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World Health Organization

Food and Agriculture Organization of the United Nations

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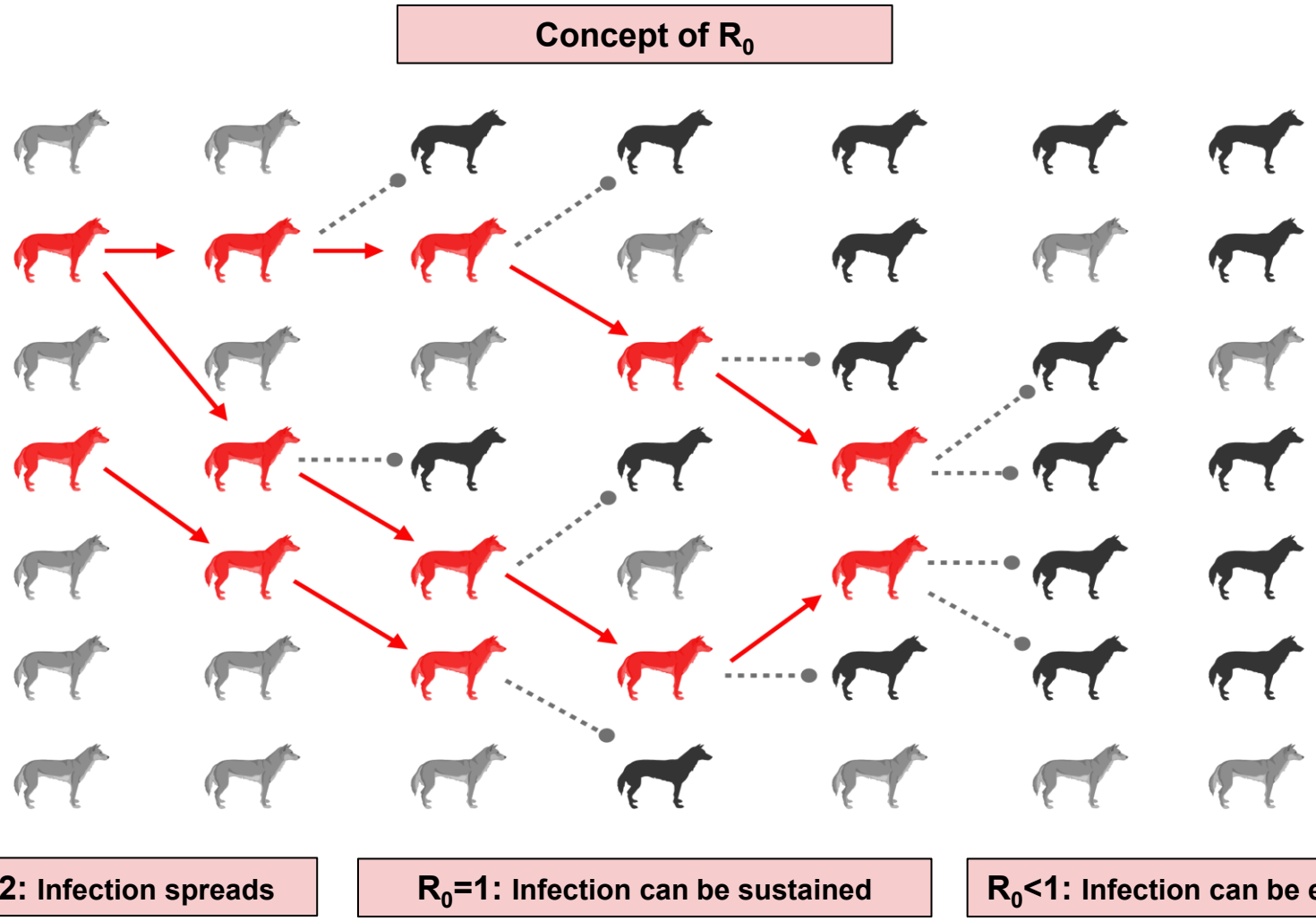
Oral Rabies Vaccination (ORV) in Dogs: History, Principles, Concepts and Requirements for Vaccines

Thomas Müller
Conrad Freuling

Vaccinating dogs is key to herd immunity



Cleaveland et al., 2018

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Parenteral vaccination – Increased inadequacies

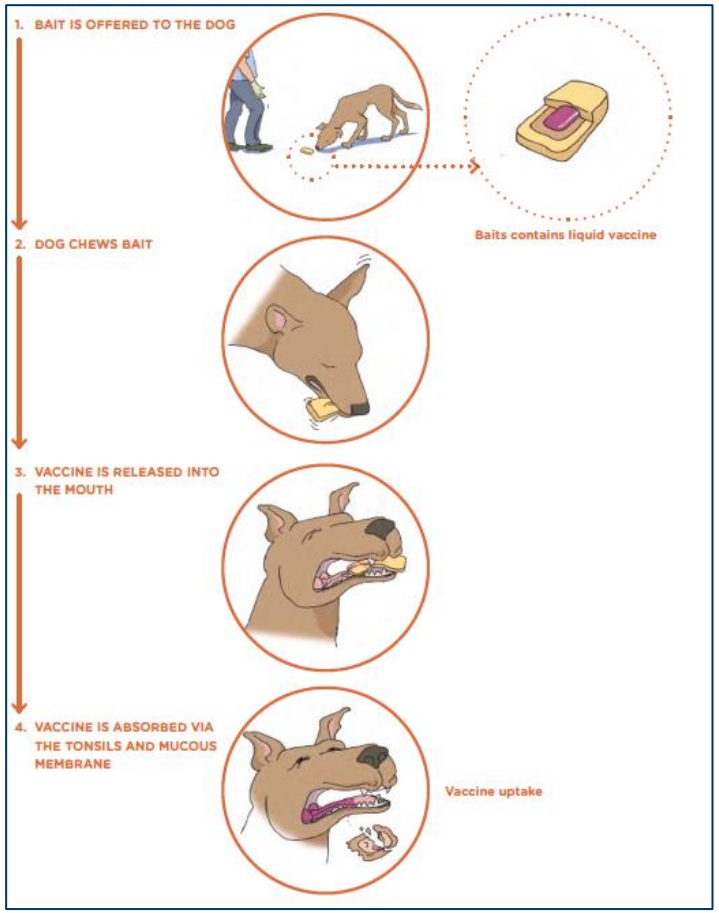
Table 1. Examples from the published literature of vaccination campaigns that have met or failed to meet vaccination targets

Successful vaccination programs			Unsuccessful vaccination programs		
Country	Vaccination coverage, %	Reference	Country	Vaccination coverage, %	Reference
Zambia	80	(*29*)	Chad	19	(*30*)
Mexico	>90	(*31*)	Chad	24	(*32*)
Chad	74	(*30*)	Kenya	29	(*33*)
Thailand	70	(*34*)	Nigeria	17	(*35*)
Bolivia	85	(*36*)	South Africa	56	(*37*)
Tanzania	68	(*38*)	Tanzania	9	(*38*)

Wallace et al. 2020

The problem of vaccinating free-roaming dogs

ORV of dogs – a promising alternative



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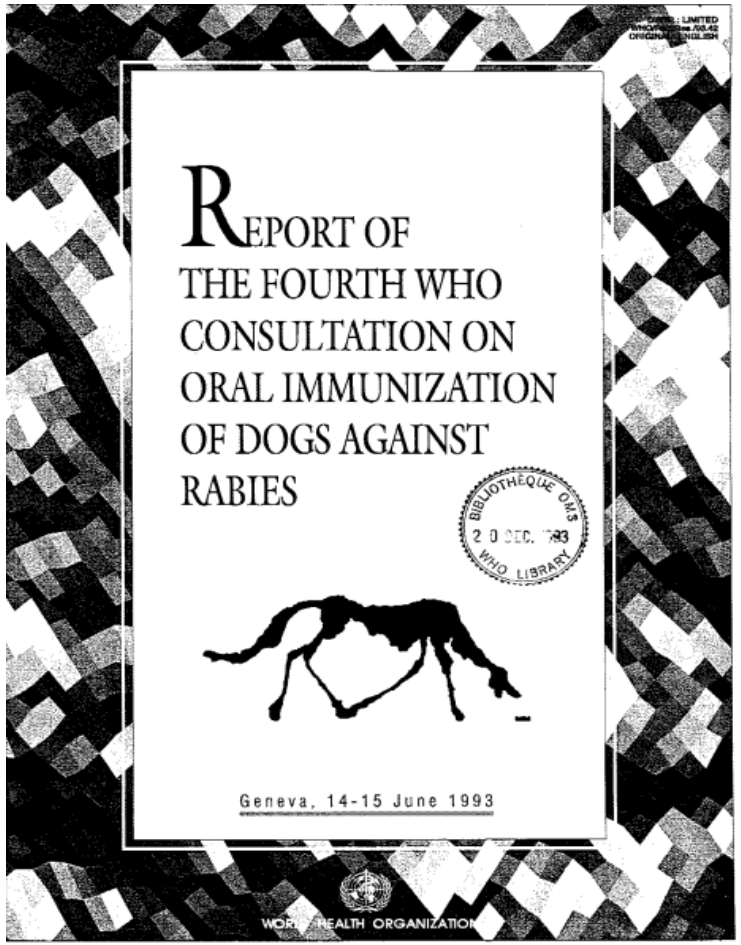
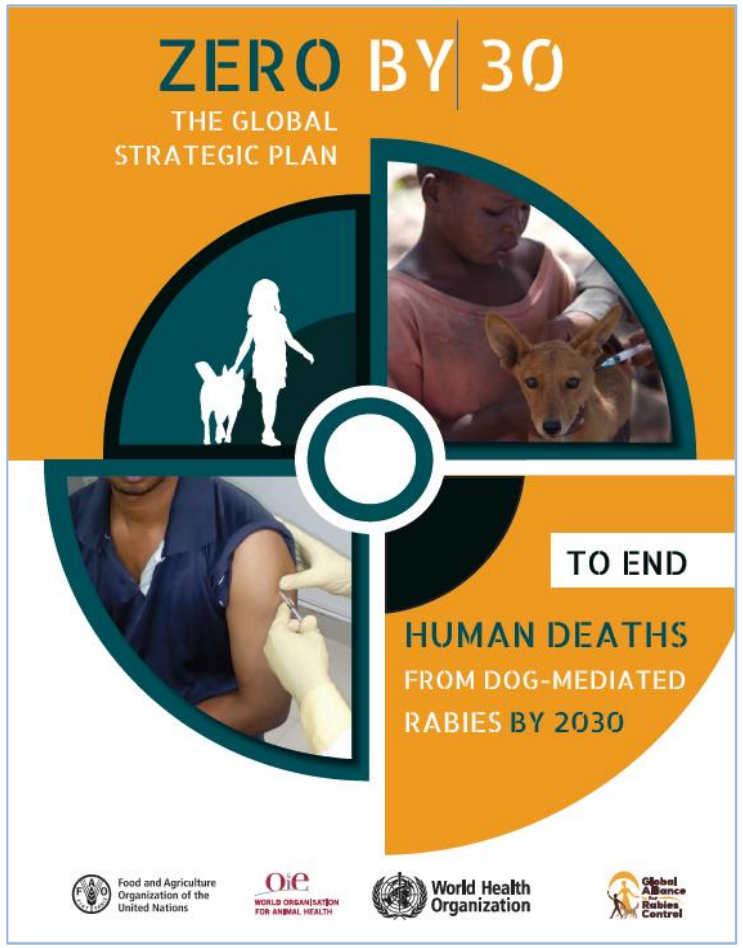
ORV of dogs – revival of an old idea



- WHO in collaboration with WOAH played an important role in promoting international collaboration and coordinating research through informal groups of subject matter experts and international stakeholders

- 13 international consultations and meetings in the past 35 years

ORV of dogs – revival of an old idea



REVIEW Open Access

Oral vaccination of dogs: a well-studied and undervalued tool for achieving human and dog rabies elimination

Florence Cliquet[1*], Anne-Laure Guiot[2], Michel Aubert[3], Emmanuelle Robardet[1], Charles E. Rupprecht[4] and François-Xavier Meslin[5]

ONLINE REPORT

Role of Oral Rabies Vaccines in the Elimination of Dog-Mediated Human Rabies Deaths

Ryan M. Wallace, Florence Cliquet, Christine Fehlner-Gardiner, Anthony R. Fooks, Claude T.
Alvaro Aguilar Setién, Changchun Tu, Vlad Vuta, Boris Yakobson, Dong-Kun Yang, Gideon B
Conrad M. Freuling, Lea Knopf, Artem Metlin, Patricia Pozzetti, Pebi Purwo Suseno, Sean V. S
Gregorio Torres, Marco Antonio Natal Vigilato, Bernadette Abela-Ridder, Thomas Müller

ORV of dogs – revival of an old idea

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Oral rabies vaccine: a new strategy in the fight against rabies deaths

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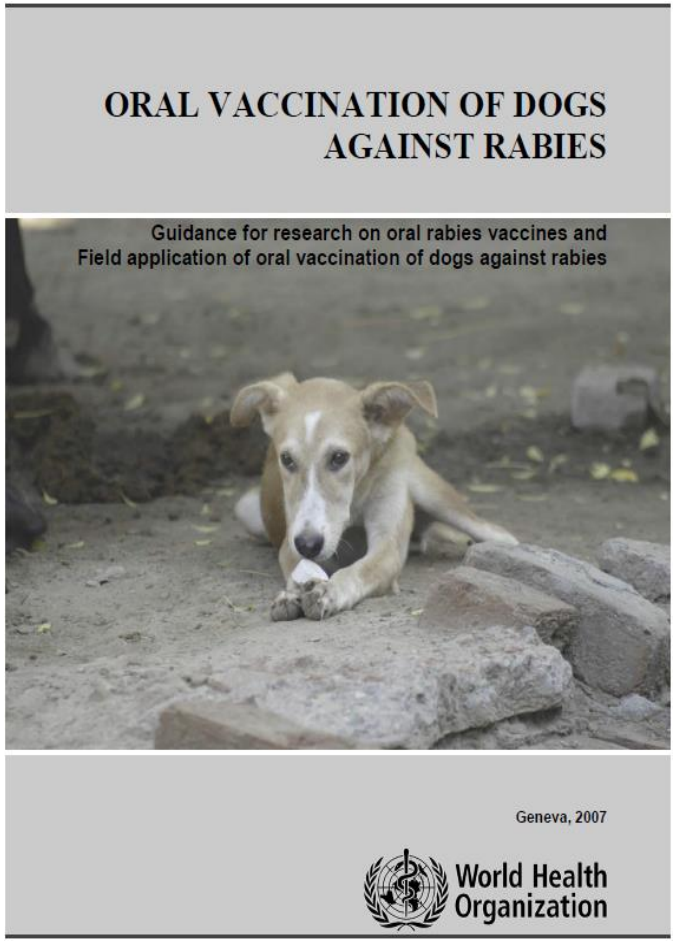
Promoting Oral Rabies Vaccines for Free Roaming Dogs

ORV of dogs – guidance needed



UNITED AGAINST RABIES FORUM ZERO BY 30 *One Health in Action*

DECEMBER 2020

PARTNERING FOR SUCCESS

ELIMINATING RABIES IS AN ACHIEVABLE GOAL,
IF WE WORK TOGETHER

- revision of the 2007 WHO recommendations on ORV of dogs
- transition from experimental to field application of ORV
- New joint WOAH/WHO/FAO document

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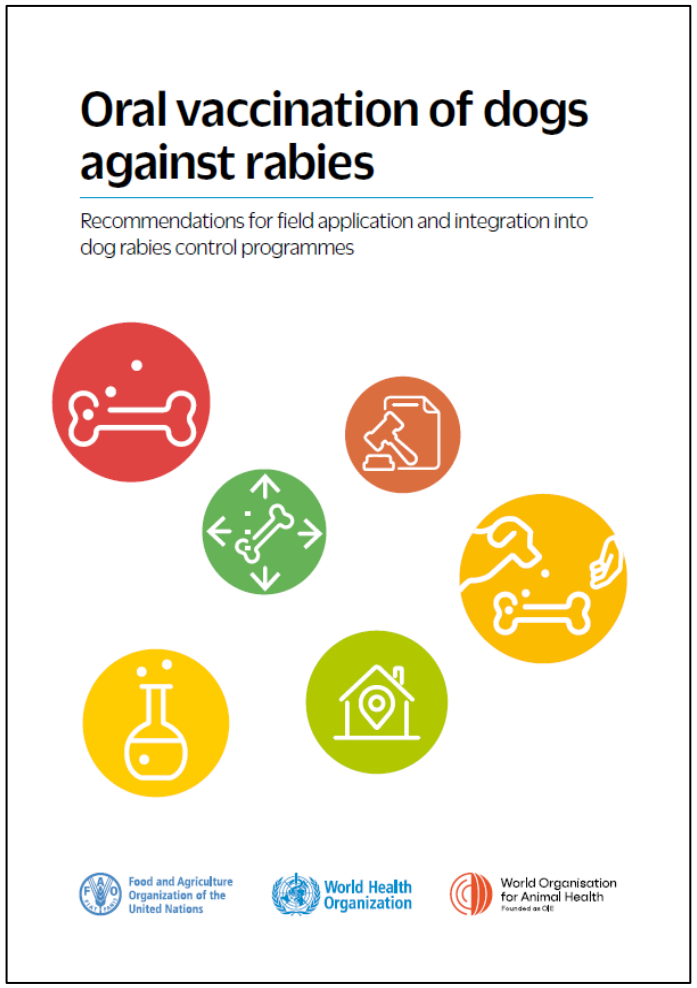
ORV of dogs – new recommendations



Contents

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ORV of dogs – main pillars

ORAL RABIES VACCINE

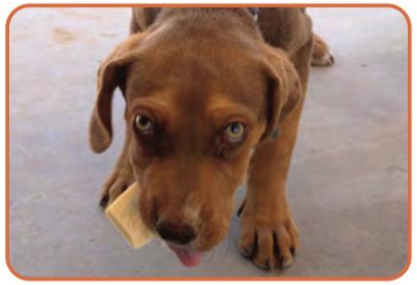
- safe
- efficacious
- effective

BAIT/BLISTER/SACHET

- highly attractive
- optimal release of vaccine in oral cavity

DISTRIBUTION SYSTEM

- optimising bait availability to target species
- limiting non-target species contact including humans
- hand-out & retrieve model
- distribution to dog owners
- wildlife model



MAIN PILLARS OF THE ORAL VACCINATION CONCEPT FOR DOGS

ORV of dogs – Vaccine production

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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USDA Animal and Plant Health Inspection Service
U.S. DEPARTMENT OF AGRICULTURE

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National regulatory requirements

international production guidance

- WOAH - CHAPTER 1.1. 8 . Principles of Veterinary Vaccine Production
- EMA - General Scientific Guidelines on Requirements for the Production and Control of Immunological Veterinary Medicinal Products Including Vaccines
- FDA - Guidance for Industry - General Principles for the Development of Vaccines to Protect Against Global Infectious Diseases
- USDA/APHIS/CVB - Biologics Regulations and Guidance

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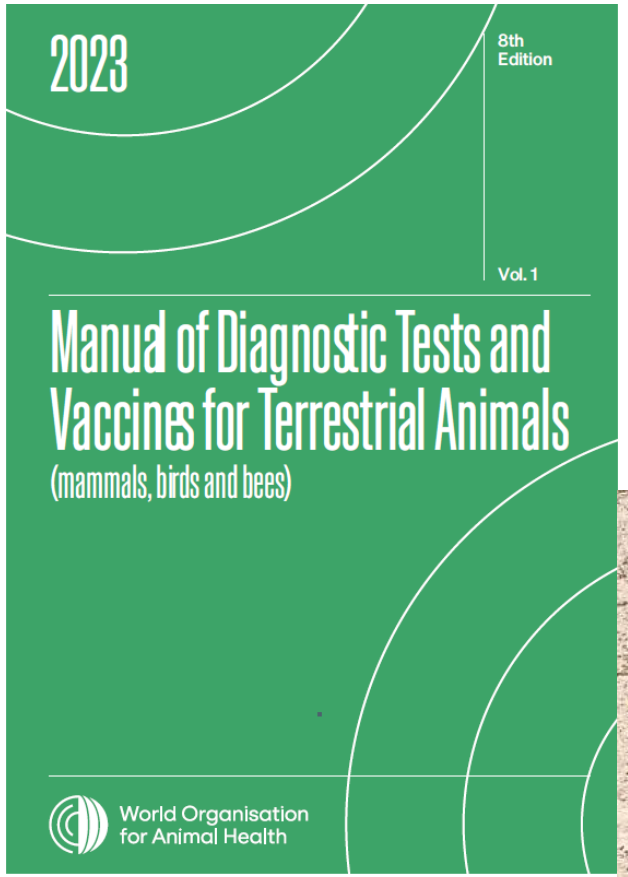
ORV of dogs – minimum requirements for vaccines



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

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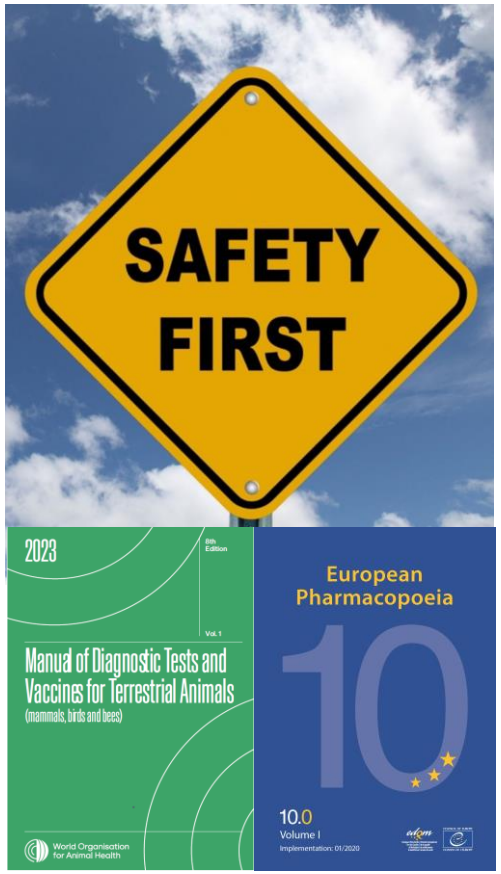
ORV of dogs – minimum requirements for vaccines



	Target species	Non-target species				
Requirements	**Dogs**	**Cats**	**(Wild) rodents**	**Suckling mice#**	**SCID nude mice**	**Humans**
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

animal studies

non-animal studies

X required by WOAH

X required by EMA

X required by both

SCID = severe combined immunodeficiency genetically affecting both B and T cells
Nude mice = genetically inhibited immune system due to a greatly reduced number of T cells

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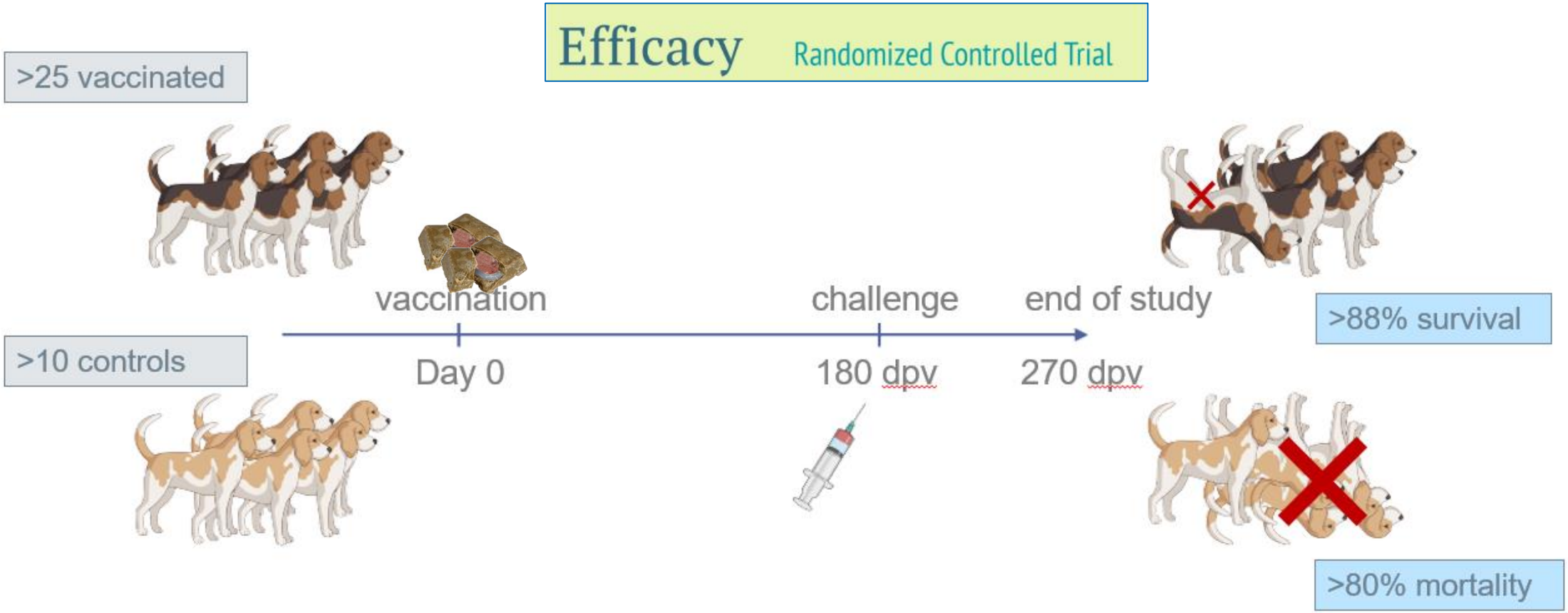
ORV of dogs – minimum requirements for vaccines



ORV of dogs – oral rabies vaccines

CONTINUOUS INFORMATION

First Oral Rabies Vaccine for Dogs

vaccines

MDPI

Article

Efficacy of Oral Rabies Vaccine Baits Containing SPBN GASGAS in Domestic Dogs According to International Standards

Katharina Bobe [1], Steffen Ortmann [1], Christian Kaiser [2], David Perez-Bravo [1], Jörn Gethmann [3], Jeannette Kliemt [4], Sophia Körner [1], Tobias Theuß [1], Thomas Lindner [1], Conrad Freuling [4], Thomas Müller [4] and Ad Vos [1,*]

When it comes to free-roaming dogs, oral rabies vaccination (ORV) may play a crucial role in the global fight against canine rabies and could revolutionise the progress towards the 'Zero by 30' global strategic plan. For the first time, and according to scientific literature, there is an oral rabies vaccine for dogs.

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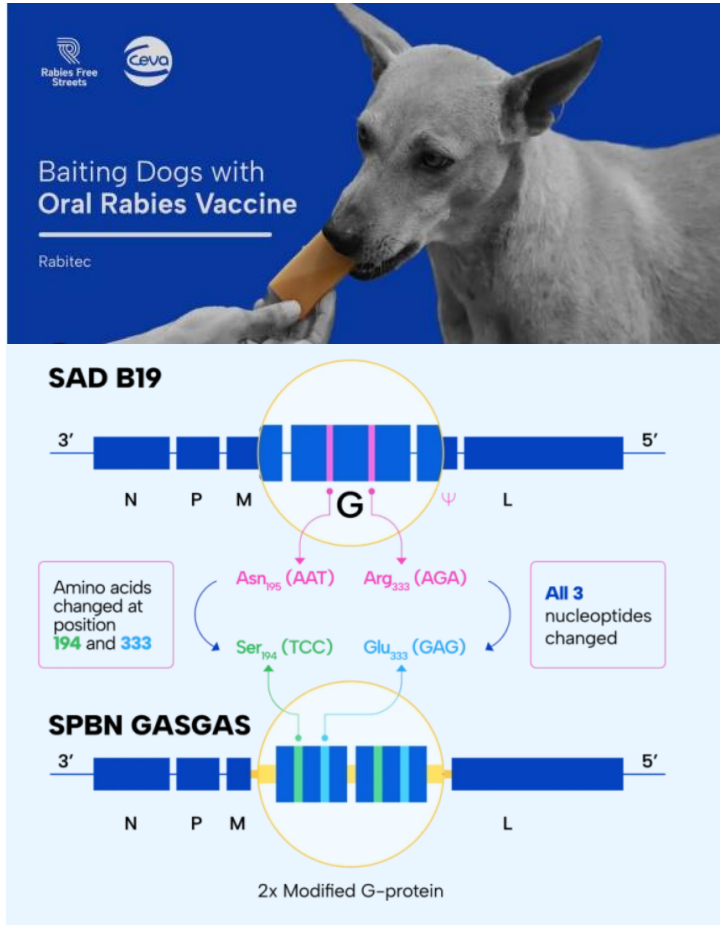
ORV of dogs – vaccine strain SPBN GASGAS



General information					Characteristics				Efficacy				Safety
	License				Vaccine				studies performed'		Fullfilling WOAH standards		Fullfilling WOAH standards
Vaccine strain	Centralized (EMA or EAC)	National/ decentralized	Wildlife	Dogs	GMO	Vector	type	generation *	Wildlife	Dogs	Wildlife	Dogs	
SPBN GASGAS	+	+	+	+	+	RABV	A	3	+	+	+	+	+
SAG2	+	+	+	-	-	RABV	A	2	+	+	+	NI	NI
SAD B19	-	+	+	-	-	RABV	A	1	+	+	+	NI	NI
SAD Bern	-	+	+	-	-	RABV	A	1	+	+	+	NI	NI
VRG	-	+	+	-	+	VACV	R	-	+	+	+	NI	NI
AdRG1.3	-	+	+	-	+	HAdV5	R	-	+	NI	+	NI	NI
SAD Clone'	-	+	+	-	-	RABV	A	1	+	NI	+	NI	NI
VRC-RZ2	-	+	+	+	-	RABV	A	1	+	+	NI	NI	NI
KMIEV-94	-	+	+	-	-	RABV	A	1	+	+	NI	NI	NI
VRG	-	+	+	+	+	VACV	R	-	+	+	NI	NI	NI
RV-97	-	+	+	-	-	RABV	A	1	+	NI	NI	NI	NI
RV-97	-	+	+	-	-	RABV	A	1	+	NI	NI	NI	NI
ERA G333	-	+	+	-	+	RABV	A	3	+	NI	NI	NI	
RV-97	-	+	+	-	-	RABV	A	1	+	NI	NI	NI	
SAD Bern SAD B19 like	-	+	+	+	-	RABV	A	1	NI	NI	NI	NI	
ERA G333	-	+	+	-	+	RABV	A	3	NI	NI	NI	NI	NI

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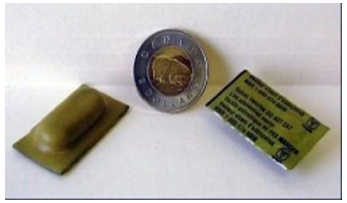
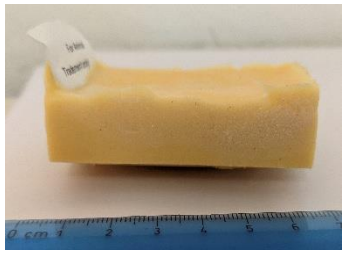
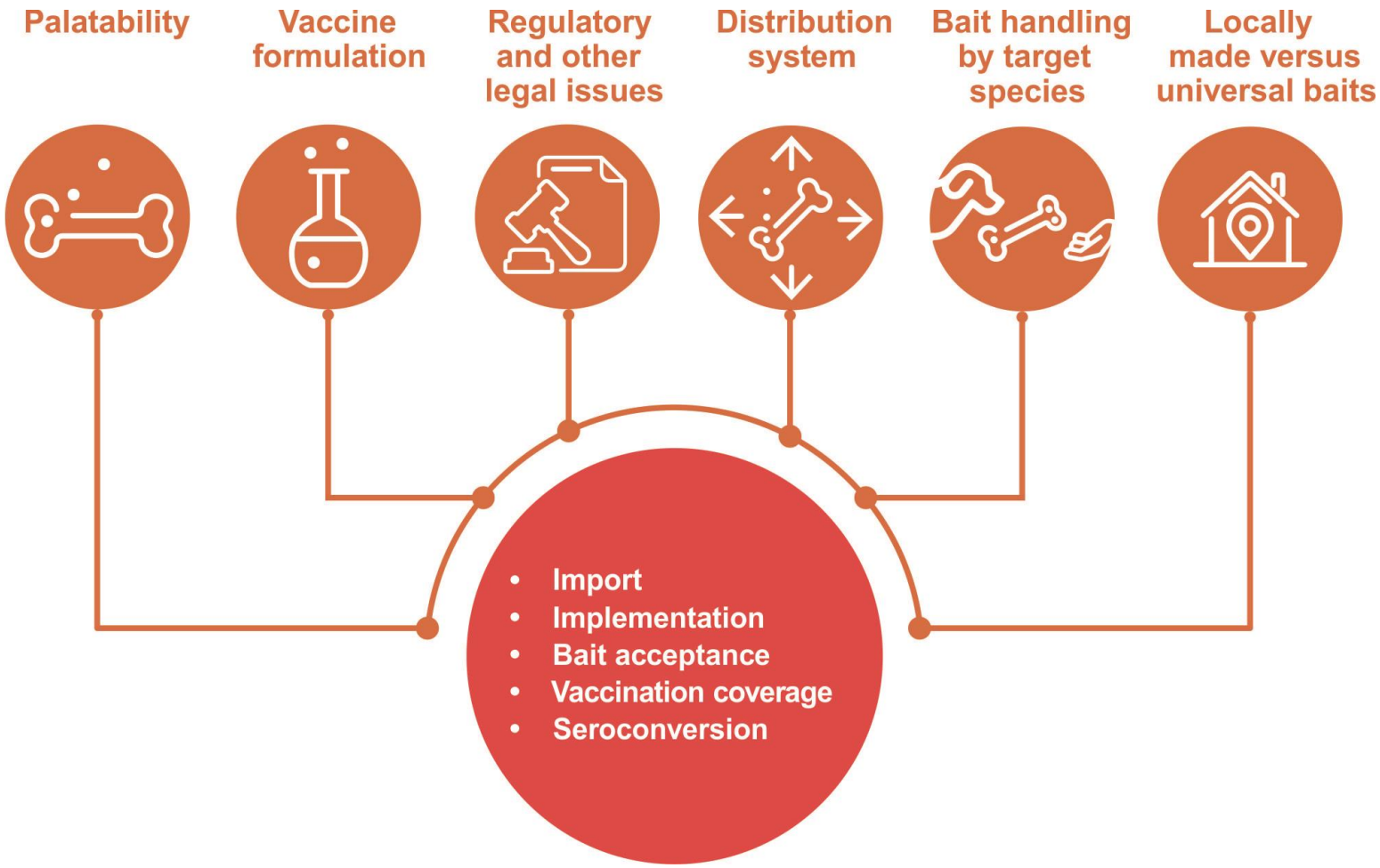
ORV of dogs – bait specifications & challenges







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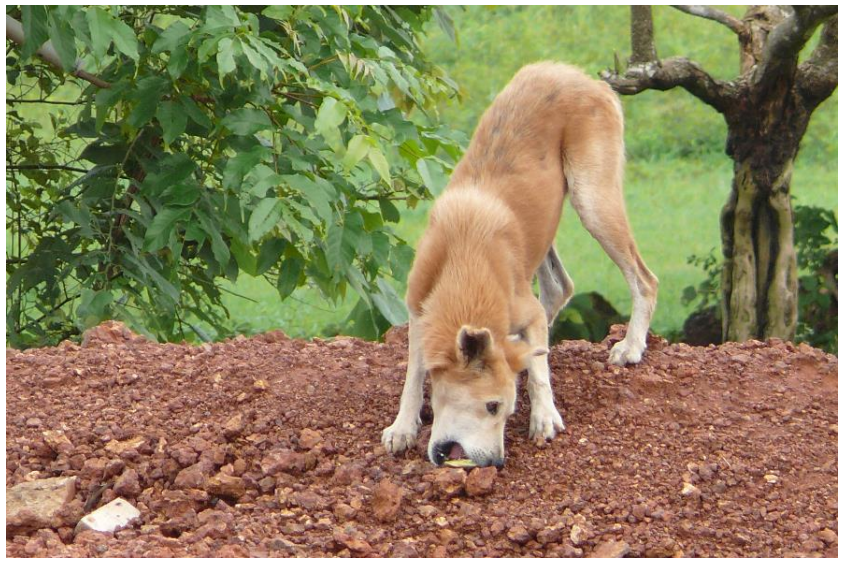
ORV of dogs – storage & transport

Long term storage
-20°C

Transport – frigerated temperatures

ORV of dogs – distribution systems

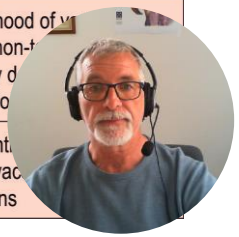


- Hand out and retrieve
- Distribution to dog owners
- Wildlife model

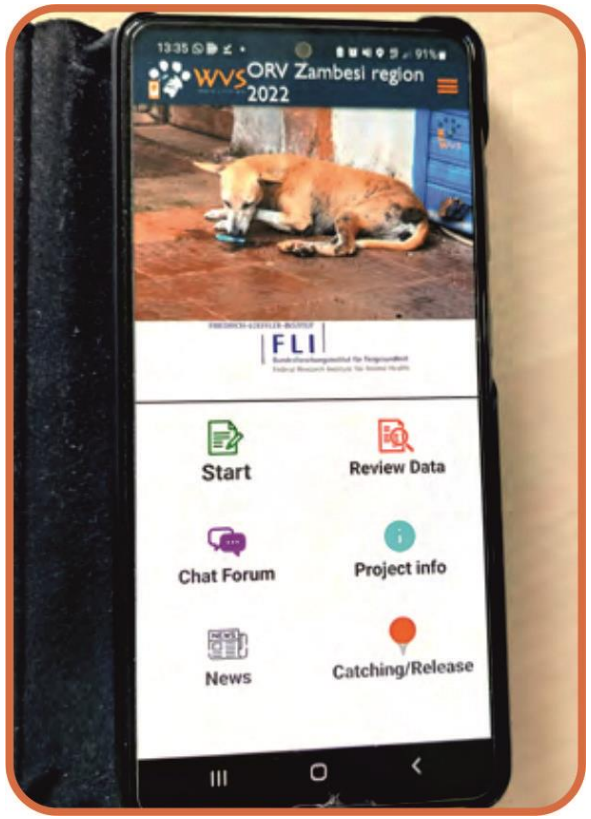
ORV of dogs – distribution systems

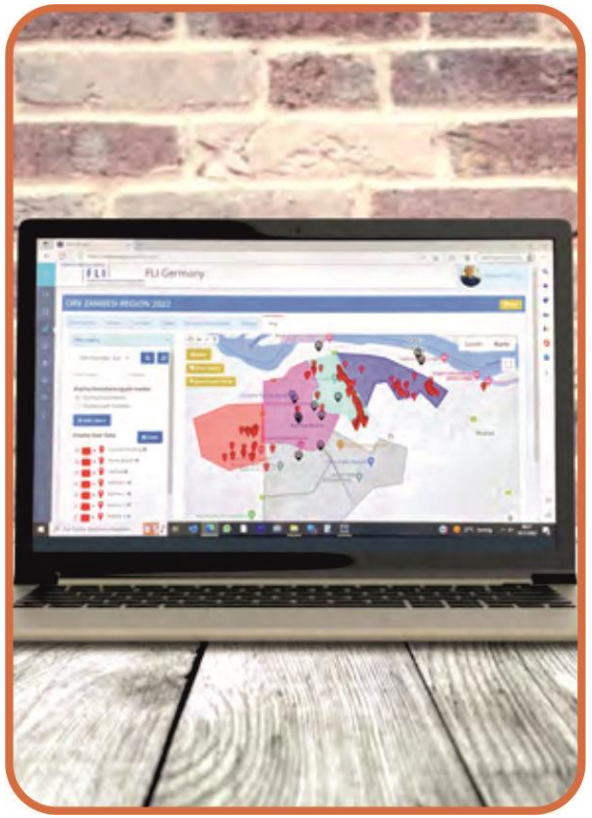
	Categories	Hand-out and retrieve model	Distribution to dog owners	Wildlife model
Advantages	**Target** (for reaching 70% vaccination coverage)	• any owned or ownerless dog (not accessible for parenteral vaccination)	• any owned dog (not accessible for parenteral vaccination)	• dogs that cannot be approached and offered a bait directly
	Logistics	• requires little training and animal handling experience	• requires little training and animal handling experience	• requires little training and animal handling experience
		• provides the best supervision of baits distributed and spatial coverage	• requires fewer human resources	• requires fewer human resources
	Costs		• reduces distribution costs through time savings and travel efficiency	• reduces distribution costs through time savings and travel efficiency
	Other	• reduces waste of vaccine baits (hardly any baits are not or taken by non-target species)	• dogs do not have to be present during distribution	• dogs not encountered during a systematic search can still locate a bait
		• reduces potential direct human contacts with vaccine (baits)	• close bonds between owners and dogs may increase likelihood of vaccination	• bait distribution can be done at a larger scale and in a time-efficient way
		• limits environmental pollution (discarded blisters)		• potentially vaccinates secondary wildlife vectors that may be partial/occasional reservoirs

	Categories	Hand-out and retrieve model	Distribution to dog owners	Wildlife model
Disadvantages	**Target** (for reaching 70% vaccination coverage)	• requires targeting individual dogs	• has negligible effect in areas with a high proportion of ownerless, hard to reach, free-roaming dogs	• lowers probability that target dogs will locate and consume a vaccine bait
	Logistics	• requires using people trained in approaching and offering baits to dogs	• last phase of supply chain unknown (cold chain)	• requires people with local knowledge of habitats frequented by dogs
				• might require effort (time/ money) to get permission to access where dogs are
				• estimation of vaccination coverage is more difficult to assess
	Costs	• requires more human resources	• requires higher number of vaccine baits	• requires a higher number of vaccine baits distributed in the environment
			• potential increase of human contact with the vaccine	• sophisticated delivery equipment may be required (aerial distribution)
	Other	• time-consuming compared to other methods	• reduced control over fate of vaccine baits (human contacts, waste disposal)	• increased likelihood of v bait uptake by non-t species thereby d availability for do
			• increased risk of human contact with the vaccine	• increased potenti target species vac including humans



ORV of dogs – data capturing





- critical for programme monitoring and interpretation of campaign effectiveness
- No paper records!
- Free and easy-to-use mobile data-gathering platforms

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ORV of dogs – regulatory affairs

- Import requirements can vary from country to country
- May require different set of documents and/or different governmental departments for approval and (customs) clearance
- Consult the competent national authorities prior to initiating the importation process to become familiar with the procedure and to avoid problems and unnecessary delays
- Import
  - of licensed oral rabies vaccines
  - for emergency use of oral rabies virus vaccines
  - for experimental use of oral rabies vaccines

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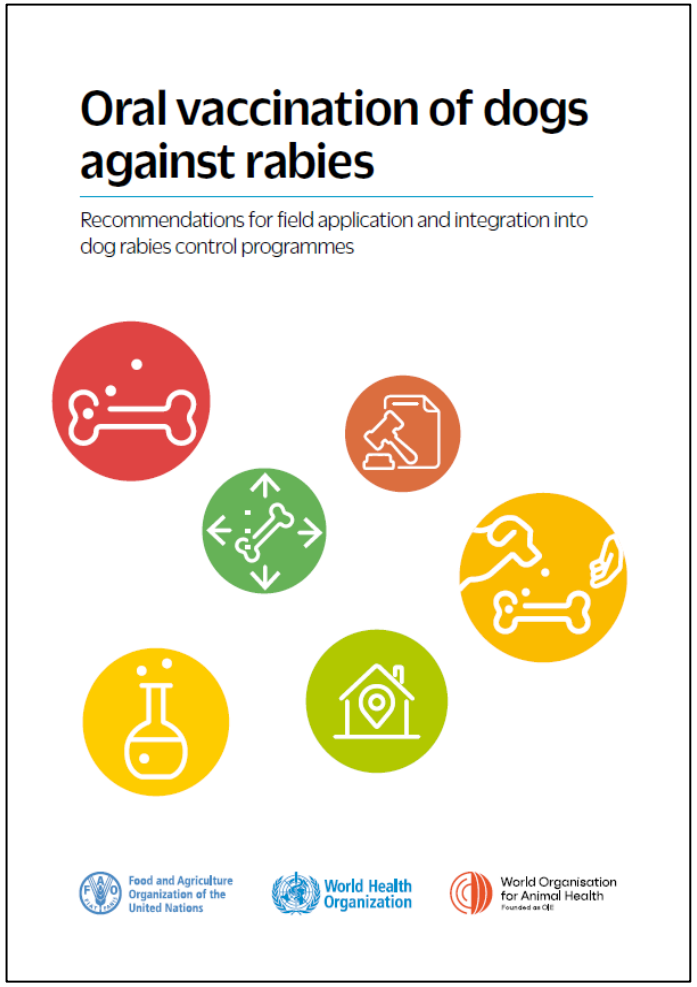
ORV of dogs – Annexes



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/publications/oral-vaccination-of-dogs-against-rabies-recommendations-for-field-applications-and-integration-into-dog-rabies-control-programmes/

Annex C. **Sugested 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.or g/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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ORV of dogs – FQAs

Frequently Ask Questions

Q1	What is in the vaccine bait?
	The vaccine bait contains a blister or sachet filled with the liquid vaccine. See also section 3.2.1.
Q2	How does it work?
	If the dog is chewing on the bait the blister or sachet filled with the liquid vaccine will be perforated and the vaccine is released into the oral cavity where vaccine uptake takes place. *See also section 3.2.1. and 3.2.4.*
Q3	What do I do when I find a vaccine bait / discarded sachet?
	Due the high attractiveness of the baits for dogs and the preferred distribution system, vaccine baits will be rarely found in the field. If you find a vaccine bait / discarded sachet simply do not touch it.
Q4	What if my child finds a vaccine bait / discarded sachet?
	If the vaccine bait/sachet is/was still intact there is no reason to be concerned about. In case, the vaccine bait does/did show chewing marks indicating that the sachet was punctured this might indicate an potential exposure and medical advice should be sought. See also sections 2.3., 6.9, 6.11. and Annex….
Q5	Has there been any reported human vaccine induced rabies cases with ORV?
	No there has been no vaccine induced rabies case reported due to ORV. Only vaccines with the highest safety profile according to international standards should be used for ORV of dogs. See also section 2.2 and 2.3.
Q6	Is there a risk for vaccinators or other people that handle the vaccine baits?
	No, as touching or handling of an intact bait system does not pose a risk. However, any staff member or person involved in dog rabies control activities or mass dog vaccination campaigns should preferably receive preventive rabies vaccination. See also section 6.5.
Q7	What is the withdrawal time of orally vaccinated dogs (dog meat consumption)?
	ORV does not impact dog meat consumption at all.
Q8	How to store and transport baits (cold chain)?
	Proper storage and transport are crucial for maintaining the effectiveness of the oral rabies vaccine. See section 6.3.
Q9	Is the vaccine thermostable and how long does the vaccine stay viable in open air conditions?
	No, since oral rabies vaccines are based on replication-competent live viruses the vaccine is not viable for very long periods outdoors. High outdoor temperatures and ultraviolet light kill the vaccine in a very short time. See section 6.3.
Q10	In case that the sachet is 'open' (perforated) how long does the vaccine remain efficacious?
	Since oral rabies vaccines are based on replication-competent live viruses the vaccine is not viable for very long outdoors. High outdoor temperatures and ultraviolet light kill the vaccine in a very short time. See section 6.3.
Q11	What about cats and ruminants (goats, cows), can they be vaccinated with the bait?
	Oral rabies vaccines for dogs are unlikely to induce an immune response in cats and ruminants because they have not been optimised for non-target species.
Q12	Can dogs develop an appetite for animal species from which material has been incorporated in the baits ?
	It is highly unlikely that the occasional consumption of egg bait (depending on the number of campaigns it is one or two baits per year) will change a dog's food preferences. So far, there are no indications or reports that give cause for concern in this regard.
Q13	How to mark dogs that were orally vaccinated?
	Orally vaccinated dogs cannot be marked externally. To do this, you would have to catch the dogs and then you could have vaccinated them parenterally. Methods such as adding a tissue dye to the vaccine are non reliable and may impact vaccine potency. Other tissue markers used for ORV are no alternative. See section 3.2..
Q14	What happens when a dog eats multiple baits and how can this be prevented?
	Overdose studies (simulating a dog consuming multiple baits) are part of the safety assessment of the oral rabies vaccine (see section 2.2.). So this is no problem. The right distribution method and the skills and experience of vaccinators can prevent consumption of multiple baits by the same dog in most cases.
Q15	What is the difference between an oral and parenteral vaccine?
	While a parenteral vaccine has to be injected into the muscle or under the skin using a syringe and needle, oral vaccinesare easier to administer because they elicit an immun response via uptake in the oral cavity.
Q16	What is the cost of the oral vaccine?
	This is difficult to say. Oral vaccines will definitely be more expensive than inactivated (parenteral) vaccines. However, there is no global fixed price both for oral and parenteral vaccines, as this is determined by many factors, incl. country specific costs.
Q17	Are the vaccine capsules (sachets) biodegradable or absorbable in the animals?
	Unfortunately, none of the currently available sachets are yet biodegradable or absorbable. However, the problem is not trivial and manufacturers are working hard to look for solutions.
Q18	What is the coverage period i.e how often would you need to repeat ORV in a given population?
	As with mass parenteral mass vaccination of dogs, ORV must be conducted recurrently in a given population until the rabies incidence is zero. I… population in an area should be vaccinated for at least up to two… last recorded case of rabies. That's why rabies surveillance a… ORV campaigns is crucial. See sections 6.4. and 6.10.
Q19	Is the vaccine (bait) accessible to anyone?
	No. The procurement and supply of vaccines is the sole respo… supervision of the respective competent authorities or its' repre…
Q20	Baits that were not accepted by a dog can they be used again?

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Acknowledgements

Authors

- Thomas Müller
- Conrad Freuling
- Richard Chipman
- Ryan Wallace
- Rachel Tidman
- Ad Vos

Federal Ministry for Economic Cooperation and Development

Federal Ministry of Agriculture, Food and Regional Identity

Reviewers

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