northward; 2) extend the current Ohio vaccination zone south into West Virginia, tying to the Appalachian Mountains to prevent raccoon variant from spreading west; and 3) provide additional cooperative federal funding to assist Texas in restoring the ORV gray fox project to its previous scope.

In response to external cooperator support, WS received an increase in appropriated and emergency funding through CCC funds to implement the proposed ORV expansion to contain raccoon and gray fox rabies (Table 1). To conduct these initiatives in 2001, WS completed a programmatic environmental assessment to comply with the National Environmental Policy Act (NEPA) requirements (USDA 2001). Public input provided for under NEPA was favorable and the projects were completed as proposed (Figure 4). Environmental compliance at all levels of government will continue to be essential for the operation of long-term ORV programs.

The establishment of a Memorandum of Understanding between the Rabies Section at CDC and WS was a key initiative completed in 2000 that is designed to enhance cooperation among all parties involved or likely to become involved in ORV. Formalizing this relationship facilitates combining wildlife management expertise in WS with the federal public health infrastructure already in place at CDC in the form of special ORV expertise, epidemiological investigation, training, and reference laboratory support critical to long-term program success. Interagency agreements between CDC and WS are currently in place to help augment critical funding needs to meet increasing requests for assistance with ORV programs to CDC.

Given that economic considerations are central to the use of ORV for rabies control, WS commissioned a broad-based study that was initiated to try to put the high costs of ORV in the context of long-term financial benefits based on preventing the spread of raccoon rabies westward (Kemere et al. 2002). Providing guidance for this study was an early undertaking of the Rabies Management Team. This study was designed to assess the costs and benefits of a scenario-specific ORV strategy to contain raccoon rabies from spreading to unaffected areas west of the current distribution for raccoon variant. The findings from this study were used help formulate WS budget requests and proposals. The results of this study are encouraging and along with other economic studies (Uhaa et al. 1992, Meltzer 1996, Aubert 1999) provide a basis for future analyses of increased sophistication and sensitivity. Economics will continue to be a central issue to ORV, given that conventional public

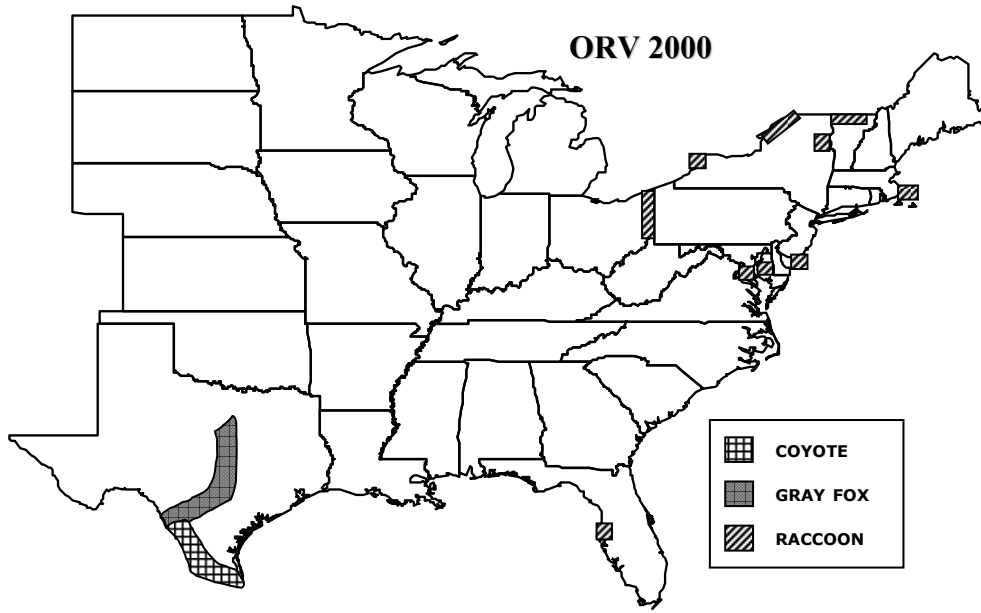


Figure 3. ORV zones by terrestrial wildlife rabies reservoir species in 2000.

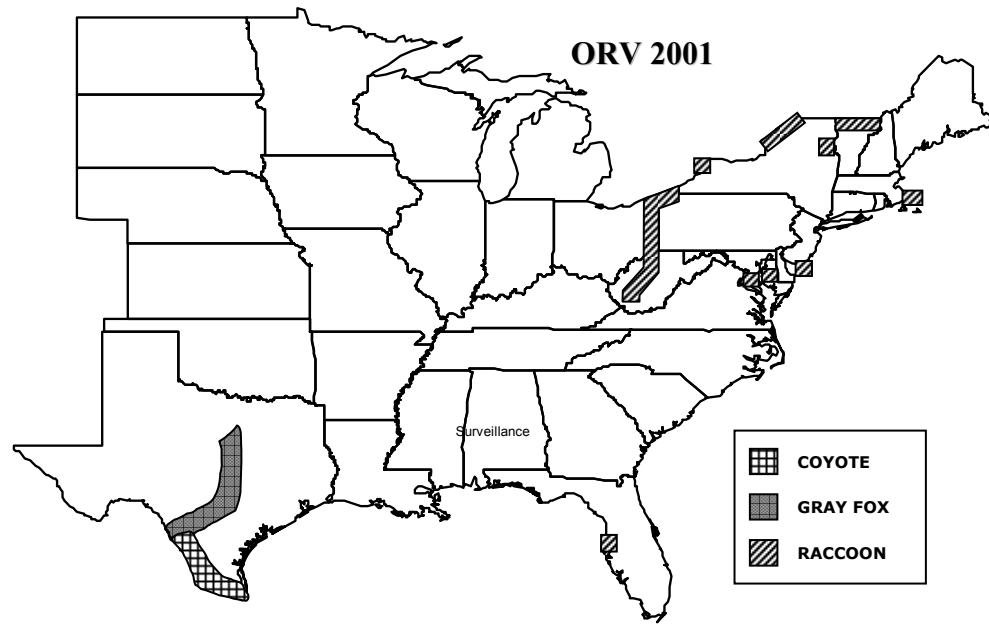


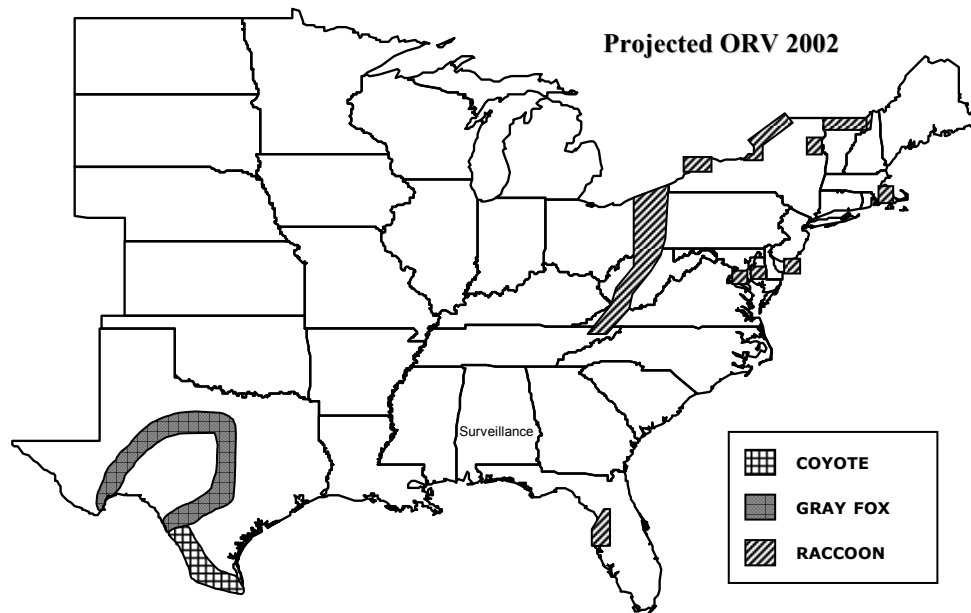
Figure 4. ORV zones by terrestrial wildlife rabies reservoir species in 2001.

health approaches in the absence of ORV have succeeded in preventing human rabies deaths.

**2002 and Beyond**

Completing ORV that began in 2001 to vaccinate mountain gaps and other corridors that may facilitate the spread of raccoon rabies to the west remains the highest

priority. The 2002 WS budget and cooperator resources allow for this interim goal to be met through expansion of the existing barrier from Lake Erie south to the high mountain of eastern Tennessee (Appalachian Ridge Project). In addition, other important initiatives in 2002 include: ORV expansion eastward into Pennsylvania, continuing efforts in the Northeast, and a full restoration



**Figure 5. Projected ORV zones by terrestrial wildlife reservoir species and continued enhanced raccoon rabies surveillance in Alabama in 2002.**

of the gray fox ORV project in west-central Texas (Figure 5). During 2002, about 4.2 million baits are projected to be distributed at 75 baits/km<sup>2</sup> in the Appalachian Ridge Project. The vaccination zone in Pennsylvania represents the largest ORV effort in an area where raccoon rabies has been enzootic, as well as the first time baiting will occur in a major U.S. metropolitan area—the City of Pittsburgh. Post-baiting evaluation will focus on two key issues: the relationship of bait uptake and immunity (based on serologic titers of virus neutralizing antibodies) for a late summer bait drop (time of year), and for varying bait densities (75, 150, and 300 baits/km<sup>2</sup>). The results will be compared to previous findings to evaluate optimal baiting strategies.

In anticipation of ORV projects of increasing project scope in 2002, the Rabies Management Team has established 10 functional teams composed of diverse expertise to address critical issues that are integral to sound project evolution (Table 2). Each team is charged with evaluating state-of-the-art or science in each area and recommending courses of action for the future.

The Contingency Action Planning Team has evaluated practical alternatives to address rabies threats that may compromise the integrity of ORV efforts. The team is finalizing contingency action recommendations that may be taken if: rabies intensifies approaching an immune barrier; “hot spots” occur within a barrier; rabies breaches a barrier, but is detected just beyond the vaccination zone; or if rabies occurs as an isolated focus sufficiently distant from a barrier to suggest translocation, intentional or unintentional, was the source of the focus.

The Communication Planning Team is developing a

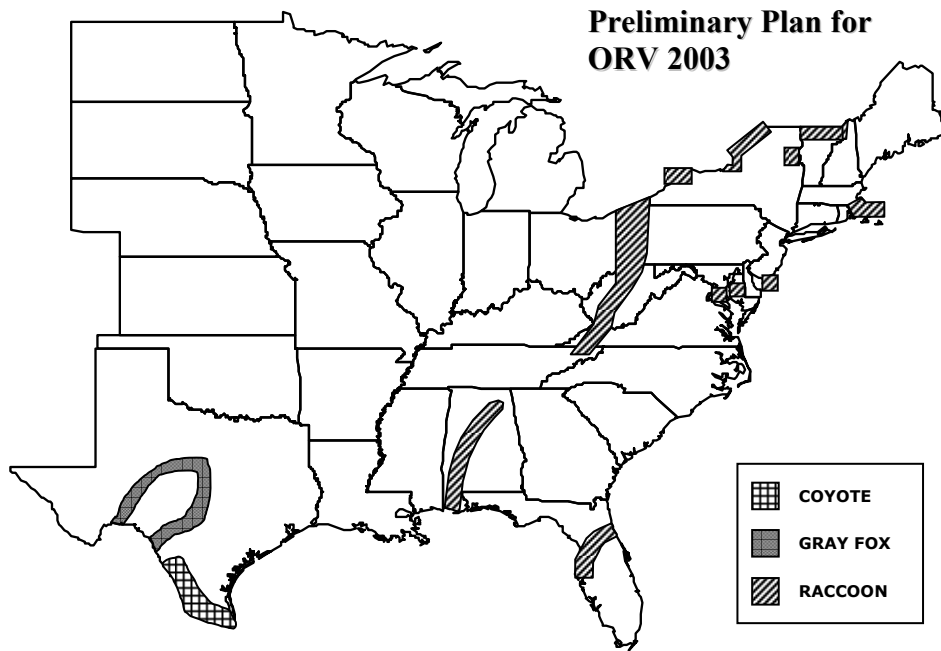
variety of means to enhance interaction with the public on ORV, including web site creation. However, an immediate charge for this team is to bring together all key interests including raccoon hunters, dog trainers, rehabilitators, nuisance wildlife control operators, and agency personnel to seriously address translocation of rabies reservoir species, which could jeopardize national efforts to control terrestrial variants of rabies. Translocation of raccoons from the southeastern U.S. to western Virginia and West Virginia in the late 1970s was the probable origin of the epizootic mid-Atlantic region that had not formerly experienced raccoon rabies (Nettles et al. 1979).

**Table 2. Ten interdisciplinary teams charged with evaluating critical subject areas integral to effective ORV and providing guidance to cooperative rabies control planning.**

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

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**Figure 6. Preliminary planning projection for ORV zones by terrestrial wildlife reservoir species in 2003.**

The Economic Analysis Team is providing guidance on an analysis of the benefits and costs of a hypothetical skunk rabies elimination program with ORV in Santa Barbara County, California. The results of this effort may provide a foundation for future statewide and national analysis for skunk rabies control.

The ORV Evaluation Team is formulating standardized approaches to assess the integrity of ORV efforts. Standardization will make comparisons among projects more meaningful. The ability to evaluate project progress will hinge heavily on CDC in the form of reference laboratory support, testing of surveillance samples, serological analysis, and epidemiological investigations. In addition, the Surveillance Team has recommended that the Rabies Laboratories in New York and Virginia provide additional regional support for ORV.

The other teams (Table 2) are focusing on a variety of issues, including: new oral vaccines to complement the existing recombinant vaccine (Hanlon et al. 2002), NEPA analysis for ORV on National Park-managed lands, air delivery capability alternatives for the future, and WS and external research priorities to close important gaps in our understanding of ORV.

NWRC scientists began several research initiatives in 2002 designed to enhance our understanding of ORV strategies, rabies reservoir species, and non-target species issues. The relationship of bait uptake to bait and target species density is a priority project planned for Pennsylvania that will allow for comparison to a similar study conducted in Ohio in 1999, once those results are published. Other studies include: vaccinia (the virus vector for rabies glycoprotein in Raboral V-RG®) dynamics in captive commensal rodent populations,

placebo bait preference in skunks in the western U.S., and bait uptake by raccoons in Ohio. WS operations, in collaboration with NWRC, will continue to apply its raccoon density index protocol and complete a 2-year project that began in 2001, designed to assess variation in density indices associated with plot size and trapping effort.

The WS Rabies Control Business Plan, Programmatic Environmental Assessment for ORV (USDA 2001), and Strategic Plan, as well as other supporting documentation (e.g., Hanlon et al. 1999) will serve as foundation to develop a more comprehensive National Rabies Management Plan. This plan will provide guidance and recommendations for linking regional raccoon rabies control plans, additional initiatives to be taken to ensure that ORV technology becomes available for use in the field for skunks and mongooses, ORV surveillance, and research prioritization, as well as other key planning issues.

The 2003 budget projection for WS looks promising, with the President's budget recommending a \$13.7 million increase. Decisions on ORV in Alabama, where raccoon rabies appears to now to be slowly spreading westward, will be based on enhanced raccoon rabies surveillance that has been conducted in Alabama since 2000. If an ORV zone is justified in Alabama on the basis of contemporary enhanced surveillance, it would represent the largest new initiative during 2003 (Figure 6). Planning and research will continue on prospective baits and oral vaccines for use in skunks that could also complement Raboral V-RG®. Effort will also be directed toward GIS analysis of baiting strategies that may have applicability in terrestrial rabies elimination. Ensuring adequate surveillance to measure ORV needs and



progress will remain a priority. A benefit:cost analysis focusing on the dynamic of raccoon rabies variant elimination is in the early planning stage and scheduled to begin in 2003.

## SUMMARY AND CONCLUSIONS

ORV shows promise as a control method for specific rabies virus variants that persist in wildlife reservoirs in the U.S. As a result of increased public interest manifested through the U.S. Congress, WS received increasing federal funding to cooperate in and help coordinate multi-state efforts to control rabies in terrestrial carnivores. In 2001, the ORV zone established in Ohio beginning in 1997 was extended southward to southern West Virginia to prevent raccoon rabies from spreading west and compromising the commitment in place in Ohio. The ORV zone will also be extended south in 2002 to interface with the high mountains in east Tennessee, in an attempt to integrate favorable geographic features with the vaccination zone to create a "barrier" at reduced cost to prevent raccoon rabies from spreading to new areas to the west. Enhanced surveillance currently in place in Alabama will provide data on the course of action to take from the southern end of the Appalachians to the Gulf of Mexico. The cooperative gray fox ORV project in west-central Texas has been restored to its original schedule through cooperative federal funds and WS participation with the Texas Department of Health as the lead agency.

Other key steps being taken with guidance from the Rabies Management Team include: ensuring adequate surveillance, pursuing additional safe and effective oral vaccines, conducting priority research to address data gaps so that decisions remain science-based, addressing translocation of rabies reservoir species near ORV projects, and developing and implementing effective communication strategies. Economic analysis and NEPA compliance have been identified as critical elements of an evolving ORV program with national goals and objectives. The stability of ORV programs in the near term will be critical to evaluate if such programs can be optimized to effectively meet long-term objectives of partial or full elimination of specific rabies virus variants in terrestrial wildlife reservoirs.

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