

Oral vaccination of dogs against rabies

Recommendations for field application and integration into dog rabies control programmes



Food and Agriculture
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Organization



World Organisation
for Animal Health
Founded as OIE

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Working group members:

- Thomas Müller, World Health Organization Collaborating Centre for Rabies Surveillance and Research/World Organisation for Animal Health Reference Laboratory for Rabies, Institute of Molecular Virology and Cell Biology, Friedrich-Loeffler-Institut, Greifswald-Insel Riems, Germany;
- Conrad M. Freuling, World Health Organization Collaborating Centre for Rabies Surveillance and Research/World Organisation for Animal Health Reference Laboratory for Rabies, Institute of Molecular Virology and Cell Biology, Friedrich-Loeffler-Institut, Greifswald-Insel Riems, Germany;
- Ad Vos, Veterinary Public Health, Ceva Innovation Center GmbH, Dessau-Rosslau, Germany;
- Richard Chipman, United States Department of Agriculture, Animal and Plant Health Inspection Service, Wildlife Services National Rabies Management Program, Concord, New Hampshire, United States of America;
- Ryan M. Wallace, Poxvirus and Rabies Branch, Division of High-Consequence Pathogens and Pathology National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia, United States of America.

Declarations of interest

All members of the working group declared their interest according to WOH standard procedures. None of the interests declared were found to be significant.

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Preamble

This technical report replaces or supersedes issue-related contents in previous World Health Organization (WHO) foundational documents on oral rabies vaccination of dogs:

- Report of WHO Consultation on Oral Immunisation of Dogs against Rabies, Geneva, 26–27 February 1988; World Health Organization. Veterinary Public Health Unit (WHO/Rab. Res./88.26. Unpublished, 1988);
- Consultation on Requirements and Criteria for Field Trials on Oral Rabies Vaccination of Dogs and Wild Carnivores, Geneva, 1–2 March 1989; World Health Organization. Veterinary Public Health Unit (WHO/Rab.Res./89.32. Unpublished, 1989);
- Report of the Second WHO Consultation on Oral Immunisation of Dogs against Rabies, Geneva, 6 July 1990; World Health Organization. Veterinary Public Health Unit (WHO/Rab. Res./91.37, 1991);
- Report of the Third WHO Consultation on Oral Immunisation of Dogs against Rabies, Geneva, 21–22 July 1992, World Health Organization. Veterinary Public Health Unit; Office International des Epizooties (WHO/Rab.Res./92.38. Unpublished, 1992);
- Suggestions for the Development of a Research Project for the Field Evaluation of Several Vaccine-Bait Delivery Techniques to Vaccinate Dogs Orally against Rabies Matter, Hans C.; World Health Organization. Veterinary Public Health Unit (WHO/Rab.Res./93.40, Corr.1. Unpublished, 1993);
- Report of the Fourth WHO Consultation on Oral Immunisation of Dogs against Rabies, Geneva, 14–15 June 1993; World Health Organization. Veterinary Public Health Unit (WHO/Rab. Res./93.42. Unpublished, 1993);
- Report of the Fifth Consultation on Oral Immunisation of Dogs against Rabies, Geneva, 20–22 June 1994; World Health Organization. Veterinary Public Health Unit (WHO/Rab.Res./94.45. Unpublished, 1994);
- Report of the Sixth WHO Consultation on Oral Immunisation of Dogs against Rabies, Geneva, 24–25 July 1995; World Health Organization. Division of Emerging and Other Communicable Diseases Surveillance and Control; World Organisation for Animal Health (WHO/EMC/ZDI/98.13, 1998);
- Field Application of Oral Rabies Vaccine for Dogs: Report of a WHO Consultation – WHO Consultation on Field Application of Oral Rabies Vaccine for Dogs (1998: Geneva, Switzerland); World Health Organization. Division of Emerging and Other Communicable Diseases Surveillance and Control; World Organisation for Animal Health (WHO/EMC/ZDI/98.15, 1998);
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- WHO Expert Consultation on Rabies: Second Report; World Health Organization. <https://apps.who.int/iris/handle/10665/85346> (WHO/TRS 982, 2013);
- WHO Expert Consultation on Rabies: Third Report; World Health Organization. <https://apps.who.int/iris/handle/10665/272364> (WHO/TRS 1012, 2018).

Acronyms

BDV	biotechnology-derived vaccines (genetically modified organisms)
CDC	Centers for Disease Control and Prevention, Atlanta, USA
EMA	European Medicines Agency
EP	European Pharmacopoeia
FAO	Food and Agriculture Organization of the United Nations
MLV	modified live vaccines
ORV¹	oral rabies vaccination
PEP	post-exposure prophylaxis
SCID	severe combined immunodeficiency disease
USA	United States of America
USDA/APHIS/CVB	United States Department of Agriculture, Animal and Plant Health Inspection Service, Center for Veterinary Biologics
VICH	International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products
WHO	World Health Organization
WOAH	World Organisation for Animal Health (founded as OIE)
WVS	Worldwide Veterinary Service

¹ In rabies science throughout the Americas and Europe, the abbreviation ORV stands for 'oral rabies vaccination'. It is not used as an acronym for oral rabies vaccines.

About this document

This technical report replaces or supersedes issue-related contents in previous WHO foundational documents on oral rabies vaccination (ORV) of dogs (see the [Preamble](#)). In contrast to the 2007 WHO recommendations [1], this report will shift focus from the development of suitable vaccines and baits for dogs towards providing guidance for practical implementation of ORV as a tool integrated into national strategies to control rabies in dog populations. This report therefore mainly addresses basic regulatory considerations for licensing and selection of appropriate oral vaccine candidates, logistics, distribution strategies in the field, communication, activities to be implemented in relation to ORV campaigns, and monitoring of campaigns.

It should be emphasised that it is impossible to establish a universally valid and applicable blueprint for the integration of ORV into national strategies for the control of canine rabies. This is not least due to country-specific circumstances, including sociocultural aspects, epidemiological situation, local dog population structures, funding and available resources. Therefore, countries should use this guiding document to find their own strategic and practical approach.

Disclaimer

This document was developed under the United Against Rabies Forum Working Group 2, Workstream 4 on oral vaccination of dogs and is supported by the World Health Organization, the World Organisation for Animal Health and the Food and Agriculture Organization of the United Nations. The views expressed in this document are those of the contributors (see [Acknowledgements](#)) and may not necessarily comply with the official policy of their institutions.

Methodology

To develop this document, the United Against Rabies (UAR) Forum, on request of, in collaboration with and under leadership of the UAR Forum Steering Group (consisting of representatives of FAO, WOAHA and WHO), engaged a group of rabies experts and stakeholders. A UAR Forum group was established in January 2022 to develop this operational document outlining considerations for recommendations for field application and integration of oral rabies vaccination (ORV) of free-roaming dogs into dog rabies control programmes, in response to needs expressed by countries.

The steps included in the development of the document were as follows:

1. A UAR Forum group was established, including leadership and technical staff from WOAHA reference laboratories, WHO Collaborating Centres for rabies, and USDA, APHIS, Wildlife Services. The team also included rabies experts with a background on and/or specialisation in vaccine production and ORV of rabies reservoir species, in particular dogs. DOIs were requested from all group members and reviewed by the Tripartite for possible conflicts of interest.
2. The group searched and reviewed a range of resources, including existing guidance documents, WHO/WOAHA meeting reports and literature relevant to ORV of dogs. Additionally, the team examined the WOAHA Manual of Diagnostic Tests and Vaccines for Terrestrial Animals, European Pharmacopoeia and USDA/APHIS/CVB standards regarding safety and efficacy requirements of oral rabies vaccines. The team also executed an intensive search on characteristics of commercial oral rabies vaccines for potential use in dogs, including availability, licensure, information on safety and efficacy studies, promotional events, and whether the vaccines meet WOAHA standards.
3. The searches were carried out between 2022/02/01 and 2022/09/01, in various online databases including the WHO Institutional Repository for Information Sharing (IRIS), PubMed, Web of Science, Google and company websites, in English and partly Russian language.
4. Following the literature review and analysis, the group solicited feedback on the document production through a broad consultative and iterative review process.
5. The document was peer-reviewed by FAO, WHO, WOAHA and independent experts from various global, regional, and national levels (see Acknowledgments section). Reviewers' comments and suggestions for changes were subject to a consensus decision by the group, with subsequent integration of appropriate revisions into the document.
6. In addition, the draft document and key recommendations were presented at the UAR Forum webinar in May 2023, reaching a diverse audience. Attendees were from dog rabies-endemic countries, where the recommendations will be increasingly considered in the future. These attendees offered valuable insights, providing feedback on document clarity and offering suggestions for further improvement.

The group met monthly to oversee and steer the project's progress and reported to the UAR Steering Group every two months.

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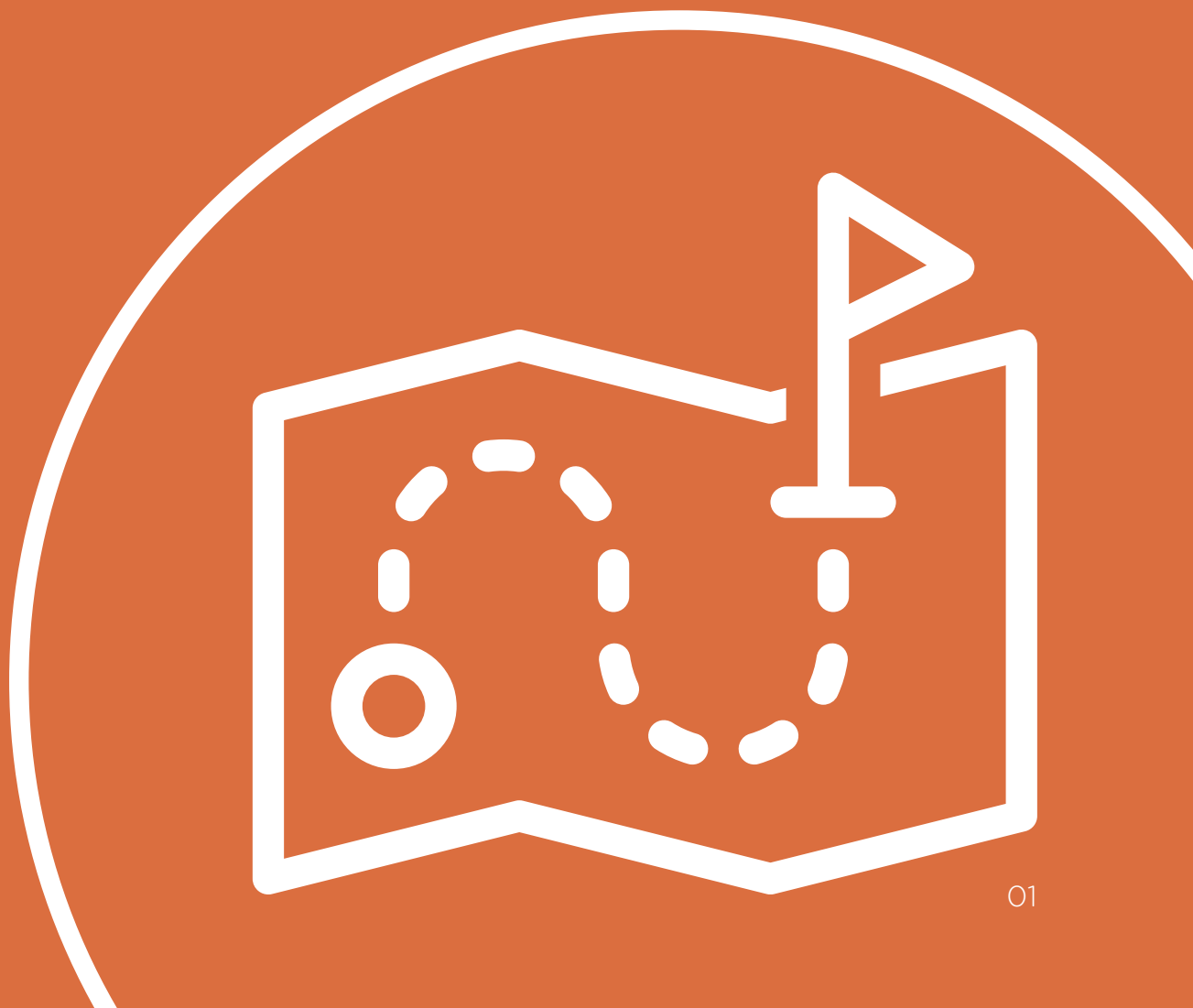
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The oral vaccination of dogs against rabies



Currently, mass vaccination of dogs with parenteral (injectable) vaccines is the principle approach to large-scale control of dog-mediated rabies, but implementation can be challenging, especially in resource-poor settings. There are increasing reports of the inadequacies of this approach in key subpopulations of susceptible dogs [2]. Maintaining adequate herd immunity in dog populations remains a significant challenge; vaccinating free-roaming dogs can be especially difficult [3].² Among other factors, perceived barriers to effective vaccination of these high-risk free-roaming dog populations have led to stagnation of vaccination efforts in many middle- and low-income countries in Africa and Asia. This dilemma urgently calls for alternative, viable and cost-effective vaccination approaches if the goal of zero dog-mediated human rabies deaths by 2030 is to be achieved.

A promising alternative for hard-to-reach dog populations is oral rabies vaccination (ORV) (Figure 1). While this method has been crucial in the targeted elimination of rabies virus variants in regional wildlife populations, ORV still has only theoretical value in the control of dog-mediated rabies. The targeted use of ORV for rabies control in dog populations was recognised as early as the late 1980s as a novel strategy that had the potential to significantly increase vaccination coverage in dogs (especially of free-roaming and poorly supervised dogs) when applied exclusively or in combination with parenteral vaccination [4]. From the beginning, the WHO in collaboration with WOAHA played an important role in promoting international collaboration and coordinating research through informal groups of subject matter experts and international stakeholders as documented by numerous international meetings (see the Preamble). Unfortunately, these efforts have not led to large-scale application of ORV as an integrated strategy for the control of dog-mediated rabies primarily because of (i) safety, (ii) immunogenicity and efficacy in dogs, (iii) licensure and production capacity for oral rabies vaccines, (iv) their role of within a vaccination programme and (v) benefit-cost of including ORV into national programs [2].

Considerable laboratory- and field-based research has been conducted, including the evaluation of several oral rabies vaccine strains in dogs [5–10], determination of dog-specific bait preferences [11–23], immunogenicity studies conducted in native dogs [24–28], efficacy studies [29–30], field applications [31–36], and benefit-cost analysis [37–38]. However, ORV has not yet been firmly integrated into practical control strategies at the national level in any country. It remains an underused and undervalued tool for eliminating dog rabies [2–39].

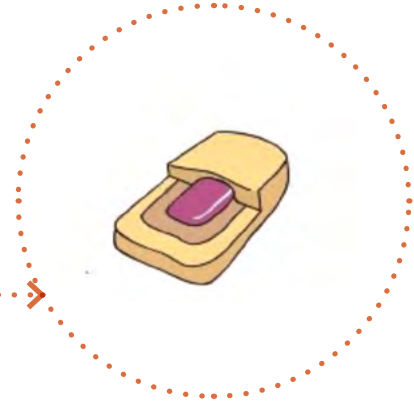
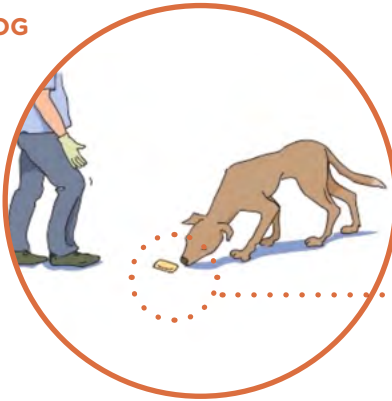
With the proclamation of the Global Strategic Plan for the Global Elimination of Dog-Mediated Human Rabies by 2030 [40], ORV for dogs has gained renewed momentum. This strategy is being promoted by WHO, WOAHA and FAO, as it is a promising complementary tool to mass parenteral vaccination of dogs and provides a management strategy that can better target free-roaming dogs [2]. There is an urgent and critical need to generate field data to optimise ORV application directed at a diversity of dog populations in a variety of habitats and under a range of socioeconomic conditions. Only through practical field application and experience can the full potential of this method be realised.

² According to the WOAHA *Terrestrial Code*, a free-roaming dog is any owned or unowned dog that is without direct human supervision or control, including feral dogs [2].

Figure 1: Oral vaccination of free-roaming dogs

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1. BAIT IS OFFERED TO THE DOG



Baits contains liquid vaccine

2. DOG CHEWS BAIT



3. VACCINE IS RELEASED INTO THE MOUTH



4. VACCINE IS ABSORBED VIA THE TONSILS AND MUCOUS MEMBRANE



Vaccine uptake

Vaccines



Vaccines form one of the three main pillars of the oral vaccination concept for dogs (Figure 2). Oral rabies vaccines, both modified live vaccines (MLVs) and biotechnology derived vaccines (BDVs), are based on replication-competent live viruses (either attenuated or recombinant). Modified live vaccines can be categorised into first, second and third generation oral rabies vaccines period. First generation vaccines include progeny produced by continued passage and adaptation to cell culture. Second generation vaccines represent selection variants as a result of targeted anti-G monoclonal antibody application. Third generation vaccines consist of virus constructs generated through reverse genetics. With each generation, the safety profile of MLVs has also been significantly improved. Recombinant oral rabies vaccines can use different vector viruses expressing the rabies virus glycoprotein. The latter, as well as third generation MLVs, are BDVs [41]. All are designed to replicate within the host, thereby invoking an immune response in the oral-pharyngeal lymphoid tissue. Oral replication-competent vaccines differ from most parenteral vaccines, which are killed viruses and cannot replicate. Review articles on oral rabies vaccines for potential use in dogs are available [2,41,42].

Figure 2: Main pillars of the oral vaccination concept for dogs

© First and third: Friedrich-Loeffler- Institut, Federal Research Institute for Animal Health, Germany;
Second: ORV project team Thailand

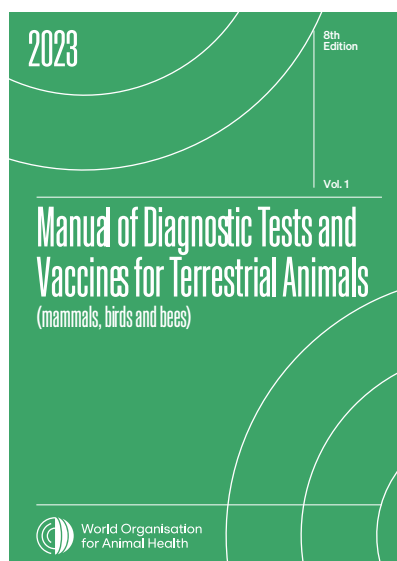


Safety and efficacy are of utmost importance and crucial for licensure of these vaccines. General scientific guidelines (from the European Medicines Agency [EMA], the United States Department of Agriculture, Animal and Plant Health Inspection Service, Center for Veterinary Biologics [USDA/APHIS/CVB], and WOAAH) have established requirements for the production and control of immunological veterinary medicinal products, including vaccines [43-45].

This section highlights best practices and basic requirements for oral rabies vaccines in terms of efficacy and safety as should be considered when integrating ORV into dog vaccination campaigns. Because rabies is a fatal disease, WOAAH (Figure 3) and WHO have set international standards that require the highest level of safety and efficacy for both parenteral (injectable) and oral rabies vaccines [44,46]. Because rabies is a fatal disease, WOAAH (Figure 3) and WHO, building on EMA requirements [45], have set international standards requiring the highest level of safety and efficacy for both parenteral (injectable) and oral rabies vaccines [44,46]. These standards have been adapted by international regulatory agencies such as the USDA/APHIS/CVB [47].

Figure 3: Outline of the World Organisation for Animal Health *Terrestrial Manual* Chapter 3.1.18, which provides an overview of WOAAH minimum requirements for oral rabies vaccines (both modified live vaccines and biotechnology derived vaccines) relevant for regulatory approval

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Chapter 3.1.18	
Rabies (Infection with rabies virus and other lyssaviruses) version adopted in May 2023	
	Rabies vaccines for oral use
3.1	Background
3.2	Outline of production and minimum requirement for vaccines
3.3	Requirements for relevant regulatory approval
3.3.1	Manufacturing process
3.3.2	Safety requirements
3.3.3	Efficacy requirements
3.3.4	Stability
3.3.5	Bait requirements and characteristics

1.1 Efficacy

It is important to note that there is a difference between vaccine *efficacy* under laboratory conditions and vaccine *effectiveness* in the field.

- **Efficacy** refers to the ability of the given oral rabies vaccine, under ideal conditions, to produce the intended effect in the vaccinated dogs, i.e. protection against rabies. Efficacy is a precondition for licensing. Like for parenteral vaccines, the efficacy of oral rabies vaccines is measured in a controlled experimental study and is based on how many vaccinated dogs develop rabies after a challenge infection compared to how many unvaccinated dogs from the control group develop the same outcome. After the study is completed, the number of dogs that succumbed to rabies in each group is compared. In terms of measuring efficacy, according to WOA, no distinction is made between MLVs and BDVs [44]. Efficacy must be demonstrated in at least 25 vaccinated dogs (offered a vaccine bait) and ten control dogs, using the minimum recommended dosage of the relevant candidate oral rabies vaccine and a subsequent challenge with a target species-adapted rabies virus strain 180 days after vaccination. Efficacy is achieved if, after 90 days post-challenge observation, at least 88% of the vaccinated dogs survives the challenge and at least 80% of the control dogs succumb to rabies (Figure 3) [44].
- **Effectiveness** refers to how well the oral rabies vaccine in question performs under field conditions based on reduction in rabies cases and serologic evidence of rabies virus antibodies or other measures of a vaccine-induced immune response in the target species.

1.2 Safety

The potential benefits of an effective oral rabies vaccine must be weighed against the potential risk of an adverse event in an individual animal following immunisation with that vaccine. Because oral rabies vaccines are administered through distribution into specific locations and habitats, safety studies must consider both the individual animal that was targeted for vaccination as well as any other non-target species (including humans - see section 1.3) that could be unintentionally exposed.

Vaccine-associated risk comprises the probability of an adverse or unwanted outcome and the severity of the resulting health impact (including vaccine-induced rabies or vector virus-induced infections) following immunisation. The WOA has issued basic standards to ensure the safety of the vaccine recipients and surrounding ecosystems, and any oral vaccine intended for ORV must meet these minimum requirements [44].

By their nature, live replicating vaccines pose a risk of genetic drift and shift, which could lead the viral construct to revert to virulence. Any vaccine product that is being considered for use should comply with WOA standards; namely, the vaccine should have limited potential for replication and leave no live virus (active shedding) in saliva and faeces after inoculation to exclude onward (horizontal) transmission. To prove that replication-competent vaccines are safe for the intended animal, requirements include overdose studies, repeated vaccination studies and viral dissemination studies.

To prove that these vaccines are safe for distribution into the environment and for target and non-target species, requirements may include overdose and repeated vaccination studies in species likely to be exposed to the vaccine, studies of viral shedding in target species, and horizontal and vertical transmission studies. In addition, the genetic stability of the vaccine must be demonstrated; i.e. it must be shown that the master seed virus and the virus from the subsequent serial passaging are identical at the consensus level. The WOH also requires additional safety studies in immunocompromised hosts, as well as a human safety risk assessment (Table 1). There are slight differences in safety requirements between MLVs and BDVs. There are only two regulatory authorities that specifically address the safety of oral rabies vaccines; for more details, see the WOH *Terrestrial Manual* [44] and the EMA *European Pharmacopoeia* (EP) guidelines [45].

Table 1: Licensing requirements for oral rabies vaccines (both modified live vaccines and biotechnology derived vaccines) according to the WOH *Terrestrial Manual* and the European Medicines Agency (EMA) *European Pharmacopoeia* (EP) [44,45]. Studies required by either WOH or the EP or both are highlighted in different colours

Requirements	Target species	Non-target species				Humans
	Dogs	Cats	(Wild) rodents	Suckling mice [#]	SCID nude mice	
Repeated dose	x					
Overdose	x	x	x			
Dissemination	x					
Shedding (saliva)	x					
Horizontal transmission	x		x			
Reproductive performance (vertical transmission)	x					
Genetic stability (increase in virulence)				x		
Immunocompromised host					x	
Biological properties (of vaccine strain)*	x					
Risk or genetic reassortment*	x					
Risk assessment						x
Likelihood of contacts						x

Key:

- * for BDVs only
- # serial passaging
- animal studies
- non-animal studies / other tests
- x test required by WOH
- x test required by EMA
- x test required by both

Definitions:

- SCID:** severe combined immunodeficiency genetically affecting both B and T cells
- Nude mice:** specimens with a genetically inhibited immune system due to a greatly reduced number of T cells

1.3 Risk assessment in humans

A product's compliance with WHO and WOHAI standards supports a robust safety profile and minimal threat to people, animals and the environment. However, additional steps must be put in place to monitor for unintended bait contact events and adverse reactions to vaccination in target and non-target species (including humans) due to the (albeit negligible) risk of (partial) reversion to virulence.

A human risk assessment must be performed to estimate the probability that a person will come in contact with the vaccine and the potential health impacts of that contact. Such a risk assessment is more robust than a safety trial using a limited number of non-human primates. Recently, a standardised approach was suggested that maps exposure pathways by which distribution of oral vaccines may result in human contacts with the vaccine virus; this approach estimates the number of severe adverse events by applying a Markov chain model [48]. For example, the risk of human deaths associated with an oral rabies vaccine of the first generation was predicted to be low when distributed to foxes, but, consistent with international concern, 19 times greater when distributed to dogs. The model predicted no deaths from a third generation oral rabies vaccine. This human risk assessment model can be applied to any proposed oral rabies vaccine virus that has completed the necessary safety studies described in [Table 1](#).

It is important to note that **touching an intact bait system is not an exposure** (but may warrant an assessment). Only exposure to the vaccine has the potential to result in an adverse event in humans. Whether post-exposure prophylaxis (PEP) may be required after accidental contact with an oral rabies vaccine will depend upon the vaccine construct and will be defined in the risk assessment. Certain recombinant oral rabies vaccines contain relatively benign viral strains that can result in mild respiratory illness (adenovirus-based recombinant constructs) or rash (vaccinia-based recombinant constructs). Depending on the level of attenuation, MLVs may cause rabies, necessitating more stringent PEP actions. Regarding bait contact, adverse reaction reporting and possible PEP, see [section 5.1](#) and [Annexes B and C](#).

1.4 Commercially available oral rabies vaccines

A number of oral rabies vaccines have been developed, some of which meet all or most of the efficacy and safety requirements mentioned above ([Annex A](#)). It is expected that the landscape of oral rabies vaccines will continue to evolve; whether all constructs will reach the market remains to be seen. Broad-scale use of products not yet approved for experimental use or licensed for dogs is strongly discouraged.

Vaccine baits



The bait is an integral part of the product and serves multiple purposes. It is the carrier through which the vaccine is delivered to the target species. Depending on the product, vaccine baits may consist of a sachet that contains the vaccine surrounded by a bait matrix, or the vaccine may be directly integrated into the bait matrix (Figures 1, 4). The bait also protects the vaccine against environmental stress.

Even the safest and most efficacious vaccine will not be effective unless it is offered in a bait that is attractive to the target species (Figure 2). Additionally, baits must be appropriate in terms of size and composition to ensure proper uptake of the vaccine once the bait is consumed.

It is important to note that no single vaccine bait is suitable for all species. A bait designed for one target species may not necessarily be attractive or effective for other target species.

2.1 Basic requirements

The WOAHP has established detailed requirements for the development of vaccine baits in the *Terrestrial Manual* under section C 'Requirements for vaccines', Chapter 3.1.18 'Rabies (infection with rabies virus and other lyssaviruses)' [44]. These requirements can be summarised as follows.

Bait and sachet (when used) should:

- be designed so that they are readily consumable by large and small dogs;
- have scents that are attractive, and flavours and textures that are palatable, to the target dog population;
- contain materials and ingredients that are safe for target and non-target species;
- be composed of materials that do not impact or interfere with the vaccine's potency or stability;
- allow optimal release of the vaccine into the oral cavity;
- be adapted to the intended method of distribution (e.g. hand baiting versus aerial distribution);
- be economical to produce, particularly if large-scale application is considered.

Importantly, inappropriate use of locally sourced or imported animal products for bait production could result in disease spread with impact on livestock, other economically important domestic animals, or wildlife, and must be avoided.

2.2 Bait types

A number of baits have been specifically developed and tested for dogs based on local food preferences and canine behaviour (Figure 4 upper row; see Module 1). In addition, commercially available baits for targeting wildlife have been field tested for free-ranging dogs (Figure 4 lower row). To date, only one industrially manufactured bait (an egg-based bait) has proven highly attractive to free-roaming dogs in many parts of the world [14,20,21,49,50]. Locally produced baits have been made, often using animal parts such as intestines to enclose a vaccine sachet. While these have been successful in reaching dogs, large-scale preparation of bait and oral rabies vaccines by this method is impracticable.

Figure 4: Examples of baits field tested for oral rabies vaccination of wildlife and dogs

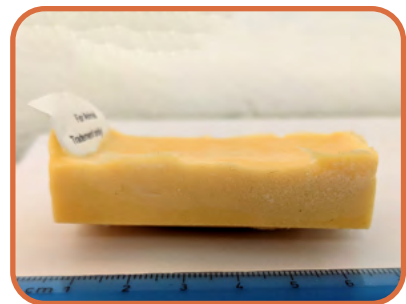
© Top left to right: CEVA Santé Animale, France; Bottom left to right: (two first) USDA, APHIS, Wildlife Services; (third) Friedrich-Loeffler- Institut, Federal Research Institute for Animal Health, Germany



Meatball (köfte) bait



Boiled intestine bait



Egg-based bait



Coated sachet



Fish meal coated sponge bait



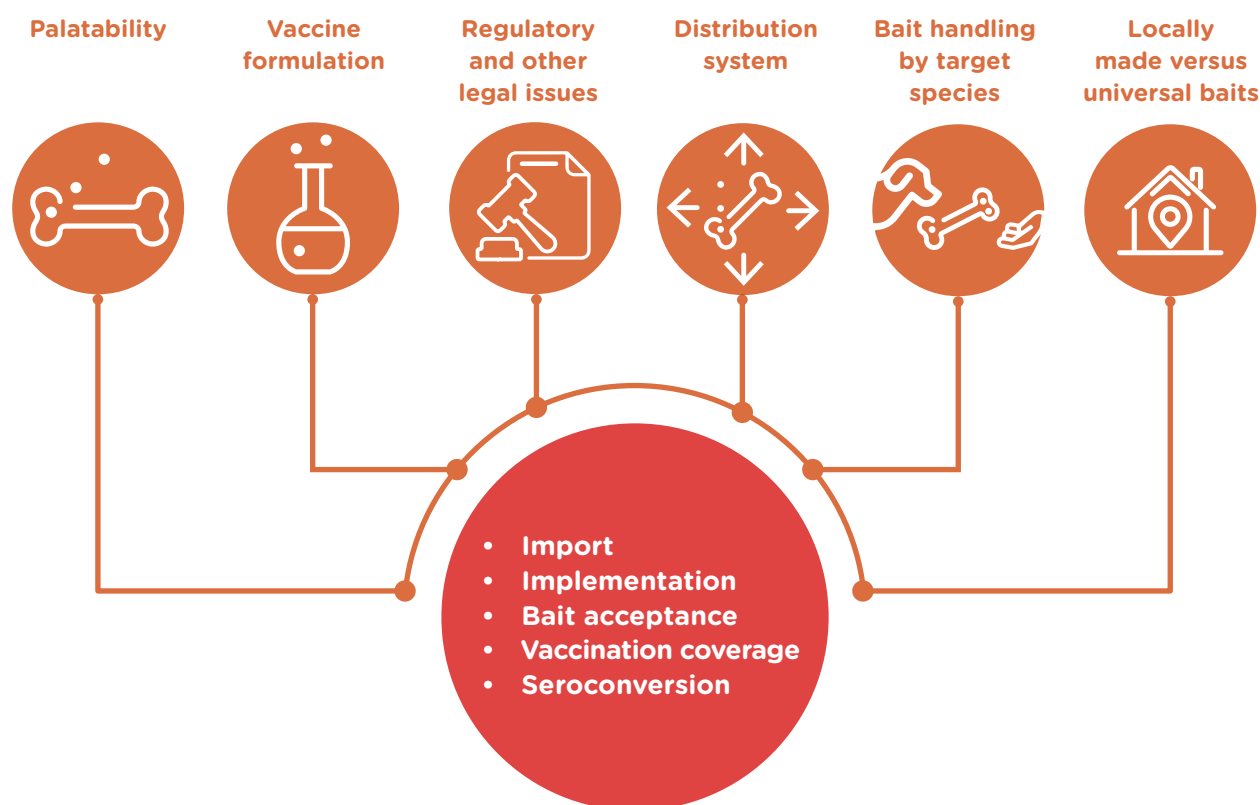
Blister pack coated with fish meal and fat

2.3 Other considerations for vaccine bait development and selection

In addition to the basic requirements for the development of vaccine baits, a number of other issues need to be considered, or require further exploration, if ORV is to be successful (Figure 5).

Figure 5: Issues to be considered if oral rabies vaccination is to succeed

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2.3.1 Palatability

A bait that is palatable to the dog will encourage consumption and mastication, ensuring release of the vaccine in the oral cavity where vaccine uptake should occur. Taste, smell, appearance, size, texture and temperature are important sensory characteristics of a bait and factors in its palatability. As the target dog spends more time investigating the vaccine bait prior to consuming it, there is an increased risk that bait uptake will be unsuccessful. Adding flavour enhancers can increase bait acceptance. It should be noted that ingredients can have both positive and negative impacts on the vaccine bait

product. For example, a flavour enhancer can increase bait acceptance but at the same time lower the melting point of the bait matrix.

A bait matrix is not always required. In some cases, the primary packaging (a sachet or gelatine capsule) is already sufficiently attractive for the target species, and there is no need to add a bait matrix. For example, the sachet can be dipped into an attractive mass that partially sticks to the sachet or an attractive sticky substance can be smeared on the outer surface of the sachet.

2.3.2 Vaccine formulation

If a vaccine is liquid, the vaccine bait must use a sachet. The sachet can have different properties (it might be soft or hard, be in the form of plastic polymer or gelatine capsules, etc.), but it should always be made of materials that are a suitable size so as not to cause oesophageal or intestinal impaction. The sachet will also play an important role in ensuring vaccine stability as it protects the vaccine against direct interference with some of the bait matrix substances and external factors such as heat stress and ultraviolet light. From a regulatory point of view, the sachet is often regarded as primary packaging material, and thus the material that can be used for the sachet and the subsequent filling process are highly regulated. For example, the labelling requirements of the primary packaging material (sachet) need to be considered.

The vaccine does not have to be in liquid form. It can, for example, also be freeze-dried, foam-dried or spray-dried. Another approach would be encapsulating the vaccine in microspheres or nanoparticles that are homogeneously mixed within the bait matrix.

2.3.3 Distribution strategy

The best characteristics for a vaccine bait will depend on intended distribution strategies. For example, wildlife baits are distributed in habitats where the target species must locate the baits by visual or olfactory clues; hence, olfactory and visual attractants can be incorporated in the bait matrix to enhance its detectability. However, bait consumption by non-target species including humans should be minimised. Since target species locate baits primarily by olfactory clues, vaccine baits should not be conspicuous; colouring agents can be added to the bait matrix to enhance camouflaging and reduce human encounters.

Some distribution strategies will require that baits not disintegrate when exposed to the prevailing weather conditions. For example, when exposed to high temperatures or rain, the bait matrix should not melt or dissolve too quickly. It may be necessary to add preservatives and stabilisers to prevent rapid microbial contamination. Also, the baits should not crack or fall apart when hitting the ground or vegetation. These considerations become less important when baits are offered directly to the dogs by hand.

2.3.4 Bait handling by target species

A readily accepted bait is essential, but its subsequent handling by the target species is equally important. The size, shape and texture of the bait matrix and sachet must be considered when identifying suitable bait candidates. Dogs tend to swallow food items without chewing, particularly if there is competition from other dogs. For most candidate

vaccine baits, however, the liquid vaccine needs to be released in the oral cavity. If a sachet is used, the material must be easily perforated by the dog's teeth upon acceptance of the bait, assuring timely release of its contents. When a dog swallows a bait without chewing, the vaccination attempt fails.

2.3.5 Regulatory and other legal issues

Because the bait matrix is sometimes considered an integral part of the final oral rabies vaccine product, it must be defined during the registration process. This can have a significant impact on further research and development to optimise and adapt the bait matrix after the vaccine bait has been licensed. Depending on the changes made and whether they may impact the product's safety or efficacy, additional (animal) studies may be required.

Local legal regulations and cultural mores can also limit the selection of bait candidates. For example, in some countries, no substances from (terrestrial) animal-derived sources can be distributed into the environment. In addition, local cultural considerations can rule out otherwise suitable baits including, in some parts of the world, porcine- or bovine-derived materials.

2.3.6 Locally made baits

It was initially suggested that baits should be made from locally available material like chicken heads or intestine segments (Figure 4); imported, machine-manufactured baits were thought to represent an unnecessary cost and limit bait flavour availability. In addition, it was assumed that due to the food preferences of local dog populations living in a diversity of habitats, a universally well-accepted bait would not be feasible. However, preparing baits from local materials is labour-intensive and requires a dedicated onsite production staff. Also, the availability of local material to produce the baits can fluctuate, resulting in an unpredictable supply chain.

For most vaccine candidates, a cold chain (with storage below -20 °C, for example) is essential (see section 5.3), and during local bait preparation, there is substantial risk that the vaccine temperature parameters will be violated, thereby compromising the quality of the vaccine.

Altogether, selecting a suitable bait is essential for the success of ORV, but there is much more to consider than palatability (Figure 5). A bait made from locally available material may on first consideration be the most promising candidate, but considering all other factors, a well characterised and tested manufactured bait will likely be more standardised, accessible, and readily available for large-scale use. Irrespective of the bait selected, a small-scale field trial to assess bait acceptance in the local dog population is advised. The trial will assess not only palatability and acceptance, but also the effectiveness of the vaccine to induce a protective immune response.

2.4 Biomarkers

To facilitate monitoring of rabies control programmes and vaccine bait uptake in wildlife populations, a bait biomarker like tetracycline or iophenoxic acid is sometimes added to the bait matrix.³ However, if following the hand-out and retrieve model the use of biomarkers is likely unwarranted as it does not provide any additional information. Smartphone tools (Figure 11) to track oral rabies vaccine distribution can provide additional information to evaluate vaccine uptake and vaccination coverage.

³ Biomarkers are chemical substances and should not affect bait attractiveness or harm target or non-target animals but can be detected in animal tissues or blood as proof of bait consumption.

Regulatory affairs



3.1 Licensure considerations

In the *Terrestrial Manual*, WOAHA has established general requirements for oral rabies vaccines for licensing⁴ under section C ‘Requirements for vaccines’, Chapter 3.1.18 ‘Rabies (infection with rabies virus and other lyssaviruses)’ [44]. Only oral rabies vaccines that meet these criteria should be authorised for use in rabies management programmes. These WOAHA standards may be supplemented, as regulatory authorities in certain countries may have their own standards for licensing of veterinary vaccines.

In general, international licensing, such as that ensured by the EMA and USDA/APHIS/CVB, should be considered for oral rabies vaccines for dogs that follow WOAHA requirements [44]. Presently, the licensing procedure – from submission of the dossier to obtaining licensure – can take many years. It requires that adequate scientific studies have been conducted and presented to appropriate regulatory authorities (Table 1). Also, the manufacturing processes and facilities need to meet certain standards and therefore must be evaluated by the authorities. Considering that the most recently developed, and therefore safest, vaccine constructs are BDVs, additional evaluation for environmental release may be required.

Given that dog-mediated rabies is present in over 100 countries, and in the light of clear and thorough international standards for the production, licensing and use of animal vaccines from WOAHA’s *Terrestrial Manual*, authorities should encourage regulatory convergence of already licensed oral rabies vaccines [2]. To achieve regulatory convergence, international agencies adopt a set of standard regulatory requirements and maintain global dossiers. Standard regulatory procedures or good regulatory practices as promoted by VICH guarantee predictability regarding, for example, review and licensing timelines and market access.⁵ Regulatory convergence would allow for oral rabies vaccine products to be safely evaluated by qualifying regulatory programmes using a science-based and transparent process, thereby assuring national rabies programmes that the products are safe and effective for use.

According to WOAHA, any use on dogs of oral rabies vaccines that are licensed for other target species should be considered an ‘off-label use’.

⁴ There do not seem to be strict rules for the use of the terms ‘regulatory approval’, ‘registration approval’, ‘licensing’, ‘permitting’, ‘marketing authorisation’ and ‘authorisation’ for medicinal products, and so these terms can be used interchangeably. Depending on the country, a registration approval can also refer to different things, such as Good Manufacturing Practices accreditation of the site, testing of samples, etc. The term ‘marketing authorisation’ is commonly used in the European Union (EU), and the marketing authorisation holder is the company that owns the product, even though in many non-EU countries, there is no marketing authorisation holder. To avoid confusion, the term ‘licensing’ is used throughout this document.

⁵ The full name for VICH is International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products. It is a trilateral (EU–Japan–United States of America) programme aimed at harmonising technical requirements for veterinary product registration (<https://www.vichsec.org/en/>).

3.2 General considerations regarding importation

Import requirements for veterinary biologicals can vary from country to country, and thus procedures for importing oral rabies vaccines may require different sets of documents and different governmental departments for approval and (customs) clearance. It is strongly recommended to consult the competent national authorities prior to attempting to import oral vaccines and become familiar with the procedure to avoid problems and unnecessary delays. The following sections outline some of the universally important considerations regarding importation of oral rabies vaccines.

3.3 Import of licensed vaccines

The importation of oral rabies vaccines usually requires registration of the product. In some countries, importation requires local (batch) testing before the product is released for use. In most instances, veterinary vaccines and regulated medical devices containing ingredients derived from animals may be imported once the appropriate national authorities have granted approval. However, there may be additional considerations and regulations for importing. For example, biotechnologically derived modified live vaccines (BDVs) may be considered genetically modified organisms and may be subject to additional approvals. If the oral vaccine licence does not include the bait matrix itself, any components of the vaccine bait derived from animals or animal products may be subject to country-specific regulations and may need to be approved by the competent authorities at the port of arrival before entry.

3.4 Import permit for emergency use

Generally speaking, depending on the country and legal situation, regulatory or other competent authorities may approve the use of experimental or licensed vaccines in emergencies to prevent the spread of serious diseases, if certain criteria are met. Exemptions from the national regulatory authorities (emergency licensing) may be sought to address an emerging rabies epizootic in a defined area where ORV of specific susceptible target dog populations is the only option to control the epizootic. In this case, only products that have a licence for use in dogs (be it an international licence or national licence in another country) should be used. The importation and use of such a product could be considered under special conditions (conditional licence, import permit for emergency purposes, etc.) and supervision.

3.5 Import permits for experimental use

Oral rabies vaccines not licensed for dogs or wildlife may be considered for import and experimental use (e.g. comparative or immunogenicity studies) under special conditions. In this case, it is essential for decision-making authorities to evaluate rigorously the data provided by the manufacturer regarding safety and efficacy of the candidate oral rabies vaccine. Products should comply with WOAHP safety recommendations (see [sections 3.2](#) and [3.3](#)). If an import permit is granted, conditions of use should be clearly specified, such as area of distribution and number of baits to be imported. The use of the experimental oral rabies vaccine should be fully supervised.

The large-scale distribution of oral rabies vaccines that have not been licensed in any country is strongly discouraged, whereas the use of oral rabies vaccines licensed in other countries is encouraged.

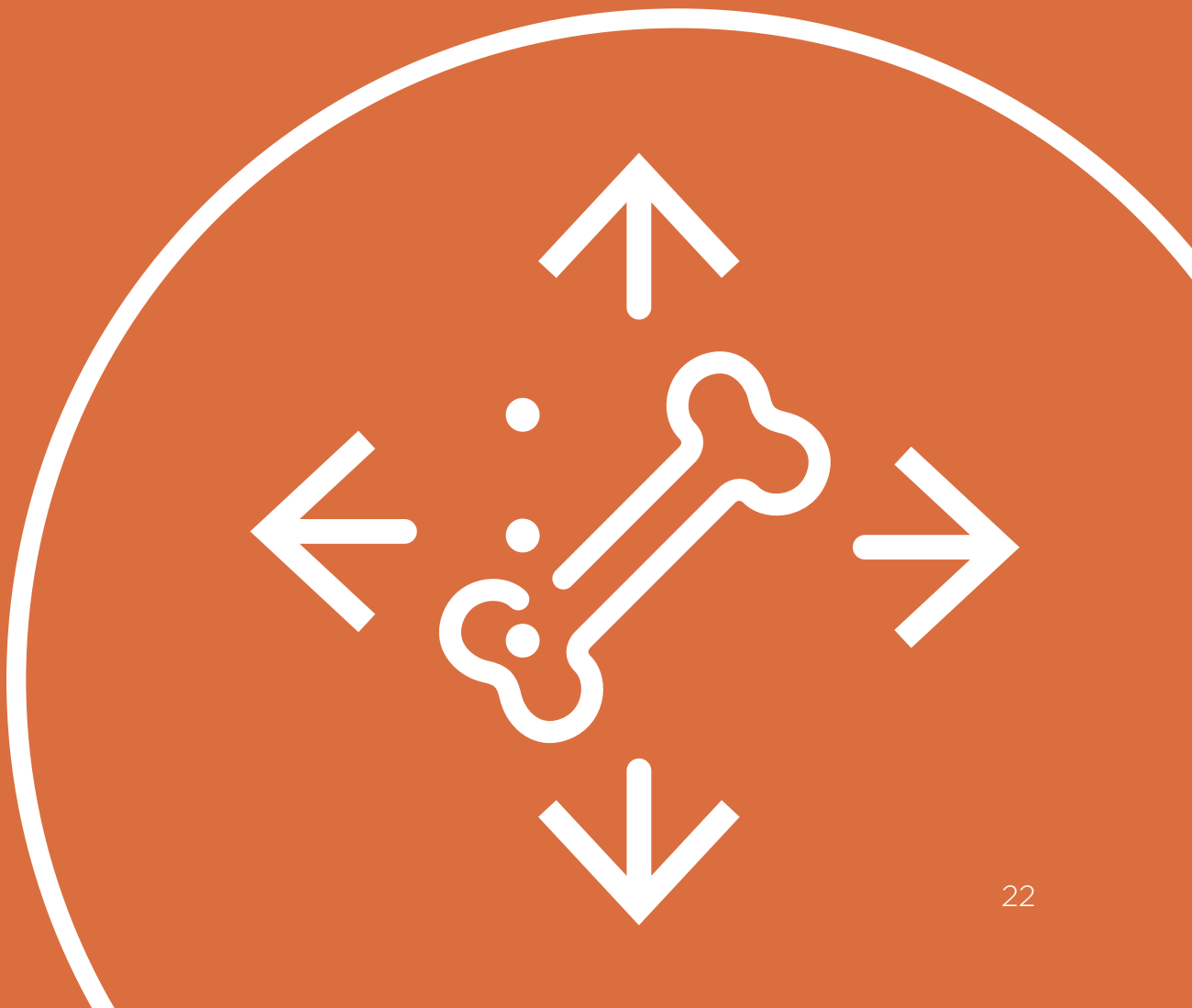
Thailand example

Importation of a non-licensed oral rabies vaccine for dogs

In Thailand, the Drugs Act, B.E. 2510 (1967), Chapter 2 'Application and issuance of licenses concerning modern drugs' specifies that drugs used in Thailand must receive a licence from the licensing authority. However, this regulation does not apply to importation by ministries, sub-ministries and departments that have a duty to prevent or treat disease. This exception allows the authorised organisations to import and utilise critical medicinal products to treat, prevent and control diseases.

The Department of Livestock Development is responsible for animal rabies control and envisions integrating ORV into the animal rabies control to programme dog-mediated rabies by 2030. Thus, the Department, through technical cooperation with the vaccine producer company and experienced institutes, imported and studied an oral rabies vaccine that was licensed for wildlife and showed scientific evidence for safety and efficacy in domestic animals. The Department controlled the usage in experimental and field settings while collecting data to support the licensing process.

Distribution systems



The vaccine bait distribution system is the third main pillar of the ORV concept (Figure 2) and should optimise bait availability to the target subpopulation of dogs, while reducing bait uptake by non-target species and dogs not intended to be orally vaccinated. Furthermore, all bait distribution strategies should consider the potential impact to human health and safety and the likelihood of people coming into contact with the vaccine. As a result, the selected bait distribution system is predominantly determined by the targeted dog population, vaccine safety profile and associated risk to human, target and non-target populations.

Three basic bait distribution systems have been identified:

- a) hand-out and retrieve model
- b) distribution to dog owners
- c) wildlife model.

Each system targets different segments of the local dog population (Table 2).

In general, all of these distribution systems require less training and animal handling experience than needed for parenteral vaccination. For this reason, oral rabies vaccine may be distributed by trained local community members with relatively minimal resources, leading to reduced personnel costs.

However, a basic knowledge of the dog population demography, including the level of ownership and restriction, is required for selecting the most appropriate bait distribution system. Including ORV in dog rabies control programmes makes sense only when it increases the vaccination coverage and herd immunity to levels sufficient to interrupt the rabies virus transmission cycle. Even in areas free of dog-mediated rabies, preventive dog rabies vaccination campaigns that include ORV can be used to prevent re-emergence of rabies in the dog population. In certain areas with wildlife-mediated rabies, particular subsets of the dog population have an increased risk of exposure to wildlife (e.g. feral dogs visiting dump sites or shepherd dogs).

4.1 Hand-out and retrieve model

The hand-out and retrieve model targets free-roaming dogs, owned or ownerless, which are not accessible to parenteral vaccination without special effort. Hand-out and retrieve is the preferred method for ORV of dogs and can be easily integrated into mass vaccination campaigns, irrespective of whether they are conducted through central point vaccination sites or door-to-door visits. Every dog that remains difficult to handle or restrain can instead be offered a vaccine bait (Figure 4). If the dog does not accept the bait, the bait can be collected by the vaccinators and reused (within the storage and use parameters of the vaccine). Discarded used sachets should also be collected after bait consumption to reduce impact on the environment (Figure 6).

Figure 6: Vaccinators practising the hand-out and retrieve model to orally vaccinate dogs



Asia © CEVA Santé Animale, France



Africa © Friedrich-Loeffler- Institut, Federal Research Institute for Animal Health, Germany



North America © USDA, APHIS, Wildlife Services



Retrieval of chewed vaccine blisters/sachets
© Friedrich-Loeffler- Institut, Federal Research Institute for Animal Health, Germany

4.2 Distribution to dog owners

In areas with sparse human populations and a high number of free-roaming dogs, it can be inefficient to systematically search for dogs. Often, the owners or caretakers are not aware of the whereabouts of their dogs, and vaccination coverage remains low. Under such circumstances, distribution to dog owners offers an opportunity to reach the free-roaming dogs that cannot be presented for vaccination at central point vaccination sites or during door-to-door campaigns. Vaccine baits can be given to dog owners at a central point, and owners can offer the baits to their dogs themselves later when returning home.

Of course, such a distribution system implicates contact of the dog owner with the vaccine bait and an interruption of the cold chain (see [sections 5.3](#) and [5.11](#)). Hence, this method is only feasible with the highest safety profile and relatively thermostable vaccine strains.

4.3 Wildlife model

The wildlife model of bait distribution is an approach adopted from ORV of wildlife target species. This method is suitable for free-roaming (feral) dogs that avoid human contact and cannot be approached within a distance that allows the bait to be offered directly. Vaccine baits are distributed in targeted habitats by various means (e.g. aerial distribution, bait stations, baited enclosures) at prescribed densities to maximise the likelihood of detection and consumption. Habituation (pre-bait feeding) of such dogs can be helpful before the actual vaccination baits are offered [51]. This system can be used in rural, urban and suburban habitats. Strategies should be incorporated that minimise vaccine bait contacts with people and non-target animals. The wildlife model should only be used in limited situations and only with the most attenuated vaccines, which have demonstrated a high safety profile.

4.4 Comparison of the three distribution systems

Each of the three distribution systems for oral rabies vaccination has several advantages and disadvantages. These should be considered when choosing the appropriate distribution system for each context. Advantages and disadvantages of one system may outweigh the advantages and disadvantages of another ([Table 2](#)). In addition, depending on the circumstances, more than one of these distribution systems might be considered in combination.

Table 2: Overview of the comparative advantages and disadvantages of the three distribution systems

	Categories	Hand-out and retrieve model	Distribution to dog owners	Wildlife model
Advantages	Target (for reaching 70% vaccination coverage)	<ul style="list-style-type: none"> any owned or ownerless dog (not accessible for parenteral vaccination) 	<ul style="list-style-type: none"> any owned dog (not accessible for parenteral vaccination) 	<ul style="list-style-type: none"> dogs that cannot be approached and offered a bait directly
	Logistics	<ul style="list-style-type: none"> requires little training and animal handling experience 	<ul style="list-style-type: none"> requires little training and animal handling experience 	<ul style="list-style-type: none"> requires little training and animal handling experience
		<ul style="list-style-type: none"> provides the best supervision of baits distributed and spatial coverage 	<ul style="list-style-type: none"> requires fewer human resources 	<ul style="list-style-type: none"> requires fewer human resources
	Costs	—	<ul style="list-style-type: none"> reduces distribution costs through time savings and travel efficiency 	<ul style="list-style-type: none"> reduces distribution costs through time savings and travel efficiency
	Other	<ul style="list-style-type: none"> reduces waste of vaccine baits (hardly any baits are not or taken by non-target species) 	<ul style="list-style-type: none"> dogs do not have to be present during distribution 	<ul style="list-style-type: none"> dogs not encountered during a systematic search can still locate a bait
<ul style="list-style-type: none"> reduces potential direct human contacts with vaccine (baits) 		<ul style="list-style-type: none"> close bonds between owners and dogs may increase likelihood of vaccination 	<ul style="list-style-type: none"> bait distribution can be done at a larger scale and in a time-efficient way 	
<ul style="list-style-type: none"> limits environmental pollution (discarded blisters) 		—	<ul style="list-style-type: none"> potentially vaccinates secondary wildlife vectors that may be partial/occasional reservoirs 	
Disadvantages	Target (for reaching 70% vaccination coverage)	<ul style="list-style-type: none"> requires targeting individual dogs 	<ul style="list-style-type: none"> has negligible effect in areas with a high proportion of ownerless, hard to reach, free-roaming dogs 	<ul style="list-style-type: none"> lowers probability that target dogs will locate and consume a vaccine bait
	Logistics	<ul style="list-style-type: none"> requires using people trained in approaching and offering baits to dogs 	<ul style="list-style-type: none"> last phase of supply chain unknown (cold chain) 	<ul style="list-style-type: none"> requires people with local knowledge of habitats frequented by dogs
		—	—	<ul style="list-style-type: none"> might require effort (time/money) to get permission to access where dogs are
		—	—	<ul style="list-style-type: none"> estimation of vaccination coverage is more difficult to assess
	Costs	<ul style="list-style-type: none"> requires more human resources 	<ul style="list-style-type: none"> requires higher number of vaccine baits 	<ul style="list-style-type: none"> requires a higher number of vaccine baits distributed in the environment
		—	<ul style="list-style-type: none"> potential increase of human contact with the vaccine 	<ul style="list-style-type: none"> sophisticated delivery equipment may be required (aerial distribution)
	Other	<ul style="list-style-type: none"> time-consuming compared to other methods 	<ul style="list-style-type: none"> reduced control over fate of vaccine baits (human contacts, waste disposal) 	<ul style="list-style-type: none"> increased likelihood of vaccine bait uptake by non-target species thereby decreasing availability for dogs
		—	<ul style="list-style-type: none"> increased risk of human contact with the vaccine 	<ul style="list-style-type: none"> increased potential for non-target species vaccine contacts, including humans

Campaign activities



Effective dog vaccination programmes utilising oral rabies vaccines involve many of the same considerations as parenterally focused vaccine campaigns: namely, ensuring use of a safe and effective vaccine product, creating community awareness and engagement, budgeting, selecting appropriate vaccine distribution methods and identifying competent vaccination staff. Use of oral rabies vaccines furthermore requires unique pre-campaign considerations that can include advanced cold-chain requirements, systems to detect and track unintended vaccine exposures, and capability to respond effectively in the event of a human or animal adverse event (similar to a pharmacovigilance system for parenteral vaccines). This section describes some of these unique considerations when introducing oral rabies vaccines as a component of a dog vaccination strategy.

5.1 Estimation of the dog population

Characterising and documenting the dog population in the area is a foundational component of a successful dog vaccination campaign. Such surveys are essential during initial programme planning and evaluation. Knowing the number of dogs in a community helps to inform vaccination strategies that are most likely to reach the desired level of herd immunity and, most importantly, target ORV for optimal use. These studies do not need to be extensive, and vaccination programmes should not be delayed to accommodate lengthy population studies: they can be done in coordination with vaccination activities (see [section 5.4](#)).

There are two general approaches to characterising and enumerating dog populations. These are household and community surveys and feral dog population (sight-resight) surveys. Each has unique benefits and drawbacks. In an ORV campaign, the latter is of utmost importance, as feral dogs are often targeted for ORV. Vaccination programme managers are encouraged to speak with experts in dog population characterisation to ensure that the selected survey methods will provide adequate information for the campaign. Vaccination programmes aimed at eliminating rabies must be conducted routinely for numerous years, typically with increased capacity in each subsequent campaign. It is reasonable to initiate vaccination campaigns with a basic understanding of the dog population and then adjust vaccination strategies based on new data collected during and between campaigns.

Conducting these surveys shortly after a vaccination campaign may offer a more cost-effective approach, as additional data on campaign efficacy can also be gathered. Vaccination coverages should always be calculated by the roaming status of dogs (confined versus free-roaming) to ensure that free-roaming dogs have met desired coverages. Methods for conducting dog population surveys in the context of a vaccination programme can be found here: [52,53].

5.2 Vaccine bait procurement

Only commercially available rabies vaccines licensed for dogs should be considered for procurement under national and regional canine rabies control projects. It is recommended to contact potential manufacturers of the vaccine early in the planning process to obtain information about their production times. It is also recommended to obtain information on their requirements for transport and intermediate storage of the oral rabies vaccine so that an adequate cold chain can be organised and ensured (see [section 5.3](#)).

5.3 Cold chain

The cold chain is a crucial system to maintain the effectiveness of vaccines throughout the vaccination process, from production to administration.

As with parenteral vaccines, global transportation of oral rabies vaccines is a complex undertaking. Transporting, storing and managing these products requires a chain of precisely coordinated operations in temperature-controlled environments. If vaccine storage temperatures become too high, the vaccine can lose potency (i.e. the active ingredients can degrade and become less effective). A vaccine that loses its potency is useless because potency cannot be regained or restored.

Like most other vaccines, oral rabies vaccines must be stored and shipped under defined temperature conditions as specified by the manufacturer – continuously from the time they are manufactured until use in the field. Storage temperature at the site of use (e.g. at regional or subregional cold storage facilities) may differ depending on the temperature stability claimed by the manufacturer. While for some oral rabies vaccines it may be necessary to keep them frozen, for others storage at refrigerated temperatures (4–5 °C) may be sufficient to preserve them for a couple of weeks.

Maintenance of the cold chain should be checked and documented using a temperature data logger and integrated electronic measuring during storage and transport until initiation of the campaign [54]. After deviations or breaks in the cold chain, experts should be contacted immediately for an assessment. Depending on the severity of the deviation (still frozen or thawed), different scenarios are possible (still usable, unusable/discard, additional testing needed). Besides the thermo-sensitivity of the vaccine, the bait matrix can also be susceptible in elevated temperatures, especially in high humidity environments (which may cause melting and/or moulding).

Figure 7: Storage of vaccine baits during transport

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Typical cool transport box used by specialised courier services for shipping oral rabies vaccine baits from the manufacturer to the country of destination



Removal of vaccine baits from -20°C freezers followed by intermediate storage in portable cool boxes until use in the field

From storage facilities to the field site, vaccination teams should carry vaccine baits in cool boxes or vaccine carriers [50,54]. Teams should only collect as many baits from the cold store as can be distributed in one day. Depending on the distribution method and thermostability of the product, vaccine baits should be frozen or thawed to refrigerator temperatures (4–8 °C) when arriving in the field so that they are ready for immediate use (Figure 7). It is expected that vaccine baits not used that day can be reused the following day if kept at refrigerator temperatures (4–8 °C); however, this should be verified for each vaccine bait type [50]. Avoid repeated freezing and thawing of vaccine baits, as this can impact vaccine potency.

Expiry dates of oral rabies vaccines do not affect the safety of the vaccine; rather they indicate how long the vaccines will retain their potency, and thus effectiveness, at a given storage temperature. This so-called minimum shelf life is guaranteed by the manufacturer and the regulatory authorities, provided that the corresponding storage conditions have been met and were regularly checked. Wasted doses are a cause for concern in most countries endemic for dog-mediated rabies. To avoid vaccine wastage, responsible authorities should ensure that proper plans are in place and logistics and facilities are available before procuring oral rabies vaccines.

5.4 Selecting vaccination strategies

According to WHO and WOAHA recommendations, parenteral vaccines should constitute the largest part of a dog vaccination strategy. This is due to the high efficacy, the relative low costs and the high safety profile of killed vaccines. However, parenteral vaccination strategies may fail to reach target vaccination thresholds in key dog populations. Free-roaming dogs (owned or unowned) are primarily responsible for maintaining rabies virus transmission, and in certain settings these dogs may be less accustomed to owner control and veterinary services, making parenteral vaccination difficult if not impossible. For introducing ORV as a component of a mixed-strategy vaccination programme, it is crucial to characterise the dog population and its accessibility in the targeted communities (see [section 5.1](#)).

An appropriate integrated vaccination plan should be devised prior to commencing the vaccination campaign and should include population density estimates of the target dog population. This vaccination plan should also include an estimated number of parenteral and oral rabies vaccines necessary to reach vaccination thresholds in the free-roaming dog population and considerations for the identification of vaccinated dogs to avoid revaccination. A tool called VaxPLAN has been created to guide the design of mixed-methods vaccination approaches and can be found here: <https://rabiestaskforce.com/toolkit/vaxplan> [55]. Support with implementing VaxPLAN or updated tool versions can be obtained here: rabies@cdc.gov.

It is of utmost importance that the vaccination strategy is flexible to cover a range of scenarios and to allow timely, adequate responses to changes in epidemiological conditions [46]. The extent to which ORV can be used as a complementary tool depends on the percentage and accessibility of local free-roaming dogs, which can vary from region to region. While ORV may only constitute a minor contribution in certain regions, in others it may be the only way to increase vaccination rates drastically and sustainably in the local dog population. It is necessary to decide in advance whether ORV can be of benefit to a vaccination campaign and the dog rabies control strategy already implemented, and action must then be taken accordingly.

During dog vaccination campaigns, all dogs should be vaccinated, regardless of age, weight or health (Figure 8) [56]. The dog population in an area should continue to be vaccinated for at least two years after the last recorded case of rabies with adequate case surveillance.

Figure 8: Examples of dogs that should be vaccinated

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Oral vaccination of a female dog and its puppy



Unhealthy-looking adult dog

5.5 Vaccination teams

Each vaccination programme should design a strategy and identify a workforce that is tailored to their community member preferences and the target dog population. Ideally, vaccination teams should consist of two veterinary staff members, e.g. a state veterinary officer and an animal health technician or a trained non-veterinary person or paravet (Annex D). Vehicles, e.g. mopeds, scooters and four-wheel drive pick-up trucks (Figure 9), should be equipped with cool boxes, cooling bags, gloves, rubbish bags and disinfectants for team members (Figure 10). As team members and vaccinators are likely to have a higher rate of dog-bite injuries than the public, pre-exposure vaccination is highly recommended [46].

Figure 9: Four-wheel drive pick-up trucks (top) and a moped/scooter (bottom) used for oral vaccination of dogs in Namibia and India, respectively

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Oral rabies vaccines for dogs will likely be a new strategy for most vaccinators; additional training may be necessary to ensure vaccinators understand how to safely handle the vaccines, effectively and safely distribute the vaccines to eligible dogs in the community and communicate to the public who will likely be curious about this new method. Oral rabies vaccine distribution is generally straightforward and can be supported by a non-veterinary workforce staffed from the local community. Countries should carefully assess strategies for vaccine distribution (see [section 5.4](#)) and ensure that competent vaccination staff are available to perform necessary duties.

Figure 10: Cool boxes and cooling bags used in oral rabies vaccination field trials

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Many vaccination programmes will implement an integrated approach that may include central point and door-to-door parenteral vaccination in combination with ORV. The traditional methods for disseminating parenteral vaccines require additional training, as vaccinators must physically restrain dogs prior to injection. When considering vaccination workforce needs, skillset requirements and training, it is critical to clearly document the vaccination strategy. If ORV is to be distributed concurrently with parenteral approaches, then the same workforce can likely accomplish both vaccination methods simultaneously (e.g. the parenteral teams will also have oral rabies vaccines for ad hoc distribution while operating in the community).

Alternatively, separate teams of ORV vaccinators may be selected to conduct 'mop up' vaccination. Under this approach, dogs should be marked with a temporary paint or collar when vaccinated through traditional parenteral methods. After completion of traditional vaccination, ORV vaccinators can canvass the community, offering vaccine baits to dogs without a mark of vaccination. If this workforce is responsible solely for vaccine bait distribution then animal handling and prior parenteral vaccination experience is not necessary, which could reduce costs and increase the eligible workforce. Regardless of the approach, vaccination programmes are more successful when vaccinators are familiar with the community and vice versa; when possible, local staff should conduct the vaccination activities.

5.6 Awareness campaigns

Oral rabies vaccines are relatively new for use in dogs and may not be familiar to community members. This may cause hesitation or curiosity among community members. To avoid undue concern and delays during the vaccination campaign when ORV is first being used in a community, extensive community outreach should be conducted beforehand. Outreach should provide community members standard information about the logistics

of the vaccination campaign, plain-language descriptions of the vaccines and vaccination approaches to be implemented, and key public health guidance on what to do with baits found in the community and how to respond after potential vaccine exposures. Messaging should be balanced to ensure the community is fully informed on the products their animals will receive but also will not have undue concern that may jeopardise the success of the campaign. Depending on local needs, leaflets, radio, television, newspaper, press releases and educational kits for schools may be suitable tools for informing members of the community. It is important to involve local staff in these campaigns.

5.7 Documenting vaccination efforts

While not unique to ORV projects, accurate documentation of vaccination activities is critical for programme monitoring and interpreting campaign effectiveness (Figure 11). Traditionally, activities have been documented through paper records compiled at the field level, collated by region and finally submitted to national programme managers. This approach is prone to error (intentional and unintentional) during data collection and to loss of records during the multistep submission process. Furthermore, the approach can result in significant delays in interpreting the campaign’s effectiveness and provides limited insight into improving vaccination strategies in future years.

Free and easy-to-use mobile data-gathering platforms are available for monitoring large-scale ORV programmes in dogs [50,52,57–59] (Annex E).

Figure 11: Mobile platform for monitoring large-scale vaccination

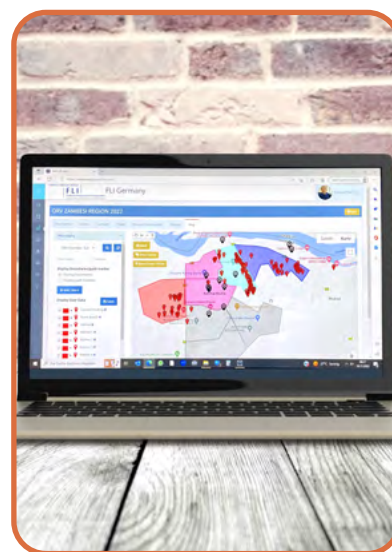
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A free and easy-to-use mobile data-gathering platform (from the Worldwide Veterinary Service [WVS]) used in an oral rabies vaccination field trial in the Zambezi Region, Namibia



A staff member from Mission Rabies provides training in data recording to Namibian vaccinators using the WVS data-collection app



Real-time assessment of orally vaccinated dogs

Here, records are often stored in cloud-based servers, which enables near real-time evaluation of campaign progress by campaign managers. While it is good practice to create documentation for all types of vaccination, the limited use of ORV for dog rabies control makes accurate and timely documentation of these campaigns even more important. The documentation of vaccination efforts should be linked to and compatible with rabies surveillance databases.

5.8 Owner consent

In some settings the owner's consent may be required, particularly if the vaccine is being used on an experimental or off-label licence. However, when targeting free-roaming dogs, having the owner's consent may be challenging or not feasible. Also, requesting consent is time-consuming and will limit the effectiveness of the campaign. Community awareness and support for rabies vaccination campaigns are critical to successful mass vaccination. As part of community engagement, materials can be created to ensure that leaders, veterinary professionals and dog owners are informed about oral rabies vaccines. In many places, rabies vaccination is compulsory due to its benefits to public health. Ensuring that legal codes and regulations also include ORV may negate the need to obtain owner consent. Free-roaming dogs with no clear owner would then not require consent to vaccinate.

5.9 Vaccination certificate

Generally, vaccination certificates have limited value if they are not linked to proper identification of the animal (e.g. by microchip or tattoo), owner data and vaccination details, and if the subsequent data is not collected and stored in a database. This is particularly true for dogs vaccinated by ORV. However, if authorities request it, or if having a certificate will incentivise dog owners, (pre-printed) ORV certificates could be issued that simply state that this dog was orally vaccinated. Public health authorities should have protocols that include rabies post-bite risk assessment criteria for dogs vaccinated with an oral rabies vaccine. The decision to consider these dogs as 'vaccinated' for public health purposes may differ based on the safety and efficacy profile of the chosen vaccine ([Annex A](#)).

5.10 Monitoring and evaluation of campaigns

As ORV is a complementary measure to improve overall vaccination coverage in canine rabies control programmes, monitoring and evaluation of ORV and mass parenteral vaccination campaigns of dogs are always interrelated. It is the spatio-temporal interaction of the two vaccination approaches that determines the success of a programme. Monitoring and evaluation of ORV campaigns in a given area should be based on a thorough analysis of dog census data (see [section 5.1](#)), documented vaccination activities (number of dogs vaccinated per region – see [section 5.7](#)) and related laboratory-confirmed rabies surveillance data [46] to estimate the vaccination coverage and identify trends in rabies incidence.

It is of utmost importance to point out that vaccination coverage and seroconversion rate are not the same thing. Vaccination coverage is the estimated percentage of dogs that have received rabies vaccines. Seroconversion is the development of rabies virus-specific antibodies above a predetermined threshold in the blood serum as a result of vaccination, and is test dependent. Seroconversion, in turn, is not the same as protection from disease; it is rather an indicator of protective immunity.

In general, serological surveys are not recommended for the assessment of vaccination coverage after ORV campaigns. If a high-quality oral rabies vaccine product is used, there should be high confidence in the efficacy of the product just as for parenteral vaccines. Serological surveys may be useful if rabies cases persist despite documented high vaccination coverage over sequential mass vaccination campaigns. The persistence of rabies may indicate a lack of vaccine efficacy or inadequate maintenance of the cold chain. However, given difficulties in accurately estimating vaccination coverage in free-roaming dog populations, persistent rabies cases are most often a result of poorly characterised dog populations and inflated estimated vaccination coverages.

Although it is recommended that 70% of dogs in a population be vaccinated to control and eventually eliminate rabies [60], it should be emphasised that it is always the rabies incidence in an area where rabies is controlled that is the ultimate proof of the efficacy of the chosen vaccination strategy [61]. Slow progress or failure to reduce the incidence of rabies in dogs in a given area, despite an implemented control strategy, can have various causes, but may not necessarily be an indicator that vaccination efforts are ineffective. Activities to verify elimination of dog-mediated rabies and subsequent declaration of rabies-free areas are defined by WHO and WOAH [3,46].

5.11 Bait contact and adverse reaction reporting

Although adverse events related to oral rabies vaccines are extremely rare in both humans and animals, such effects should be immediately analysed and reported to national health officials, the manufacturer and relevant international agencies, as for every other vaccine. While the safety precautions and the preferred hand-out and retrieve model for the ORV of dogs should significantly reduce the incidence of such events, some rare vaccine contact incidents cannot be excluded in the large-scale use of ORV. Human exposures to the vaccine can occur through direct touching of a punctured bait or through contact with an animal that has recently been exposed to the oral rabies vaccine.

Therefore, prior to vaccine distribution, public health programmes should be consulted to establish a system for community members to report exposures to oral rabies vaccine baits and bait contents. Adverse events should be thoroughly investigated to confirm that they are related to the vaccine product. Public health response to oral rabies vaccine contact (patient management) will then depend on the product used. Health officials should therefore produce guidance for the investigation of suspected adverse reactions to oral rabies vaccines, and such guidance should reflect the viral construct and safety profile of the vaccines to be used. For example, the Centers for Disease Control and Prevention has developed guidance intended for exposures in the general public to adenovirus-vectored, vaccinia-vectored, and highly attenuated rabies virus vaccines (see [Annexes B and C](#)). General guidance regarding rabies post-exposure prophylaxis is available [46].

Another adverse event is not related to the vaccine but to the vaccine blister [62]. Intestinal congestion was sporadically observed in dogs that ate multiple baits when wildlife was targeted with ORV.

5.12 Frequently asked questions

This document contains basic recommendations for the ORV of dogs. To address additional ORV-related questions and issues that seem not to be covered in this document, [Annex F](#) contains frequently asked questions that have arisen during the introduction of ORV for dogs.

Concluding remarks

Oral vaccination of dogs is a compelling, simple, effective and highly efficient means of increasing vaccination coverage in target animal populations. With strategic long-term planning and targeting, and if implemented correctly and consistently within national control programmes, ORV can reach its potential and significantly accelerate the elimination of dog-mediated rabies. With this potential, the need for commercial vaccines is expected to increase, and it is hoped that vaccine manufacturers can meet this demand. While the ORV of dogs can be a game changer, it cannot replace sustained commitment, cooperation and support in implementing conventional One Health prevention and control strategies if there are to be zero human rabies cases worldwide by 2030.

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Frequently asked questions

Annex A. **Characteristics of commercial oral rabies vaccines for potential use in dogs**

<https://www.unitedagainstrabies.org/publications/oral-vaccination-of-dogs-against-rabies-recommendations-for-field-applications-and-integration-into-dog-rabies-control-programmes/>

Annex B. **Centers for Disease Control suggested standard operating procedure for Rabitec oral rabies vaccination bait contacts**

https://www.unitedagainstrabies.org/annex2_rabitec-oral-rabies-vaccination-bait-contact_eng_jul2023/

Annex C. **Suggested standard operating procedure of oral rabies vaccination bait contacts (human)**

<https://www.ccbh.net/wp-content/uploads/2016/08/Human-bait-contact-flow-chart.pdf>

Annex D. **Instructions for lay vaccinators**

<https://www.anthc.org/wp-content/uploads/2021/07/Guidelines-for-LVs.pdf>

Annex E. **eHealth Monitoring Systems for possible application in large-scale oral rabies vaccination programmes**

- **Epicollect5**
<https://five.epicollect.net/>
- **Worldwide Veterinary Service data-collection app**
<https://missionrabies.com/app/>
- **KoboToolbox**
<https://www.kobotoolbox.org/>
- **Rabies Vaccination Tracker**
<https://rabiesalliance.org/tools/surveillance-tools/rvt>

Annex F. **Frequently asked questions**

<https://www.unitedagainstrabies.org/publications/oral-vaccination-of-dogs-against-rabies-recommendations-for-field-applications-and-integration-into-dog-rabies-control-programmes/>

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