WOAH's perspectives on Oral Rabies Vaccines (ORVs)

Regional Training of Trainers Workshop on Mass Dog Vaccination
Veterinary College, KVAFSU, Hebbal, Bengaluru, India
28 Nov – 2 December 2022

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World Organisation for Animal Health
Founded as OIE

MISSION RABIES

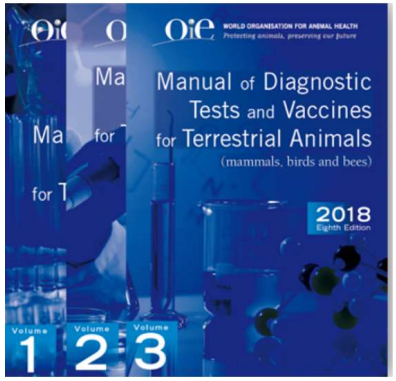
Contents

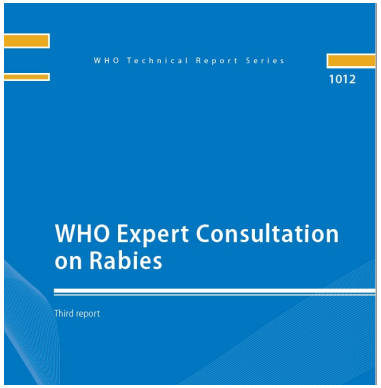
- WOAH Standards on ORV
- Key elements of ORV use in dogs
- WOAH regional activities on ORVs
- Challenges
- Way forward

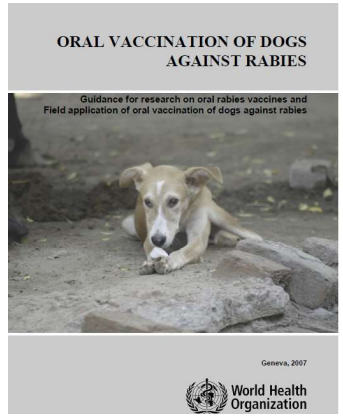
WOAH Terrestrial Manual on Rabies

Chapter 3.1.18 Infection with rabies virus and other lyssa viruses
3. Rabies vaccines for oral use
3.1 Background
3.2 Outline of production and minimum requirement
3.3 Requirements for relevant regulatory approval

- Harmonisation of WHO expert consultation and WOAH International Standards
- Joint technical articles
- Update 2007 WHO dog oral vaccination guidelines







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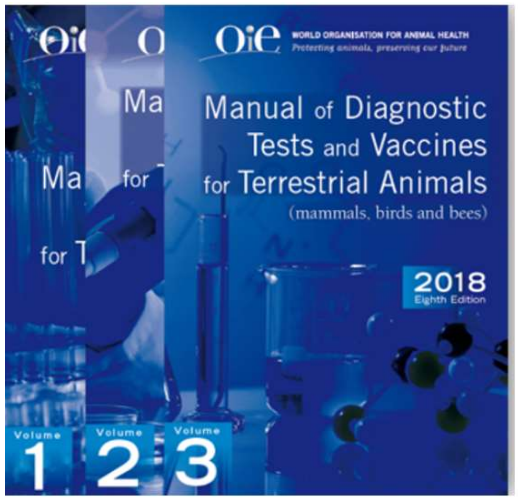


- Crucial for licensing
  - Manufacturing process
  - Safety requirements
  - Efficacy requirements
  - Stability
  - Bait requirements and characteristics

https://www.oie.int/fileadmin/Home/eng/Health_standards/tahm/3.01.17_RABIES.pdf

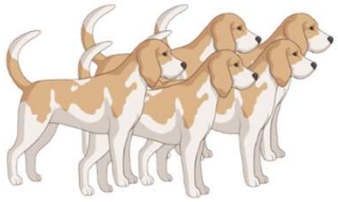
Oral rabies vaccines – WOAH minimum requirements

>25 vaccinated

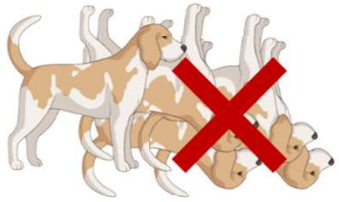
Efficacy
Randomized
Controlled
Trial

>92% survival

>10 controls



Day 0 — Day 180 — Day 270



>90% mortality

Source: Dr Thomas Muller, FLI

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Bundesforschungsinstitut für Tiergesundheit
Federal Research Institute for Animal Health

Oral rabies vaccines – Efficacy vs effectiveness

Efficacy

- refers to the ability of a given oral rabies vaccine, under ideal conditions, to
  - produce the intended effect in vaccinated dogs, i.e. protection against rabies
  - is a precondition for licensing

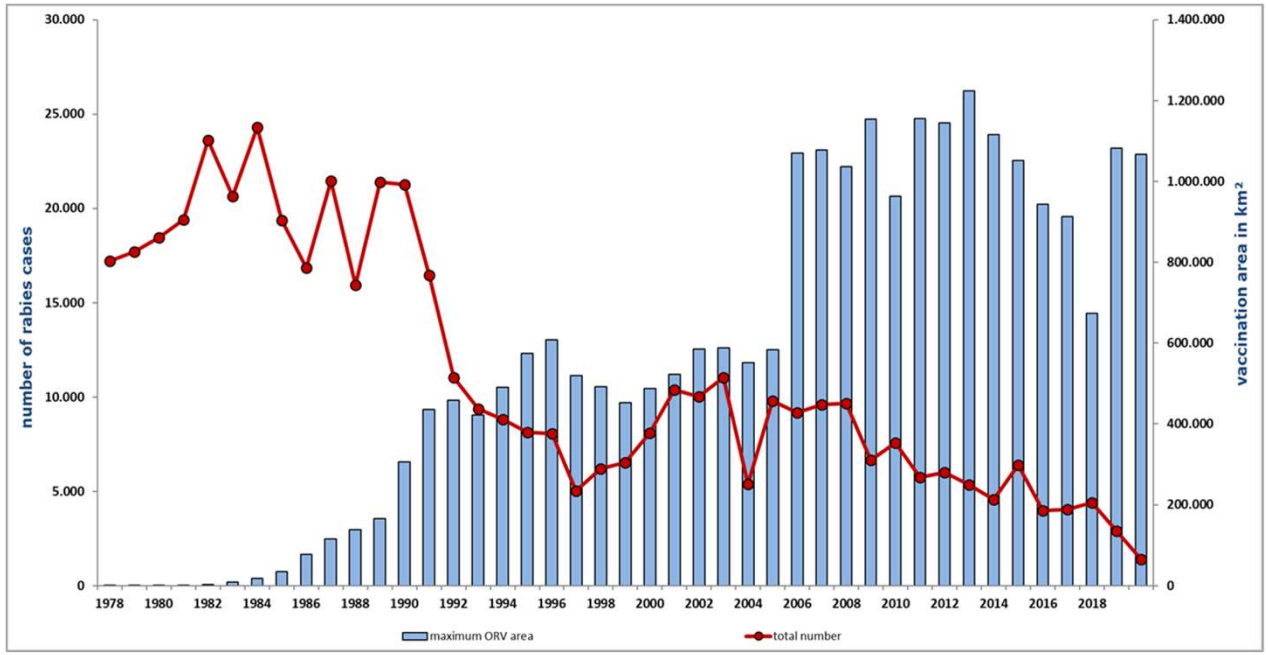
Effectiveness

- refers to how well the oral rabies vaccine in question performs under field conditions based on
  - reduction in rabies cases and
  - serologic evidence or
  - other measures of a vaccine induced immune response in the target species

Source: Dr Thomas Muller, FLI

Elimination of sylvatic rabies in Europe

- Emergence of fox-mediated rabies in Europe in 1940s to 1980s
- ORVs vaccines used since 1978 (Switzerland first country to do field trial) – 40 years in 30 European countries
- Covered 43 Million Square Kms (1978-2022)
- 13 different ORVs used; more than 860 Million ORV baits used



Europe – ORV areas & rabies prevalence

Freuling et al., 2019; Müller et al., 2015; Müller and Freuling, 2020; Friedrich-Loeffler-Institut, 2022

Can ORVs be used in dog-mediated rabies control?

- **Important points for successful dog rabies vaccination**
  - Dog population ecology – dog keeping practices, pets, free roaming
  - Vaccination methods – central point, door-to-door, capture-vaccinate-release, ORVs, combination of these
  - More than 70% vaccination coverage in the susceptible population

Source: https://helpanimalsindia.org/

- **Key issues with dog vaccination**
  - Free roaming dogs – major reservoir of rabies virus in Asia including India
  - Difficulty and costly to catch free-roaming dogs
  - Inadequate vaccination coverage

Can ORVs be used in dog-mediated rabies control?

ORVs in dogs – key points to consider

- **Safety**, not only for the target animals, but for non-target species, including humans
- **Efficacy** - should elicit protective immunity
- **ORV baits** - configuration and bait delivery systems are also critical and may require adaptation to local circumstances
- **Cost effectiveness**

Source: Ad Vos, Ceva

Safety of ORVs in dogs

Existing literature

- Many ORVs have undergone stringent process of licensure for use in wildlife in North America and Europe
- Simulation study by US CDC for ORVs in rabies endemic countries in dogs
  - 0.3 persons dead for every 1 billion baits distributed
- Simulation study by Mission Rabies for SPBN GASGAS ORV in dogs India
    - no human deaths for 10 million baits used

Recent field studies on Thailand reported no safety issues in dogs and non-target species including humans with the third generation ORVs

We could vaccinate every dog in endemic countries THREE TIMES and expect 1 human deaths from vaccination (Courtesy – Ryan Wallace, US CDC)

Efficacy of ORVs in dogs

Existing literature

- Field studies with third generation SPBN GASGAS Vaccine Strain in Haiti, Thailand etc. showed that ORVs elicit protective immunity in dogs comparable to parenteral vaccination
- Tested for rabies virus neutralizing (RFFIT) and binding (ELISA) antibodies
- Third generation SPBN GASGAS Vaccine Strain (modified live vaccine) currently undergoing trials in dogs in Namibia, Africa and in Indonesia.

Oral rabies vaccination trials in Thailand (Source: Dr Leelahapongsathon)

Cliquet et al, 2007; Smith et al, 2019; Leelahapongsathon, 2020;

Cost effectiveness of ORVs in dogs

- Currently limited ORVs produced due to less demand
- Initial cost of the ORV is high
- Although ORVs cost more than parenteral vaccines, vaccinators can reach 4 times as many dogs with oral vaccines
- *Field studies in India by Mission Rabies showed that fixed operational team cost for parenteral (catch-vaccinate-release) was 4 times higher than oral bait hand out method (ORVs)
- ORVs target the most important dog population – free roaming

- **If >65% of the dog population is free roaming, ORV is likely to be cost effective**
  - **Wallace et al, 2019**

*Gibson et al, 2019

Challenges for ORV use in dogs

- **Safety**
  - If handout and retrieval method used, ORVs are largely safe
  - Robust international evaluation need to be continued

- **Licensure**
  - Complex process of licensing and registration (live vaccines, vector-based vaccines)
  - Benchmark immunogenicity studies and field trials related to bait acceptance should form the basis for either conditional or full-fledged licensure of oral rabies vaccines for dogs
  - Policy makers to agree on interpretation of parameters of safety and efficacy
- **Production capacity and cost of vaccines**
  - Lack of demand = no incentive to produce
  - Exact costs remain unclear with no commercial ORVs for dogs
  - Strict cold chain requirements

- **Role of ORVs in national rabies control program**
  - Rabies manager should design fit-for-purpose
  - ORVs as complementary to cover inaccessible dogs

Wallace et al, 2020;

Recent publications on ORVs

Emerg Infect Dis. 2020 Dec; 26(12): e201266.
doi: 10.3201/eid2612.201266
PMCID: PMC7706920
PMID: 33219786

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. Sabeta, Alvaro Aguilar Setién, Changchun Tu, Vlad Vuta, Boris Yakobson, Dong-Kun Yang, Gideon Brückner, Conrad M. Freuling, Lea Knopf, Artem Metlin, Patricia Pozzetti, Pebi Purwo Suseno, Sean V. Shadomy, Gregorio Torres, Marco Antonio Natal Vigilato, Bernadette Abela-Ridder, and Thomas Müller

viruses
MDPI

Review

Review of Oral Rabies Vaccination of Dogs and Its Application in India

Gowri Yale [1,*], Marwin Lopes [2], Shrikrishna Isloor [3], Jennifer R. Head [4], Stella Mazeri [5,6], Luke Gamble [6], Kinzang Dukpa [7], Gyanendra Gongal [8] and Andrew D. Gibson [5,6]

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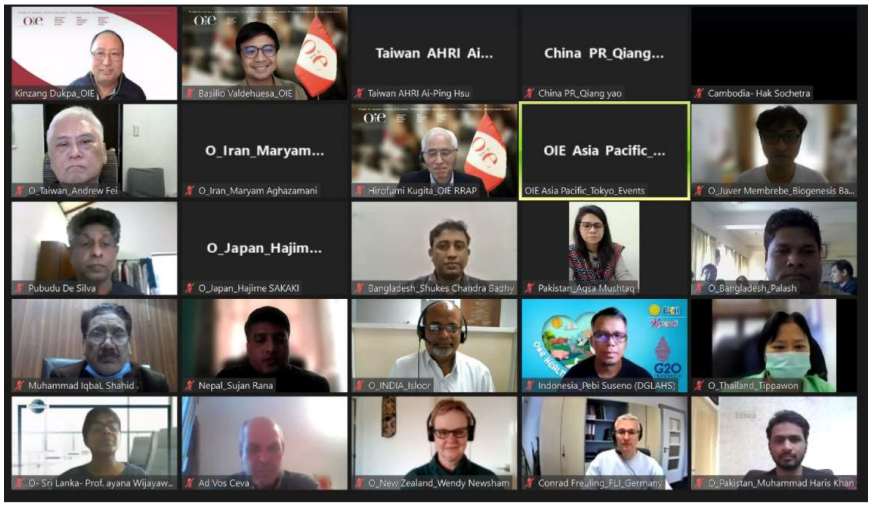
Role of Oral Rabies Vaccines in the Elimination of Dog-Mediated Human Rabies Deaths (nih.gov)

Studies on ORVs and ORV baits in Asia

Country	Type of ORV/ORV bait	Result	Reference
Indonesia (2012)	SAG2 rabies vaccine (modified live)	Immunity elicited lasted longer than parenteral	Faizah et al, 2012
India (2007	SAG2 rabies vaccine (modified live)	Safety and efficacy shown in street dogs	Cliquet et al, 2007
Sri Lanka (2000)	vaccinia recombinant rabies glycoprotein (vector-based)	Acceptability study	Perera et al, 2000
Philippines (2001)	Bait acceptance study	Boiled intestine bait was most widely accepted	Estrada et al, 2001
Thailand (2020)	SPBN GASGAS (third generation modified live)	Safe and efficacious even one year after vaccination in dogs	Leelahapongsathon et al, 2020
Thailand (2018)	Bait acceptance study	Egg-flavoured bait most successful	
Thailand (2021)	SPBN GASGAS	65.5% of the targeted free roaming dogs were vaccinated with ORVs	Chanachai et al, 2021
Thailand (2021)	SPBN GASGAS	76% of vaccinated dogs (25/33) had protective titre 90 days post vaccination	Leelahapongsathon et al, (unpublished)

Initiatives of WOAH Regional Office

- OIE Virtual Workshop on Oral Rabies Vaccines held on 28 February 2022
  - More than 120 participants from 22 countries in the Asia Pacific Region



- Country consultations with Cambodia, India, Myanmar, Philippines, Singapore, Thailand, Sri Lanka, for pilot studies

Information Session on Oral Rabies Vaccines (ORVs), 28 October 2022

https://rr-asia.oie.int/en/events/oie-virtual-workshop-on-oral-rabies-vaccines/

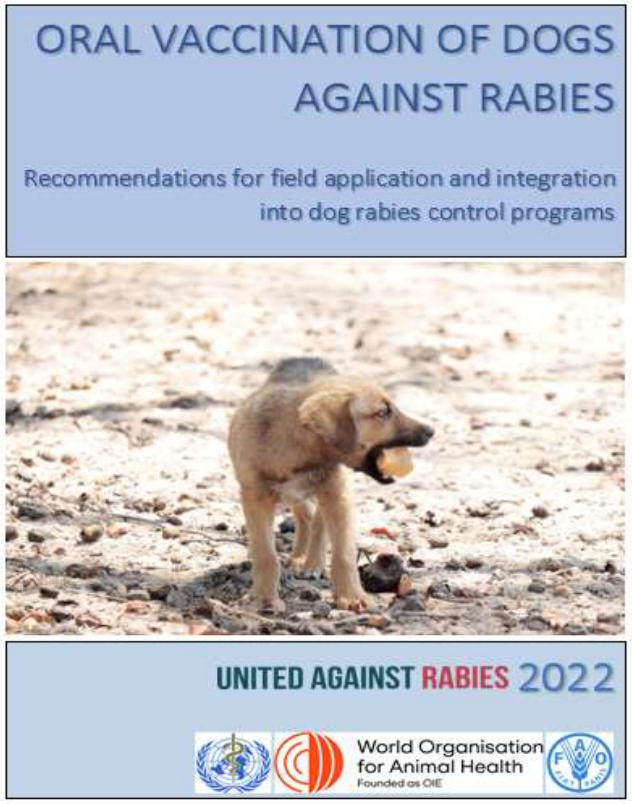
Challenges in piloting of ORVs

- **Import/registration issues**
  - **Live vaccines, vector-based vaccines**
  - **Safety concerns especially, human safety**
- **High shipment costs, high vaccine costs**
- **Technical knowledge/experiences**
  - Limited
- **Lack of guideline on ORVs**
  - Need easy to understand guideline

Questions about:
safety, efficacy when used in dogs,
costs, post-vaccination monitoring,
Reversion to virulence
Safety of vector based vaccines,

UAR Working group 2

- Workstream 4
  - revision of the 2007 WHO recommendation on ORV of dogs
  - transition from experimental to field application
  - New joint WOAH/WHO/FAO document



Courtesy: Thomas Muller, FLI

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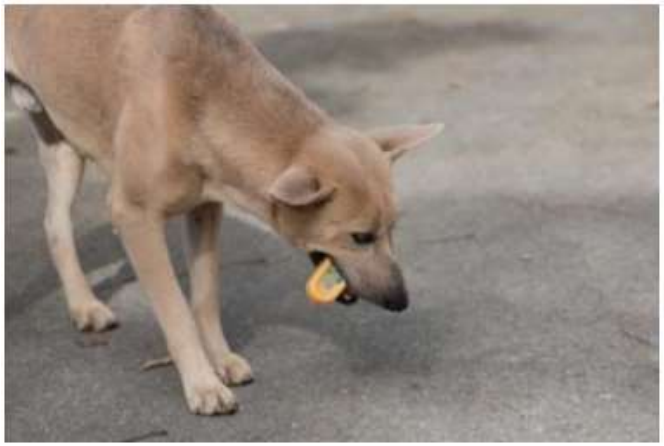
‘ Parenteral vaccination of dogs should remain the foundation of mass vaccination campaigns. […] the use of oral vaccination, especially in free-roaming and inaccessible dogs, […], should represent a complementary measure for the improvement of the overall vaccination coverage. For ORV of dogs, the handout and retrieve model should be used’



Conclusions

- Parenteral vaccination program should continue as the foundation for rabies control
- However, for inaccessible dog populations (free-roaming dogs), ORVs has an important role
- In most rabies-endemic countries, including India, free-roaming dogs are important reservoir hosts
- Critical to ensure comprehensive national vaccination strategy inclusive of free-roaming dogs

- More field studies needed for safety and efficacy of ORVs as not all ORVs are same

- ORVs likely to be a game changer

- Encourage countries to participate in field trials of ORVs to generate more data on safety, efficacy and cost-effectiveness of using ORVs.

Thank you.

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