Review Article

A Review of Oral Rabies Immunization in Dogs: Types and Usage in Pakistan

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Abstract | Oral Rabies Vaccines (ORVs) have been shown to reduce wildlife rabies in Europe and the United States since 1978. This review explores the feasibility of and need to vaccinate free-roaming dogs in Pakistan using (ORVs) as a means of controlling canine rabies. Over the last four decades, ORV technology has advanced, resulting in vaccines with improved safety and strong protective immunogenicity. This has strengthened the confidence of national government entities in using modern ORVs for dogs wherever needed, supported by strong evidence of their efficacy and safety, as well as clear endorsements from key international public health organizations. Pakistan reports among the highest global rabies prevalence rates. Although significant advances have been made in human rabies prevention, such broad and efficacious programs are scarce for canine vaccination, which can ultimately eliminate the virus at its source. While parenteral vaccination is essential, a scalable and practical method is needed to immunize the extensive and mobile stray dog population. Management plans currently in place require the deployment of large, experienced dog-catching teams, but this poses logistical and operational barriers to rapidly achieving 70% adult vaccination coverage at scale. If pursued to its logical conclusion, (ORVs) may become the solution to quickly eliminate rabies from widespread territories of South Asia. This review emphasizes the advantages of ORVs for controlling rabies in dogs, with a specific focus on how Pakistan can utilize their full potential. A campaign on risk analysis for dog vaccination using (ORVs) in Pakistan will also be examined.

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Introduction

Rabies, one of the oldest known diseases, continues to spread globally. Although vaccination efforts have been made to control rabies in dogs, resource limitations hinder widespread implementation (Rupprecht *et al.*, 2020). Globally, rabies causes an estimated 50,000 human deaths annually. Pakistan accounts for over one-third (around 35%). Annually, rabies incurs an estimated $2.2 billion in economic losses due to premature deaths, treatment costs, lost labor, and livestock depletion (Hampson *et al.*, 2015). Despite significant progress in Pakistan in increasing the availability of post-exposure prophylaxis for rabies, the persistent amplification and transmission of the virus within the canine population continue to pose a substantial risk of human exposure, leading to severe public health consequences and long-term economic burdens (Wallace *et al.*, 2020; Rupprecht *et al.*, 2020).

Unfortunately, Pakistan has one of the highest estimated burdens of rabies worldwide (WHO, 2017) and is endemic to canine rabies, with thousands of free-roaming dogs. Pakistan needs a comprehensive, systematic, and sustained annual dog vaccination campaign reaching millions of dogs over an extended time frame to achieve the ultimate objective under the Tripartite Agreement among Food and Agricultural Organization (FAO), Office International Des Epizootic (OIE), World Health Organization (WHO), and Global Alliance for Rabies Control (GARC) for zero human deaths from canine Rabies by 2030. Parenteral immunization presents logistical challenges due to the large and inaccessible canine populations in many regions of Pakistan (Tiwari *et al.*, 2019).

Oral Rabies Vaccination (ORV) has been advocated for canine rabies control for over three decades and has played a critical role in eradicating rabies from wildlife species globally for over 50 years (WHO, 1988). In addition to parenteral therapies, prominent international bodies such as the (WHO) and (OIE) are actively promoting the implementation of (ORV) for canines in regions where rabies are prevalent (Meyer, 1954; Freuling *et al.*, 2013). The establishment of efficient and scalable strategies for mass vaccination of dogs in Pakistan would not only contribute to advancing the battle against rabies in one of the most heavily impacted nations but also stimulate the adoption of similar approaches across South Asia (Wallace *et al.*, 2020). This review explores key aspects of mass dog vaccination and management in Pakistan, with a focus on risk considerations associated with the distribution of oral baits.

Rabies affects a wide range of mammalian hosts, with carnivores and bats serving as primary reservoirs. In domestic settings, dogs are the principal source of human rabies infections, especially in developing countries. Wildlife species such as foxes, raccoons, skunks, and insectivorous bats maintain the virus in sylvatic cycles globally (Ameer *et al.*, 2023, Figure 1).

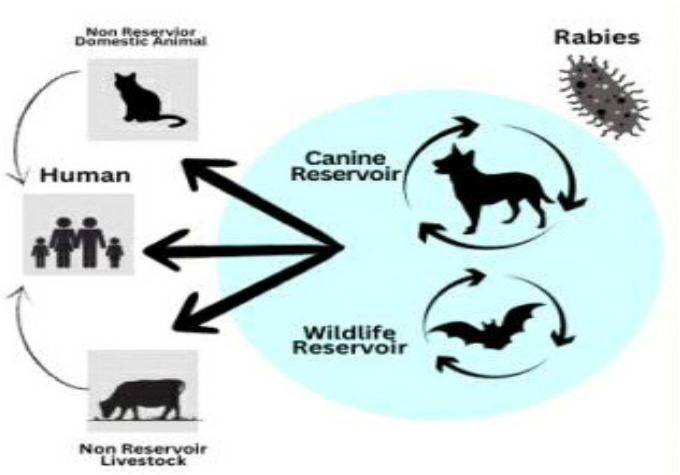

Figure 1: *Modes of rabies transmission in animal and human populations.*

History of rabies vaccine

The inception of rabies prevention dates to ancient times, specifically in the initial century (BC), when a plethora of myths and dogmas surrounded the understanding of rabies and its therapeutic interventions. Prior to the nineteenth century, no standardized diagnostic or therapeutic approach for rabies existed for diagnosing and treating rabies in both human beings and animals. Various methodologies, such as cauterization, were recommended for managing rabies-infected wounds, sometimes even resorting to extreme measures like excision or amputation. However, these practices failed to offer a definitive remedy for the alarming mortality rates observed among both human and animal populations. It was not until 25 (AD) that a shift towards a more empirical approach to rabies was witnessed. Aulus Cornelius Celsus, around that time, advocated for the prompt treatment of injuries sustained from animal bites. Later, in 1198, Moses Maimonides emphasized the protracted incubation times that people are bitten by rabid animals endured (Meyer, 1954; Freuling *et al.*, 2013).

Further advancements were made in understanding the characteristics of the rabies virus, with Giovanni

Battista Morgani pinpointing its inclination towards nerve tissues in 1769. Georg Gottfried Zink's discovery in 1804 that the contagious saliva of rabid animals was the main means of transmission was a revolutionary finding. The idea of developing rabies vaccinations was initially proposed in 1852 by the well-known French pharmacist Apollinaire Bouchardat. The first experimental vaccine against rabies was successfully administered intravenously in sheep in 1881, marking a seminal finding in the history of the illness. Renowned French veterinarian Pierre-Victor Galtier made this remarkable accomplishment feasible (Wallace *et al*., 2020; Undurraga *et al*., 2020).

Pre-Pasteurian efforts laid the foundational groundwork for vaccine development, but Louis Pasteur led the official start of rabies vaccine research in 1885 as a means of emergency response, even before the disease's causal agent was discovered. Initially, the etiology of rabies posed a challenge to Koch's Germ Theory, as attempts to isolate any causative infectious agents proved futile. Even in the latter part of the 1800s, rabies was theorized to be linked to a parasitic origin homologous to the Sporozoan. It wasn't until 1903 that concrete evidence of a "filterable agent" associated with the disease was substantiated. The true nature of the rabies virion remained elusive until 1936, and it wasn't until 1962 that an in-depth exploration of the causal agent through electron microscopy was undertaken. Pasteur and his colleagues, Chamberland, Roux, and Thuillier, were able to successfully identify the presence of the rabies virus within the central nervous system of rabid animals despite these challenges and knowledge gaps (Velasco *et al*., 2017; Wallace *et al*., 2019).

The need for dog ORV in Pakistan

Maximizing herd immunity in a remote population: Parenteral vaccinations like static point (SP), door-to-door vaccination (DDV), and capture-vaccinate-release (CVR) are three commonly utilized approaches for conducting mass vaccination of dogs on a large scale (Undurraga *et al*., 2020). The degree of dog ownership and accessibility in the target population has a significant impact on each method's ability to achieve a high level of vaccination coverage (Wallace *et al*., 2019). SP vaccination involves establishing temporary clinics where dog owners can bring their pets for immunization. In Latin America, up to 50 million dogs have been vaccinated in a single week, where this method has proven remarkably effective (Velasco-Villa *et al*., 2017; De Carvalho *et al*., 2018). Additionally, significant vaccination coverage has been noted in Africa because of SP programs (Mazeri *et al*., 2021). Since most people own dogs and most dog owners are able and ready to transport their pets to vaccination sites, the application of this strategy depends broadly on community involvement (Léchenne *et al*., 2016).

In places where the efficacy of the SP vaccine is restricted, DDV vaccination can improve coverage by sending one or two teams of immunization workers to tour communities, visit every home, and vaccinate dogs that can be securely confined for parenteral immunization (Gibson *et al*., 2016). Nevertheless, these procedures may not be sufficient in reaching large population areas, where handling a high number of dogs manually for vaccination proves challenging or unfeasible. Consequently, more intricate capture techniques like CVR are imperative to achieve an annual vaccine coverage of up to 70% (Gibson *et al*., 2015). Capture-vaccinate-release (CVR) strategies are associated with substantial fixed operational costs, necessitate a large, technically trained workforce, and may further complicate dog accessibility by inducing fear and evasive behavior in free-roaming canine populations.

Using DDV as the main immunization technique for dogs that can be controlled with their hands and subsequently, CVR to reach the inaccessible population can help reduce CVR's high fixed operational expenses (Gibson *et al*., 2015). This method, however, does not solve the core operational difficulty of managing a large, highly experienced workforce dedicated entirely to ensuring annual vaccination of the canine population across wide geographical regions (Gibson *et al*., 2019). The complex contact structure of the canine population necessitates that vaccination campaigns must be organized and synchronized, covering urban areas, peripheral areas, and rural areas where the transmission of rabies virus is maintained. Parenteral vaccinations, for which more information and resources are available, are being used to systematically immunize several hundred thousand canines annually; however, they would not be practical in the larger Indian states for the control of rabies (Colombi *et al*, 2020).

The competitive priorities for dog population management

The attention on stray dogs has frequently moved away from rabies and toward other problems brought on by their presence, such as barking, traffic accidents, and

hygiene (Srinivasan *et al*., 2019). This highlights the need for a greater public awareness of rabies however, the issue of population management of stray dogs will continue to be a priority for both public and political decision-makers. Dog culling does not help reduce the number of dogs and is frequently ineffective in managing rabies, according to a significant body of evidence (Windiyaningsih *et al*., 2004; Townsend *et al*., 2013). As a result, as part of their humane dog population management policies, many governments are searching for long-term solutions through comprehensive dog sterilization.

Mass vaccinations are simple compared to managing dog populations, which calls for extensive changes in dog ownership, dog abandonment, and reproductive control as well as the improvement of public services (such as waste disposal) and a well-organized surgical veterinary infrastructure (ICAM, 2015). While there is continuing research into less labor-intensive devices for canine sterilization, a more thorough evaluation of the impact of current surgical techniques is required. Combining the requirement for universal annual dog vaccination against rabies with the requirement to prevent canine reproduction through surgical sterilization may lessen the effects of both techniques (Taylor *et al*., 2017). ORV would make it possible to vaccinate difficult to capture dogs without the need for handling, enabling intense yearly vaccination of strays without jeopardizing efforts to regulate the dog population by capturing dogs for later sterilization.

Types of current oral rabies vaccines

Modified Live Vaccines (MLVs), Inactivated Rabies Vaccine, Adjuvanted Rabies Vaccine and Vector-Based Vaccines (VBVs) are types of Oral Rabies Vaccines (ORVs) that are now licensed for the immunization of various animal species.

Modified live vaccine

MLV is made up of a living, replicative rabies virus that still activates the body's immune system despite being altered so that it no longer causes disease. Contrarily, VBVs are made by incorporating antigenic glycoproteins from other vectors into the Rabies virus. These other vectors then express the rabies glycoprotein into the recipient, triggering an immunological response. In 1935, the United States Centers for Disease Control and Prevention (CDC) discovered a single strain of the rabies virus known as Stre*et al*abama Dufferin (SAD) (Steck *et al*., 1982). From this strain, the great majority of modified live rabies viruses (MLV) currently in use are derived. A variety of greatly reduced Rabies virus (ORS) strains, including SRB1, SRB2, SRB3, SRB4, and SRB5, were produced by extensive cross-breeding this strain with non-neuroleptic cell lines, such as hamster kidney, Pig kidney, and embryonated chicken egg.

The first generation of oral rabies viruses (ORVs) pioneered the basis for rabies eradication in Europe and is still the most extensively used (ORV) internationally (Müller and Freuling, 2020). Monoclonal antibodies were used to select mutations, which notably improved the safety of the first-generation Oral Rabies Virus (ORV) (Müller *et al*., 2015). Site-direct mutagenesis, which aims for specific modifications at specific places in the Rabies Virus genome, is now possible thanks to recent advancements in 3rd-generation MLVs. This site-specific deletion and insertion improve the existing compounds' immunogenicity and safety even further. The G-protein mutation at residue 333 (amino acid substitution) is present in both vaccines even though they are produced from different vaccine virus strains (Müller and Freuling, 2020).

Live Attenuated Rabies Vaccines are made from G-protein gene alterations, which are responsible for viral uptake, bud formation, and neurodegeneration (Mebatsion *et al*., 1999; Faber *et al*., 2002). The vaccina virus reaches palatine tissues and replicates locally (Kamp *et al*., 2020). The vaccine gene, on the other hand, blocks normal pathogen processes and promotes apoptosis (Kamp *et al*., 2020). Due to extensive exposure to a large variety of rabies antigens, little local replication occurs in oral tissues, resulting in significant and permanent immunity against rabies (Maki *et al*., 2017). Vaccina virus is removed through the gastrointestinal tract rather than the urine or feces (Vos *et al*., 2018). It is, however, detectable for several hours after intake through the oral cavity (Pfaff *et al*., 2019).

The primary concern with Modified Live Vaccines (MLVs) is the risk of reversion to virulence due to spontaneous genetic mutations, potentially restoring the virus's pathogenicity and capacity to cause rabies (Pfaff *et al*., 2019). Following the widespread use of MLV in the global battle to eradicate polio, this risk has been well-documented, with continued challenges brought on by the proliferation of vaccine-derived polioviruses (Alleman *et al*., 2020). A solid evidence base for the evaluation of this risk for (ORVs) is

provided by the continuing use of MLV for more than 40 years in the global effort to reduce rabies in wildlife. The ability to induce live attenuated vaccination after intra-cerebral inoculation into immune-compromised animals is the safety marker for attenuated live rabies vaccines (Natesan *et al*., 2023).

In immunocompetent mice, it has been shown that the initial generation of MLVs can still result in rabies following intracranial immunosuppression. Following first-generation MLV immunization, eleven vaccine-associated incidences of rabies in immune-competent mice have been documented in Europe (Müller *et al*., 2015). These instances were epidemiologically insignificant, occurring exclusively in immunosuppressed animals such as foxes, and did not result in broader transmission or public health concerns (Artois *et al*., 1992). Additionally, there haven't been any reports of second or third-generation bacteria returning to their harmful nature in the field. Additionally, no negative effects have been linked to MLV contact with humans.

Inactivated rabies vaccine

The history of inactivated vaccinations began around a century ago when certain parts of Africa and Asia were using the inactivated nerve tissue injections developed to prevent rabies. Most traditional rabies vaccinations involve whole, inactivated viruses with the same antigenic properties as wild-type viruses. Research has demonstrated that administering a fully inactivated viral vaccination to an individual stimulates helper and cytotoxic T cells, which in turn produce antibodies that neutralize the virus and protect against a lethal intracerebral rabies virus challenge (Kamp *et al*., 2020).

Worldwide, a variety of rabies virus strains have been used to produce the inactivated vaccine, including CVS 11, Pittman-Moore-NIL2, RC-HL, which is derived from the Nishigahara strain, and Pasteur virus strains. Currently, inactivated, pure rabies virus grown in cell culture or embryonated duck or chicken egg systems is used to manufacture the licensed rabies vaccines for human administration. The rabies vaccine strains are usually inactivated by UV light, phenylethylamine, beta propiolactone (BPL), or binary ethylenimine (BEI). Despite being the most widely used inactivating agent, BPL is expensive and prone to instability around 37 °C. Since formaldehyde and phenol can change the antigenic sites, they are no longer advised for virus inactivation (Vos *et al*., 2018; Pfaff *et al*., 2019).

On the other hand, BEI is easier to work with and has benefits, including good stability, affordability, and ease of preparation. However, decreased immunogenicity, high cost, and the requirement for numerous vaccination schedules for both pre- and post-exposure immunization are the main disadvantages of inactivated vaccines. Consequently, adjuvanted vaccinations have emerged because of the incorporation of antigen adjuvants into inactivated vaccines to boost the immune response (Natesan *et al*., 2023).

Vector-based vaccine

To mitigate the potential hazards associated with live vaccines, the concept of Vector-Based Vaccines (VBVs) was developed (VRVs). In these vector-borne viruses (VBVs), a cDNA sequence encoding the Rabies Virus Glycoprotein is inserted into the genome of a vector virus, which is subsequently produced in the recipient (Müller *et al*., 2009). There are now two commercially approved VBVs that express the glycoprotein of the rabies virus that can be used in wild animals: Oral Newcastle disease virus-Rabies Vaccine (ONRAB), which uses recombinant Human Adenovirus 5 (HAD5) as the vector, and RV-RG, which uses recombinant vaccinia virus (RV) as the vector. The possibility of illness brought on by the vector virus is one disadvantage of VBVs. For example, V-RG may cause a person's skin to become noticeably inflamed, especially if they already have immunological competence in the USA (Esposito *et al*., 1987).

The employment of VBVs may impede the immune response to the vector, thereby obstructing rabies absorption and immunity formation (Brown *et al*., 2014). This challenge is especially relevant for adenovirus vaccines, given the virus's prevalence in various regions. Over the past 40 years, more than 1 billion doses of Oral Rabies Vaccine (ORV) bait have been distributed across North America and Europe, mainly through helicopter and aircraft (Table 1). The initial field studies on ORV were conducted in Switzerland in 1978 to investigate rabies control in the red fox population (Rosatte *et al*., 2009), followed by successful trials and widespread adoption in other European countries during the 1980s (Rupprecht *et al*., 2005; Roess *et al*., 2012). Since 1989, the European Union has been providing financial support to Member States for ORV programs (Root *et al*., 2008).

Table 1: *Advantages and disadvantages of current rabies vaccine.*

Vaccines	Advantages	Disadvantages
MLV (Modified Live Vaccine)	Greater immunogenicity, enduring immunity after just one dosage, and affordability	The significant risk of self-inoculation with the MLV rabies vaccine, potential reversion of virulence, and increased sensitivity to temperature fluctuations all exist.
IRV (Inactivated Rabies Vaccine)	No chance for virulence to return and secure	Expensive, frequent booster doses needed, low immunogenicity
VBV (Vector base vaccine)	Pathogen-associated molecular patterns are carried by viral vectors and cause inflammatory reactions required to trigger adaptive immune responses, more immunogenic, and beneficial as potential oral rabies vaccines	The process of creating viral vectors is more difficult and expensive, and they are too reactive to be used on humans. Moreover, people who have had the vaccination may unintentionally become infected and they may develop immunity to the vector.
ARV (Adjuvanted Rabies Vaccine)	Prompting the body's immune system to create more and more durable antibodies strong cellular and humoral immunity by improving antigen presentation to immune cells that are specific to antigens.	Adverse effects included in the majority of adjuvant formulations

The development of Oral Rabies Vaccines (ORVs) has resulted in the commercial licensing of more than ten ORVs in the European Union (EU) over the last forty years, including SAG1 (SAG2), V-GR (V-GR), and SAD Bern (SAD B19). Over 30 countries in Europe have distributed almost 736 million ORV baits over an area of 2.75 million km2 (Vitasek, 2012), which is equivalent to the combined size of Pakistan's five largest states. It's vital to remember that rabies virus transmission is not limited to Europe and Canada (Muller *et al.*, 2018), as enzootic transmission can also occur in North America between skunks and raccoons (Müller *et al.*, 2014).

Modified Live Vaccines (MLVs) exhibit lower efficacy in reaching immunogenic tissues in canids due to oral anatomy variations, limiting vaccine efficiency (MacInnes *et al.*, 2001; Ma *et al.*, 2021). In contrast, VBVs have proven to elicit an immune response and are commonly used in non-canid animal populations to control rabies (Rupprecht *et al.*, 1986). ORVs are administered orally through a bait formulation tailored to the taste preferences and feeding habits of the target animal (Rupprecht *et al.*, 1989). Both MLV and VBV are enclosed in a liquid solution, and sealed in a sachet that, upon ingestion, is perforated to allow the vaccine suspension to enter the oral cavity through chewing.

Adjuvanted rabies vaccine

A chemical known as an adjuvant can enhance or change the immune response to vaccination by increasing the inflammatory reactions required for the antigen-driven activation of naive B and T cells. Due to the use of inactivated, subunit, and synthetic vaccines, adjuvants, which are essentially weak immunogens, have always attracted interest. Adjuvants are incorporated into vaccines to enhance immunogenicity by improving antigen presentation, stimulating innate immune responses, and promoting the activation of antigen-presenting cells. This leads to more robust and durable adaptive immune responses, thereby increasing vaccine efficacy. Three often used adjuvants are aluminum hydroxide, aluminum phosphate, and saponin. Many adjuvants used now, however, are aluminum salts. Despite being the first adjuvant to be approved for use in humans, alum is thought to be less effective at triggering cellular immunity and postponing the establishment of antibodies (Root *et al.*, 2008).

Adjuvants primary drawbacks are their toxicity, limited ability to act as adjuvants against antigens, and unfavorable side effects. Consequently, there has been a surge in the development of synthetic derivatives as substitute adjuvants. A few examples of these include liposomes, QS21, monophosphoryllipidA, MF-59, and immunostimulant complexes (ISCOMS). To enhance the immunogenicity and efficacy of the inactivated rabies virus vaccines, a variety of additional substances, including indigotic root polysaccharides, CpG oligo deoxynucleotides, monophosphorylate-lipid A (MPLA), β-glucans, *Staphylococcus aureus*-derived hyaluronic acid (HA), and *Bacillus Calmette-Guérin* purified protein derivative (PPD), have been studied in recent years. These proposed adjuvants have a better ability to increase immunity and provide a strong basis for the development of novel adjuvanted rabies vaccines in the future. They also have low health risk aspects (Müller *et al.*, 2018).

Table 2: *The status of the rabies vaccine right now (Natesan et al., 2023).*

Vaccines	Vaccines name	Research focus	Mode of action
Modified live rabies vaccine	ERA-G333 Leu	Reverse genetics reveals an Arg-to-Leu mutation at G333 in the ERA strain.	6-week-old mice showed enhanced protective immunity and neutralizing antibody response, as well as a higher survival rate.
Inactivated rabies vaccine	-	Vaccine for vero cell rabies various inactivating substances were used to inactivate and stabilize	Elevated levels of IgG
Adjuvanted rabies vaccine	-	The effect of β-glucans' adjuvanticity on the inactivated rabies vaccine (Rabisin®)	Enhanced Immunological Response
	RABV-ED51 mBAFF	examined how the rabies virus affected the B cell activating factor (BAFF) immunological response.	increased the creation of specific IgM, IgG, IgG2c/IgG1, and RVNA
Recombinant vaccines	NC8-pSIP409 -dRVG	Recombinant Lactobacillus plantarum NC8 provides one or two copies of G protein linked with a DC-targeting peptide (DCpep) as a novel oral rabies vaccine.	Even though the titers of the RABV neutralizing antibody (VNA) were below the threshold of 0.5 IU/mL, the NC8-pSIP409-dRVG could protect 60% of inoculated mice against the fatal RABV challenge.
Viral vector vaccines	rAAV-G	G protein produced via AAV	encouraged mice to produce long-lasting RVNAs
Intra dermal vaccines	-	Administration of the inactivated cell culture rabies vaccine to dogs by SC, IM, and ID	In dogs, ID was proven to be immunogenic and harmless.

Recent advancements in rabies vaccine development have focused on enhancing immunogenicity, reducing dosage requirements, and improving accessibility in endemic regions. According to (Natesan *et al.*, 2023), both pre- and post-exposure prophylaxis regimens have evolved, with novel vaccine platforms such as recombinant and DNA-based vaccines showing promising results. An overview of current vaccine types, their efficacy, and clinical trial progress is summarized in Table 2.

Oral rabies vaccinations of dogs

The most effective technique to vaccinate dogs against ORV is to use a bait construct that is made to maximize the vaccine's effectiveness in the mouth, much like it is for wild animals. The bait's palatability and the ease with which the dog can chew through the vaccination are greatly influenced by its smell, taste, and size (Knobel *et al.*, 2002). If the bait is too small and the dog doesn't swallow it without breaking the sachet, they won't get immunized. A lot of studies have been done to see which bait casing materials people prefer and it looks like there's a lot of variation depending on where you're from. For example, studies from India, Bangladesh, and Thailand all showed that egg-based baits got the most out, but with a high perforation rate. The fact that egg-based baits are more socially and culturally acceptable and can be mass-produced using simple equipment is another benefit (Bonwitt *et al.*, 2020).

Dogs in metropolitan settings can receive ORV by being given oral bait. It works by having two people travel by bike and inject dogs that are too tough to handle. They toss baits to the dogs from a distance, making sure not to scare them. The dog eats the baits, and the vaccine packaging and other baits are collected and thrown away safely. It's been proven to be cost-effective and works well in places like Goa, Haiti, Morocco, USA, Tunisia, Turkey, Philippines, Guatemala, and Sri Lanka (Berentsen *et al.*, 2016; Bender *et al.*, 2017; Gibson *et al.*, 2019).

Evaluation of available ORVs for use in dogs

A national regulatory body is mandated to assess the safety and efficacy of a product in target species, non-target animals, and humans as part of the formal process of vaccine approval. This procedure is typically costly and challenging, often prompting ethical dilemmas during investigations (Dellepiane and Wood, 2013). While seeking licensure at every usage site was deemed unfeasible, the emergence of global health initiatives in the 1970s necessitated the establishment of uniform standards for vaccine quality, safety, and efficacy. There is a widespread consensus that Oral Rabies Vaccines (ORVs) require international oversight to ensure the availability of essential evidence for national regulatory agencies to make informed decisions on ORV implementation. However, no such protocols have been developed for the veterinary vaccine sector. Recently, updated

guidelines for evaluating ORV candidates intended for field application have been issued by renowned institutions such as the Centers for Disease Control and Prevention (CDC), the World Organization for Animal Health (OIE), and the World Health Organization (WHO), among others (Perera *et al.*, 2000). The CDC, OIE, WHO, and various other bodies have recently issued revised recommendations for assessing ORV candidates considered for field deployment.

The off-label use of vaccines is prevalent, even in nations with robust immunization initiatives where safety and efficacy have been verified but formal registration is pending. Consequently, the WHO and OIE have stressed the importance of continuing with the licensing procedures (Wallace *et al.*, 2020); however, they have also underscored that this should not be a prerequisite before commencing field trials of ORVs that have been deemed safe and effective (Neels *et al.*, 2017).

Safety risk analysis

Many ORVs have undergone rigorous licensing procedures in North America and Europe for wildlife use. An in-depth evaluation of human safety concerning distribution in areas near human settlements is a crucial component of this licensing process by regulatory bodies such as the European Medicines Agency and the US Department of Agriculture Center for Veterinary Biologics (Head *et al.*, 2019).

The CDC formulated a Markov chain model to assess the human safety implications of the environmental distribution of ORVs for canine vaccination. Apart from China and Pakistan, computer simulations were conducted for potential dog ORV initiatives using SAD B19 (1st generation MLV) and SPBN GASGAS (3rd generation MLV). The simulation involving the 3rd generation MLV, SPBN GASGAS, projected zero human fatalities, unlike the simulation with the 1st generation MLV, SAD B19, which estimated 3.36 human deaths per 10 million baits distributed (Ortmann *et al.*, 2018).

To assess the human safety of a hypothetical canine vaccination program in India, a model incorporating regional characteristics of Goa State was utilized. During the simulated initiative, 40,000 SPBN GASGAS baits were dispersed across urban and rural areas over 12 days. A comprehensive study based on local data sources and published literature was carried out, along with a sensitivity analysis employing Latin Hypercube sampling of potential parameter values. One thousand simulations were run for each analysis, and the 2.5th and 97.5th percentiles of the results were used to calculate the 95% confidence interval (Faber *et al.*, 2019).

The standard study indicated that a median of 32,006 dogs would be vaccinated, preventing both dogs and non-target animals from contracting rabies. No significant adverse events involving human fatalities were reported during the campaign or extrapolated per 10 million baits distributed. Instead, an average of 5.1 human exposures (95% CI: 0, 14) resulted in 4.0 additional medical visits (95% CI: 0, 11). The simulations did not anticipate any cases of vaccine-induced rabies among dogs or non-target animals per 10 million baits administered (Gibson *et al.*, 2019).

Sensitivity analysis simulations indicate that there would be no cases of vaccine-induced rabies and an average of 27,919 dogs and 201 non-target animals immunized. 3.4 more medical visits, 4.9 more people exposures, and no significant adverse events or fatalities were predicted by the model. When compared to the sensitivity analysis results, the accuracy of values is anticipated to increase with the inclusion of predicted parameters based on available data. Since it illustrates the range of possible outcomes inside the parameter space, the range of values investigated in the sensitivity analysis is crucial. In the worst-case scenario, there were 22 medical visits and 24 exposures, but no fatalities or significant adverse events were reported (Neels *et al.*, 2017).

Candidate ORV for Pakistan

It is expected that ORV will supplement current parenteral dog vaccination methods in both urban and rural environments. Nevertheless, due to the close interaction between canines and humans in Pakistan, ensuring vaccine safety is of utmost importance. The analysis utilizing modeling techniques indicated that employing the hand-out approach would lead to remarkably low levels of human contact in such regions (Perera *et al.*, 2000).

The prediction that there won't be any serious side effects or human deaths for every 10 million SPBN GASGAS bait distributions highlights the third-

generation MLV's exceptional safety record. SPBN GASGAS was created by carefully altering the SAD-B19 immunization strain, changing all three nucleotides at amino acid positions 194 and 333 to lower the likelihood of a spontaneous mutation turning virulence back into a possibility (Faber *et al*., 2002).

SPBN GASGAS, recognized as Rabitec®, is presently sanctioned for administration to foxes and raccoon canids in the European Union and the United States. Conversely, the importation and utilization of SPBN GASGAS in Pakistan necessitate prior approval from regional and national regulatory bodies. Its relatively limited stability under high temperatures (exceeding 20 ˚C) poses practical challenges when deployed in tropical and subtropical regions. The proposed method of dispensing oral baits directly to each dog, thereby ensuring immediate consumption, would minimize environmental exposure effectively (Faber *et al*., 2009).

Conclusions and Recommendations

In circumstances when dogs are challenging to confine or vaccinate, the efficacy of Oral Rabies Vaccination (ORV) for dog immunization has been demonstrated to increase the reach of extensive vaccination programs. The ongoing and growing support provided by the World Health Organization (WHO), the World Organization for Animal Health (OIE), and other international bodies for the implementation of ORV preliminary field operations gives national governments confidence when assessing the suitability of ORV products. Tens of millions of canines wander freely throughout Pakistan, which is known to have the highest rate of both human and canine rabies in the world. Pakistan, hence needs a competent and practical operational solution for the mass immunization of difficult to manage canines.

While parenteral vaccination remains essential for immunizing accessible dogs, incorporating oral rabies vaccination (ORV) enables rapid expansion of mass vaccination campaigns by effectively targeting free-roaming and hard to reach canine populations, thereby enhancing overall vaccination coverage and accelerating progress toward rabies elimination goals.

Extensive participation in dog vaccination campaigns across Pakistan, including Punjab, Sindh, Balochistan, and KPK. West Bengal and Maharashtra also lack a similar instrument in India's efforts to meet the Zero by 30 targets for eliminating dog-mediated human rabies by 2030, demonstrating the efficacy of Oral Rabies Vaccine (ORV) as a supplement to parenterally administered vaccination techniques for the expeditious containment of canine rabies.

Novelty Statement

This review highlights the current status, types, and application of oral ra-bies vaccines in dogs with a special focus on Pakistan, where such approach-es remain underutilized and underreported.

Author's Contributions

Haleema Sadia and Muhammad Adil: Developed the main idea, contributed to writing, and finalized the manuscript.
Farrah Deeba and Muhammad Tariq: Supervised the work and reviewed the final draft.
Ahmad Muhammad: Structure the manuscript and improve readability.
Patricio De los Ríos-Escalante and Eliana Ibáñez-Arancibia: Assisted in organizing and clarifying the content.
Muhammad Kashif Ismail: Assisted in gathering references.

Conflict of interest
The authors have declared no conflict of interest.

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