REVIEW OF ORV STRATEGY USING RABORAL V-RG® FOR MITIGATING PUBLIC HEALTH RISKS FROM RABIES VIRUS CIRCULATION IN U.S. RACCOON POPULATIONS

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Executive summary

Approximately 90% of rabies cases reported annually in the U. S. occur in wildlife species. RABORAL V-RG®, an oral rabies vaccine delivered by edible bait, has been used for over 20 years in the field setting to vaccinate wildlife against rabies virus and has been shown to be a safe and effective product for reducing risks from wildlife rabies. Oral rabies vaccine programs contribute to wildlife rabies control by reducing rabies virus transmission in target species such as coyotes, grey foxes, and raccoons. Local oral rabies vaccine programs have successfully mitigated human health risks associated with raccoon rabies outbreaks in heavily populated areas. Regional barrier programs have prevented or slowed spread of raccoon rabies into uninfected wildlife populations. Review of previous and on-going ORV programs demonstrates that successful and cost-effective ORV campaigns require careful tailoring of bait delivery parameters to meet specific program goals. There is no one-size-fits-all strategy for effective use of ORV for wildlife rabies control. Raccoons live in heterogeneous landscapes and have highly variable population demographic dynamics in different habitat types. ORV program design must take into account these local ecological and landscape factors that affect bait uptake by target and non-target species when determining bait density, bait distribution method, and distribution timing.

Background

Annually approximately 90% of reported rabies cases in the United States are wildlife species (*1*). Oral rabies vaccination (ORV; *2*) programs were implemented in the early 1990s in response to an expanding raccoon rabies epizootic on the eastern seaboard through the immunization of free-ranging raccoons (*Procyon lotor*; 3-*7*). This on-going raccoon rabies outbreak began during the mid-1970s following translocation of raccoons infected with raccoon rabies virus variant to hunting camps in the mid-Atlantic region of the United States (*8*). After this translocation event, raccoon rabies rapidly spread to neighboring states (*6*).

The first U. S. field trial using RABORAL V-RG® occurred during 1990. Prototype baits containing oral rabies vaccine were distributed on a barrier island (Paramore Island, Virginia) to immunize an isolated population of raccoons. After bait distribution, greater than 80% of animals tested positive for antibiotic biomarkers, showing strong evidence of uptake when vaccine baits were distributed at relatively high density (1000 baits/km^2; *9-10*). After this first trial, several state public health agencies initiated raccoon rabies control programs using RABORAL V-RG® to combat the expanding eastern U. S. raccoon rabies epizootic. Early raccoon ORV programs in Williamsport, Pennsylvania in 1991(*11*); and Cape May, New Jersey in 1992-1994 (*12*) were deemed successful in both public health safety and vaccine efficacy

Over the next ten years, ORV bait campaigns targeting raccoons were implemented by a number of state agencies, including Ohio, New Jersey, Massachusetts, Maryland and New York. A federal program initiated in 1998 created a multi-state rabies vaccination barrier along the Appalachian Mountains to prevent the westward spread of the raccoon rabies variant, adding territory to existing ORV barriers in Pennsylvania, West Virginia, eastern Tennessee, Alabama and Georgia, as well as additional ORV zones to upstate New York, Vermont and Maine. In each case, program managers strived to maximize ORV program effectiveness – in terms of both reducing rabies virus circulation in target raccoon populations and protecting of domestic animals and humans from rabies virus exposure – while minimizing baiting program costs. Over time, economic studies of ORV programs have repeatedly shown that ORV can be a cost-effective approach to wildlife rabies management with benefit:cost ratios well in excess of 1 due to reductions in domestic livestock losses to rabies and reductions in human post-exposure prophylaxis administration (*13*).

Measuring ORV efficacy in the field

Documenting the success of an ORV campaign can be challenging due to the dynamic nature of wildlife populations. Two approaches used for monitoring ORV efficacy in the field setting are surveillance of laboratory confirmed rabid animal cases and prevalence of rabies neutralizing antibodies in animals captured from vaccination zones (*3*).

Laboratory confirmed rabies case counts are typically obtained through passive surveillance of animals submitted to diagnostic laboratories for rabies testing after human or domestic animal exposures. Such sampling methods leave rural areas poorly monitored for rabies circulation. Thus, enhanced surveillance (e.g., collection of road kill, testing of animals collected by animal control officers or nuisance cases) is increasingly used to supplement passive surveillance to identify rabid animals that would not otherwise be tested (*3*). Limiting post-surveillance to human exposure cases can lead to erroneous assumptions of declining trends when rabies "hot-spots" still exist in areas with poor surveillance coverage.

Rabies virus neutralizing antibody levels peak at 4-8 weeks after vaccine ingestion and then decline quickly such that observed seroconversion rates from serum samples collected after 8 weeks may incompletely reflect existing population-level protection against rabies virus transmission. Despite declines in circulating antibodies, animals that have ingested vaccine may remain protected against rabies virus infection for months after ingestion of vaccine (*14*). Conversely, high seroconversion rates post-baiting may not extinguish rabies virus circulation in raccoon populations that have high demographic turnover rates or seasonally receive many unvaccinated migrants from areas outside the baiting zone.

Holistic use of all available post-bait distribution monitoring provides vital feedback on progress towards program goals and can allow for dynamic adjustment of program parameters.

Factors contributing to ORV campaign efficacy

ORV campaign success is equally contingent on the vaccine product, program structure, and perseverance in the form of political will for providing adequate funding and in-kind support for a sufficient period of time to reach program goals. Multiple programmatic factors can influence program efficacy, including local understanding of raccoon ecology and demography, presence of additional susceptible species such as skunks or foxes, the size, shape, and natural features of the target area, and bait distribution parameters including bait density, seasonal timing of distribution, frequency of distribution and distribution method (i.e. hand baiting, bait station, or aerial distribution). Key parameters to consider when structuring an ORV program include:

- Availability of pre-ORV epidemiologic analysis
- Presence of geographic barriers (e.g., mountains, rivers, roadways)
- Ability to limit animal movements (e.g., prevent translocation)
- Number of campaigns per year
- Surveillance before and after ORV campaigns
- Feasibility of different bait distribution methods (e. g., air, vehicle, bait station)
- Communication of ORV campaigns to the public
- Strategic goals – slow spread, barrier to spread, local or regional elimination
- Primary target species and potential spill-over into other wildlife species
- Habitat complexity and presence of urban or suburban residential zone
- Bait density required to deliver optimal number of doses sufficient number of target species

While many of these parameters are inherent to target bait distribution areas, bait density and distribution strategy can be more easily modified to best match with the characteristics of the bait distribution area and program goals. Bait densities have varied among ORV programs, ranging from 27 baits/km^2-250 baits/km^2 (Table 1). Lower bait densities appear to be effective for maintaining barriers to migration of rabid animals into unaffected areas, but higher bait densities may be needed for local and regional raccoon rabies elimination programs or for areas with particularly high raccoon densities.

Table 1. Historical and contemporary examples of ORV programs by program goal

Goal	Target Species	Location (type)	Years	Area	Target Bait Density	Time to Goal	Reference
Local Barrier	Raccoon	Cape May, NJ (isthmus)	1992-1994	552 km^2	64/km^2	Barrier maintained 3 yrs, discontinued prior to breach of barrier in 1995	*12*
Local Barrier	Raccoon	Cape Cod, MA (isthmus)	1994-2004	207 km^2	50-200/km^2	Barrier maintained 10+ years, breached shortly before discontinued	*4*; *15*
Local Control/ Elimination	Raccoon	Cape Cod, MA (peninsula)	2006-present	Variable: ~400-700 km^2	100+/km^2	On-going program to eliminate rabies from peninsula, establish barrier to re-entry	*16, 17*
Local Control/ Elimination	Raccoon	Anne Arundel Co., MD (mainland, entire county)	1998-2007	186 km^2	75-100/km^2	5 yrs field trials on small peninsulas, 4 yrs to near local elimination from full county	*18*
Local Control/ Elimination	Raccoon	Long Island, NY (island, parts of two counties)	2004-2010	~1500 km^2	Up to 250/km^2	5 yrs to elimination	*19, 20 L. Bigler unpublished data*
Regional Barrier	Raccoon	Ohio-Penn Border (regional)	1998-present	10,000-12,000 km^2	≥75/km^2	On-going, barrier maintained for over 18 years, breach in2004 contained by aggressive efforts including trap-vaccinate-release	*3, 17, 21*
Regional Elimination, Regional Barrier	Coyote	South Texas (regional)	1995-present	20,000-50,000 km^2	19-27/km^2	12 yrs to elimination, on-going barrier at U. S.-Mexico border	*22, 23*
Regional Elimination	Gray Fox	West Central Texas (regional)	1996-present	40,000-80,000 km^2	27-39/km^2	15+ yrs, nearing elimination: One gray fox case during 2013	*22, 23*

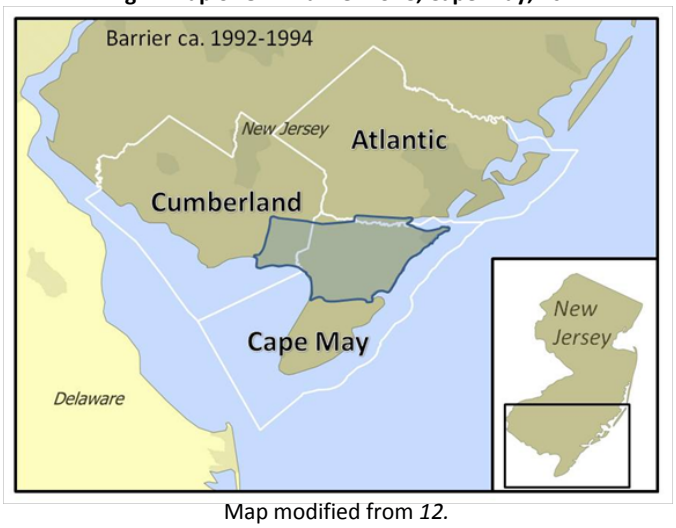
CASE STUDY 1: ORV bait distribution strategy on Cape May, NJ (1992-1994;*12*)

Goal: Barrier to Rabies Spread

Rabid raccoons were first detected in New Jersey during 1989. The peninsular geography of the southern tip of New Jersey presented the first opportunity to evaluate use of RABORAL V-RG® in the United States for establishing a barrier to raccoon rabies migration into an uninfected land area.

An experimental 18 km-wide barrier was established during 1992-1994 using a bait density of 64/km^2 (Fig. 1). Baits were distributed biannually in the spring and fall by helicopter and vehicle.

Fig 1. Map of ORV Barrier Zone, Cape May, NJ



Map modified from *12.*
Shaded areas indicate urban populations.
Blue area indicates baiting zone ca. 1992-1994.

Rabies neutralizing antibody seroprevalence in captured raccoons ranged from 7% to 71%, with notable increases in seroprevalence between pre- and post-baiting testing. At this relatively low bait density, raccoon rabies did challenge and then invade the barrier vaccination zone, but the estimated rate of raccoon rabies migration in this zone was lower during 1992-1994 (15 km/yr) than after the

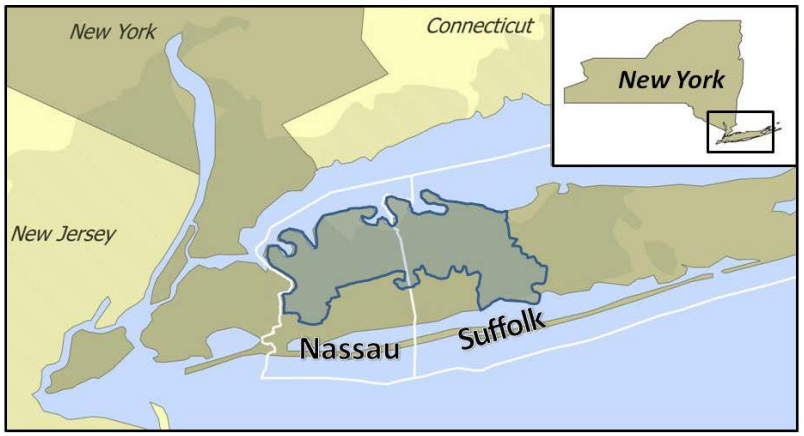
bait distribution program was discontinued (43 km/yr). Once raccoon rabies had entered the bait distribution zone, rabid raccoon prevalence was noted to be less in the bait zone during bait distribution (8-10%) than in a neighboring unbaited surveillance zone (53-65%).
This barrier program was discontinued during 1994 due to lack of continuing funding and raccoon rabies established on the peninsula shortly after discontinuation.

Subsequent ORV barrier programs, including the long-standing barriers protecting Cape Cod, Massachusetts from 1994-2004 and the federal program barrier along the Appalachian ridge have successfully applied bait densities of ≥75 baits/km^2 to preventing raccoon rabies spread into uninfected areas (*3-4,15-17, 21*).

CASE STUDY 2: Long Island, New York (*19-20*)
Goal: Local Elimination

Rabid raccoons were first detected on Long Island, New York during 1993, but raccoon rabies was not fully recognized as an established epizootic in Nassau County until 2004. The outbreak quickly spread east into Suffolk County (Fig. 2). An aggressive oral rabies vaccination campaign using RABORAL V-RG® oral rabies vaccine (ORV) baits was initiated in 2006 to mitigate the human health threat posed by raccoon rabies in this densely populated area.

Fig 2. Map of Nassau and Suffolk Counties, Long Island, NY



Map modified from *19.*
Shaded areas indicate urban populations.
Blue area indicates baiting zone during the 2010 campaign.

This intensive campaign relied on:

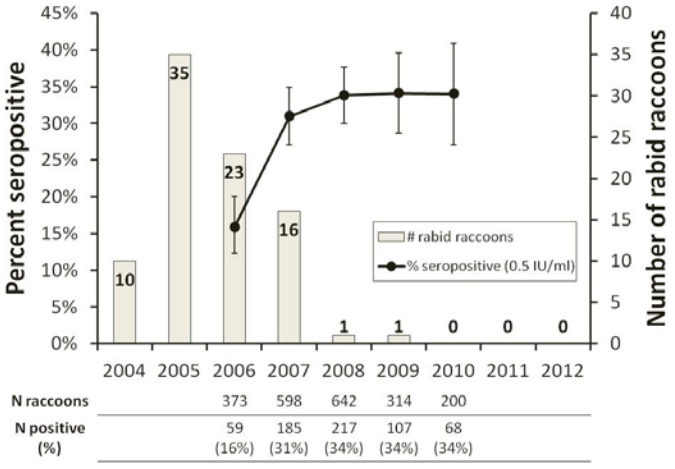
a. high-density baiting (target bait densities up to 250 baits per km^2)

b. multi-modal bait distribution by helicopter, ground vehicle, and bait stations to accommodate Long Island's heterogeneous landscape and densely populated residential areas, and

c. biannual baiting during the fall and summer seasons to target both adult and juvenile raccoons.

During 2006-2010, serologic monitoring of target raccoon populations demonstrated a rapid rise to a sustained population-level immunity of approximately 35% (Fig. 3). Concurrent with this rise, reports of rabid raccoon declined quickly from over 30 cases in 2005 before this intensive baiting campaign began to zero rabid raccoon reports on Long Island in 2010, 2011 and 2012.

Fig 3. Trends in rabid raccoon reports and seroconversion of raccoon populations exposed to RABORAL V-RG® baits, Long Island, NY – 2004-2012 (L. Bigler unpublished data)



This campaign led to the successful elimination of raccoon rabies from Long Island, New York over a relatively short period, demonstrating how a high-intensity efforts and careful planning can result in a cost effective and successful campaign to mitigate human health risks in a geographically defined area. Given the peninsular geography of this region, continued baiting along the narrow eastern edge of New York might prove a cost-effective strategy for preventing reintroduction of rabies to Long Island raccoon populations.

While high bait densities appeared to be a key factor on Long Island for accomplishing rapid increases population immunity to rabies and concurrent declines in rabies virus circulation, it is important to note that habitat heterogeneity and a relatively high density of raccoons were both important determinants of this high bait density requirement. The bait density required for local or regional control of rabies virus circulation for the

purposes of establishing a barrier to viral migration or even elimination will be highly contingent on unique combinations of such key parameters and could be higher or lower than that used on Long Island.

Large-scale Programs and Prospects for Raccoon Rabies Elimination

Today, the federal ORV program immunizes sufficient numbers of raccoons in the eastern U. S. to maintain an immunological barrier that protects Midwestern states such as Illinois, Michigan, Indiana, Kentucky and western Tennessee against the raccoon rabies variant expansion and associated financial costs of raccoon rabies introduction despite practical and financial challenges (*3, 11, 17*). The northern edge of the barrier along the Ohio/Pennsylvania state line requires an unusually high investment level of resources in ORV baiting campaigns on an annual basis to prevent the spread of rabies beyond Cleveland. Northeastern regions along the Canadian border remain difficult to control despite many years of effort and a breach of the barrier occurred during 2004 in the Ohio-Great Lakes region that has required extended ORV zones, addition of a trap-vaccinate-release strategy, and enhanced surveillance to contain (*3, 21*). Recently rabies control has faced decreased support from state and local partners and a stable but inadequate federal budget for demands placed on the National Rabies Management Program. Despite these challenges, the Appalachian ORV barrier has prevented the western spread of raccoon rabies for nearly 20 years.

The challenges for long-term maintenance of an ORV barrier program have also driven increasing interest in garnering financial and political support for pursuing regional elimination of the raccoon rabies virus variant. Such efforts would cost more on the short-term, but could ultimately reduce financial investment in rabies control and postexposure prophylaxis over the long-term. However, established program parameters that have been used to successfully maintain barriers and accomplish local elimination may be insufficient to achieve elimination. In particular, re-evaluation of bait density and bait distribution strategies may be required to ensure delivery of the optimal number of baits per target animal to achieve sufficient population-level protection in diverse habitats.

Maximizing cost-effectiveness and impacts on mitigating risks to human health remain a critical goal of rabies ORV programs. Understanding of landscape and raccoon population characteristics in bait zones is critical for designing an appropriate bait distribution strategy to reach program-specific goals. Decisions concerning programmatic features such as target bait density, bait distribution method(s), and timing of bait distribution are very important for a successful and cost-effective campaign to reduce or eliminate raccoon rabies virus circulation in the target population in order to mitigate human health risks from rabies.

Conclusions

Strategic use of RABORAL V-RG® by public health officials has been proven to reduce rabies infection rates in raccoon populations to support barrier and local elimination programs targeting raccoons. These programs not only protect wildlife from this deadly disease but also reduce pet, livestock, and human exposures to the rabies virus. Consideration of regional elimination efforts for raccoon rabies will require continued partnership and research to determine program parameters that will support an elimination goal across the variable landscapes of the eastern United States. There is not a one-size-fits-all strategy for successfully using ORV to control wildlife rabies. Bait delivery and dosing consideration must take into account local ecological and landscape factors that affect bait uptake by target species and must be dynamically adjusted based on post-baiting surveillance observations to achieve programmatic goals. Wildlife rabies control using ORV can be a cost-effective strategy (*13*) and a short-term financial surge to support raccoon rabies elimination efforts could yield dramatic cost-savings from reduced animal and human rabies deaths and rabies virus exposures over the longer term.

Previous successes using RABORAL V-RG® in the field setting demonstrate that ORV is an important component of a holistic rabies management approach that combines wildlife and pet vaccination with strong surveillance and public education efforts. However, even with optimal product and program parameters, elimination of raccoon rabies virus variant on a regional or continental scale remains most reliant on obtaining sufficient public, political, and financial support for durable and sustained ORV programs.

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