REVIEW ARTICLE

Oral Rabies Vaccines: A boon in control of rabies in free ranging dogs in India?

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ABSTRACT

Oral rabies vaccines have been in use for the control of sylvatic rabies for years. While the global rabies burden is carried by Asian and African countries, the control programs for the disease have been more effective in North America and Europe. This peculiarity is attributed to the use of oral method of vaccination. The broad reservoir host range for rabies, with it being canine mediated in India demands the need to modify our current control practices. Oral vaccines have been proven to be safe and induce protective antibody titres in dogs against rabies. Furthermore, with an increasing threat of wildlife rabies in different parts of India, there is an urgent need for the use of such vaccines in rabies endemic countries. This short review article is a collective data of the published literature available on different oral rabies vaccines, their field studies and their applicability in animal rabies control.

Key words: Oral rabies vaccines, Rabies, Dogs, Baits

1. INTRODUCTION

Rabies is a fatal zoonotic viral encephalitis that causes 59,000 human deaths annually, 35% of which i.e. 20,000 occurs in India. The obviousgap in terms of affordability and accessibility to post-exposure treatment, rabies awareness and risks of exposure to rabid dogs is evidencedby 10 to 18 times higher deaths in rural than urban areas with 40% of the victims being less than 15 years of age25.For endemic countries like India with itslarge stray dog population, control methods such as mass dog vaccination, animal birth control and waste management falls short. Global pressure to end canine rabies throws light into a rather new aspect in India- Oral Rabies Vaccines (ORVs) for dogs.

In early 20th century, rabies control was by eliminating reservoirs through hunting, trapping or poisoning which eventually raised animal rights issues. In 1978, Street Alabama Dufferin (SAD)rabies strain inserted in chicken headsused as baits laid the foundation for ORVs. Since then, dog mediated rabies has been eliminated in many European countries and the USA22 through the use of viral vectored and live attenuated vaccines. It is also a valuable tool for rabies control in India in terms of dog accessibility, cost and labor requirement11.Although ORV use for sylvatic rabies is common in North America and Europe, dearth of dog specific ORVs, tapered vaccine licensing regulations and inadequate clinical trials impede ORV use for dogs in Asian and African countries.

2. ORAL RABIES VACCINES

Oral rabies vaccines are classified into 3 generations. First generation vaccines contain live attenuated strains obtained by repeated passaging such as SAD, ERA, SAD Bern, SAD B19, RV-97, KMIEV 94, VRC- RZ2. Their use is limited by their

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residual pathogenicity indicated by mortality on intracerebral inoculation in mice. Second generation includes viral vectored vaccines such as RABORAL- VRG, ONRAB and antibody escape mutants such as SAG1, SAG2 that have evaded neutralization by monoclonal antibodies (mAbs). These are limited by their side effects in humans in the former and reversion to virulence in the latter. Third generation vaccines strains such as SPBN GASGAS, ERA 333 claim to overcome these limitations through reverse genetics, by inducing irreversible mutations at specific amino acid sites of rabies glycoprotein. Vaccine types have been described in Table 2.

2.1. RABIES VACCINAL STRAINS AND VECTORS

Street Alabama Dufferin(SAD) strain was isolated from a rabid dog in Alabama, USA in 1935, passaged on mice, chick embryos and cell lines to obtain Evelyn RokitnickiAbelseth (ERA) strain. SAD Bern strain is a cell-adapted derivative of the ERA strain while SAD B19is derived from SAD Bern. The SAG2 strain (SAD Avirulent Gif), is a modifiedlive virusstrain derived from SAD Bern by two sequential mutations, was constructed in a two-stepselection process using neutralizing mAbs where an amino acid at position 333 was replaced by lysine which was again replaced by glutamic acid17. Although they are widely used in rabies vaccines, their safety is undermined by residual pathogenicity or vaccine induced rabies specifically for SAD Bern, SAD B19, SAD P5/88. Different vaccinal strains have been described in Figure 1.

Recently, site directed mutagenesis at selected region through reverse genetics has led to safe and efficacious vaccines. SPBN GASGAS is a similar strain derived from SAD B19 that lacks pseudogene (Ψ) has a mutation at 194 and 333 amino acid sites and a second identical glycoprotein gene10.Viral vectors such as vaccinia used in RABORAL- VRG18or adeno used in ONRAB12 have rabies glycoprotein inserted into them. Currently ORVs used are biotechnology derived vaccines (RABORAL-V-RG®, ONRAB®) and modified live vaccines (RABIGEN®, RABITEC®). ORVs have been described in Table 1.

2.2. BAITS AND MARKERS

The vaccine component is packaged into suitable baits. Commercially fish flavoured baits have attracted wildlife18whereas dog baits depend on acceptancein target species, socio-cultural acceptance and efficacy of the delivery system25.Canine bait preferences to fish meal crumble3, bacon flavor2, boiled bovine intestine1 and poultry meal6was observed in North America where asintestine baits were preferred in Bangladesh, Philippines and Thailand 84 15. Baits are required to have ideal shape, optimum vaccine release, be economical and be resilient to extreme environmental and storage25. As part of baits, markers are indicators to assess uptake of baits by the hosts, such as surface markers (Rhodamine B), tissue markers (Iophenoxic acid) or calciphilic markers (Tetracycline) that are detected on hair and skin, tissues and teeth respectively25. Different ORV bait vaccines depicted in Figure 2.

2.3. VACCINE EFFICACY AND SAFETY

Vaccine efficacy, safety and immunogenicity is verified by protective antibodies of106.6 FFU/mL with SPBN GASGAS in foxes10 and 108 TCID50/dose of SAG2 in badgers14. In dogs, vaccine efficacy is assessed by direct oral instillation, in baits in caged dogs and baits in field25. SAG2 was shown to induce protective antibodies upto 109 days post vaccination with 108.5 TCID50and was safe in dogs5.OIE requirements for sterility, identity, purity, safety and potency need to be met. Safety in target species i.e. dogs and non-target species such as monkeys, rodents or other domestic animals that may encounter ORVs meant for dogs, non-human primates, and immune suppressed animals need to be assessed25. An ORV vaccinal candidate requires distinct details of manufacturer, vaccine construct, dosage, instructions, warnings, post-exposure prophylaxis details, laboratory and field trials, approvalof international public health agency, optimized cost- benefit ratio and sero-surveillancestudies24.

Humoral mediated protective immune response has been observed in rabies by parenteral or oral routes. Rabies virus has been attributed to mucosal immunity pathways based on anatomical structure of the oral cavity. The tonsils are suspected to play a major role in mucosal immunity with the involvement of CD20+ B cells, few CD3+ T cells and IBA1+ macrophages and activation of NFκB genes23.

2.4. STUDIES IN DOGS

ORV studies in dogs are initiated with the bait acceptability studies. Acceptability to intestine and egg baits8 4 15was higher. Efficacy studies found SAG2 has induced protective and long term antibody titres in dogs5 9while 87.5% of the Adeno vector vaccine immunized dogs developed virus neutralizing antibodies (VNA) that lasted upto 2 years26.Safety of SAG2 was validated by the absence salivary excretion and replication in brain and salivary glands of vaccinated dogs. A titre of 108.5 TCID50 per dose was efficacious5. Third generation vaccines was revealed to have neutralizing antibodies20that lasted over 3 years with salivary rabies specific IgA21. SPBN GAS-GAS was predicted to be the ideal vaccine for dogs13 16.Door to door model was more productive at 77% bait uptake7while hand out model was operationally feasible, economical and effective at accessing the free roaming dogs11. Regrettably excessive bait consumption in dogs has also caused gastrointestinal and behavioural symptoms19. Currently no approved dog ORVs is available 24.

3. VACCINE DISTRIBUTION AND PUBLIC HEALTH

Distribution methods for ORVs in wildlife include aircraft distribution to cover large areas and wildlife immunization model, where baits are placed at selected sites for target species. In dogs, door to door model (DDM), wildlife immunization model (WIM) and handout model25 are encouraged.DDMensures safe administration of vaccine baits to dogs by professionals although it is time consuming. WIMallows vaccination of free-roaming and feral dogs where they gather, such as garbage dumping grounds, slaughter houses and markets. Handout models have proven to be most efficiently in owned and free-roaming dogs. Interestingly, GPS enabled mobile applications for dog identification in vaccine distribution has proven to be useful11.

ORVs a crucial means of rabies control in animals can turn hazardous to humans. Vaccinia vectored ORVs have known to cause skin rashes and blisters in immunosuppressed and pregnant individuals18. Adeno vectored ORVs have revealed to cause respiratory infections in children below 5 years12. Modified live attenuated vaccines are feared to have a reversal to virulence. These issues are magnified when the ORVs are used to target domestic dogs that live in close association to human habitat. Consequently the use of warning labels, contact information and instructions and the recent rise of third generation ORVs can aide overcome these limitations. Such uncertain public health risks can be managed with extensive clinical trials, setting up surveillance systems, mandatory pre-exposure and post exposure immunization and by generating public support through extension programmes.

Table 1. Oral Rabies Vaccines

VACCINE NAME	STRAIN/ CONSTRUCT	MANUFACTURER	LICENSE STATUS (For wildlife)	RESIDUAL PATHOGENICITY	DOG STUDIES AVAILABLE
Raboral V-RG®	Recombinant vaccinia	Boehringer Ingelheim, Gennany	Europe and USA	No	Yes
ONRAB®	Recombinant adeno	Artemis, Canada	Canada	No	Yes
Rabitec®	SPBN GASGAS	Ceva, France	Europe	Low	Yes
Rabigen®	SAG2	Virbac, France	Europe	Low	Yes
Rabivac0/333®	ERA G333	Prokov, Russia	Russia	Low	Yes
Fuchsoral®	SAD B19	Ceva, France	Europe	Moderate	Yes
Rabifox®	SAD P5/88	IDT, Germany	Europe	Moderate	-
Lysvulpen®	SAD Bern	Bioveta, Czech Republic	Europe	Moderate	-
Rabadrop®	SAD Clone	Bioveta, Czech Republic	Europe	No	-
Rabistav®	RV-97	Stavropol Biofactory Russia	Russia	Moderate	-
Oralrabivac®	RV-97	Shelkovo Biological plant, Russia	Russia	Moderate	-
Sinrab®	RV-97	FGBI ARRAIH, Russia	Russia	Moderate	-
VRC-RZ2	VRC-RZ2	Knzakhstan	Knzakhstan	-	Yes
KMIEV-94	KMIEV-94	Institute of Veterinary Experimental, Belarus	Belarus	Moderate	-

Table 2. Types of ORV

VACCINE	TYPE	ORAL RABIES VACCINES
First generation	Live attenuated by repeated assaging	SAD, ERA, SAD Bern, SAD B19, RV-97, KMIEV 94, VRC- RZ2
Second generation	Antibody escape mutants	SAG1, SAG2
	Viral vectored vaccines	RABORAL- VRG, ONRAB
Third generation	Reverse genetics	SPBN GASGAS, ERA 333

Figure 1. Rabies vaccinal strains

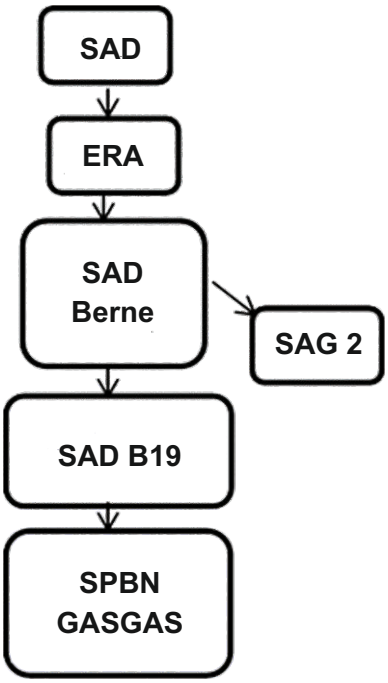

Figure 2. Oral vaccines baits

Vaccinia based
(Maki et al., 2017)

Adeno based
(Berentsenet al., 2021)

Adeno based
(Berentsenet al., 2021)

4. CONCLUSION

India, endemic to canine rabies, is a suitable country to step into ORV control programs.ORVs known for its ease of distribution, immunogenicity, safety and stabilityhave to be evaluated in dogs in the Indian scenario. Currently the absence of any ORVs in India pushes the need to expand international vaccine license, carry out bait preference studies and finally manufacture indigenous vaccines. ORVs are claimed to be complementary to parenteral vaccines in the challenge of dog rabies elimination and the success of ORVs is not only determined by vaccine quality alone but also on socio-cultural acceptance. The recent launching of National Action Plan for Elimination of dog mediated Rabies (NAPRE) in India is a major mile stone in achieving Zero rabies by 2030. However, one of the major limitations in achieving minimum 70 % per cent coverage of free roaming dogs for anti-rabies vaccination is catching dogs for conventional parenteral vaccination. This limitation can be overcome by simultaneous administration of ORV in free roaming dogs under the strict vigilance. If this becomes a reality soon, then India can be a leader in the region in evolving strategies for the successful control of dog mediated human rabies in the years to come.

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