CONTROL OF WILDLIFE RABIES USING RABORAL V-RG®
These companies combined to form Pasteur and Merieux, a world leader in vaccine development. Under Epizootic Field Conditions, the need for chemical adjuvants, is shown. This is the first recombinant vaccine, which eliminates the need for chemical adjuvants, and has a multivalent effect.

Today, Boehringer Ingelheim offers a variety of global field conditions. The US is the first oral, canarypox-vectored rabies vaccine. Since its development, it has become one of the most extensively tested animal vaccines ever developed, and it has shown extraordinary success against wildlife rabies under a variety of global field conditions.

RABORAL V-RG® is the world's first oral, vaccinia-vectored rabies vaccine. It provides a three-year duration of immunity against rabies in dogs, cats and sheep, and one year for cattle, horses and ferrets.

PUREVAX® Feline Rabies is the first recombinant vaccine for cats. This genetically engineered recombinant vaccine, which eliminates the need for chemical adjuvants, is available as a monovalent providing one or three year duration of immunity in cats as well as multivalent combinations.

Boehringer Ingelheim, one of the world's largest research, development, and manufacturer of vaccines for animal health, has a unique combination of outstanding products, unparalleled technical expertise, and a history of individualized customer care.

As raccoon rabies invaded the mid Atlantic region, it began to move through populated areas, and human exposure to rabies increased. In 1989, a new orally active recombinant rabies vaccine, RABORAL V-RG, was evaluated in the US for use in wildlife. After successful large-scale use in Europe and extensive testing in the US, this novel vaccine was conditionally approved for use in New Jersey in 1994. Soon, other states began to follow suit. RABORAL V-RG was licensed for use in raccoons in April 1997.

In 1995 and 1996, ORV programs in Texas began to address racies outbreaks in coyotes and gray foxes, respectively. The coyote program stopped the expansion of the canine rabies outbreak in coyote populations of south Texas. A coyote claim was added to the V-RG license in May of 2002. The CDC declared the canine variant eliminated from the US in 2007. A second ORV program dramatically reduced the impact of gray fox rabies in west-central Texas.

For total rabies control and prevention, a comprehensive program includes the veterinary vaccination of domestic animals complemented by the application of RABORAL V-RG in target wildlife populations. This partnership of products offers the most promising way to prevent the spread of wildlife rabies in North America.

RABORAL V-RG®: Proven Protection Under Epizootic Field Conditions

Wildlife racies account for nearly 91% of the reported racies cases in the United States (US) each year with raccoons accounting for a significant portion of these cases. These reports originate from Center’s for Disease Control and Prevention in Atlanta, GA (CDC). The CDC also publishes a map locating various wildlife racies reservoir species. To understand the value of oral racies vaccination (ORV) programs, it is helpful to review the history of racoon racies in the US. It is also of value to learn about successful oral racies vaccination (ORV) programs in Texas targeting coyotes and gray foxes. Raccoons (Procyon lotor) were identified as a racies reservoir in the southeastern US since the 1950s. For many years, racies was considered a wildlife disease of rural areas, posing little threat to human populations. Rabies cases were reported, but little else was done. At that time no practical means of effective wildlife racies control was available to prevent an outbreak.

Beginning in the 1970s racoon populations increased in rural and urban environments. Intentional or unintentional transportation of raccoons from the south to a hunting camp in Virginia is thought to be the cause of an outbreak that spread northward along the Atlantic Coast and into New England. As racoon racies invaded the mid Atlantic region, it began to move through populated areas, and human exposure to racies increased.

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The Evolution of Orally Active Recombinant Rabies Vaccines

New ground was broken in the field of veterinary medicine with the development of a different sort of rabies vaccine—a vaccine designed specifically to orally vaccinate wildlife in their natural habitat. It began with a most appropriate step. Looking back for inspiration to pioneering studies in immunization, researchers started with the same carrier virus (vector) that had been used successfully in the worldwide campaign to eradicate smallpox. Employing the latest genetic engineering techniques, scientists combined this vector with a single very important part of the rabies virus—the glycoprotein gene that elicits immunity to rabies disease. Because only a small portion of the rabies virus surface protein was included, the vaccine cannot cause rabies. The new vaccine was effective when given orally. It also proved very stable, even under wide temperature fluctuations as would be found in the field. Even before development of the new vaccine was complete, wildlife biologists and other researchers began looking for an attractive, stable, cost-effective bait method to deliver the vaccine. Several edible substances were found to work well. For raccoons, researchers chose fish meal. Wild raccoons seem to find it palatable. This fish meal and a special polymer were mixed to form a hardy bait into which a sealed vaccine-filled package, called a sachet, could be inserted. A raccoon eagerly biting down on the bait would puncture the sachet and immunize itself as the vaccine was released into its mouth and throat.

Trials demonstrated up to 85% raccoon bait acceptance.7 Bait contact has been reported as high as 99% on day-two post-deployment.7 Tests in Virginia and Pennsylvania, under the direction of the United States Department of Agriculture—Animal and Plant Health Inspection Service (USDA-APHIS), demonstrated the vaccine was environmentally safe.8

In April 1997, the USDA granted license to RABORAL V-RG for ORV in raccoons. Its utility for controlling rabies in European red foxes was well established. In 2002, based on successful trials in Texas against the canine strain in coyotes, RABORAL V-RG was granted license for use in coyotes. In the American South-west, under experimental use, the oral vaccine was demonstrated to be effective against gray fox variant rabies.9

RABORAL V-RG has been successfully used in Alabama, Arizona, Florida, Georgia, Maine, Maryland, Massachusetts, New Hampshire, New Jersey, New Mexico, New York, North Carolina, Ohio, Pennsylvania, Tennessee, Texas, Vermont, Virginia, and West Virginia.

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1. A section of DNA is removed from the vaccinia virus allowing the insertion of a cDNA copy of the rabies glycoprotein gene by recombination. The new recombinant vaccinia virus expressing the rabies glycoprotein becomes the vaccine strain RABORAL V-RG®.
2. The recombinant vaccinia virus infects the host cell where it loses its viral coat. The inserted gene is transcribed and translated into glycoprotein. Progeny recombinant virus is also produced.
3. The rabies glycoprotein is expressed on the host cell surface.
4. Lymphocytes recognize the rabies glycoprotein as foreign and respond by producing antibodies and cellular immune responses.
Introduction

RABORAL V-RG® has three unique distinctions as a veterinary vaccine. It is the first oral vaccine, it is the first wildlife rabies vaccine and it is the first recombinant vector vaccine approved for environmental release. Thus it is likely the most thoroughly tested veterinary vaccine in US history. The product is specifically designed to impede or prevent the spread of lethal rabies disease in wildlife populations. Since rabbies is spread by animal-to-animal contact, vaccination of a significant number of raccoons or coyotes may effectively establish a barrier between rabies enzootic and uninfected areas. Over time, repeated vaccination campaigns reduce the transmission of the virus within the population and allow it to be eliminated from vaccination zones.

The main objective of any rabies vaccination program is to limit the exposure of domestic animals to rabid wild animals. Because people are more likely to come in contact with domestic animals, the ultimate goal is to protect the human population from rabies.

An ORV program does not and is not intended, in any way, to eliminate the need for vaccination of pets or other domestic animals. RABORAL V-RG is not intended nor approved for use in pets. All animal owners are encouraged to have their animals vaccinated in accordance with local, state, or federal regulations by licensed veterinarians.

Indications

RABORAL V-RG is recommended for the oral vaccination of raccoons and coyotes against disease caused by the pathogenic rabies virus. The vaccine is restricted for use in raccoon control programs approved and directed by an appropriate federal or state agency. Control of the use of the vaccine rests with the sponsoring agency which has the responsibility for defining conditions for proper use in its program. Assessment of such factors as target species population, baiting densities, competitive species, habitat, methods and frequency of distribution, public awareness, safety precautions, and any appropriate parameter is the responsibility of the sponsoring state or federal agency.

Composition

RABORAL V-RG is composed of vaccine-filled plastic sachets contained in fishmeal polymer baits or coated in wax and fishmeal crumbles. The vaccine is a Type III recombinant virus which means it contains a live virus vector which carries and expresses a foreign gene. In this case, the viral vector is vaccinia virus, and the expressed gene product is rabies virus glycoprotein. This vaccine cannot cause rabbies because it expresses only the antigen which is important in inducing immunity. It has been shown to be safe in more than 60 species of animals including primates. It has also been shown to be effectively protecting raccoons against virulent rabbies challenge in controlled studies in the United States.

Route of Administration

This vaccine is effective when administered by the oral route.

Packaging and Storage

Shipped refrigerated. Store refrigerated 2-7°C (35-45°F). Do not freeze. Each bait contains one single-dose sachet ready for field use.

Quality Control

The quality of RABORAL V-RG is confirmed by testing under guidelines put forth by USDA-APHIS (9CFR) for:

- **PURITY** - Tested for bacteria, fungi, and mycoplasma to assure no detectable contaminants.
- **POTENCY** - Tested to assure each lot meets or exceeds the viral content required in accordance with Production Outline specifications.
- **SAFETY** - Tested for safety to assure no adverse effects are attributable to the vaccine.

**IDENTITY** - Tested to ensure the vaccinia virus identity and to confirm the expression of rabbies.

Precautionary Measures

Labels are printed on each bait, clearly identifying the recombinant vaccine and listing a toll-free phone number to contact the appropriate public health authorities. Public education should be conducted prior to distribution of the baits. This education may include newspaper articles, local television and radio reports, public meetings, and the distribution of brochures and posters. In certain areas, it may be appropriate to post signs at the periphery and at strategic points within the distribution area notifying visitors of the baits. This education includes newspaper articles, local television and radio reports, public meetings, and the distribution of brochures and posters. In certain areas, it may be appropriate to post signs at the periphery and at strategic points within the distribution area notifying visitors of the baits.

Rabies incidence rates and serum antibodies against rabbies are the primary tools used to determine the success of an ORV campaign. Biomarker analysis is useful but requires additional laboratory cost and technical support. Since the biomarker is a permanent record of yearly rabies control, the number of lines detected in a single animal tooth or bone shows the number of baits consumed over time.

The key personnel conducting the rabbies control programs should be trained in the appropriate precautions and techniques for handling and distributing the vaccine-filled baits. All personnel who will be handling the vaccine should be nonpregnant adults at least 18 years of age, who are free of any known immunosuppressive conditions.

Tetracycline Biomarker

The fishmeal polymer bait contains the antibiotic tetracycline hydrochloride. Following consumption of a bait the antibiotic binds to calcium in growing bones and teeth. This interaction creates a detectable line in the bone that can be seen microscopically by ultraviolet light detection. This “biomarker” line is a permanent record of bait consumption. Tooth and bone samples collected from animals within the baited zones demonstrate bait uptake. Such post-baiting surveillance data can be used to determine the percentage of targeted and non-targeted wildlife in a given area that may have been vaccinated.

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Baiting Patterns: Stopping Rabies In Its Tracks

While an effective ORV program begins with the availability of an efficient, efficacious vaccine, it doesn’t end there. Success depends on decisions about area of coverage, time and method of vaccination, and a host of epidemiological, geographic, climatic, biologic, and economic factors. Timing and spacing of bait deliveries are particularly important, because they often determine what proportion of the population will be successfully vaccinated.

The cycle of disease in a rabies-infected population can be broken if enough animals are immunized and if rabid animals do not come into contact with susceptible animals. Ideally, the disease will die out in the population. Rabies can be kept from penetrating into a new area in the same way. In either case, the immunized portion of the target animal population presents a barrier against rabies that is as real and effective as a physical barrier would be.

The barrier concept for preventing wildlife rabies is similar to — and complementary to — the current philosophy of rabies control in domestic animals. This strategy is based on producing a buffer of immunized animals around humans. Because pets are the animals with the most day-to-day contact with people, such programs usually focus on canine and feline rabies vaccination. For effective wildlife rabies control, concurrent domestic animal vaccination plans must be continued. Additional measures which help to increase the effectiveness of pet vaccination include reducing contact among pets, preventing free roaming of pets, and reducing pet contact with wildlife.

RABORAL V-RG can be a very efficient system for immunizing wildlife populations when combined with effective vaccine distribution strategies. These strategies, in turn, are based on the status of raccoon rabies in the targeted area, e.g. Is rabies already entrenched at a low enzootic level? Has it exploded onto the scene as a major animal epizootic? Or, is it absent now but threatening to move into the area?

Rabies viruses exist as different variants which tend to be host specific. Thus, rabies tends to be geographically limited based on wildlife animal populations. Taking advantage of this knowledge will help you design an effective program. Cross-infection or spillover to domestic species is common, especially during an outbreak. So consider injectable vaccination campaigns for dogs, cats and other species to complement your wildlife program. Unvaccinated pets and livestock are often the first victims exposed to wildlife rabies during an outbreak. Following are some possible distribution scenarios.

Barrier programs:

A. Keeping rabies out

Immune barriers may be created in multifaceted fashions which depend upon the area threatened with rabies (see opposite page for some examples). Scientific experiences and field use of RABORAL V-RG suggest that successful barrier programs depend on:

1. The barrier or vaccination zone must be large enough to impede the spread of rabies.
2. Applying the vaccine at sufficient frequencies and/or densities which tend to be host specific. Thus, rabies tends to be geographically limited based on wildlife animal populations.
3. Vaccinating behind the barrier to eliminate the establishment of enzootic rabies.
4. Determining if vaccine should be administered once or twice per year to gain control.
5. Vaccine densities for outbreaks should be higher than barrier densities and may require multiple applications to reach sufficient immunity in target populations.
6. Surveillance to ensure that the outbreak has been stopped.
7. Developing an exit strategy after the epizootic has been wiped out.

B. Confronting an epizootic

Dealing with an epizootic front of rabies requires a campaign which includes several phases. Short- and long-term planning includes:

1. Vaccinating the target species ahead of and within the advance of the epizootic front.
2. Creating a barrier of immunity to prevent the advancement of the front.
3. Vaccinating behind the barrier to eliminate the establishment of enzootic rabies.
4. Determining if vaccine should be administered once or twice per year to gain control.
5. Vaccine densities for outbreaks should be higher than barrier densities and may require multiple applications to reach sufficient immunity in target populations.
6. Surveillance to ensure that the outbreak has been stopped.
7. Developing an exit strategy after the epizootic has been wiped out.

C. Baiting in a rabies enzootic area

Enzootic rabies may be established following the progression of an epizootic front if no other control measures are taken. Whether the disease becomes enzootic is dependent on the residual population of the target species which may be extremely low or rising. The enzootic area may be quite large so program goals should be well defined and measurable (e.g., create barriers to protect human populations). The following aspects must be considered in developing such a program:

1. The area to be covered must be clearly designated and defined.
2. A surveillance program for the target species should be established.
3. Vaccine densities, frequencies, and targeted habitats must be determined.

Options for Vaccine Treatments

<table>
<thead>
<tr>
<th>Rabies Infected Area</th>
<th>RABORAL V-RG Vaccine Barrier</th>
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<tbody>
<tr>
<td>Rabies Free Area</td>
<td>Direction of Rabid Animal Movement</td>
</tr>
<tr>
<td>Line of Observation</td>
<td>Water</td>
</tr>
</tbody>
</table>

A. Keeping rabies out

A linear oral vaccine barrier is useful to block unidirectional progression of rabies. This approach is effective if geographical features of the rabies-free area help to isolate the territory. Oral vaccination of the rabies-free area should not be necessary unless the barrier is broken. In that case, complete treatment becomes advisable.

B. Confronting an epizootic

A circular barrier encompassing a small outbreak may be used where no geographical barriers are present and the direction of movement of the rabies epizootic can be predicted. Preventing the spread of rabies into populated areas is a potential strategy. This approach should include treatment of the rabies-free area and its perimeter.

C. Baiting in a rabies enzootic area

When rabies is enzootic, control must include both complete coverage of the affected area with vaccine and surveillance at the periphery to detect potential spread.

4. Design a barrier to prevent further disease spread and/or eliminate rabbits from a specific geographic area.
5. Maintain or expand the barrier to meet the original objectives.
Keys to a Successful ORV Program

We can assist you in developing an ORV program tailored to control and prevent wildlife rabies in your area. What follows are steps to building a typical oral rabies vaccination program using resources that may be available within your state.

1. Gather pertinent background information

Detailed information on the target species and the rabies problem in your area is vital to the design and implementation of a successful program.
- Status of rabies in the proposed control area — Number and location of rabies cases reported in the targeted area and species in which these cases have occurred. When were the first cases reported? Is there an outbreak or is the disease enzootic? Similar data for adjacent areas are useful and may reveal the source of the infection.
- Population estimates — Number of humans, domestic and wild animal species in the area, concentration or dispersal of the targeted wildlife, local laws concerning confinement or movement of domestic animals and translocation of wildlife species.
- Habitat information — Physical and demographic maps of the targeted geographical area are necessary to determine how and where the baits will be distributed.
- Activities of target species — Local biological data on behavioral seasonality of the target species, including such factors as breeding cycles and animal movement associated with seasonal variations in food supply. These data will help determine the timing of the campaign.
- Presence of non-target species — Number of other wildlife species in the area that may be susceptible to rabies (i.e., spillover cases) and non-target species, which may compete for bait uptake.

2. Determine what you want to accomplish and who may be able to help

The objectives and rationale of your ORV program must be clearly stated at the outset. Identify methods for assessing the results of the program (e.g., post-ORV surveillance, laboratory reports, animal complaints, etc.). Identify the types of civic, service, educational, medical, and governmental organizations that might be supportive and useful in helping carry out your program. Contact the leaders of these organizations to solicit their assistance and support.

3. Learn about products available for your use

Those administering the ORV program must know the properties of the vaccine and the baits.

4. Begin program development

Depending upon the status of wildlife rabies in the targeted area, your program will be a customized version of one of three basic approaches: 1. Vaccination to develop a barrier against the intrusion of the rabies virus; 2. Vaccination in the face of an epizootic; 3. Vaccination of a target species potentially already exposed to rabies virus because the disease is enzootic within the targeted area. Sample scenarios appear under “Baiting Patterns” in this brochure.

5. Establish cooperation with appropriate agencies

A State Veterinarian or other proper state official must approve an ORV program but obtaining that approval is just the beginning. The most successful programs have been widely cooperative in nature. There are many potential partners to consider in an ORV program. The United States Department of Agriculture - Wildlife Services (USDA-WS) is the lead federal agency in controlling wildlife rabies and carries out a multi-state program. Protecting the public against transmissible diseases is the responsibility of the U.S. Centers for Disease Control and Prevention (CDC). You may also want to work with organizations such as your State Veterinarian’s Office, your state departments of Health, Agriculture, and Fish and Wildlife; state veterinary schools or veterinary science departments; state and local medical and veterinary medical associations; state and local animal control officials; wildlife rehabilitators, local politicians, or law enforcement officials.

6. Estimate the budget and identify funding sources

After the scope of the program has been determined, the cost estimates of conducting such a program will have to be developed. Vaccine and bait costs are available from Boehringer Ingelheim Animal Health USA, Inc. Other budget items will vary according to local costs, available personnel and equipment. An important part of the budget includes evaluation tasks, such as post-vaccination surveillance, in addition to vaccine distribution costs.

Typical ORV programs require funding over multiple years, as no ORV program will be successful from a single baiting. Data on costs incurred in the implementation of other on-going programs or published economic analyses can help to estimate the cost of your ORV program.

7. Cultivate positive public relations

It is vitally important — and never too early — to set up a framework for sharing information regarding a planned ORV program. All successful programs have included a variety of communications to organizations, groups, and the general public. An informed public is usually a supportive public. Information to be shared should include potential benefits from baiting, as well as address possible safety issues that may be raised by various individuals and groups.
- The medical community — Physicians, hospitals, and veterinarians in the community should be informed about the public health significance of the program including answers to commonly asked questions. (Please see www.raboral.com).
- Public officials — Letters, brochures, and news clippings can inform public officials so that they can be knowledgeable on the vaccination program when interacting with their constituents. Point papers for staff of appropriate legislative committee members are very helpful.
- Schools — Give presentation in schools using video clips that describe the program, and distribute informative brochures to the students. The children can take the brochures home to tell their parents what they learned in school.
- Broadcast media — Plan an orchestrated release of information regarding: program planning, targeted areas, supporting organizations, interviews with personnel, vaccine information, pictures of baits, method of distribution, etc. Most newspapers are willing to print several preliminary informational articles, cover the distribution...
of the vaccine, and communicate the results of the program.

- Radio programs interview people with various public concerns. Control of rabies is a popular topic when a community is threatened. Areas targeted for control, the extent of the disease, the number of baits, precautions to be taken, and the timing of events are pertinent topics.
- Television reporters want visually graphic news. Some stations have special news features on the problem of raccoon rabies and the dangers it presents to the community, pets, and livestock. Invite local television stations to film the distribution of the baits and interview the personnel associated with the distribution, along with the program administrators, and public health officials.
- Utilize social media where appropriate such as web pages, You Tube, Facebook, Instagram, blogs, etc.

8. Distribute baits according to a well-designed plan, with continuous evaluation and fine-tuning

This step, which everyone generally thinks of first, actually comes quite late in the overall campaign, after much detailed planning. The actual distribution requires a surprisingly large amount of planning, careful coordination, and follow-up.

A comprehensive ORV control program is complex, but its potential benefits can be correspondingly great. Program success is measured by a decline in reported rabies cases in the target species, serology results, and other parameters. Armed with an effective oral rabies vaccine and guided by experience with other successful programs, Boehringer Ingelheim stands ready to help you in this endeavor. Working together, we can help to control wildlife rabies cases threatening your area.

9. ORV Programs Network

Becoming an expert in ORV programs is a matter of time, study, patience, setting achievable and meaningful goals, and most importantly, the adaptability to work as part of a team, not only in your geographical area but also in conjunction with other states. Taking advantage of the experience already gained by other states, regions, counties, and agencies using RABORAL V-RG®, is a key factor for the success of a new program.

Any adverse reactions observed in the areas where the recombinant rabies vaccine is used should be reported immediately to Boehringer Ingelheim, who will forward the information to the USDA-APHIS, Center for Veterinary Biologics.

Related Web Sites

The following links are provided only as a means of learning more about rabies or communicating with State Health Organizations about rabies. Note that these sites are current as of the date of publication, and their content may not be devoted entirely to rabies. Boehringer Ingelheim does not endorse, nor is it affiliated with, any of the links or their sponsors.

GENERAL RABIES INFORMATION
http://www.cdc.gov/rabies/
https://rabiesalliance.org/
https://www.who.int/rabies/en/
https://medlineplus.gov/rabies.html

RABIES INFORMATION BY STATE
Florida:
https://www.youtube.com/watch?v=_ABU6Gp38&amp;feature=youtu.be
North Carolina:
New York:
Texas:
https://www.dshs.state.tx.us/idcu/disease/rabies/orvp/
Virginia:

RABIES INFORMATION FOR CHILDREN
https://www.cdc.gov/rabiesandkids/
https://www.aahealth.org/rabies-elementary-school-curriculum/
References

1. Based on product label for IMRAB.


