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Authors: Rupprecht, Charles E., Buchanan, Tore, Cliquet, Florence, King, Roni, Müller,, Thomas, et al.

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PERSPECTIVE

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A Global Perspective on Oral Vaccination of Wildlife against Rabies

Charles E. Rupprecht,[1,8] Tore Buchanan,[2] Florence Cliquet,[3] Roni King,[4] Thomas Müller,[5] Boris Yakobson,[6] and Dong-Kun Yang[7] [1]College of Forestry, Wildlife and Environment, College of Veterinary Medicine, Auburn University, 602 Duncan Drive, Auburn, Alabama 36849, USA; [2]Wildlife Research and Monitoring Section, Ontario Ministry of Natural Resources and Forestry, Trent University, 2140 East Bank Drive, Peterborough, Ontario K9L1Z8, Canada; [3]ANSES, Nancy Laboratory for Rabies and Wildlife, European Union Reference Laboratory for Rabies Serology, European Union Reference Laboratory for Rabies, WHO Collaborating Centre for Research and Management in Zoonoses Control, WOAH Reference Laboratory for Rabies, Technopôle Agricole et Vétérinaire, Domaine de Pixérécourt, CS 40009 Malzeville, France; [4]Israel Nature and Parks Authority, Am V'Olamo 3, Jerusalem 95463, Israel; [5]Institute of Molecular Virology and Cell Biology, Friedrich-Loeffler-Institut, Federal Research Institute for Animal Health, WHO Collaborating Centre for Rabies Surveillance and Research, WOAH Reference Laboratory for Rabies, Südufer 10, 17493 Greifswald-Insel Riems, Germany; [6]WOAH Reference Laboratory for Rabies, Kimron Veterinary Institute, Ministry of Agriculture, Derech HaMaccabim 62, Rishon Lezion, 50250, Israel; [7]Viral Disease Division, Animal and Plant Quarantine Agency, Ministry of Agriculture, Food and Rural Affairs, 177, Hyeoksin 8-ro, Gimcheon-si, Gyeongsangbuk-do, 39660, Republic of Korea; [8]Corresponding author (email: charleserupprechtii@gmail.com)

ABSTRACT: The long-term mitigation of human–domestic animal–wildlife conflicts is complex and difficult. Over the last 50 yr, the primary biomedical concepts and actualized collaborative global field applications of oral rabies vaccination to wildlife serve as one dramatic example that revolutionized the field of infectious disease management of free-ranging animals. Oral vaccination of wildlife occurred in diverse locales within Africa, Eurasia, the Middle East, and North America. Although rabies is not a candidate for eradication, over a billion doses of vaccine-laden baits distributed strategically by hand, at baiting stations, or via aircraft, resulted in widespread disease prevention, control, or local disease elimination among mesocarnivores. Pure, potent, safe, and efficacious vaccines consisted of either modified-live, highly attenuated, or recombinant viruses contained within attractive, edible baits. Since the late 1970s, major free-ranging target species have included coyotes (*Canis latrans*), foxes (*Urocyon cinereoargenteus*; *Vulpes vulpes*), jackals (*Canis aureus*; *Lupulella mesomelas*), raccoons (*Procyon lotor*), raccoon dogs (*Nyctereutes procyonoides*), and skunks (*Mephitis mephitis*). Operational progress has occurred in all but the latter species. Programmatic evaluations of oral rabies vaccination success have included: demonstration of biomarkers incorporated within vaccine-laden baits in target species as representative of bait contact; serological measurement of the induction of specific rabies virus neutralizing antibodies, indicative of an immune response to vaccine; and most importantly, the decreasing detection of rabies virus antigens in the brains of collected animals via enhanced laboratory-based surveillance, as evidence of management impact. Although often conceived mistakenly as a panacea, such cost-effective technology applied to free-ranging wildlife represents a real-world, One Health application benefiting agriculture, conservation biology, and public health. Based upon lessons learned with oral rabies vaccination of mesocarnivores, opportunities for future extension to other taxa and additional diseases will have far-reaching, transdisciplinary benefits.

Key words: baits, biomarkers, diagnosis, lyssavirus, oral vaccination, rabies, serology, surveillance, zoonosis.

INTRODUCTION

Historically, infectious diseases at the human–domestic animal–wildlife interface were considered by some as a basic, natural "... struggle for existence among different forms of life ..." and a "... pitiless war ... without quarter or armistice ..." (Zinsser 1935). Since the 16th century, management of wildlife diseases has fallen between the varied realms of indifference and overreaction (Wobeser 2006; Gortazar et al. 2015). Significant zoonoses, such as rabies (an acute, progressive, incurable viral encephalitis of warm-blooded vertebrates) caused by lyssaviruses, such as rabies virus (RABV), and perpetuated globally by bat and mesocarnivore reservoirs, were no exception (King et al. 2004). Although options were considered for other zoonoses, the major methods of the control of rabies in wildlife during the 20th century involved indiscriminate killing,

bounties, unrestricted hunting, night shooting, trapping, cyanide, and carbon monoxide gassing at dens, and strychnine poisoning via baits (Geiger 1916; Sellers 1923; Records 1932; Lewis 1966; Blancou and Meslin 2000). Major conflicts over the concepts of lethal predator control vs. conservation erupted and led to early and deep schisms among professionals, such as the U.S. Bureau of Biological Survey and the American Society of Mammologists (Schmidly and Naples 2019).

Although amenable to prevention and control, rabies is not a candidate for eradication, because of the breadth of mammalian reservoirs and the diversity of lyssaviruses (Rupprecht et al. 2008). However, this was not always thought to be the case. By the end of World War II (before the broader global comprehension of bat rabies and the taxonomic recognition of multiple species of lyssaviruses), complete disease elimination using lethal control was viewed as an achievable goal (Steele and Tierkel 1949). A basic assumption underlying these considerations was that the speed of disease spread was influenced by a reduction in the affected population, such that when density fell below a critical threshold, an "epidemic wave" could be stopped (Zinn 1966; Bögel et al. 1976; Schneider 1977; Gunson et al. 1978). Besides random culling of animals, other strategies, such as habitat modifications, use of chemosterilants, or the introduction of infectious diseases, were also considered as techniques to manage mesocarnivore populations (Davis and Wood 1959; Sikes 1970; Winkler 1975; Wood 1954; Wood and Davis 1959).

Recognizing the considerable expense, questionable ethics, and ultimate futility of widespread, long-term depopulation programs alone, other strategies emerged. Because of the improvement in available biologics, the use of mass dog immunization, and the increasing importance of wildlife in disease perpetuation via cross-species transmission (CST) impacts on humans and domestic animals, researchers considered alternatives, such as vaccination (Black and Lawson 1970; Schmidt and Sikes 1968; McLean 1970; Baer 1988). In prescient fashion, Plummer (1954) opined that "... one might be inclined to wish that a vaccine which would be active by the oral route might be devised ..." Rather than concentrating upon parenteral inoculation as practiced in domestic species, the concept of oral rabies vaccination (ORV) of wildlife developed (Baer et al. 1971; Black and Lawson 1973). The objectives of this perspective are: To demonstrate progress in wildlife ORV over the past 50 yr within Europe, North America, the Middle East, Asia, and Africa; to discuss the critical parameters to measure continued programmatic success; and, based upon evident challenges, to suggest improvements towards future applications.

VACCINES

Precursors

Over the past 100 yr, rabies biologics have morphed considerably, from original concepts to field applications (Rupprecht et al. 2016). By the end of the 19th century, medical consensus emerged regarding the fundamental causation and pathobiology of rabies, including the acceptance of vaccinology for disease prevention in humans (Carter 1982; Schwartz 2022). However, the idea of extension from humans to wildlife evolved slowly, decades after human and domestic animal vaccine introduction. As an original demonstration of a reverse One Health application, the development of veterinary rabies products copied the human medical approach, as crude nervous tissue derivatives, made by the same method introduced for human postexposure prophylaxis (PEP) in the 1880s by Pasteur and his team (Cavaillon and Legout 2022). Such nerve-tissue–based vaccines were produced by inoculation of RABV into animal brains (initially in rabbits, and later in sheep, dogs, rodents, etc.). After clinical signs of rabies appeared in these infected animals, central nervous system tissues were harvested and RABV was inactivated partially by drying, irradiation, or the addition of chemicals, such as phenol (Wiktor et al. 1972). However, residual RABV remained in these vaccines, which could lead to a productive infection, with severe adverse events or death. Gradual

improvement of safety and efficacy of rabies vaccines occurred after Pasteur's original model from the 19th century. Following small-scale proof-of-concept demonstrations, practical utilization in domestic animals began by successful mass parenteral immunization of dogs in Japan, before major programmatic interruption imposed by World War II (Umeno and Doi 1921).

After World War II, vaccinology underwent a veritable renaissance. During the late 1950s, to increase product potency, modified-live viral vaccines (MLV) were generated and refined by serial passage of RABV in chicks and avian embryos, or by culture in primary hamster, canine, or porcine kidney cells (Kissling 1953; Koprowski 1954; Fenje 1960). By the later 20th century, multiple "street" (i.e., wild-type) RABV, isolated from naturally infected animals, served as the primary source materials for so-called "fixed" (i.e., laboratory-derived) vaccine seed viruses, by multiple passages in animal brains or in cell culture. These included those descended via Pasteur's 1882 isolate from a rabid cow, the Pasteur virus (PV), and the derived challenge virus standard (CVS) from the 1940s; avianized options, such as the low egg passage (LEP) and high egg passage (HEP) strains, the former obtained from a 1939 human rabies case; and the Street-Alabama-Dufferin (SAD) strain, isolated originally during 1935 from a rabid dog, and its derivative, the Evelyn-Rokitnicki-Abelseth (ERA) strain (Rhodes 1981; Sacramento et al. 1992).

Several of these fixed laboratory RABV strains were used as the basis for research and development of inactivated or MLV vaccines in humans and domestic animals, as well as the first source material applied to wildlife, focused primarily upon red foxes (*Vulpes vulpes*), a major reservoir in Europe and North America. As one example, Baer (1962) administered the CVS or LEP RABV strains to captive foxes by gastric intubation, but only 1/5 animals given the former, and 0/6 in the latter group, developed virus-neutralizing antibodies (VNA) and survived a lethal RABV challenge, in which all six controls succumbed. At that time, the critical role of lymphoid tissue in the buccal cavity, as an active site of oral vaccination, was not fully appreciated, nor was the deleterious impact of the gastric environment of carnivores upon the stability of such biologics as MLV (Orciari et al. 2001; Te Kamp et al. 2020).

In another attempt, an inactivated neural tissue RABV vaccine was delivered into the mouths of foxes (Supplementary Material Fig. S1), using a slightly modified explosive "humane coyote getter" (Robinson 1943). Six of the 14 vaccinated foxes developed VNA and survived laboratory challenge against a virulent RABV, with all six controls succumbing (Baer et al. 1963). Considering a different technique for remote delivery, Hudson et al. (1968) used a device in which a spring-propelled needle and syringe could administer either inactivated or MLV vaccine to animals (Supplementary Material Fig. S2). Cost and the need for applicability over large landscape scales limited this application.

Despite relative novelty and ideal intentions, such early inventions were impractical and not readily transferable to later widespread applications, which would require a self-replicating virus delivered to the host's oral cavity via an edible bait for successful proof of concept in the field (Bögel and Winkler 1992). The viral antigenic load contained within inactivated vaccines was inadequate to produce adequate immunity per os and the relatively large amount of purified antigens was cost prohibitive to provide efficacy by the oral route (Rupprecht et al. 1992a).

MLV progression

The CVS and LEP strains were not efficacious in the original laboratory applications, but progress towards the use of another RABV was forthcoming. After its original isolation during 1935, the SAD strain was adapted to cell culture and passaged serially to derive the attenuated vaccine, ERA, for veterinary use (Abelseth 1964; Lawson et al. 1967). This vaccine strain was the progenitor of all later laboratory research and field work with MLV in ORV (Baer et al. 1971; Mayr et al. 1972; Black and Lawson 1973; Debbie et al. 1972). Administration of a sufficiently potent MLV elicited

the induction of VNA and subsequent protection against a lethal RABV challenge infection after oral vaccination (Supplementary Material Fig. S3).

After the initial laboratory proof of concept of ORV in captive foxes during the 1970s, demonstrating the oral cavity as the primary site of viral replication (Baer et al. 1975), the ERA strain (confusingly referred to as SAD, because of the proprietary use at that time of ERA as a veterinary vaccine) was transferred to European investigators for further development in the field. From the first Swiss trials during 1978, multiple ERA/SAD MLV were derived and used throughout Europe, with >650 million doses distributed, of which the SAD strain was the most deployed (Steck et al. 1982; Müller et al. 2015b). In contrast, within Canada, the only RABV used as a MLV for wildlife ORV from 1985 was ERA-BHK21, with tens of millions of doses distributed (MacInnes et al. 2001). Except for experimental proof of concept, no MLV were used in the field for wildlife ORV in the United States. Although efficacious, these first-generation MLV vaccines for ORV were associated with residual pathogenicity and occasional vaccine-associated cases of rabies from ERA/SAD viruses (Fehlner-Gardiner et al. 2008; Müller et al. 2009; Hostnik et al. 2014; Vuta et al. 2016; Calvelage et al. 2020; Smreczak et al. 2022). New, more attenuated, second-generation MLV biologics consisted of antigenic variants of RABV, originally selected under neutralizing monoclonal antibody (MAb) pressure in vitro (Wiktor and Koprowski 1980). Selection for variations in the antigenic determinants of the RABV glycoprotein resulted in apathogenic variants (Coulon et al. 1983; Dietzschold et al. 1983; Tuffereau et al. 1989). One of these apathogenic variants derived from the SAD Bern strain, with a single nucleotide alteration in the RABV glycoprotein, was called Street Alabama Gif (SAG1), and was shown to immunize foxes orally (Le Blois et al. 1990; Follmann et al. 1992; Artois et al. 1997). The SAG1 vaccine was used for red fox ORV in both Switzerland and France. Isolation of another avirulent mutant from SAD, having two nucleotide differences at codon 333 in the RABV glycoprotein, resulted in a more genetically stable virus, known as SAG2 (Schumacher et al. 1993; Lafay et al. 1994). These apathogenic viral vaccines were used at high concentrations and were quite effective (Mähl et al. 2014; Masson et al. 1996). Starting during 1993, the SAG2 vaccine was used more widely for ORV of wildlife in several European countries, including Switzerland, France, Estonia, Finland, Italy, and Greece (Mähl et al. 2014). In addition to field efficacy, after distribution of >20 million doses of SAG2, no vaccine-associated cases of rabies had been detected (unlike first-generation ERA/SAD MLV vaccines), attesting to the safety of this second-generation ORV biologic.

Design of recombinant viruses

Given potential safety and stability concerns over first-generation MLV vaccines, alternatives were sought during the 1980s. Experience gained during the global smallpox eradication campaign, and considerable molecular insights into orthopoxviruses, provided an opportunity for development of a recombinant vaccinia-rabies glycoprotein (V-RG) virus (Wiktor et al. 1984; Kieny et al. 1984). The V-RG vaccine elicited VNA (via the incorporation of the ERA RABV glycoprotein gene into vaccinia virus) after parenteral administration and protected laboratory rodents against experimental RABV challenge, but without the ability to cause rabies. Extension of V-RG vaccine safety and efficacy by the oral route to important mesocarnivore reservoirs included both red foxes and raccoons (*Procyon lotor*), as well as other taxa (Blancou et al. 1986; Rupprecht et al. 1986; 1992b). To date, hundreds of millions of doses of the V-RG vaccine have been used extensively for ORV programs in Europe (e.g., Belgium, France, Luxembourg, Ukraine), Asia, the Middle East, and North America (Maki et al. 2017). Several other pox virus-vectored recombinant vaccines were designed later (Paoletti 1996; Jones et al. 2014). However, only the V-RG vaccine has been used extensively in ORV field programs for wild mesocarnivores since the 1980s.

Besides orthopoxviruses, adenoviruses have also been considered as major candidate recombinant viral vectors against rabies (Prevec et al. 1990; Li et al. 2006). One candidate selected for wildlife ORV was a first-generation human adenovirus type 5 RABV glycoprotein virus (AdRG1.3), developed as a vaccine in Canada, again focused upon the insertion of the ERA viral glycoprotein gene (Yarosh et al. 1996). As with the orthopoxvirus-based biologics, such adenovirus-vectored vaccines were safe and efficacious, without the ability to cause rabies (Knowles et al. 2009). The AdRG1.3 vaccine was recommended for ORV of foxes, raccoons, and skunks in Canada and used experimentally in laboratory/field trials in the USA (Rosatte et al. 2009b; Mainguy et al. 2012; Slate et al. 2014; Gilbert et al. 2018a).

In addition to the use of orthopox- and adenoviruses, RABV has also been employed as an effective cloning and expression vector system itself, with the potential for creation of highly attenuated recombinant biologics intended for wildlife ORV (Schnell et al. 1994; Faber et al. 2009). For example, the recombinant SPBN GASGAS virus (derived from the SADB19 virus), with two copies of modified RABV glycoprotein genes, was stable after serial passages (Borutzki et al. 2022). Another third-generation vaccine, based upon the ERA strain, was constructed (ERAG333), using a reverse genetics approach for focal point-mutation at site 333 of the RABV glycoprotein gene, shifting Arg333 to Glu333 (Franka et al. 2009). To date, both these recombinant RABV vaccines have been deployed in Europe and the Russian Federation for wildlife ORV (Bankovskiy et al. 2008; Shulpin et al. 2018; Vos et al. 2021).

BAITS

To target free-ranging wildlife taxa, vaccines must be provided remotely via attractive containers (i.e., baits) delivered to the field by hand, via aerial distribution, or at stations. Although the earliest research attempts used vaccines administered orally (Supplementary Material Fig. S3), or injected directly into or on baits, to remain pure and potent, liquid vaccines should be distributed in primary containers, such as plastic sachets or blister packs. Today, all products used in wildlife ORV campaigns reside in such containers placed within edible baits (Supplementary Material Fig. S4). More biodegradable primary packaging may be anticipated for future ORV use.

A great variety of potential baits have been considered over the last 50 yr. These included eggs, sausages, chicken heads, offal, and various waxes, fats, oils, etc., or polymers containing fishmeal or other components (Table 1). The original vaccine-laden baits of the 1970s were prepared laboriously by hand. Thereafter, products were constructed commercially, en masse, for ORV programs (Supplementary Material Fig. S5).

FIELD ASSESSMENTS

Biomarkers

After initial vaccine development in laboratory and captive trials, determination of which species consumed baits under field conditions was a critical part of wildlife ORV assessment (Cliquet and Aubert 2004; Slate et al. 2009; Freuling et al. 2013a; Fehlner-Gardiner 2018). Although the programmatic intent of ORV was maximum engagement with target mesocarnivores towards rabies prevention, control, and ultimate disease elimination within an ecological community, bait fate was dependent upon multiple environmental factors and collective consumption via a myriad of invertebrate and vertebrate nontarget species (Dixon et al. 2023). Data on animal acceptance and handling of baits may be obtained in real time, such as by direct observation of events by investigators concealed from view within blinds (Hanlon et al. 1989). Given drawbacks to such in-person evaluations, remote camera traps have also been used for bait fate estimations (Smyser et al. 2015). Indirect measurements included bait distribution and subsequent collection of bait fragments, combined with detection of evidence such as footprints within sand pits or on tracking tile stations over time (Winkler et al. 1975; Linhart et al. 1994, 2002; Roscoe et al. 1998).

TABLE 1. Examples of bait types that have been used for oral rabies vaccination of wildlife.

Type	Citation
Embryonated chicken eggs	Debbie (1974)
Wax-coated dog biscuits	Winkler et al. (1975)
Plastic straws within smoked sausages	Winkler and Baer (1976)
Lyophilized vaccine within fish oil-coated plastic envelopes	Black and Lawson (1980)
Blister packs inserted under the skin of chicken heads	Steck et al. (1982)
Blister packs coated with fishmeal and fat in molds	Wachendörfer (1986); Schneider et al. (1987)
Gastrointestinal-resistant tablets	Brochier et al. (1985)
Beef tallow-coated polyurethane sponge cubes	Lawson et al. (1987)
Capsules enclosed by a mixture of fat, bone, and fishmeal	Brochier et al (1988)
Wax ampules in fishmeal polymer cylinders	Hanlon et al. (1989)
Polyurethane foam cubes coated with a wax-tallow mixture and covered with a mackerel-water slurry, placed into plastic bags	Hadidian et al. (1989)
Polyurethane sponges heat-sealed into a polyethylene film, coated with soybean oil and sardines, placed into plastic or wax bags	Perry et al. (1989)
Polystyrene blister packs coated with tallow, oil, and chicken flavor, in plastic bags with liver slurry or meatballs	Bachmann et al. (1990)
Wax ampules in batter-coated, deep-fried polyurethane sleeves	Linhart et al. (1991)
Dog-food flavored polymer cubes	Farry et al. (1998a)
Sachets covered in beef stock, wax, and oil, with added attractants (i.e., banana-bees wax, cheese, honey-bees wax, peanut butter, seafood-cod oil, or sugar-vanilla flavors)	Rosatte et al. (1998)
Marshmallow-flavored wax lard cakes	Steelman et al. (1998)
Plastic blister packs with a paper-laminated aluminum foil lid, embedded in a fat-wax matrix flavored with chicken essence	MacInnes et al. (2001)
Poultry-flavored sachets	Linhart et al. (2002)
Polyethylene plastic sachets inserted into fishmeal polymer-based square or rectangular baits	Cliquet et al. (2008)
Blister packs coated with partially hydrogenated vegetable shortening, wax, stearine, icing-sugar, vegetable oil, artificial marshmallow flavor, artificial sweet flavor, and a fat-soluble food dye	Rosatte et al. (2009a, b)
PVC/aluminum blisters embedded in a mixture of fat, fishmeal, fish flavor, paraffin, and a polymer	Mahl et al. (2014)
Polymer/aluminum blisters embedded in a matrix of fishmeal, palm fat, coconut fat, and paraffin	European Medicines Agency (2021); Vos et al. (2021)

Another part of such environmental ORV studies used the addition of biomarkers to baits (Supplementary Material Fig. S6). Biomarkers are substances added to baits for subsequent detection in the bait-consuming animal (Table 2). Such substances must be safe, stable, inexpensive, compatible with the vaccine, and easy to evaluate. Detection of the biomarker confirms bait contact and at least partial consumption by an animal. However, biomarker detection does not provide information on immunological response in the host, because animals may consume a bait irrespective of vaccine contact, leaving the vaccine container untouched. In addition, some biomarkers may be long-lasting, such as tetracycline, and could suggest bait ingestion from a prior field season (Supplementary Material Fig. S7).

As with testing expertise in diagnosis and serological evaluation, demonstration of proficiency also extends to detection of biomarkers, but they remain in widespread use (Robardet et al. 2012). Although critical during initial research and development, after years of using

TABLE 2. Common biomarkers used in wildlife oral rabies vaccination programs.

Biomarker	Samples	Examples
Tetracycline	Teeth, bones	Linhart and Kennely (1967); Johnston and Voigt (1982); Johnston et al. (1988); Hanlon et al. (1989); Perry et al. (1989); Müller et al. (1993); Fearneyhough et al. (1998); Algeo et al. (2013)
Sulfadimethoxine	Plasma	Hanlon et al. (1993); Southey et al. (2002)
Rhodamine B	Hair, vibrissae	Lindsey (1983); Hable et al. (1992); Southey et al. (2002)
Oil Blue A dye	Adipose tissue	Linhart et al. (1993); Creekmore et al. (1994)
Iophenoxic acid	Plasma	Larson et al. (1981); Linhart et al. (1994); Follmann et al. (1987); Hadidian et al. (1989); Sillero-Zubiri et al. (2016); Berentsen et al. (2019, 2020a, 2020b)
Plastic beads	Feces	Robardet et al. (2019b)

a given licensed vaccine, an attractive bait, and a defined distribution system for a selected mesocarnivore species, continued ORV programmatic utilization of a biomarker is debatable, especially with adequate laboratory-based rabies surveillance (Middel et al. 2017; Davis et al. 2021). In addition, cessation in the use of some biomarkers (e.g., tetracycline) may be in line with best practices to minimize environmental contamination with antibiotics.

Serology

Serology is a laboratory tool used during wildlife ORV to assess an appropriate immune response to the RABV glycoprotein Moore (2021) component of a vaccine, to gauge herd immunity. Typically, 4–8 wk after ORV, blood from carcasses may be obtained via hunters, or animals may be trapped, sedated, bled, and serum separated for laboratory testing. Alternatively, blood in tissues of recently dead animals may be stored on filter paper strips (Wasniewski et al. 2014). Although innate immunity may be important, most laboratory testing is dependent upon the measurement of VNA after exposure to the RABV glycoprotein in inactivated, MLV, or recombinant vaccines. The two major neutralization tests for determination of VNA against RABV are the fluorescent antibody virus neutralization test (FAVNT) and the rapid fluorescent focus inhibition test (RFFIT). Both use serial dilutions of test sera against a standard challenge RABV concentration (compared to a positive control standard) and are considered equivalent measures of VNA (Smith et al. 1973; Cliquet et al. 1998; Briggs et al. 1998; World Health Organization 2018). In most wildlife ORV programs, the cut-off value selected as indicative of the induction of VNA after vaccination is 0.5 IU/mL. However, other VNA cut-off values have been operationally defined in various investigations, from approximately 0.06 to 0.1 IU/mL, and below this range may be considered negative for evidence of VNA (Moore and Hanlon 2010). Determination of immune responses after vaccination has also included ELISAs (Cliquet et al. 2000; Knoop et al. 2010; Sobey et al. 2010; Wasniewski et al. 2013). Such serological methods infer detection of a RABV-specific immune response from the vaccination, but cannot confirm efficacy. Biomarker detection and serological determination used in conjunction attempt discrimination between vaccinated and naïve individuals, but confounding variables are operative in this interpretation (Table 3). In one study, the ELISA specificity was evaluated at 95%, after being tested on more than 900 foxes, with 5% false positive response in serology; these foxes were negative for evidence of biomarker uptake (Cliquet et al. 2000).

Moreover, serology is a tool for inference, whereas protection against rabies is complex, due in part to multiple factors such as viral dose, route, severity, and so on. Immunity is a dynamic concept, and VNA are only a surrogate for a potential outcome when a host contacts a pathogen (Moore and Hanlon 2010). In rabies,

TABLE 3. Assessment of potential biomarker and antibody outcomes in animals during oral rabies vaccination monitoring activities.

Biomarker status	Antibody status	Interpretation
Positive	Positive	Animal consumed bait successfully and adequate immunological response to vaccine (also, VNA may be indicative of residual passive immunity in juveniles, or prior RABV exposure and abortive infection)
Positive	Negative	Bait consumption (as above), but without adequate viral vaccine exposure (or waning immunological response); bait consumption only (i.e., blister, capsule or sachet with vaccine discarded from the bait casing); false negative result (i.e., lack of diagnostic sensitivity of the test)
Negative	Positive	Inadequate bait consumption, but exposure to vaccine container, vaccine virus from another animal (e.g., mother–young grooming), passive immunity (e.g., in juveniles), or prior RABV exposure (i.e., abortive infection); false positive result is also a concern (i.e., lack of diagnostic specificity of the test)
Negative	Negative	Inadequate contact with bait (or waning biomarker) and vaccine (or waning immunological response)

there is no absolute "seroprotective" VNA titer, only arbitrary laboratory values from serial dilutions of serum that measure the reduction of RABV foci in cell culture. Such correlates of protection are relative, in the sense that higher VNA levels may be quantitatively more advantageous than lower values, but occasional failures in efficacy may occur even in a vaccinated host demonstrating an "acceptable" defined titer (Moore et al. 2017). For example, in one laboratory study on efficacy of wild-caught raccoons in an ORV area, 24% of seronegative animals survived RABV challenge in which 17% of seropositive animals (with a titer >0.1 IU/mL at the time of challenge) succumbed (Blanton et al. 2018). Thus, seemingly seronegative animals may survive a virulent infection (presumably because they were vaccinated in the field appropriately, but their VNA levels had declined to baseline over time) and apparently seropositive animals may succumb (potentially because their immune system was overwhelmed in the variable host–pathogen race after viral challenge). An anamnestic response may be more important in the flux between a productive infection and protective immunity, rather than a single titer as indication of a whole-host response against an agent with the highest case fatality of any infectious disease (Rupprecht and Dietzschold 1987). Such discrepancies between VNA levels and efficacy are well known in the field, but perhaps less appreciated when trying to gauge true herd immunity in nature, such as with ORV, compared to parenteral vaccination in which an operator may be more assured of delivery of a full dose via needle and syringe (Rupprecht et al. 1990, 1993; Cliquet et al. 2000, 2007; Bobe et al. 2023). Dependence upon a correlate of protection alone may be misleading for some management decisions, particularly if VNA levels in properly vaccinated animals wane by the time of sampling, irrespective of the utility of an anamnestic response upon future pathogen exposure. Hence, one biologic that yields a mean value of approximately 60% seropositivity in animals over unit time is not necessarily twice more effective than another vaccine that routinely produces a VNA seroprevalence of about 30% in a target host, without an otherwise objective measure of herd immunity.

Laboratory-based surveillance and monitoring

The most important demonstration of ORV program utility is efficacy under field conditions. Postmortem samples of brain tissue may be obtained via passive public health surveillance of suspects that expose humans or other animals

(Ma et al. 2022, 2023; Kunkel et al. 2023). Passive surveillance may be combined with enhanced rabies surveillance (ERS) of suspect animals acting abnormally or found dead, such as road-killed specimens (Davis et al. 2021). Common tests include the direct fluorescent antibody test (DFAT) and the rapid immunohistochemical test (RIT), which detect RABV antigens within the central nervous system of affected animals (World Health Organization 2018; Patrick et al. 2019). The latter test may use unconjugated antibodies, such as MAbs, for binding to RABV antigens, in an indirect fashion (i.e., IRIT), which may also be utilized for antigenic typing of variants (Dyer et al. 2013). Alternatively, the antibodies may be conjugated to another molecule, such as biotin, and used directly (i.e., DRIT) for detection of RABV antigens in the brain of suspect animals by light microscopy (Kirby et al. 2017). In addition to the DFAT and RIT, lateral flow tests (LFTs) have been used during some surveillance activities, but unsatisfactory findings in commercial kits demonstrate a persistent lack of appropriate test validation and necessary quality controls (Klein et al. 2020; Mauti et al. 2020). In addition, the need for brain homogenates in LFTs raises biosafety concerns. For epidemiological investigations, positive samples for viral antigen can be confirmed by RT-PCR and used for sequencing to characterize the RABV in the affected animals (World Health Organization 2018; Marston et al. 2019). The combination of public health surveillance and ERS has been the fundamental basis of measuring the primary success of wildlife ORV programs on a global level during the past 50 yr.

REGIONAL APPLICATIONS

Europe

Since the 1970s, European investigators have contributed significantly to the concept and application of wildlife ORV. Thanks to an ingenious idea by workers in North America and its enthusiastic pursuit and further development by European research groups, this novel method of "controlling disease at the source" led to the virtual disappearance of wildlife-mediated rabies in western, northern, and large parts of central Europe (Baer et al. 1971; Dubreuil et al. 1979; Steck et al. 1982; Cliquet and Aubert 2004; Müller and Freuling 2018; Robardet et al. 2019a).

In the mid-20th century, when Europe was in the final stages of eliminating canine rabies, intervention measures were challenged by the inexorable spread of fox-mediated rabies (Lloyd 1976; Pastoret et al. 2004; Müller et al. 2012). Since the first estimated occurrence during the 1930s, fox rabies spread in Europe over 80 yr to an area estimated at 4.7 million km^2. The epidemiological events were shaped primarily by the spatial-temporal circulation of various phylogenetic lineages of RABV in the red fox (Bourhy et al. 1999; Kuzmin et al. 2004; McElhinney et al. 2008; Turcitu et al. 2010; Robardet et al. 2014; Horton et al. 2015). The epizootic appears to have been further accelerated by the raccoon dog (*Nyctereutes procyonoides*), an invasive species in Europe. After the red fox, the raccoon dog is the second most affected mesocarnivore species and harbors the same RABV lineages (Niin et al. 2008; Singer et al. 2009; Zienius et al. 2011; Freuling et al. 2013a). Raccoon dogs share a common range with foxes, especially in northeastern Europe (Kauhala and Kowalczyk 2011; Kochmann et al. 2021). Thus, rabies prevalence continued to increase throughout Europe during the 20th century, peaking in 1984 with about 24,315 reported cases, posing a serious threat to human and animal health.

As in North America, awareness and management shifted forcibly to wildlife rabies from mid-century onwards (Rupprecht et al. 2008; Müller et al. 2012). Considering the vast geographical area affected by wildlife rabies and the failure of other, less ethical management techniques (e.g., unrestricted population reduction, fumigation of fox dens, and broad poisoning of foxes), ORV was proven to be the ideal option for rabies control in fox populations (Aubert 1992; Rupprecht et al. 2001).

Field applications: The first ORV field experiment was conducted during 1978 in Switzerland and is considered a milestone for ORV in Europe (Steck et al. 1982). The ORV

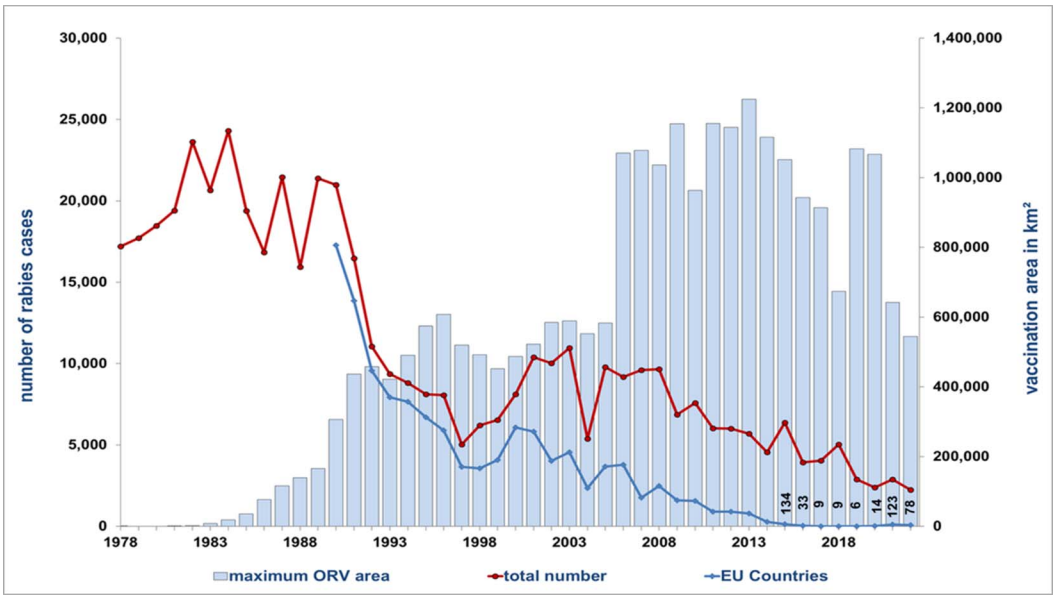


FIGURE 1. Development of rabies cases and vaccination areas in Europe between 1978 and 2022 (bat rabies cases not included). The total number of rabies cases for 2018–2022 is an approximation that may be underestimated because of irregular or missing data reporting from Belarus, Russia, and Ukraine, where rabies virus (RABV) remains endemic and is not efficiently controlled. For better visualization RABV cases in EU countries for the years 2015–2022 are indicated by numbers.

strategy, which evolved over time, was based on three main components: Effective oral rabies vaccines, attractive edible vaccine-laden baits, and an appropriate distribution system (Aubert et al. 2004; Cliquet and Aubert 2004; Freuling et al. 2019). Between 1978 and 1990, no detailed protocol for field applications was available for countries pioneering ORV. Both vaccines and baits were under development and subject to improvement (European Commission 2002; Freuling et al. 2019). The current, more refined ORV strategy relied heavily on both primary research and simple trial and error in the field, especially in the early stages, complemented by a lively exchange of experiences with other research groups, always communicating setbacks and lessons learned (Aubert 1994; Rupprecht et al. 2008; Müller et al. 2012).

Widespread introduction of ORV, coherent transboundary activities, and almost universal coverage of the entire endemic area did not occur until the early 1990s, when additional European countries benefited from earlier experiences and alternate vaccines (Aubert 1994; Freuling et al. 2013b; Robardet et al. 2019a). This process was facilitated greatly by the European Union (EU) policy of giving high priority to rabies control and the introduction of targeted and sustainable cofinancing for ORV programs for both EU Member States and non-EU countries (European Commission 2015, 2017; Robardet et al. 2019a). During the periods 1991–2005, and 2006–2017, a mean of 519,000 and 1,073,000 km^2 were continuously under vaccination, respectively, followed by a decline in ORV areas, due to regional success in recent years (Fig. 1). The geographical area covered by ORV in Europe was about 2.9 million km^2, and the cumulative vaccination area, depending on seasonal vaccination campaigns, was estimated to be 47.4 million km^2 (Fig. 2).

A total of 14 different attenuated RABV MLV and recombinant vaccines were used in the field in varying numbers overlapping in time (Müller et al. 2015b). Since 1978, nearly a billion vaccine baits have been distributed

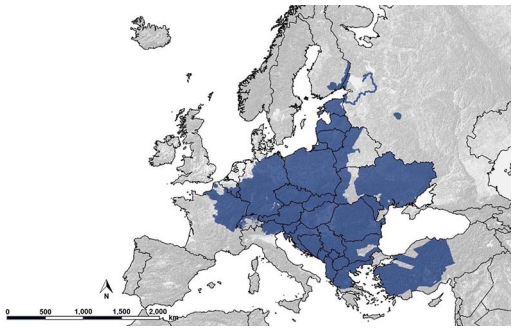


FIGURE 2. Area covered (in blue) by wildlife oral rabies vaccinaion in Europe between 1978 and 2022.

in 30 European countries, mainly using aerial distribution (Table 4).

The ERS and continuous monitoring of European ORV campaigns in the fox population remained key elements of rabies control programs (European Union 2017). The original World Health Organization (WHO) recommendations for a minimum sample size for RABV surveillance (approximately 8 foxes per 100 km^2/yr), adopted by the EU in 2002 to ensure a rabies-free status, was found to be inappropriate as increasing testing of healthy animals to meet the sampling requirement did not add additional value. Thus, a sample size for passive surveillance could not be established. Since 2005, only a reduced sample size (4 foxes per 100 km^2/yr) has been applied to the monitoring of ORV campaigns (World Health Organization 2013). This monitoring includes the evaluation of bait uptake by biomarker tests and seroconversion (i.e., RABV-specific VNA) in foxes and raccoon dogs, intended to assess the effectiveness of bait vaccines used, particularly at the beginning of ORV campaigns (European Food Standards Agency panel on Animal Health and Welfare, EFSA AHAW 2015). Biases in sampling, different quality of samples, and the use of different serological tests (RFFIT, FAVNT, direct and indirect ELISA) led to large discrepancies and made it difficult to compare results among European countries (Cliquet et al. 2010, Robardet and Cliquet 2011, Wasniewski et al. 2013, 2016, 2019). Comparative studies resulted only in partial improvements. Later, when it was realized that rabies prevalence was the best indicator of the success of ORV campaigns, such serological

TABLE 4. Estimated number of vaccine baits distributed in Europe between 1978 and 2022 according to vaccine. As no exact figures were available, the number of vaccine baits distributed is an approximation based on the size of the area covered by each vaccine and an assumed bait density of 20 baits/km^2. Given that bait densities have varied between 15 and 30 baits/km^2 over time, the figures given are only the minimum numbers and vary slightly depending on the vaccine.

Vaccine type	Stage of development	Vaccine strain	Cumulative area covered	Number of vaccine baits	Proportion of total number in %
MLV	First generation	SAD Bern	19,499,342	389,986,839	43.05
		SAD B19	15,558,246	311,164,925	34.35
		SAD P5/88	2,684,858	53,697,168	5.93
		RABIVIT-VBF	488,862	9,777,232	1.08
		Vnukovo 32	410,462	8,209,247	0.91
		SAD Clone	387,680	7,753,596	0.86
		RV 97	142,761	2,855,210	0.32
		SAD VA1	82,929	1,658,572	0.18
	Second generation	SAG-1	516,457	10,329,144	1.14
		SAG-2	1,633,713	32,674,267	3.61
MLV/recombinant	Third generation	ERA G333	213,847	4,276,942	0.47
		SPBN GASGAS	155,204	3,104,087	0.34
Recombinant		VRG BROVARABIS	2,851,230	57,024,592	6.29
		VRG	669,055	13,381,097	1.48
		Total	45,294,646	905,892,917	100

monitoring became less important (World Health Organization 2018).

Challenges: Since 1990, rabies cases in mesocarnivores have decreased by 80% across Europe, in the EU and the West Balkans (Lojkić et al. 2021). Although many European countries eliminated fox rabies and declared themselves free of (RABV) rabies according to international standards set out by the World Organisation for Animal Health (WOAH 2022), the EU has not achieved its goal of becoming rabies-free by 2020 (Robardet et al. 2019a). This is mainly because of repeated incursions of fox rabies from neighboring rabies-endemic countries, as documented during 2021 in Poland, and in Hungary, Romania, and Slovakia near the borders with Belarus, Ukraine, and Moldova (Smreczak et al. 2023). This highlights the disproportionally greater effort required in the final phase of elimination, but also the fragility of "rabies-free" status, the border repercussions from sociopolitical and economic turmoil, and the critical role of surveillance for early detection (Freuling et al. 2013b; Cliquet et al. 2014).

This in no way detracts from the theory of ORV in concept or the recognized substantial achievements in wildlife rabies control in Europe, which are unprecedented in the continent's history European fox rabies blueprint 2013. However, preventing the introduction of rabies into the EU will remain a major future challenge, as maintaining a 100-km-wide vaccination belt along the common borders in Eastern Europe is a costly long-term task requiring constant political and financial engagement as well as sufficient motivation to pursue intensive ERS (Müller et al. 2015a; Cliquet and Wasniewski 2018). In addition, bidding procedures for both vaccines and field delivery are becoming increasingly competitive and often lead to legal proceedings, with ORV campaigns in affected countries sometimes having to be suspended. Whether raccoons (*Procyon lotor*) and golden jackals (*Canis aureus*) will become potential new reservoir hosts in Central Europe and the Balkans, respectively, remains to be seen (Lanszki et al. 2006; Müller et al. 2015a). Furthermore, in addition to RABV, multiple bat lyssaviruses, including Bokeloh bat lyssavirus, European bat lyssaviruses 1 and 2, Lleida bat lyssavirus, Kotalahti bat lyssavirus, and West Caucasian bat virus, are endemic in strictly protected bat populations in Europe. These bat lyssaviruses appear largely host restricted. Unlike in North America, with European bat lyssaviruses, although rare CSTs have been reported, resultant host switching has not occurred; thus these lyssaviruses do not seem to pose a major threat of causing a rabies enzootic in mesocarnivore populations. Nevertheless, true elimination of rabies in Europe is not possible under the current limitations (Schatz et al. 2013; Fooks et al. 2021). This reaffirms a basic concept that wildlife rabies may be prevented, controlled, and selectively eliminated, but this zoonosis is not a candidate for eradication (Rupprecht et al. 2008).

North America

Wildlife rabies is widespread in North America, from the Arctic to the Tropics (Simon et al. 2021; Ma et al. 2022; Ortega-Sánchez et al. 2022). Although probably present much earlier, historical reports among wild mesocarnivores only appeared during the 1700s, some two centuries after the Columbian Exchange (Held et al. 1967; Crosby 1972; Tabel et al. 1974; Vos et al. 2011). During the 20th century, the apparent case burden varied dramatically throughout the continent, based on national surveillance data (e.g., reported highs of >2,400 cases in Canada during 1972, mainly wildlife; approximately 15,000 in Mexico during 1978, mainly dogs; and >10,000 in the USA during 1946, with a combination of domestic animals and wildlife). Current major wildlife reservoirs include Arctic (*Vulpes lagopus*), both red and gray (*Urocyon cineroargentus*) foxes, raccoons, skunks (*Conepatus*, *Mephitis*, and *Spilogale* spp.), and bats of multiple taxa (e.g., *Desmodus*, *Eptesicus*, *Lasiurus*, *Lasionycteris*, *Myotis*, *Parastrellus*, and *Tadarida* spp.). Like many other wild canids, coyotes (*Canis latrans*) are reservoir-competent, but a specific RABV focus maintained within this species at the Mexico–USA border appears to have been eliminated via ORV (Sidwa et al. 2005). Other wild reservoirs, such as skunks or coatis (*Nasua*

narica), may perpetuate the disease in Mexico, given the country's mammalian biodiversity (Aréchiga Ceballos et al. 2022). Within the Caribbean, the nonnative, small Indian mongoose (*Urva auropunctata*) maintains RABV within Cuba, Grenada, Hispaniola, and Puerto Rico, with CST to domestic animals and humans, and serves as a risk for introduction to multiple jurisdictions believed free of the disease (Seetahal et al. 2018). Wildlife ORV has occurred only in Canada and the USA, focused upon a few of the major mesocarnivore reservoirs (Fehlner-Gardiner 2018; Ma et al. 2022). With the recent elimination of canine rabies in Mexico by mass vaccination, ORV may be considered a future option in wildlife health management there, based on the results of enhanced laboratory-based surveillance (Garcés-Ayala et al. 2017).

Canada

At nearly 10 million km^2, stretching between the Atlantic and Pacific Oceans, and northward from the border with the USA to the Arctic Ocean, Canada is the second largest country by total area. The impact of RABV, the viral variants that occur, the reservoir species that perpetuate the disease, and the interventions used to manage this zoonosis across this vast expanse are diverse and regional. Following the successful control of imported canine rabies in domestic dogs in Canada during the early 20th century using quarantine procedures, reporting regulations, dog muzzling orders, and parenteral vaccination in the midcentury and onwards, awareness and management shifted to rabies reservoirs in wildlife populations (Tabel et al. 1974).

Distinct RABV variants in wildlife perpetuate throughout the country. Multiple bat RABV variants occur, but management of bat rabies has not been attempted. A skunk RABV variant is established in the western prairie regions, after spreading north from the USA (Charlton et al. 1988; Pybus 1988; Davis et al. 2013). An Arctic fox RABV variant was enzootic in the Arctic and sub-Arctic regions spreading southwards into most Canadian provinces in the 1950s (Plummer 1954). The raccoon RABV variant entered eastern Canada several times from the USA (Rosatte et al. 2001; Nadin-Davis et al. 2006a, 2020; Trewby et al. 2017). When Canadian jurisdictions have attempted direct wildlife rabies management or elimination, ORV programs have been the most frequently used method.

History: The earliest experimental field use of ORV in Canada occurred during 1985 to manage an Arctic fox RABV variant, following its incursion and spread across most of Ontario, establishing as an enzootic across an estimated 100,000 km^2 of intensely populated southern portion of the province (Bachmann et al. 1990; MacInnes et al. 2001). A mean of 1,532 rabies cases were diagnosed annually in Ontario between 1964 and the large-scale implementation of ORV in 1989 (Tinline and Rosatte 2020). Political impetus for attempting to control (and eventually eliminate) the outbreak in Ontario came from mounting case numbers; livestock losses; rising costs of human PEP; and two human fatalities in 1959 and a third in 1967, despite prophylaxis administration in accordance with the WHO recommendations (Filejski et al. 2020). Considering the vast geographical area involved and the drawbacks of other management techniques such as population reduction, contraceptive management interventions, or parenteral vaccination, ORV was selected as the best option to manage the Arctic fox RABV variant in Ontario. Between 1972 and 1989, numerous aspects of an ORV program, including development of oral vaccines, baits for delivery, distribution techniques, baiting densities, and monitoring of program effectiveness, were either adapted from European programs or specifically designed in Ontario to meet local rabies program objectives. Three different biologics were used in Canadian wildlife ORV programs.

ORV biologics: The first oral rabies vaccine distributed in Ontario was the MLV ERA vaccine (Bachmann et al. 1990). Following successful field trials, large-scale management with this vaccine was implemented in 1989. A total of 17.2 million baits were distributed, in Ontario (16.1 million between 1985 and 2009),

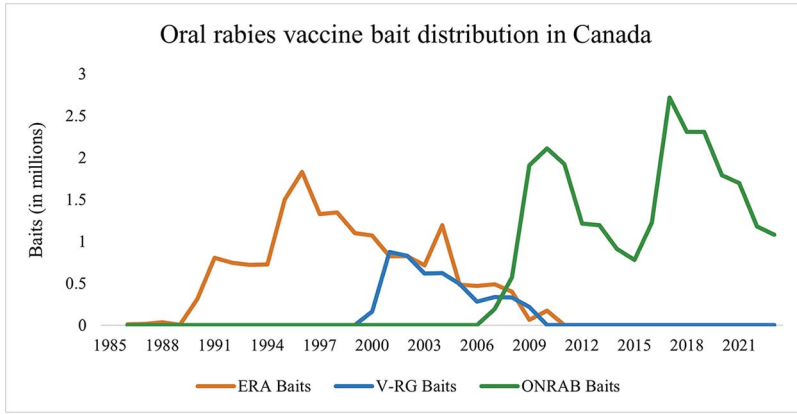


FIGURE 3. Graph showing the numbers of oral rabies vaccine baits distributed in Canada 1985 to 2022 and the change over time in the use of Evelyn–Rokitnicki–Abelseth (ERA), recombinant vaccinia-rabies glycoprotein (V-RG), and human adenovirus rabies glycoprotein recombinant vaccine (ONRAB) baits.

Quebec (0.45 million between 1995 and 1999), and Newfoundland and Labrador (0.6 million in 1988 and 2003), using the ERA vaccine (Figs. 3 and 4). The Arctic fox RABV variant was eliminated from most of the endemic area in southern Ontario, except a small part in the southwestern portion of the province, where rabies persisted in the striped skunk (*Mephitis mephitis*) population (MacInnes et al. 2001; Nadin-Davis et al. 2006b; Rosatte et al. 2009b). The ERA vaccine-laden baits were effective at vaccinating red foxes, the primary

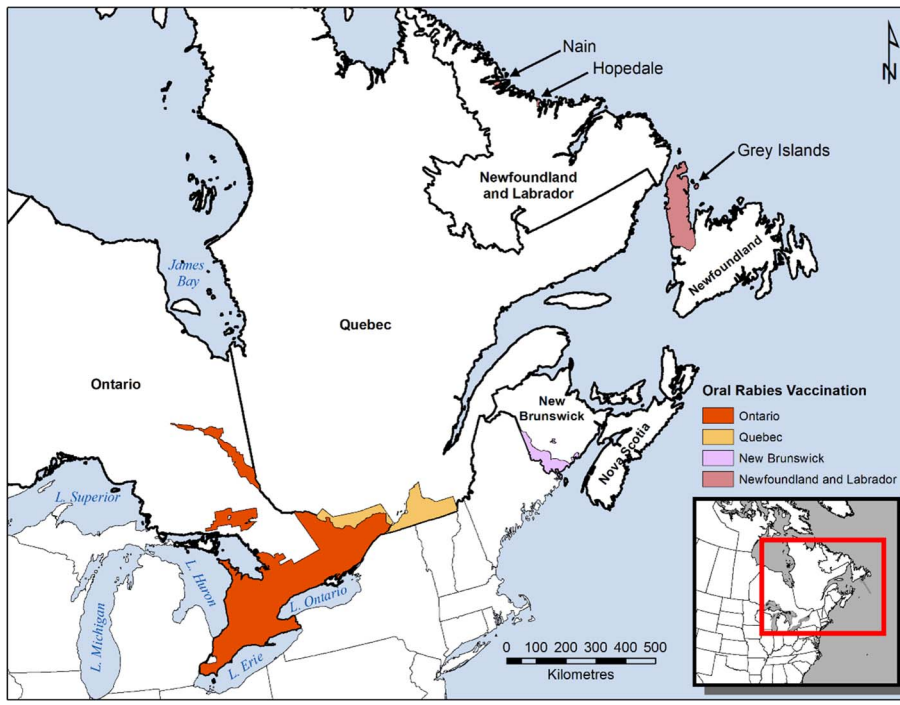


FIGURE 4. Extent of wildlife oral wildlife vaccination (ORV) programs in Canada by province between 1985 and 2022 (colored areas depict locations of ORV; white coloration denotes no vaccination).

reservoir of the Arctic fox RABV variant in southern Ontario, but this was not adequate to eliminate this RABV variant from all areas of the province. The ERA vaccine inadequacies included ineffective vaccination of secondary reservoir or vector species (i.e., raccoons and skunks) as well as safety issues as a MLV RABV vaccine. At least nine instances of ERA-vaccine–associated rabies cases were detected in Ontario animals between 1989 and 2004, during the interval when most of this vaccine was used in Ontario (Fehlner-Gardiner et al. 2008). Thereafter, the ERA vaccine was phased out for consideration of newer biologics for ORV.

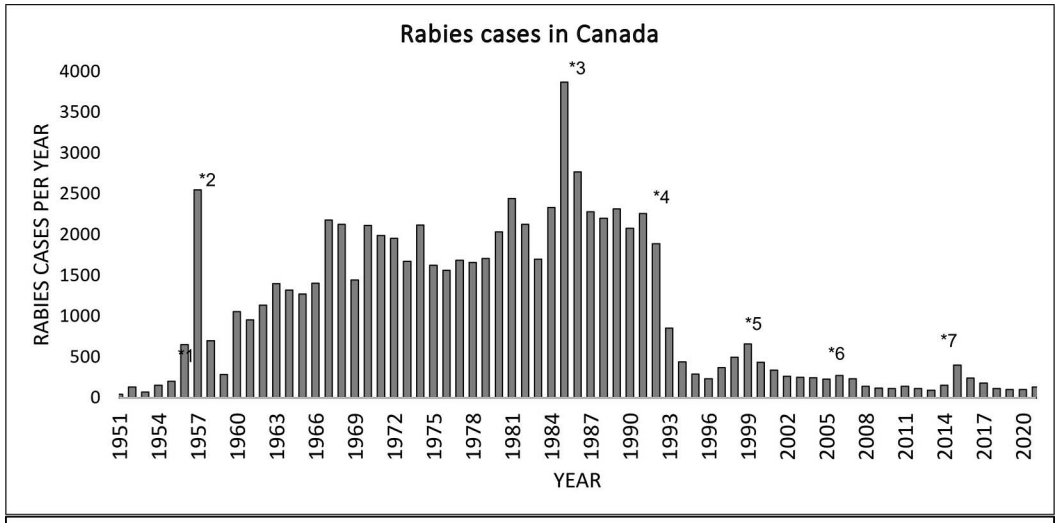
With the incursion of the raccoon RABV variant into eastern Canada from the USA in 1999, the V-RG vaccine, field tested in the USA during 1990, was used in Canada. A total of 4.8 million V-RG vaccine doses (embedded within either fishmeal polymer, coated sachet or Ontario slim baits) were distributed in Ontario (3.8 million between 1999 and 2005) and Quebec (0.98 million between 1999 and 2008), as a component of raccoon rabies elimination programs in those provinces (Figs. 3 and 4).

Safety concerns with the MLV ERA vaccine and its inadequacy in orally vaccinating striped skunks and raccoons led to development of a new oral vaccine in Ontario, known as ONRAB. This recombinant vaccine used the human adenovirus type 5 (AdRG1.3) virus to express the RABV glycoprotein (Yarosh et al. 1996). More than 25.1 million ONRAB baits have been distributed in Canada since the first field trial in 2006, including in Ontario (13.2 million between 2006 and 2022), Quebec (8.6 million between 2007 and 2020), and New Brunswick (3.2 million between 2015 and 2022), as components of dual Arctic fox and raccoon rabies elimination programs in those provinces (Figs. 3 and 4).

ORV program monitoring: The development of ORV programs in Canada relied heavily on both primary research and refinement of ORV techniques within the country. Moreover, the program incorporated experience and research development across the globe, especially from Europe and the USA. The different RABV variants, target species, habitat types, season, and oral vaccine type all caused variation in specific ORV program success. Evaluating the success of Canadian ORV programs has been measured through three principal methods: tetracycline biomarker evaluations of bait uptake by targeted wildlife; the measurement of rabies VNA in targeted species as indication of immunization; and through ERS to monitor for program impact on cases of rabies in wildlife populations. Often, all three methods have been used in concert.

In Canada, only the biomarker tetracycline hydrochloride was used to evaluate oral bait acceptance rates. Use of this biomarker helped develop and refine ORV program efficiencies. However, related to issues of tetracycline supply (Fry and Dunbar 2007), environmental concerns (Daghrir and Drogui 2013), and marking reliability (Johnston et al. 2005; Rosatte et al. 2008; Sobey et al. 2013), tetracycline-impregnated baits were last used broadly in Canada during 2012, and finally for smaller-scale research in 2019, both in Ontario. Developing biomarkers such as iophenoxic acid may hold promise for the future (Berentsen et al. 2019).

Assessments of vaccination effectiveness in wildlife have been estimated both through captive animal trials (Lawson et al. 1997; Brown et al. 2012, 2014a, 2014b) and in post-program field study of live-trapped targeted wildlife for serological analysis of RABV specific VNA (Rosatte et al. 2008, 2009b, 2011; Fehlner-Gardiner et al. 2012; Mainguy et al. 2013; Elmgren and Wandeler 1996). The success of rabies management actions, including ORV programs, has been monitored and evaluated through ERS programs designed specifically by wildlife rabies managers to target specific species, locations, and risk factors to directly and in near-real time provide measurable indications of ORV program effectiveness and early detection of new rabies cases (Kirby et al. 2017). In Canada, ERS programs were established in Ontario, Quebec, and New Brunswick for early detection of new RABV incursions and to measure elimination program effectiveness (Middel et al. 2017; Rees et al. 2011; Allan et al. 2021).



*1 Arctic fox RABV spreads from arctic Canada south into Manitoba (1951), Alberta and Saskatchewan (1952), British Columbia and Quebec (1953), and Ontario (1954).
*2 Arctic fox RABV spreads into southern Ontario in 1956 and establishes.
*3 Rabies cases peak in Canada in 1986 at 3,872 cases, 85% of cases are in Ontario.
*4 Oral rabies vaccination implemented in eastern Ontario in 1989 and expanded to most of southern Ontario in 1994.
*5 Raccoon RABV enters Ontario in 1999 and New Brunswick in 2000.
*6 Raccoon RABV enters Quebec in 2006
*7 Raccoon RAV re-enters Ontario late 2015

FIGURE 5. Graph showing how rabies cases in Canada have declined steadily with the use of wildlife rabies vaccination during the late 1980s.

As ORV programs matured in eastern Canada, many program budgets prioritized resources to applying rabies management techniques and ERS, versus the emphasis on research and development in the earlier years. European wildlife rabies researchers also emphasized ERS to define areas for ORV (Freuling et al. 2013b). The development of simple, sensitive, specific, and affordable RABV diagnostic screening tests, such as the DRIT, was implemented in Canada in 2010 and has been widely adopted in the Ontario, Quebec, and New Brunswick wildlife rabies control programs (Middel et al. 2017; Allan et al. 2021). Much emphasis has been placed on monitoring rabies cases and response to ORV programs in near-real time (Fig. 5).

ORV successes: The ORV programs initiated in Canada have been overwhelmingly successful at controlling or locally eliminating RABV variants. Often, ORV was used in conjunction with other control methods, such as trap–vaccinate–release (TVR), where targeted wildlife species are live-trapped and vaccinated parenterally, and historically with population reduction of targeted wildlife vector species. Most successful RABV variant outbreak eliminations from Canada have included ORV, except for the elimination of Arctic fox rabies from Alberta in the 1950s and skunk rabies from the 1970s (Ballantyne and O'Donoghue 1954; Rosatte et al. 1986), which apparently was achieved solely via local population reduction. Successful rabies outbreak eliminations from Canada, which were either primarily ORV-focused or at least incorporated ORV elements, included: Arctic fox RABV variant from eastern Ontario in 1996 (MacInnes et al. 2001); Arctic fox RABV variant from the city of Toronto in 1996 (Rosatte et al. 2007b); Arctic fox RABV variant from the island of Newfoundland in 2003 (Nadin-Davis et al. 2008); raccoon RABV variant from Wolfe Island, Ontario in 2000 (Rosatte et al. 2007a); raccoon RABV variant from New Brunswick in 2002 (Goltz et al.

2020); raccoon RABV variant from eastern Ontario in 2005 (Rosatte et al. 2009a); and raccoon RABV variant from Quebec in 2009 (Belanger et al. 2020). The ORV programs have also either greatly contained or eliminated recent raccoon RABV variant outbreaks in New Brunswick in 2020 (Government of New Brunswick 2022) and Arctic fox RABV variant from southwestern Ontario in 2018 (Ontario Government 2022). There are no examples of ORV programs in Canada failing to eliminate an outbreak of rabies.

When is ORV used?: The use of ORV in Canada has often been a matter of economics and political pressure. Delivery of the human universal health care system and management of wildlife populations are both provincial mandates within Canada. Therefore, control of rabies in wildlife populations has been the decisions of the provinces. Provinces have embarked on specific RABV variant elimination campaigns when deemed economically beneficial through offsetting the perpetual costs to the health care system and other losses to the economy. Pressure from the public (such as following the death of a young girl during 1967), has also prompted wildlife rabies control. Use of ORV in Canada to date has been either in areas with higher human densities, such as southern Ontario or southern Quebec for Arctic fox and raccoon RABV variants, or in areas where a new RABV variant incursion had recently been detected, such as southern New Brunswick for the raccoon RABV variant and the island of Newfoundland for Arctic fox RABV variant. In the western Canadian provinces of Manitoba and Saskatchewan, where skunk RABV variant is endemic, and in the Canadian Arctic, ORV has not been attempted, because of the vast areas and low offsetting economic incentives of eliminating those RABV variants.

Future challenges: Despite successes in Canada with the elimination of dog rabies and control of epizootic outbreaks of raccoon and Arctic fox RABV variants, several challenges remain for Canadian wildlife rabies managers. Maintaining public and political support for rabies management, and the ability for rabies control programs to deliver effective return on investment for the economy, will be crucial. For the foreseeable future, rabies epizootics remain an ongoing risk to more populated areas of southern Canada. Such risks include spread or translocation of raccoon RABV endemic in the eastern USA; Arctic fox RABV endemic in northern Canada; and skunk RABV endemic in the central and western USA and central Canada. Another future scenario that could warrant wildlife rabies management with ORV could be the intensification of skunk RABV in larger urban metropolitan areas in western Canada. Localized wildlife rabies management may also be feasible in predominately indigenous settlements within the endemic Arctic fox area of northern Canada. This area of the endemic Artic fox RABV in Canada (and Alaska) is vast, but the number and area of the communities are relatively small and conducive to scaled ORV to reduce rabies risk within the areas surrounding those communities.

United States

History: Although the concept of ORV originated with investigators in the USA during the 1960s, implementation of this idea followed only after widespread use in Europe and Canada (Baer 1988). One of the major reasons for the delay was based on the primary rationale for application. The red fox was a major reservoir for focus in other field applications in Canada and Europe. However, by the latter 1970s, red foxes were no longer the major RABV reservoir in the USA, compared to skunks, and later raccoons (Held et al. 1967; Kappus et al. 1970; Carey 1982; Carey et al. 1978; Gremillion-Smith and Woolf 1988; Davidson et al. 1992). In addition, a laboratory-acquired RABV infection in a researcher halted further national work on first-generation MLV for ORV (Tillotson et al. 1977). Given these two facets (i.e., the lack of a market focused on red foxes and adverse events associated with the use of MLV), no serious commercial interests arose until an alternate technical evolution during the 1980s (Paoletti 1996).

TABLE 5. Examples of initial local pilot studies of a vaccinia rabies glycoprotein recombinant virus vaccine in the eastern USA during the 1990s for safety and efficacy assessments of wildlife vaccination.

Location and date	Purpose	Citation
Parramore Island, Virginia, 1990	Assessment of safety within an island animal community	Hanlon et al. (1989)
Pennsylvania, Sullivan County, State Gamelands 13, 1991	Assessment of safety within a northern temperate mainland animal community	USDA, APHIS (1991); Hanlon and Rupprecht (1998)
Cape May Peninsula, New Jersey, 1992–1994	Prevention of the local geographical spread of raccoon rabies virus into southern New Jersey	Roscoe et al. (1998)
New York, 1994 to date	Control of raccoon rabies virus spread	Hanlon and Rupprecht (1998)
Cape Cod, Massachusetts, 1994 to date	Prevention of the spread of raccoon rabies virus from the mainland to Cape Cod	Robbins et al. (1998); Algeo et al. (2008)
Pinellas County, Florida, 1995–1997	Local intervention for raccoon rabies control in a highly urbanized environment	Olson and Werner (1999); Olson et al. (2000)
Anne Arundel County, Maryland, 1998–2007	Animal rabies control in an enzootic area	Horman et al. (2012)

The translocation of raccoon rabies from the southeastern states to the mid-Atlantic states during the late 1970s provided a major impetus towards further applied research (Rupprecht and Smith 1994). The development of recombinant biotechnology allowed the construction of the V-RG vaccine as an alternative to the use of MLV for wildlife ORV (Wiktor et al. 1984, 1985; Rupprecht et al. 1986, 1988, 1992a, b, 1993), with obvious benefits: the V-RG vaccine was effective orally in all mesocarnivores tested in the laboratory, and it would not cause rabies. After proof of concept from captive studies in target and nontarget species during the 1980s, the primary focus on the experimental use of the V-RG vaccine from 1990 to 1995 was a demonstration of its safety and efficacy under field conditions (Table 5).

These initial small-scale field trials with fishmeal polymer cylinders or cubes (later focused on coated polyurethane sachets) demonstrated the safety and efficacy of the V-RG vaccine for raccoon rabies prevention and control, and the stability of the vaccine under environmental conditions, which provided a pathway towards a licensed vaccine (conditionally licensed for raccoons in 1994), and paved the way for larger geographical operations for additional species throughout the country (Maki et al. 2017).

Broad-scale operations: After initial proof of concept with the V-RG vaccine in the laboratory and field, more widespread coordinated ORV applications began in Texas and in the eastern USA, in response to separate foci of rabies among different mesocarnivores in 1995 (Slate et al. 2005). This targeted progress on ORV was timely, because by the mid-1990s, raccoon rabies stretched from New England at the Canadian border to Florida, east of the Appalachian Mountains. With the accumulated encouraging data on safety and efficacy from laboratory and field studies, the V-RG vaccine was approved for use in raccoons during 1997 as a USDA licensed veterinary biologic (Maki et al. 2017). In 1998, the USDA Wildlife Services received federal appropriations for ORV and began coordinated expansion of programs into Ohio, Vermont, and other eastern states, with the goal of preventing the westward expansion of the raccoon RABV variant and its eventual elimination within the ensuing decades (Slate et al. 2005; Elmore et al. 2017). In 1999, this concept was formalized as part of the US National Rabies Management Program (Slate et al. 2009). From less than 4,000 baits

placed only by hand on a barrier island in 1990, by 2006, more than 12 million baits were being distributed annually over 18 states, primarily by aerial distribution in the eastern region (USDA 2006). As in the Canadian and European ORV programs, bait distributions occurred in line with target species biology and relative abundance in rural and urban environments, utilizing geographical features such as topography (e.g., the Appalachian Mountains), bodies of water (e.g., the Great Lakes), and so on, as potential barriers to the expansion of wildlife rabies (Arjo et al. 2008). Such features and the detection of rabies cases determined the geographic shapes and patterns of ORV programs by 2006 (Supplementary Material Fig. S8). In addition to the testing of animals from traditional public health laboratory reporting based upon exposures to humans to ensure appropriate prophylaxis, ERS from clinically suspect and road-killed animals by wildlife biologists allowed additional case detection to meet ORV programmatic goals of containment at the source (Blanton et al. 2006; Slate et al. 2009, 2017; Algeo et al. 2017; Kirby et al. 2017).

Typically, ORV for raccoons occurred during the autumn, with densities of approximately 75–150 baits/km^2, and aerial flight lines about 0–50 km wide (Slate et al. 2008, 2009). As an index to herd immunity via ORV using the V-RG vaccine, mean raccoon seroprevalence against RABV was around 33% from 1997 to 2007 (Slate et al. 2009). In general, raccoon seroprevalence after ORV tended to increase as bait density increased (Sattler et al. 2009; Pedersen et al. 2018; Johnson et al. 2021). Contingency actions occurred ad hoc, such as during 2004–2007 in Ohio, and elsewhere based upon the detection of new cases, such as the serendipitous detection of the raccoon RABV variant in a feral kitten within Omaha, Nebraska during the autumn of 2023 (Slate et al. 2008, 2009; Lederhouse 2024). Such emergency responses were expensive, involving ERS activities, additional bait drops (e.g., twice a year), or higher bait densities (e.g., 150–300 baits/km^2), augmented with additional methods (e.g., TVR). To maximize raccoon vaccination and to help minimize bait contact by nontarget species such as humans, domestic cats, or opossums (*Didelphis virginiana*), bait stations were employed, particularly in suburban and urban environments (Boulanger et al. 2006; Bjorklund et al. 2017; Haley et al. 2017; Bastille-Rousseau et al. 2024).

Besides the licensed V-RG vaccine for raccoon ORV in the eastern USA, experimental use of the Canadian AdRG1.3 recombinant virus vaccine began in 2011 in West Virginia (Slate et al. 2014). In 2012, use of this adenovirus recombinant vaccine expanded into other states, including New York, Vermont, and New Hampshire, with a mean associated RABV seroprevalence in raccoons of 68.5% over a 3-yr period of ORV (Gilbert et al. 2018b). In a related study, VNA seroprevalence of 58% was found after 3 yr of baiting during 2013–2015 in St. Lawrence County, New York, with a lower level detected in juveniles compared to adults (Pedersen et al. 2019). These findings were supportive, notwithstanding that "Although serology results are an important component to the evaluation of ORV success, the ultimate factors are the absence of raccoon rabies cases in the currently treated zone, and those areas from where ORV has been shifted away..." (Bjorklund et al. 2017).

Since its historical detection within the southeastern states and translocation to the mid-Atlantic region during the 1970s, raccoon rabies has not declined to extinction spontaneously from any state. In contrast to the situation in most of Europe for foxes, the disease has not yet been eliminated in the eastern states. Rather, to date the national ORV plan has focused on containment and gradual diminution of the raccoon RABV enzootic in the eastern states since institution of active management during the 1990s (Supplementary Material Fig. S9).

Based upon surveillance data and epidemiological modeling, ORV appears to have been effective in raccoon rabies control, particularly against the predicted threat of epizootic westward expansion (Russell et al. 2005; Ma et al. 2010, 2023; Recuenco et al. 2012; Plants et al. 2018; Davis et al. 2023; Anderson et al. 2014). The raccoon RABV variant has not spread and established itself westward, with this

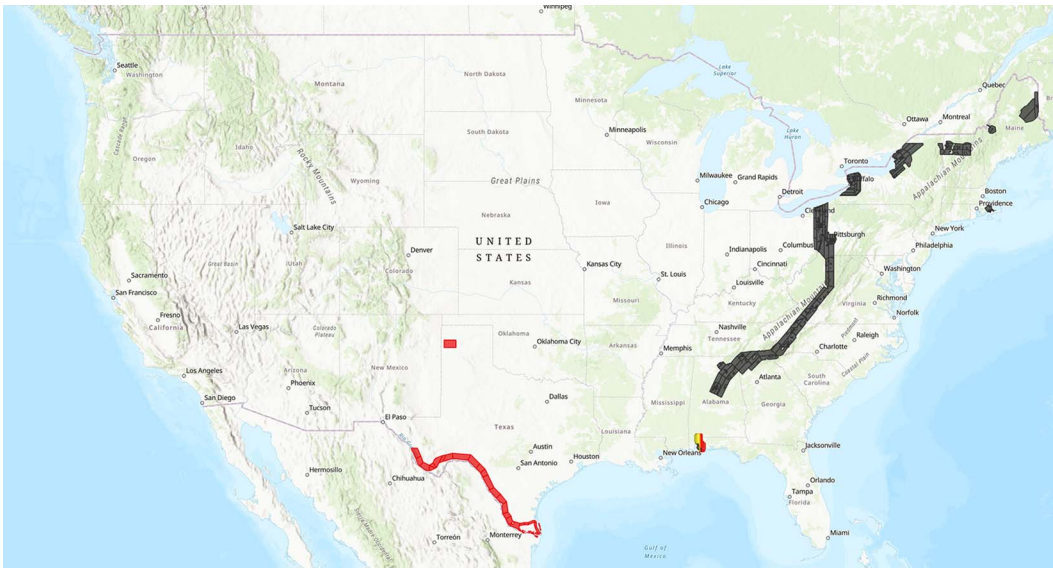


FIGURE 6. Map of the USA showing the coverage of wildlife ORV applications during 2023–2024 (courtesy of US Department of Agriculture, Animal and Plant Health Inspection Service, Wildlife Services).

apparent success of the national program being the result of the innovative flexibility of the program in response to enhanced surveillance, overall case distribution (as summarized annually in the CDC national reports), and apparent topographic barriers to disease expansion that assist in routine decision making for bait distribution (Fig. 6).

Texas ORV program: Texas is a large, southern US state with a diverse history of wildlife rabies reported in coyotes, gray foxes, skunks, bats, and many other individual mammalian species, due to CST from the major reservoirs (Sullivan et al. 1954; Eads et al. 1955; Clark et al. 1981; Pool and Hacker 1982; Texas Department of Health 2021). Before the 1980s, overall reports of rabies in coyotes were sporadic throughout the western US states, typically associated with canine RABV (Records 1932; Anonymous 1931). However, more than 160 cases in coyotes and 180 in dogs were reported between 1988 and 1993 in southern Texas (Clark et al. 1994). In addition, transient translocation of this coyote–dog RABV variant from Texas to Alabama and Florida dogs occurred during 1993 and 1994, respectively (CDC 1995; Krebs et al. 1995). Concomitant with the coyote epizootic, rabies in gray foxes emerged in west-central Texas as a new region, after gradual southwestern spread from a focus observed in the eastern portion of the state during the 1940s–1950s (Rohde et al. 1997). In context, considering the success towards the control of rabies in domestic dogs nationwide that began by the end of World War II, these expanding epizootics among highly mobile wild canids posed significant local, regional, and national risks to humans, domestic animals, and other wildlife during the mid-1990s (Supplementary Material Fig. S10).

Given the severity of these two outbreaks (including at least two associated human fatalities), during 1994, Texas Governor Ann Richards declared rabies a state health emergency and convened an expert group to consider possible solutions, including oral vaccination of wildlife (Texas Department of State Health Services 2004). In response, applied research on the use of placebo baits and distribution strategies by hand or at stations found between 83% and 87% of marked coyotes, at a density of 19–58 baits/km^2, and candidate bait and attractant investigations began for gray foxes (Farry et al. 1998a, b; Steelman et al. 1998, 2000; Meehan 1995). During 1995, the Texas Department of State Health Services began a cooperative

state–federal ORV initiative with the V-RG vaccine, as a multiyear program with a goal of creating zones of vaccinated coyotes, with the inclusion of gray foxes during 1996, by aerial distribution of V-RG vaccine-laden baits (Supplementary Material Fig. S11). In contrast to the ORV of raccoons at higher northern latitudes in the eastern USA (and the red fox programs in Canada and Europe), presumed bait availability for mesocarnivores in Texas was longer during the cooler winter than the hotter summer months, due in part to interference by fire ants (*Solenopsis invicta*).

Based on collective data analyzed via biomarker, serologic, and surveillance activities, significant rabies prevention, control, and eventual elimination occurred in both wild canids from these coordinated programs (Supplementary Material Fig. S12). Akin to these findings in the field, a licensure claim was added for V-RG use in coyotes during 2002 (Maki et al. 2017). As a gauge of herd immunity, seroprevalence against RABV after ORV was a mean of 56% for coyotes and 62% for gray foxes (Sidwa et al. 2005). No further cases appeared after 2005 associated with the coyote–dog RABV variant, and none related to the gray fox RABV variant after a rabid cow in 2013 (Fearneyhough et al. 1998; Sidwa et al. 2005; Ma et al. 2023). Since 1995, more than 53 million doses of vaccine have been distributed for wildlife ORV in Texas (Texas Department of State Health Services 2023). Estimated economic benefits ranged from $89 to $346 million, with total program costs of $26,358,221 from 1995 to 2006 (Shwiff et al. 2008). Today, more than a decade after coyote and gray fox rabies elimination, the southern and the west-central Texas ORV zones have been combined into a single barrier strategy for bait distribution, to prevent potential reintroduction of nonindigenous wildlife RABV along the southern border with Mexico (Fig. 7).

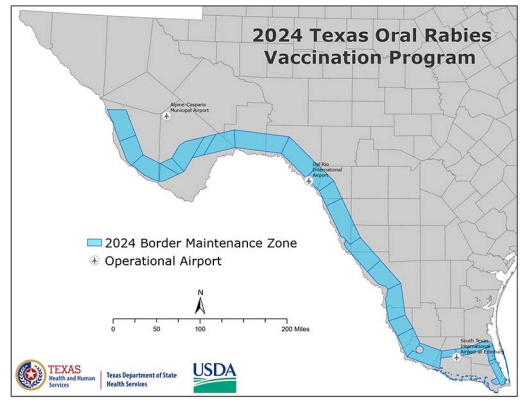


FIGURE 7. Map of Texas, USA, showing the area covered by the Texas Oral Rabies Vaccination Program (blue shaded area) during 2024 (courtesy of the Texas Department of State Health Services, https://www.dshs.texas.gov/sites/default/files/LIDS-Zoonosis/ORVP/OrvpBaitMap.pdf).

Current and future challenges in the region: Although coyote and gray fox rabies have been eliminated in Texas, and raccoon rabies is under operational control in the east, other challenges loom. For example, the current raccoon rabies control program will need to regroup towards an elimination of raccoon rabies (ERR) model for the continent, requiring major resources to accomplish such a task, and tactical alterations over the next several decades (Slate et al. 2009; Sterner et al. 2009; Acheson et al. 2023; Davis et al. 2023). Given the broad distribution, relative abundance, extreme adaptability, and high vagility of this mesocarnivore, the ERR program is feasible, but will not be simple, rapid, or inexpensive. Moreover, outside Texas, gray fox foci perpetuate in the southwestern region, together with other mesocarnivores, with no enhanced surveillance, ORV, or other interventions (Garcés-Ayala et al. 2022; Ortega-Sánchez et al. 2022). Quite curiously, the CST of bat RABV clusters among foxes and skunks in Arizona are unique globally and continue to reemerge, without adequate explanation (Leslie et al. 2006; Kuzmin et al. 2012; Ma et al. 2023). Whether this "Flagstaff phenomenon" will expand into a permanent regional focus among foxes, skunks, and other mesocarnivores requires additional ERS and applied research.

Throughout North America, skunk rabies control is difficult compared to ORV of raccoons and other reservoir species (Oertli et al. 2009; Gilbert et al. 2018; Wohlers et al. 2018; Te Kamp et al. 2020; Johnson et al. 2022). Similarly, rabies control in Alaska (and the

broader Arctic ecosystems) has not begun and is less well understood than wildlife rabies at more populated lower latitudes, but the need is likely to be exacerbated by climate change (Kuzmin et al. 2008; Kim et al. 2014; Baecklund et al. 2021; Elmore et al. 2022). Within insular environments, rabid mongoose throughout the Caribbean, such as on Puerto Rico, pose problematic issues of relative abundance and distribution, especially under both tropical and dry forest habitat conditions (Berentsen et al. 2015, 2020a,b; Sauvé et al. 2021; Browne et al. 2021). Hence, the region of the Americas provides ample opportunities for future ORV engagement among a diverse population of mesocarnivores and RABV variants.

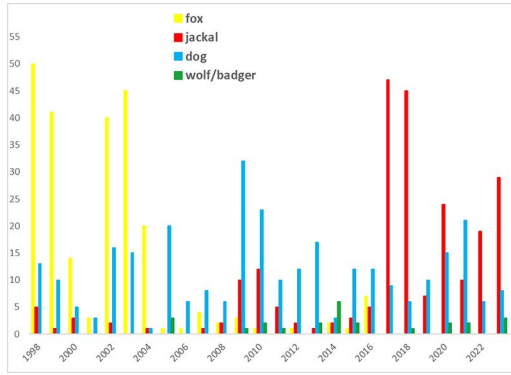


FIGURE 8. Graph showing the prevalence of rabies cases in Israel associated with wild and domestic carnivores during 1998–2022.

Middle East

Israel: Regionally, rabies has been described since antiquity throughout the Middle East, predominating among domestic and wild canids (Seimenis 2008; Horton et al. 2015). Despite this, the only country in the region to use ORV of wildlife is Israel. Throughout Israel, rabies has been monitored since 1948 (David et al. 2000; King et al. 2004). During the last 70 years, the disease has varied between urban and sylvatic cycles, with dogs, foxes, and jackals as reservoirs and vectors (Yakobson et al. 1998; King et al. 2004). Urbanization, agricultural development of rural areas, and relatively poor sanitation contributed to an uncontrolled increase in the population of wild canids and increased the contact rate of wildlife with humans and domestic animals.

Historically, rabies has occurred in most parts of Israel, compared to the current situation limited to the border areas (see Fig. 8). Before 1958, rabies was mainly urban, common in dog populations (Yakobson et al. 1998, 2006). From 1950 to 1970, the golden jackal (*Canis aureus*) was the major reservoir of wildlife rabies (Yakobson et al. 1998; Mähl et al. 2014; Maki et al. 2017; Linhart et al. 1997). Because of the implementation of massive poisoning (targeted at jackals), the initiation of compulsory annual dog vaccination, and the elimination of stray dogs, during the mid-1970s Israel experienced a major transition from urban dog rabies to sylvatic fox (*Vulpes* spp.) rabies, with a significant increase in cases. Foxes became the primary rabies reservoir in Israel from 1988 to 1997, accounting for 49% of all rabies cases during this period (Yakobson et al. 1998). Following three human rabies cases in 1996 and 1997, and an increase in animal rabies incidence, ORV of wildlife was considered (Yakobson et al. 2006, 2014; Maki et al. 2017). The project began with trials in captivity, to evaluate the safety of the SAG2 vaccine in local nontarget species and its efficacy in the target species (Mähl et al. 2014). Concurrent field tests were conducted to determine the ideal bait matrix, as there were no commercial products at that time for specific use in hot climates nor in jackals (Yakobson et al. 2006). Because commercial vaccines were not registered for jackals, in 1998 a comparative study was performed of the efficacy of two vaccines (V-RG and SAG2) given orally. Both vaccines were shown to be safe and efficient under captive conditions, but as their thermal and mechanical stability were tested under field conditions, the SAG-2 bait was excluded due to its incompatibility with the local high summer heat conditions, melting in direct sunlight (Mähl et al. 2014; Maki et al. 2017).

Acceptance rate of baits in the field by the target species was evaluated using tracking stations (70–120 baits per location) within vaccination zones. Analysis of over 2,500 bait-uptake events revealed an acceptance rate of

40%–90% during the first night (Maki et al. 2017). Starting in the autumn of 1998, ORV campaigns were conducted targeting jackals and foxes, with yearly increasing geographical extension to cover most of the country, extending since 2004, including the West Bank (in total approximately 21,000 km^2).

Following European recommendations, baits were distributed at a minimal density of about 15 baits/km^2 (World Health Organization 1989). The distribution was performed originally by helicopters, later by light aircraft, which flew in lines 300 m apart. Active monitoring of bait acceptance, demonstrated by using the biomarker tetracycline, showed variation from 35% to 55% during 1999–2021. Animal brain samples were examined using the DFAT, with each positive sample confirmed by virus isolation and PCR. The RABV variant was determined by viral sequencing and compared to data on viruses that were present in Israel before the start of ORV.

Before implementation of the ORV program, an extensive survey was conducted using molecular epidemiological methods, to characterize the RABV variants and map their distributions (David and Yakobson 2011). Six different variants were identified among foxes, jackals, and dogs. Five years after the beginning of ORV, sylvatic rabies had been eliminated: The variants that had been circulating prior to ORV had disappeared.

In 2005, a new variant (V7), which originated from Turkey, was involved in an outbreak among dogs that appeared in Israel from Syria (David et al. 2007). This RABV variant became dominant, circulating between dogs and jackals (David et al. 2009). The increase of rabies in dogs triggered a field study to determine bait acceptance and the feasibility of ORV in packs of livestock guardian dogs. Coated sachets and fishmeal polymer baits of V-RG (Merial, USA) were hand-fed to individual dogs. The estimated immunogenicity of ORV by the RFFIT was very low (i.e., a maximum of 28%). Observations of canine behavior demonstrated unequal consumption of the baits, as dominant animals took multiple baits, while subordinates were repressed. Also, the competitive situation led to gulping of the baits without chewing. Thus, ORV of pack dogs using the baits designed for wildlife did not appear to be effective (Yakobson et al. 2008).

The relative stability of local rabies epidemiology was upset in 2009 by an outbreak of rabies in a dense jackal population adjacent to the border with Jordan. The disease spread within a limited area, reaching not more than 15 km inward from the border. A targeted ORV campaign, doubling the density of baiting from 20/km^2 to 40/km^2, was quite effective, stopping the outbreak within 18 mo. In collaboration with the Jordanian veterinary services, the baiting area was extended across the border, adding a strip of about 5 km (in total, about 1,200 km^2 within Jordan). Since 2011, approximately 37,000 baits have been dispersed annually in the Kingdom of Jordan.

From 2012 to 2016, annual rabies cases numbered 30 or less, located near the borders and attributed to intrusion of infected animals from the neighboring countries of Lebanon, Syria, and Jordan (Maki et al. 2017). A second, more severe outbreak of rabies occurred in 2017–2018. The outbreak lasted for 6 mo (October 2017– March 2018) and 68 rabies cases in jackals were reported from an area of about 500 km^2 in and around the Bet Sha'an and Jezreel Valleys. Most jackals diagnosed as rabid were juveniles, born in the spring, and had not been exposed to the baits distributed in the spring of 2017. The disease became established and RABV circulated throughout the population. Intensive aerial and automobile-delivered ORV distribution (up to 150 baits/km^2) was implemented, beginning in October 2017. The area was rich with fishponds, so it was important to evaluate the removal (consumption) rate of the baits manufactured with fishmeal attractants. The bait uptake (percentage of baits taken in one night) was 97%. The ORV was combined with a focal population reduction strategy, as had been used in Texas for coyotes (Sidwa et al. 2005). More than 6,000 jackals were culled by shooting over an area of approximately 850 km^2, to reduce the number of incubating rabies and lower the potential of viral transmission. The outbreak ceased by March 2018 with the peak of positive cases occurring in

November 2017 to January 2018. In total, 41 jackals were found rabid, based on the passive surveillance data, as detailed (Supplementary Material Fig. S13).

Based on this experience, an additional bait distribution was performed in August 2019, targeting young jackals born in the spring, thus not exposed to the October–April ORV vaccination campaign. Because of the high temperatures at this time (the mean daily temperature in the area during August–October is 35 C in the shade) the baits were distributed towards sunset. Summer night baiting was repeated in 2020–2022.

The ORV program was continuously assessed by laboratory-based surveillance and monitoring of baiting efficacy. Bone samples of wild carnivores were examined for presence of tetracycline as a biomarker, with approximately 200–400 samples tested annually. The incidence of positive rabies cases in the previous 2 yr was used in deciding the number and density of the bait distribution, which varied from 19–45 baits/km^2 per distribution in different areas. Serology results were not taken into consideration, because of the limited number of samples examined.

From March 2018 until September 2022 there have been no rabies outbreaks, despite a dramatic increase (about threefold) in the estimated jackal population in the same area, as detected by line transects. Since 1998, more than 10 million vaccine-laden baits have been distributed in the country, about 400,000-700,000 annually, according to the Israeli Veterinary Services Annual report. Such an ORV strategy targeting young wild carnivores in high-risk areas during the summer, before they disperse, should significantly contribute to preventing future outbreaks. So-called "migratory waves" of rabies occurrence in dogs, jackals, and foxes crossing international frontiers remain the most serious threat. Until a comprehensive regional approach is adopted, Israel is obliged to continue annual ORV campaigns to maintain wildlife herd immunity, to restrict the disease to such intrusive foci and prevent extensive rabies outbreaks. Currently in 2022, rabies is limited to the border of Israel with Lebanon, Syria, and Jordan (see Fig. 9).

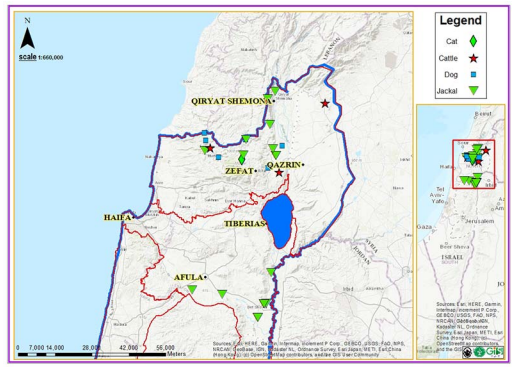


FIGURE 9. Map showing rabies cases in Israel in 2022.

Asia

Republic of Korea: Understandably, the surveillance of wildlife rabies is less than ideal in Asia, due to the greatest burden of any continent, perpetuated substantially by canine-mediated RABV (Hampson et al. 2015). Apparent CST of RABV infection from dogs to other canids includes foxes, jackals, and wolves (Reddy et al. 2019; Feng et al. 2022). Significant mesocarnivore reservoirs in Asia include Arctic foxes, ferret badgers (*Melogale* spp.), mongooses, and raccoon dogs, while others await documentation (Karunanayake et al. 2014; Shih et al. 2018; Shulpin et al. 2018). Several lyssavirus species have also been detected, but surveillance among bats is poor throughout the continent (Mani et al. 2017; Chen et al. 2018; Hsu et al. 2019; Seidlova et al. 2020). Despite the seemingly rather widespread occurrence of wildlife rabies, the only country in Asia to utilize ORV with V-RG vaccine-laden baits for control among mesocarnivores is South Korea, officially known as the Republic of Korea (ROK). Raccoon dogs are responsible for the transmission of animal rabies in South Korea (Supplementary Material Fig. S14).

History: As elsewhere in the region, canine rabies was enzootic throughout the Korean peninsula, with the first case diagnosed in 1907 (Kim et al. 2006). With implementation of control among domestic animals during the later 20th century following the Korean War, total cases declined steadily in the ROK from 1976 to 1984 (Fig. 10).

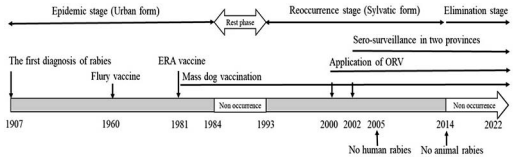


FIGURE 10. History of rabies prevention in the Republic of Korea, including parenteral vaccination of domestic animals and oral rabies vaccination (ORV) of wildlife.

After massive dog vaccination, no RABV cases were reported from 1985 to 1992. Rabies reemerged in the ROK during 1993–2013, indicating that dog-mediated rabies was controlled by 1984, but sylvatic rabies was reported in 1993. All cases occurred in only three parts of the ROK, Seoul, Gyeonggi, and Gangwon, with most counties bordering the demilitarized zone (DMZ) with the Democratic People's Republic of Korea (DPRK; see Fig. 11).

Based upon comparisons with samples from China and Russia, Korean RABV isolates had the closest phylogenetic relationship with Arctic-like viruses originating from rabid raccoon dogs in northeastern Asia (Hyun et al. 2005; Yang et al. 2011a,b).

Since 1907, 16,134 cases of animal rabies have been reported in the ROK (Fig. 10). Between 1962 and 2007, more than 750 cases of rabid dogs were reported, with 350 human cases during that same period (Joo et al. 2011). The majority occurred prior to 1980. Overall, poor laboratory-based surveillance in the mountainous areas of the DMZ limited case detection among wildlife, after the control of canine rabies by 1985. Recognizing these limitations, public health, wildlife health and veterinary programs were augmented in a One Health context (Yang et al. 2011b; Park et al. 2013; Oem et al. 2013; Cheong et al. 2014). Following dog rabies control, improved laboratory-based surveillance and viral characterization of cases showed raccoon dogs as important in RABV transmission (Oem et al. 2014). After the reemergence of wildlife rabies in the ROK, the prevalence of antibodies against RABV in raccoon dogs was investigated in Gyeonggi and Gangwon provinces.

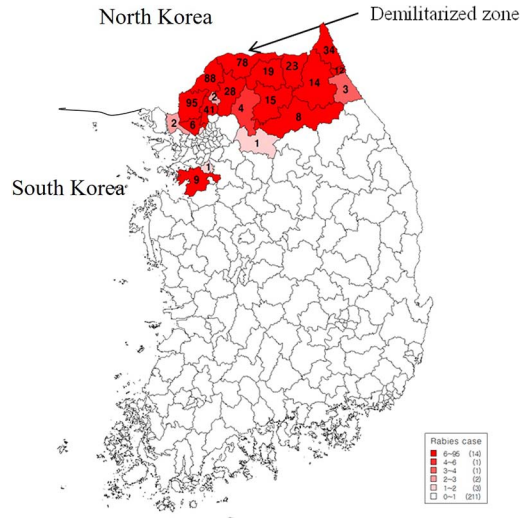


FIGURE 11. Map showing the distribution of animal rabies cases in the Republic of Korea since 1993. Numbers indicate animal rabies cases in the region. Regions where rabies has occurred (in red) have been designated as major risk areas. Oral rabies vaccination of raccoon dogs began during 2000.

The seropositivity of Korean raccoon dogs in enzootic areas ranged from 13.7% (20/146) to 40% (20/50) over time (Oh et al. 2012; Yang et al. 2017).

Regarding public health, from 2005 to 2009, approximately 2,500 animal bite cases were investigated (Han et al. 2012). Unvaccinated dogs were responsible for most of these human exposures. Given that no human rabies cases have been reported since 2005, while animal rabies was present, PEP and the National Animal Bite Patient Surveillance to monitor animal bite incidents played a significant role in the prevention of human rabies.

Raccoon dog ORV: Recognizing the threat from raccoon dogs, ORV was applied in the mountains in rabies risk regions (Supplementary Material Fig. S15). To date, millions of ORV doses have been distributed into rabies risk regions since 2000 and cases have declined (Fig. 12).

Such use of ORV has been effective in control of rabies among raccoon dogs and no further cases have occurred since 2014 (Yang et al. 2018a, b). Current studies have focused upon improvements to traditional RABV

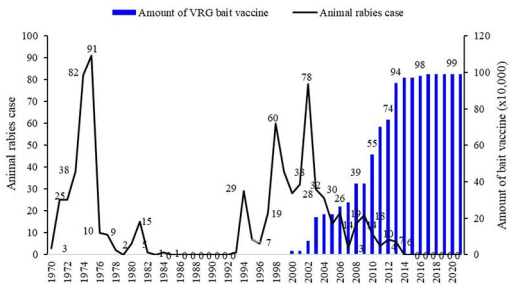


FIGURE 12. Comparison of animal rabies cases (1970–2020) and oral rabies vaccination (ORV) bait doses of vaccinia-rabies glycoprotein recombinant virus distributed in the Republic of Korea (ROK). After initiation of ORV during 2000, the ROK has reported no animal rabies cases since 2014.

serology, the use of camera traps, and improved surveillance among target and nontarget species (Yang et al. 2019; Cho et al. 2020; Kim et al. 2020; Yang et al. 2021). Enhanced laboratory-based surveillance and application of ORV into and north of the DMZ would provide greater reliability on the relative risk of disease reintroduction into the ROK.

Africa

Ecological conditions seem to only support wild carnivore–mediated rabies in the grasslands, savanna, semidesert, scrub, and woodlands (open canopy) of southern Africa. Here, several mesocarnivore reservoirs have been identified or are suspected to harbor distinct genetic lineages of RABV independently, such as black-backed (*Lupulella mesomelas*) and side-striped (*Lupulella adustus*) jackals (Bingham and Foggin 1993), the yellow mongoose, *Cynictis penicillata* (Everard and Everard 1988; King et al. 1993; van Zyl et al. 2010), bat-eared foxes, *Otocyon megalotis* (Swanepoel et al. 1993), and African civets, *Civettictis civetta* (Sabeta et al. 2008). Also, reports of thousands of rabies cases in the greater kudu (*Tragelaphus strepsiceros*) from Namibia (and a assumed novel mode of viral transmission) provided grounds for speculation whether this woodland antelope, distributed widely throughout eastern and southern Africa (IUCN Species Survival Commission 1999), could act as an herbivore RABV reservoir (Barnard et al. 1982; Scott et al. 2016). Alternatively, this phenomenon may form part of the same broad epidemiological jackal cycle of rabies in Namibian wildlife, via CST (Bellan et al. 2012; Hikufe et al. 2019; Müller et al. 2022).

Although mass vaccination of coyotes, foxes, raccoons, raccoon dogs, and so on is considered the primary approach to managing wildlife-mediated rabies in the Northern Hemisphere, in Africa ORV of wildlife has, unfortunately, never been used as an integrated control strategy, on a small or a large scale. This is partly because in lower- and middle-income countries (LMIC), wildlife rabies surveillance remains inadequate. The primary focus of management is the dog, which is the major reservoir and vector of RABV and thus poses the greatest threat to public health and agriculture throughout LMIC (Hampson et al. 2015). In addition, the prevention, control and eventual elimination of canine rabies in Africa is already a major challenge, especially in resource-poor areas (Haselbeck et al. 2021). Applying ORV techniques to control wildlife rabies, if it is a problem, could overwhelm most LMIC, as already-limited resources need to be targeted and used wisely, without distracting from the ambitious global goal of eliminating dog-mediated rabies in humans by 2030 (Abela-Ridder et al. 2018).

The success of ORV in Europe and North America sparked early scientific interest in exploring whether this approach could also apply to potential African mesocarnivore reservoirs or critically endangered canid species. As a result, a few experimental studies have been conducted in African species. These included black-backed and side-striped jackals (Bingham et al. 1995, 1999), African wild dogs, *Lycaon pictus* (Knobel et al. 2003), and the greater kudu (Müller et al. 2022; Hassel et al. 2018), showing that replication-competent viral vaccines, either attenuated MLV or recombinant vectors (Müller and Freuling 2020), are immunogenic after oral application, inducing VNA that are highly likely to be effective against challenge with a street RABV variant (Table 6).

TABLE 6. Experimental studies in African species of jackals, black-backed (*Lupulella mesomelas*) and side-striped (*Lupulella adusta*), wild dogs (*Lycaon pictus*), and greater kudu (*Tragelaphus strepsiceros*) using various rabies vaccines.

	Oral vaccination				Challenge		
Species	Vaccine strain	Dose[a]	Route	Immune response	Dose[a,c]	Survival	Reference
Jackal	SAD B19	7.3	doa[b]	13/13[d]			Schneider (1991)
Black-backed jackal	SAD Bern	6.3	doa	2/2[d]		2/2	Bingham et al. (1995)
		6.8		2/2[d]	3.3[c]	2/2	
		7.5		4/4[d]	3.3[c]	4/4	
		7.5	bait	2/2[d]	3.3[c]	2/2	
			controls	0/2[d]	3.3[c]	0/2	
Side-striped jackal	SAD Bern	6.3	doa	1/1[d]	3.3[c]	1/1	
		6.8		2/2[d]	3.3[c]	2/2	
		7.5		4/4[d]	3.3[c]	4/4	
			controls	0/1[d]	3.3[c]	0/1	
Black-backed jackal	SAG 2	6.5	doa	3/3[d]	3.3[c]	3/3	Bingham et al. (1999)
		7.5		3/3[d]	3.3[c]	3/3	
			controls		3.3[c]	0/2	
Side-striped jackal	SAG 2	6.5	doa	2/3[d]	3.3[c]	3/3	
		7.5		2/3[d]	3.3[c]	2/3	
			controls		3.3[c]	0/3	
	SAG2	8.0	bait	5/5[d]	3.3[c]	5/5	
		7.0		3/5[d]	3.3[c]	3/5	
			controls		3.3[c]	0/5	
Black-backed jackal	VRG	8.0	bait	8/8[e]			Koeppel et al. (2022a)
			doa	0/2[e]			
			controls				
African wild dogs	SAG2	8.3	bait	8/11[d]			Knobel et al. (2003)
			controls	0/3[d]			
Greater kudu	SPBN GASGAS	8.1	doa	5/3[d]	5.3[a]	3/10	Hassel et al. (2018)
			controls	0/4[d]	5.3[a]	0/4	
				0/4[d]	3.3[a]	1/4	
	SPBN	8.1	bait	5/11[d]			Müller et al. (2022)
	GASGAS	9.1	doa	4/5[d]			
		9.3		6/7[d]			

[a] log 10 tissue culture infectious dose 50% ($TCID_{50}$)/mL.
[b] Direct oral administration.
[c] log 10 mouse intracerebral lethal dose 50% ($MICLD_{50}$)/0.03 mL.
[d] Cut-off: 0.5 IU/mL.
[e] Cut-off: 0.2 IU/mL.

However, safety of oral rabies vaccines has been a major concern for their use under African settings, where many people have a weakened immune system, which may pose a substantive risk when encountering ORV baits. For example, in one study of the first MLV generation candidates (e.g. SAD Bern), the vaccine was pathogenic in 2/4 Chacma baboons (*Papio ursinus*) when administered orally with a dose of 2 mL of $10^{7.5}$ $TCID_{50}$/mL vaccine (Bingham et al. 1992). Second and third generation ORV, such as SAG2 and SPBN GASGAS, were shown to be safe in baboons, mongooses and several other non-target species (Bingham

et al. 1997; Ortmann et al. 2018a, 2018b; Vos et al. 2018). These findings underscore the longstanding recommendation that only biologics with a very high safety profile should be given priority (World Health Organization 2018; Yale et al. 2022).

Small-scale ORV field trials, using SAG2 ($10^{8.6}$ $TCID_{50}$/mL) and V-RG ($10^{8.0}$ $TCID_{50}$/mL) vaccine-laden baits in free-ranging Ethiopian wolves (*Canis simensis*) and black-backed jackals have not been as successful to date; seroconversion rates have been unsatisfactory depending on the serological tests and cut-offs used (Sillero-Zubiri et al. 2016; Koeppel et al. 2022a). Even though there are positive developments in this regard, no general conclusions can be drawn from the current findings of these trials. The methodological approaches used still leave many questions unanswered. Thus, further applications, including bait development, enhanced laboratory-based surveillance, and epidemiological parameters to measure program success, are needed to develop efficient ORV strategies suitable for African wildlife reservoirs. Moreover, application to other potential reservoirs (bat-eared foxes, yellow mongoose, etc.) should also be explored.

In addition to wildlife, the potential of ORV for the control and elimination of canine rabies was quickly recognized. Historically, the use of mass parenteral dog vaccination has led to major success in the regional program of control in the Americas, as well as more recent progress in smaller scale projects, such as in Goa, India (Freire de Carvalho et al. 2018; Gibson et al. 2022). The use of ORV in dogs makes particular sense in an African context, as there are large numbers of free-ranging dogs in almost every region of the continent, making parenteral mass vaccination campaigns difficult (Horton et al. 2015; Morters et al. 2014a, b; Wallace et al. 2020). Despite enormous efforts, prior approaches may fail to achieve sufficient herd immunity in free-ranging dogs parenterally, such that infectious cycles would be interrupted, and rabies would gradually disappear from these epidemiologically important susceptible subpopulations (Lembo et al. 2010; Wallace et al. 2020; Sambo et al. 2022). Initially, during the 1990s, the WHO played a major role in coordinating and promoting international research and cooperation in the field of ORV of dogs, as illustrated by numerous WHO working group reports. However, after successful experimental proof-of-principle ORV studies in dogs with various vaccine candidates (Vos 2019), very few baiting studies (Kharmachi et al. 1992; Matter et al. 1995, 1998; Aly et al. 2022), immunogenicity research (Haddad et al. 1994; Hammami et al. 1999; Cliquet et al. 2007; Molini et al. 2021), or field trials had been reported (Darkaoui et al. 2014; Freuling et al. 2022), mainly from Tunisia, Morocco, and Namibia.

Unfortunately, as in other countries where canine rabies is endemic, all such efforts have failed to lead to large-scale application of ORV as an integrated strategy for the control of dog-mediated rabies in Africa. Hence, ORV still remains an underutilized and undervalued tool for achieving canine rabies management (Cliquet et al. 2018; Wallace et al. 2020). Hopefully, this could change radically with the implementation of the Global Strategic Plan calling for the global elimination of dog-mediated human rabies by 2030 (Abela-Ridder et al. 2018). Meanwhile, there are high expectations placed upon the concept by WHO, WOAH, Food and Agriculture Organization and other international stakeholders, that as a complementary tool to mass parenteral vaccination, ORV may become a game changer in the prevention, control, and eventual elimination of rabies in difficult-to-reach dogs (Wallace et al. 2020). Considering CST between dogs and wildlife, this would augment existing programs. Clearly, whether focused upon wildlife reservoirs or free-ranging dogs, applied research must be accelerated if ORV is to ever develop its full potential throughout Africa.

ADDITIONAL CHALLENGES

Inarguably, over the past 50 yr, major progress has occurred in the field of wildlife ORV, leading to disease prevention, control, and even

elimination in several free-ranging species at a landscape scale, based upon ERS. Nevertheless, ORV is not a panacea (Slate and Decker 2003). Most concentration has been focused upon only a few key mesocarnivores, such as coyotes, foxes, jackals, raccoons, and raccoon dogs, whereas other taxa await similar application. For example, ferret badgers are important reservoirs in Asia (Shih et al. 2018; Miao et al. 2023). Several other species may maintain rabies in Africa, including the yellow mongoose (*C. penicillata*), slender mongoose (*Galerella sanguinea*), African civet (*Civettictis civetta*), bat-eared fox, meerkat (*Suricata suricatta*), aardwolf (*Proteles cristatus*), spotted hyena (*Crocuta crocuta*), and others (Sabeta et al. 2020; Binkley et al. 2022; Koeppel et al. 2022b). Outside of Canada and the USA, elsewhere in the Americas, the crab-eating fox (*Cerdocyon thous*), hoary fox (*Lycalopex vetulus*), coatí (*Nasua nasua*), and common marmoset (*Callithrix jacchus*) have been implicated in RABV transmission, among others (Caraballo et al. 2021; Aréchiga Ceballos et al. 2022; Benavides et al. 2022). Moreover, the observation that "… notably, no single vaccine has proven efficacious under field conditions for all relevant species …" remains a valid concern since the advent of the technology (Slate et al. 2009). A thorough understanding of the basic mechanisms involved in ORV of different taxa will be a major improvement in additional biologics (Te Kamp et al. 2020).

Besides mesocarnivores, bats are major lyssavirus reservoirs on a global basis (Coertse et al. 2021; Leopardi et al. 2021; Poleshchuk et al. 2023). Preliminary attempts to vaccinate bats under captive conditions have produced variable, yet somewhat promising results, exploiting social grooming to assist in vaccine spread to conspecifics (Setien et al. 1998; Almeida et al. 2005; Stading et al. 2017). However, given their global distribution and more than 1,400 species, extreme abundance, unique biology, and diversity of lifestyles, the concept of realistic application of ORV to the Chiroptera in the same capacity as in mesocarnivores seems remote in the near term (Rupprecht et al. 2004). Moreover, notwithstanding their association with more than 17 lyssavirus species globally (beyond multiple variants of RABV), upon which all human and veterinary vaccines are based, no current vaccines provide adequate cross reactivity against the most genetically divergent members of the genus (Fooks et al. 2021). The somewhat imaginative concept of a transmissible vaccine, using an infectious recombinant virus that could spread spontaneously throughout a population to overcome potential limiting barriers, remains controversial, with overt ecological, epidemiological, pathobiological, regulatory, and ethical concerns, even if only at a modeling stage (Griffiths et al. 2023; Rupprecht et al. 2023). In retrospect, regardless of faunal focus, an extension of the WEIRD (i.e., western, educated, industrial, rich, and democratic) concept from the behavioral sciences is also apt for other disciplines, including immunization (Henrich et al. 2010). In this context, no comparable wildlife ORV program exists in a LMIC. Today, perhaps the greatest benefit that wildlife ORV may play globally, using safe and effective biologics that have already been field tested using an evidence based-approach, is as a pragmatic real-world example for the oral vaccination of free-ranging dogs (Yale et al. 2022; Freuling et al. 2023; Megawati Saputra et al. 2023; WHO Expert Consultation on Rabies 3rd consultation). Until the time that canine rabies is eliminated finally, wildlife ORV may be deemed a luxury only for the WEIRD among us (Acharya et al. 2022).

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SUPPLEMENTARY MATERIAL

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