



Current and Future Perspectives of Vaccine Development for ORFV Infection: Opportunities and Challenges

Ghazala Shaheen^{1*}, Muhammad Khalid Mansoor¹, Nahl Jameel², Talha Ahmad³, Nouman Tariq^{4*}, Muhammad Shahzaib Ashfaq⁵, Samavia Abid⁵, Badar Rasool⁶, Ruqayyah Moiz², Anam Tariq⁷, Ghulam Hussain⁸, Mubasher Hussain⁴ and Ali Hamza⁴

¹Department of Microbiology, Faculty of Veterinary and Animal Sciences, The Islamia University, Bahawalpur 63100, Pakistan; ²Faculty of Life Sciences, Institute of Microbiology, Government College University Faisalabad, Pakistan; ³School of Science and Engineering (Centre of Anatomy and Human Identification) University of Dundee, Scotland, United Kingdom, ORCID: 0009-0003-3215-1102; ⁴Faculty of Veterinary Science, University of Agriculture Faisalabad, Pakistan; ⁵Faculty of Veterinary and Animal Sciences, University of Poonch Rawalakot, Pakistan; ⁶Department of Wildlife and Ecology, University of Veterinary and Animal Sciences, Lahore, Pakistan; ⁷ Department of Biochemistry, Government College University Faisalabad, Faisalabad, Pakistan; ⁸Department of Animal Breeding and Genetics, Faculty of Animal Production and Technology, University of Veterinary and Animal Sciences, Lahore, Pakistan

*Correspondence: ghs.rao02@gmail.com; noumantariq0208@gmail.com

ARTICLE INFO

ARTICLE HISTORY: CVJ-25-1105

Received: August 28, 2025
Revised: October 31, 2025
Accepted: November 03, 2025
Published online: November 05, 2025

Key words:

Orf virus (ORFV)
Zoonotic disease
Livestock, dermatitis
Modified vaccines

ABSTRACT

Contagious ecthyma (CE), caused by the Orf virus (ORFV), is a globally prevalent zoonotic disease that primarily affects sheep and goats, leading to significant economic losses in livestock production. Despite decades of research, vaccine development against ORFV remains challenging. Currently, live attenuated vaccines are the only commercially available option, yet they pose safety risks due to potential reversion to virulence and provide only short-term protection. The virus's genetic diversity and its ability to evade host immunity further complicate vaccine efficacy. Recent advances in molecular virology and immunology have, however, opened new avenues for vaccine design. Novel approaches, including recombinant and genetically modified vaccines, DNA and subunit vaccines, and vector-based strategies, show promise in eliciting robust and durable immune responses. Additionally, ORFV is being explored as a vaccine vector and immunotherapeutic platform due to its strong immunomodulatory properties. This review highlights the limitations of current vaccination strategies and discusses emerging perspectives that may pave the way toward safer, more effective, and sustainable vaccines for controlling ORFV infection in livestock populations worldwide.

To Cite This Article: Shaheen G, Mansoor MK, Jameel N, Ahmad T, Tariq N, Ashfaq MS, Abid S, Rasool B, Moiz R, Tariq A, Hussain G, Hussain M and Hamza A, 2025. Current and future perspectives of vaccine development for ORFV infection: opportunities and challenges. *Continental Vet J*, 5(2): 199-206. <http://dx.doi.org/10.71081/cvj/2025.052>

INTRODUCTION

Parapoxvirus ovis (PPVO or ORF virus) is an epitheliotropic oval-shaped linear double-stranded DNA virus, which is widespread across the globe and stands as a major pathogen affecting small ruminants, especially goats and sheep. It induces a distinct mucocutaneous, inflammatory, and proliferative disease recognized as contagious ecthyma (CE), ORF, or scabby mouth. It largely affects goats and sheep, although camels, deer, muskox, reindeer, serow, cats, squirrels, and dogs have also been found to be affected. This disease is also zoonotic; however, it poses an occupational

threat to individuals who work with animals, such as shepherds, veterinarians, and farmers, due to its zoonotic nature (Reichen et al. 2025). ORFV attacks the skin surface of small ruminants, which can be identified by the rapid growth of erythematous macules, vesicles, papules, pustules, the oral mucosa, and scab lesions on the lips and around the nostrils of affected animals. It can also be identified by ulcerative wound development on less hairy body parts, i.e., the nostril, ears, muzzle, and genitalia. Within four weeks, these lesions often crust over, quickly develop scabs, and heal on their own. Scabs are considered a source of new infection and contaminate pastures and sheds. They also

retain high numbers of the virus and can shield it from environmental inactivation for months or years (Mungmunpantipantip and Wiwanitkit 2024).

However, it has been overlooked for several decades due to the common belief that it merely leads to self-limiting infection. In contrast, it has already been demonstrated to result in major cumulative economic losses in the livestock industry (Thompson et al. 2022). ORF disease can be characterized by localized, proliferating, and persisting skin nodules that can be categorized into three types: generalized, labial, and genital or mammary. It can appear in either benign or malignant forms. The latter form of ORF can persist, leading to fatality and typically causing a serious outbreak among the small ruminants. ORF is most common and fatal in young goats and lambs who have recently been infected. A vaccine, an anti-infection medication that stimulates the desired and strong immune response against infectious agents, is the most effective way to overcome this virus, especially in goats and sheep (Bukar et al. 2021). In this review, we may discuss the occurrence and vaccinated cure of ORF virus in domestic animals.

Structure and Classification of ORFV

ORF virus is the causative agent of contagious ecthyma (CE) in goats and sheep that is responsible for contagious pustular dermatitis (CPD), sore mouth, infectious labial dermatitis, and scabby mouth. A prototype ORF virus (ORFV) belongs to the genus '*Parapoxvirus*' along with closely related parapoxviruses like pseudocowpox virus (PCPV), red deer parapoxvirus in New Zealand (PVNZ), and bovine papular stomatitis virus (BPSV) (Mansoor et al. 2025). The ORFV genome is an epitheliotropic oval-shaped linear, double-stranded DNA that is about 134–139 kilobases in size (Li et al. 2023). The genome contains around 132 genes and has a GC content of up to 66%. The virus itself has dimensions of approximately 260 nm × 160 nm, as shown in Fig. 1. Essential genes, primarily situated in the central region, are critical for the formation of

infectious particles and viral DNA in the host cell's cytoplasm (Knipe et al. 2022). The assembly of the ORFV occurs within the cytoplasm of the host cell, exhibiting particular morphological characteristics, including a high GC content and a crisscross surface layout. The B2L gene produces the envelope protein (42KDA), which is highly immunogenic and is utilized for detecting pathogens and conducting phylogenetic research (Poulinlu et al. 2022). Virus isolation and cultivation, despite being time-consuming, are still considered the most reliable methods for validation. However, molecular tools, specifically PCR, provide a quick and dependable means of screening for ORF pathogens. The ORFV contains potent genes, such as VEGF and IL-10, which enhance viral infection and enable it to evade the host's immune defences (Ewies et al. 2024). The virus uses strategies that inhibit the function of immune cells and keratinocytes, which accounts for its temporary protective immunity and vulnerability to reinfection, as shown in Fig. 1.

The predominant physical characteristic of the Orf virus (ORFV) is the filamentous, tubular organization of its outer layer (Lacasta et al. 2021). The virion particle is composed of an inner membrane that is encased by a thick and dense wall. This inner membrane is made up of the nuclear membrane, the nucleoprotein, and the palisade layer. The ORFV genome, which contains 138 kilobase pairs, has 17% of significantly variable genes accountable for the virus's pathogenesis, host range, virulence, and immunomodulatory functions. The variable areas, surrounded by 3 kilobase pairs (kbp) inverted terminal repeats (ITRs), are positioned at the very ends of the genomic DNA. These regions consist of nucleotide sequences that are similar but ordered in opposite directions. Additionally, they are strongly linked by hairpin loops (Almsarrhad 2023). On the contrary, the central region of the ORFV genome that is conserved constitutes almost 80% of the total genome and plays a crucial role in viral replication, transcription, and morphogenesis (Bukar et al. 2021).

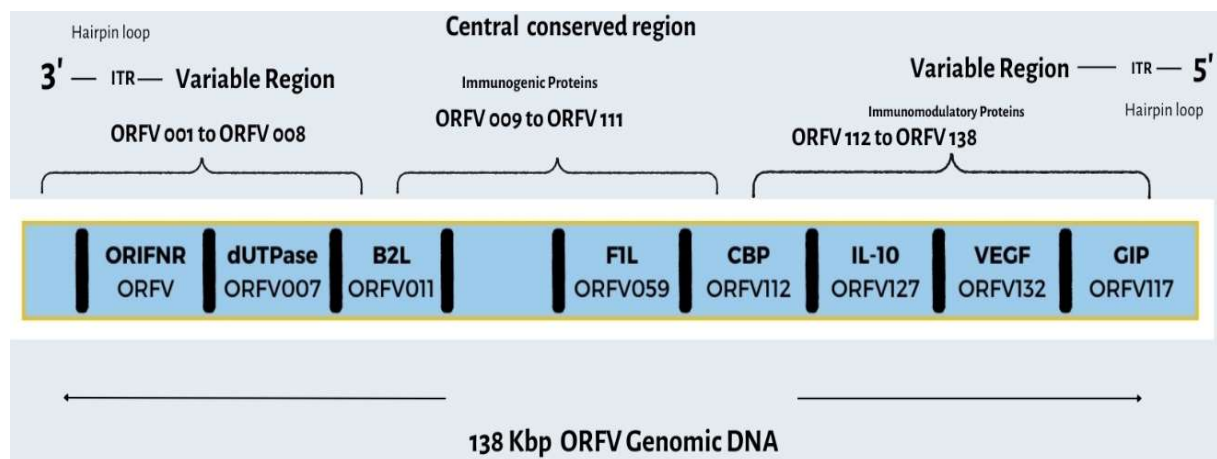


Fig. 1: Schematic illustration of ORFV Linear DNA genome. The double-stranded DNA genomic molecule (138 kb long) contains the 5' end showing the immunomodulatory genes (ORFV112 to ORFV138), the central conserved region (ORFV009 to ORFV111), and the 3' genomic end represents the variable region (ORFV001 to ORFV008). The inverted terminal repeats (ITRs) in nucleocapsid protein are closely linked with heparin loops at both the 5' and 3' ends. The central conserved region encodes 101 essential genes of the virus that are involved in replication, immunogenicity, morphogenesis, and transcription. These highly variable regions play a role in the virulence and pathogenicity of ORF.

ORFV Pathogenesis

The virus enters the body through damaged skin and replicates in the epidermal layer of skin cells, making skin lesions that progress consistently through multiple stages (Thompson et al. 2022). The infection is confined to the squamous epithelium and can affect various areas, such as the mouth cavity, eyelids, teats, and coronary band. This can make the infected animals more susceptible to secondary infections (Hussain et al. 2023). Residual skin lesions do not lose their effectiveness once the scab falls off. However, a significant amount of infectious virus is released within the scab, which can stay infectious in the environment for many years (Kassa 2021).

Viral infection is transmitted through direct contact with the highly resistant virus, which can survive for over a year in the environment (Lacasta et al. 2023). Although younger lambs are the most prevalent hosts, older sheep are occasionally affected due to grazing on coarse pastures or stubbles. It may increase the risk of scabby mouth infection due to the higher likelihood of viral entrance through oral abrasions (Abbott 2024). Morbidity caused by ORFV infection in lambs can reach 100%, while mortality can reach 50% in animals that have secondary infections or are immunocompromised (Abubakar et al. 2025). The virus is characterized by its consistent reinfections in sheep and goats and resistance to severe environmental conditions, both of which have contributed to the infection's transmission in various animal species, including dogs, guinea pigs, and deer.

Zoonotic Impact of ORFV: Hindering the Livestock Business

ORF is characterized by proliferative skin lesions, most frequently on the mouth and face, which further form through papule, vesicle, pustule, and scabs over several months (Thompson et al. 2022). While typically self-limiting in healthy animals, it causes significant economic losses due to mastitis, degraded wool quality, reduced animal value, and can be lethal in young animals (Ma et al. 2022). As a zoonosis, Orf poses a significant human health risk, primarily transmitted through contact with infected animals, especially via broken skin, and presents as pus-filled dermatitis, most often on the hands and arms; although usually self-resolving within weeks, it can lead to severe, persistent infections in immunocompromised individuals (Khan et al. 2022; Ma et al. 2022).

ORF disease is identified to be enzootic in the small ruminants in Asian, African, and many other regions worldwide (Mao et al. 2022). Small ruminants have significant economic value for humans due to their abundant supply of calcium, protein, vitamins, hides, fiber, and particularly wool, which benefits millions of people globally (Chadda et al. 2025). Nevertheless, the financial and economic consequences of viral infections are thought to be under-reported due to their severe occurrence of the disease. Furthermore, a higher proportion of the viral disorders currently hindering the livestock business are attributed to harmful animal viruses. In order to meet the significant demand in livestock farming, it is essential to protect animals against contagious viruses such as ORFV and some other veterinary pathogens. Hence, by taking measures to prevent infectious diseases in animals, it is possible to achieve the widespread elimination of viruses,

promote healthy livestock production, and subsequently enhance the life expectancy of farmers and veterinarians (Zanella 2023).

Molecular and Laboratory Diagnosis of ORFV

Cell culture is a standardized procedure used to isolate and proliferate the poxviruses. The morphologic changes (cytopathic effect) such as granulation, rounding, shrinking, degeneration, and ballooning of the cells represent the incidence of viruses in the monolayer of different cell lines (Lawan et al. 2021). At first, primary cells from lamb kidneys and testis were used to isolate the Orf virus (Sun et al. 2022). Later, cells from ovine, cattle, and caprine animals were chosen because they were better at producing cells and supporting virus replication (Galnbek et al. 2021). However, using primary cells has problems like heterogeneity and limited virus susceptibility. This is why researchers are looking to continuous cell lines as an alternative way for isolation and propagation of the Orf virus (Medina et al. 2024).

The CE virus typically grows in primary cell cultures unless it is adapted to specific cell lines, which is quite a challenging process. The adaptation of the CE virus to primary cultures can be very difficult, and it may require various passages before any visible effects can be seen (Lawan et al. 2021). The fetal lamb skin, testes, and muscle cells are suitable for isolating the CE virus, but once adapted, they can support the growth of the virus only in continuous cell lines. Alternatively, CE viruses can also be grown in embryonated chicken eggs, causing different pathological changes like oedema, haemorrhages, small greyish white foci, the development, and thickening of pock lesions in the egg's chorion-allantoic membrane (Joseph et al. 2021; Lawan et al. 2021).

Several methods, such as electron microscopy, are used to observe the parapoxvirus virus in skin biopsies that can detect CE, but they might have certain limitations in distinguishing the Orf virus (Lawan et al. 2021; Tuppurainen 2022). Molecular methods, such as PCR, help to make an obvious and definitive diagnosis, while histopathology and serologic tests, such as ELISA and VNT, help for viral antigen detection (Prasad et al. 2024). The methods used for the molecular and laboratory diagnosis of ORFV are discussed in Table 1 given below:

Immunomodulatory Genes

It is well known that parapoxvirus (ORFV) can survive many challenges to the immune reaction that is set off by the host. ORFV can get around some of the body's immune system because when it infects the mucocutaneous epidermis boundaries, it instantly releases a number of virulence proteins that weaken the host's defence (Kassa 2021). Because of this, the virus may eventually use different immunomodulatory approaches to change, avoid, or weaken the host's immune system. Some of the main immune-modulatory genes (IMGs) that ORFV encodes are OVIFNR, which stops the synthesis of proteins by blocking an enzyme called dsRNA-dependent kinase, VEGF, GM-CSF inhibitory factor (GIF), chemokine binding protein (CBP), and interleukin-10 (IL-10). These virulent genes are mostly located in the terminal end of each inverted terminal repeat (ITR) (Martins et al. 2021). Researchers have shown that ORFV gets its IMGs and

Table 1: Diagnostic Laboratory Methods for Contagious Ecthyma

Animal Species	Sample Collected	Detection	Diagnostic Lab Test	References
Sheep	Skin scraping, skin biopsies, dried scabs, crusts	B2L gene	PCR	(Ewies et al. 2024)
Sheep	Blood serum	Antibodies and B2L	ELISA and PCR	(Umitzhanov et al. 2024)
Sheep and Goats	Skin Scabs	B2L and VIR Genes	PCR	(Coradduzza et al. 2024)
Goats, Sheep, and human	Sera and scabs	Antibodies, B2L gene detection, evaluation of ovoid shape particles (290-300 × 160 nm)	Protein A-ELISA, IFAT, AGPT, EM, and PCR	(Lawan et al. 2021)
Goats	Scabs	F1L and B2L genes	PCR	(Mansoor et al. 2025)
Human	Skin lesion	Bricklike shape covered by a double-layered capsid	Electron microscopy	(Cook 2022)
Human	Scabs	B2L, and Orf045 internal region gene	PCR	(Peralta et al. 2023)
Goats	Scabs, sera, and buccal swab	B2L and VIR	PCR	(Mansoor et al. 2025)
Goats	Tissue, skin Scrapings	B2L gene	Real-time PCR	(Yatoo et al. 2023)
Goats	Serum	B2L gene	PCR	(Zheng et al. 2024)
Goats and sheep	Scab	B2L	PCR	(Shehata et al. 2022)
Sheep	Skin lesions	ORFV-539, OVS, and OVA genes	Virus isolation, PCR, and real-time PCR	(Lawan et al. 2021)
Goats	Serum samples	IgG	Indirect ELISA	(Berguido et al. 2022)
Camel	Skin biopsies	B2L gene	PCR	(Shehata et al. 2021)
Goats and sheep	Serum and scabs	IgG and B2L gene	ELISA and PCR	(Nashiruddullah et al. 2022)
Goats	Scabs	B2L and A32L genes	PCR	(Mansoor et al. 2025)
Goats and sheep	Serum	IgM antibodies	ELISA	(Zhang et al. 2022)

immunomodulatory proteins (IMPs) from vaccinia viruses and from interacting with its host over and over again. For example, GIP, CBP, VIR, and dUTP came from vaccinia virus's homologue proteins, which in turn came from ancestral poxvirus genes. So, the finding of genes that change the immune system and proteins released by ORFV may help explain how the virus avoids being killed by the host's immune system (Bukar et al. 2021).

In addition to their therapeutic effects, IMPs play a big role in how viruses cause disease and how strong they are. As a result, these benefits would bring attention to the virus's immunology, how it spreads, and possible ways to treat it. However, intracellular viruses make immune-modulatory proteins (IMPs), which manipulate the host's immune system and stop cell interaction (Gülyaz et al. 2020).

Overview of Vaccines against ORFV

Vaccination is the most effective way to prevent outbreaks of infectious diseases. Vaccines are synthetic or biological formulations of immunogens (carbohydrates, proteins, and lipids derived from microorganisms or other synthetic sources) that elicit long-lasting immunogenic memory for the antigen in the host when administered (Sam-Yellowe et al. 2021). Thus, quarantine and prophylactic vaccination are the most economical strategies for reducing the utilization of antimicrobials in sheep and goats of all ages infected with ORFV. Strict adherence to vaccination protocols, implementation of comprehensive preventive measures, including proper treatment of diseased animals, and additional containment strategies like improved sanitation appear to effectively prevent further transmission of the disease (Siddique and Terrill 2025).

Live Attenuated Vaccines

Live attenuated vaccine contains the non-virulent form of Orf virus, which will be injected in animal (Zhang 2021). Consequently, recurrent infections should be treated with ORFV vaccines, and vaccinated goats or sheep should be kept in isolation from unvaccinated animals. The immunization of lambs and young animals that are devoid

of ORFV-specific antibodies within the initial week after birth can result in substantial immunity (Bukar et al. 2021). However, the scientific literature concerning the advancement of vaccines and vaccination strategies in response to ORFV infections is minimal. The current live-attenuated vaccines designed to combat ORFV infections fail to induce protective immunity against the virus (Ravikuma et al. 2022; Kamboj et al. 2024). Hence, currently available attenuated vaccines pose a significant hazard of reverting back to their virulent state. The diverse levels of vaccine failure necessitate a reassessment of many determining factors, specifically proteins and genes participating in the virulence and pathogenesis of the virus. These factors may affect the safety and effectiveness of current vaccines designed to combat ORFV infection (Endale et al. 2022).

Genetically Modified and Recombinant Vaccines

The contagious Orf virus (ORFV) causes ecthyma, a skin disease that affects animals and humans. A genetically modified ORFV strain with two genes deleted, called rGS14-ΔCBP-ΔGIF, was developed. It was tested on lambs and shown to be completely safe and protective against a virulent ORFV challenge. This makes it a good, promising candidate for a vaccine (Zhu et al. 2022). The Orf virus (ORFV) could be used to make vaccines and treat cancer with viruses. Taking out the VEGF or CBP genes from ORFV makes it less infectious and less dangerous, especially the VEGF-deletion mutant. This highlights their potential as attenuated vectors for clinical applications (Yamada et al. 2023).

The limited host range of Orf virus (ORFV) makes primary cells from natural hosts like goats and sheep ideal for isolation and propagation. SV40 T antigen, a viral oncoprotein, can extend the life span of cells, leading to the transformation of fibroblast and testis cells (Patil and Bihari 2022; Stricker et al. 2023). These cells, FBT and GTT, show faster growth kinetics and lower serum dependency compared to parental cells (Espinoza-Hernández et al. 2025). Their prolonged life span makes

them ideal for ORFV isolation, pathogenesis studies, and efficient vaccine development (Chen et al. 2025). ORFV can be used as a therapeutic agent in vector-based medicines to fight cottontail rabbit papillomavirus (CRPV)-induced tumors. It is possible to make ORFV-CRPV recombinants that expressed early CRPV genes E1, E2, E7, or LE6 (Helmold and Amann 2025).

Using CRISPR/Cas9 to add the *S. aureus* TRAP gene to a weakened ORFV vector is a new way to make a vaccine that shows promise for controlling both ORFV and *S. aureus* at the same time with an effective gene expression that has been shown in keratinocytes (Yu et al. 2023). ORFV strain D1701-V as a novel vector for vaccine development, allowing repeated immunizations and enhanced humoral immune responses against inserted antigens. However, cellular immunity to the ORFV vector is negligible, while strong CD8⁺ T cell response is induced against the inserted transgene (Müller et al. 2022). This highlights the ORFV strain D1701-V as an attractive vector for vaccine development and outlines prerequisites for selecting T cell epitopes for ORFV-based vaccines (Helmold and Amann 2025).

Conventional and Autogenous Vaccines

Animal vaccination against ORF has a significant potential benefit, particularly for big herds of sheep or goats (Bukar et al. 2021). Some countries have manufactured many kinds of conventional vaccinations. In the past, autogenous vaccines were made without following appropriate standard procedures. The Texas Agricultural Experiment Station (presently known as Texas AgriLife Research) at Sonora, Tex., in the 1930s in the United States created the most famous and first ORF virus vaccination, which was successful in reducing farm losses (Davis et al. 2024). The Texas AgriLife Research contagious ecthyma vaccination and the other contagious ecthyma vaccine that is commercially available were found to be ineffective at shielding goats against the wild-type contagious ecthyma virus that infects goats. The fact that there are more goats in Texas than ever before and that their breed has dramatically changed from Angora to Boer cross goats may have something to do with the apparent inadequacy of the current infectious ecthyma vaccinations to protect goats. To safeguard this growingly significant animal industry, a contagious ecthyma vaccination is desperately needed (Lawan et al. 2021).

The infectious ecthyma virus has been identified in over 40 strains. Goats are likely not always protected by sheep contagious ecthyma vaccines because phylogenetic analyses show that the viral strains that cause contagious ecthyma in sheep and goats cluster on different branches of the genetic tree (Lawan et al. 2021; Alam et al. 2024). This shows that the contagious ecthyma virus strains in goats are more varied than those in sheep, suggesting that contagious ecthyma vaccines must be made using viral strains recovered from goats in order to be effective in goats (Lawan et al. 2021; Zhu et al. 2022; Alam et al. 2024).

After that, Colorado Serum Company, USA, created and distributed a commercial Orf vaccine. A vaccination based on cell culture has also been developed in Australia. Nevertheless, the vaccine only provides four to six months of protection in ewes and lambs. Germany has successfully developed another cell culture-based vaccine by using the

Orf virus strain (Orf-V D1701) by an attenuation procedure that results in mutations at the amino acid sequences of the virus's crucial virulence coding protein (Lacasta et al. 2021; Lu et al. 2022).

Scab-Derived Vaccines (Autogenous Vaccination)

To make autogenous vaccines, infected scab tissue from recently infected animals is usually used. The tissue is then ground up and mixed with a clean saline solution that contains antibiotics (penicillin/streptomycin solution) (Cao et al. 2022). After a simple mixture is made, target animals are injected by scarification on their skin, primarily on the inside of the thigh. The first widely available vaccine made from scab material worked to protect against getting the disease for two to three years. However, live, non-attenuated vaccines have been linked to induce infection when they are given, which was seen as a big problem (Britzke et al. 2025).

Tissue Culture Vaccines

Tissue culture vaccines have been demonstrated to be helpful in producing ORF virus-infected herds. To grow ORF viruses, you can use both primary and continuous cell lines, such as primary lamb testes (PLT), MDOK, Vero, and MDBK (Poulinlu 2022). If the virus is passage through these cells at least 10 to 50 times, it may become attenuated. However, a wild-type ORFV may be attenuated in primary chicken embryo fibroblast cells and subsequently used to produce a live virus vaccination (Sohaimi and Clifford 2023).

ORFV as Vaccine Adjuvant and Vector Platform

Orf virus (ORFV) strongly activates the immune system and was tested as an adjuvant to help mice improve the immune response to a porcine circovirus type 2 (PCV2) subunit vaccine. ORFV, both inactivated and live attenuated, greatly increased the activity of dendritic cells, the production of cytokines, and the Th1/Th2 immune reactions. It also decreased the amount of virus in the body and the damage it caused to the lungs, showing that it could be used as a novel vaccine adjuvant (Sun et al. 2024). The virus contains a variety of immunomodulatory genes that limit the immune system of the host and affect the development of disease. The advent of the Orf viral genome sequence allows for further study of this dynamic process, which will yield valuable knowledge on virus pathogenesis and the immunological response of the host's skin to infection (Wang et al. 2023).

DNA and Subunit Vaccines

Rats had strong immune reactions to a DNA vaccine that contained ORF virus protein and kisspeptin-54. This suggests that it serve as a bivalent vaccine against the ORF virus and for immunocastration. ORF viral protein is an effective immunomodulator to provoke antibody responses to kisspeptin-54; it could be used for powerful antibody production (Ding et al. 2023). A DNA vaccine that expresses ORFV F1L and B2L genes was developed alongside subunit vaccines containing F1L truncated protein and B2L full-length protein. Immunization trials on BALB/c mice revealed that the DNA prime-protein boost approach generated higher antibody levels, enhanced lymphocyte proliferation, and increased expression of key

cytokines like IL-2, IL-4, IL-6, TNF- α , and IFN- γ , suggesting a mixed Th1/Th2 cytokine response. It indicates that the DNA prime-protein boost method induces robust humoral and cellular immune responses, potentially effective in ORFV infection prevention (Wang et al. 2022).

Goat-Specific Vaccines

In the selection of a suitable strain of contagious ecthyma virus for a goat vaccine, twenty-five goat kids were used for vaccine development, with another hundred for efficacy evaluation. Five viral strains were assessed, with strain 47CE chosen as the seed strain due to its favourable vaccine-to-challenge scab ratio. The vaccine derived from 47CE effectively protected all vaccinated goats from wild-type virus challenge, showing promise for improved goat-specific protection against contagious ecthyma compared to existing sheep vaccines (Zhu et al. 2022).

Mutant Vaccine Candidates

The primary method of controlling CE is through vaccination, as there are no specific medications and treatments available. A recently developed ORFV mutant (rGS14 Δ CBP Δ GIF Δ 121) with a deletion in three genes has exhibited complete safety and immunological protection in goats. This mutant has shown remarkable advancements compared to earlier strains, making it an outstanding candidate for a vaccine (Shen et al. 2023). Orf virus, derived from sheep lesions, was adapted to cell culture for vaccine development. While traditional vaccine methods showed efficacy, cell culture-adapted viruses initially lacked effectiveness until a recent isolate proved promising, indicating feasibility for a cell culture-produced scabby mouth vaccine (Chandipwisa et al. 2025).

Limitations and Challenges in Current ORFV Vaccination

Despite decades of research, Orf virus (ORFV) vaccination remains constrained by several limitations. Currently, only live attenuated vaccines are commercially available, but these carry a significant risk of reversion to virulence, raising safety concerns for both animals and handlers (Tang et al. 2025). Moreover, vaccinated animals often remain susceptible to reinfection, largely due to genetic variation among ORFV strains and the global movement of livestock, which facilitates viral spread. Conventional vaccine development strategies, such as tissue culture adaptation, have shown limited success in providing long-lasting protection. These shortcomings highlight the pressing need for safer and more effective alternatives (Aribi 2024).

Other challenges include the technical and economic constraints associated with newer vaccine platforms. Recombinant viral vectors can induce robust immune responses, but their development is complex and costly (Spunde et al. 2022). Subunit and peptide-based vaccines, though safer and easier to manufacture, generally require strong adjuvants to elicit protective immunity, while nanoparticle-based vaccines remain in early experimental stages, with issues of scalability and affordability yet unresolved. Collectively, these limitations underscore the gap between available vaccines and the requirements for effective, sustainable disease control in small ruminants (Petkar et al. 2021).

Novel and Future Perspectives in ORFV Vaccination

Recent advances in immunology and molecular virology are paving the way for next-generation ORFV vaccines. Insights into host-virus interactions have revealed that while attenuated strains tend to suppress immune responses, wild-type strains stimulate interferon pathways regulated by STAT1 and STAT2, offering valuable targets for novel vaccine design. Recombinant DNA technology also allows the deletion of immunomodulatory genes (e.g., ORFV020, ORFV117, ORFV132), resulting in attenuated viruses that provoke stronger immune responses while minimizing the risk of uncontrolled infection. These approaches represent a significant step toward designing safer, genetically stable live-attenuated vaccines.

Beyond traditional methods, a variety of innovative platforms are under investigation. Recombinant ORFV vectors show promise not only as veterinary vaccines but also in cancer immunotherapy due to their ability to activate antigen-presenting cells and trigger robust CD8⁺ T cell responses. Subunit and peptide vaccines offer safety and manufacturing advantages, while nanoparticle-based systems can enhance antigen stability, protect against degradation, and improve delivery to immune cells. Additionally, immortalized ovine cell lines and optimized production systems are improving scalability and quality for vaccine manufacturing. Looking forward, the future of ORFV vaccination lies in integrating these approaches to achieve vaccines that are safe, cost-effective, scalable, and capable of eliciting durable protective immunity in diverse livestock populations.

Conclusions

This review highlights the current challenges in vaccine development. However, continuous advancements in immunology indicate that new vaccines, which are both safe and effective, will be developed in the near future. There is currently significant progress in the development of vaccines for previously untreated infections, thanks to extensive research and study on antigens, vectors, and adjuvants. CE is a widely spread health problem for the even-toed ungulates and a big risk to the small ruminant industry, with economic outcomes for humans. Frequent re-infection of already infected animals, as well as inter- and intra-species transmission, must be addressed in order to implement proper control and preventative measures and reduce economic losses caused by disease-related damages. Setting up well-equipped animal health services at different levels is also important for quick response to disease.

DECLARATION

Funding: None.

Acknowledgement: None.

Conflicts of Interest: Authors have no conflict of interest.

Data Availability: All the data is available in this paper.

Ethical Statement: This is a purely review article and no animals were harmed.

Author's Contributions: All the authors participated equally.

Generative AI Statement: The authors declare that no Gen AI/Deep Seek was used in the writing/creation of this manuscript.

Publisher's Note: All claims stated in this article are exclusively those of the authors and do not necessarily represent those of their affiliated organizations or those of the publisher, the editors, or the reviewers. Any product that may be evaluated/assessed in this article or claimed by its manufacturer is not guaranteed or endorsed by the publisher/editors.

REFERENCES

- Abubakar M, Manzoor S and Iqbal A, 2025. Concurrent peste des petits ruminant's virus infections in small ruminants. *Peste des Petits Ruminants Virus* 159–168. DOI: [10.1007/978-3-031-82214-8_9](https://doi.org/10.1007/978-3-031-82214-8_9)
- Alam MS, Akther S, Rahman MH, Ali MZ and Ahmed S, 2024. Epidemiological diversity, isolation, and molecular characterization of circulating contagious ecthyma virus (Orf virus) in goats of Bangladesh. *Egyptian Journal of Veterinary Sciences* 2024: 1–9. DOI: [10.21608/EJVS.2024.320480.2371](https://doi.org/10.21608/EJVS.2024.320480.2371)
- Berguido FJ, Gelaye E, Liu Y, Davaasuren B, Krstevski K, Djadjovski I, Ivanova E, Goujgoulova G, Loitsch A, Tuppurainen E and Chibssa TR, 2022. Development and optimization of indirect ELISAs for the detection of anti-capripoxvirus antibodies in cattle, sheep, and goat sera. *Microorganisms* 10(10): 1956. DOI: [10.3390/microorganisms10101956](https://doi.org/10.3390/microorganisms10101956)
- Britzke T, Halwe NJ, Ulrich L, Breithaupt A, Barut GT, Wylezich C, Ebert N, Trüb BS, Thiel V, Hoffmann D and Beer M, 2025. Live attenuated SARS-CoV-2 vaccine OTS-228 demonstrates efficacy, safety, and stability in preclinical model. *NPJ Vaccines* 10(1):104. DOI: [10.1038/s41541-025-01165-2](https://doi.org/10.1038/s41541-025-01165-2)
- Bukar AM, Jesse FFA, Abdullah CAC, Noordin MM, Lawan Z, Mangga HK, Balakrishnan KN and Azmi MLM, 2021. Immunomodulatory strategies for parapoxvirus: current status and future approaches for the development of vaccines against Orf virus infection. *Vaccines* 9(11): 1341. DOI: [10.3390/vaccines9111341](https://doi.org/10.3390/vaccines9111341)
- Cao D, Guo W, Cai C, Tang J, Rao W, Wang Y, Wang Y, Yu L and Ding J, 2022. Unified therapeutic-prophylactic vaccine demonstrated with a postoperative filler gel to prevent tumor recurrence and metastasis. *Advanced Functional Materials* 32(40): 2206084. DOI: [10.1002/adfm.202206084](https://doi.org/10.1002/adfm.202206084)
- Chadda A, Meena DC and Singh J, 2025. Exploring the value chain of small ruminants: a review. *Indian Journal of Small Ruminants (The)* 31(1): 1–15. DOI: [10.5958/0973-9718.2025.00019.7](https://doi.org/10.5958/0973-9718.2025.00019.7)
- Chandipwisa C, Bwala DG, Shimilimo A, Olusola V, Adetunji SI and Killo AO, 2025. A comparative evaluation of the immunogenicity of cell culture adapted fowl pox vaccines. *Nigerian Veterinary Journal* 46:1. DOI: [10.4314/nvj.v46i1.1](https://doi.org/10.4314/nvj.v46i1.1)
- Chen C, Li J, Zhou Y, Zhang Y, Huang R, Zhang Y, Li J and Chen K, 2025. Latest advances and prospects in the pathogenesis, animal models, and vaccine research of severe fever with thrombocytopenia syndrome virus. *Frontiers in Immunology* 16: 1624290. DOI: [10.3389/fimmu.2025.1624290](https://doi.org/10.3389/fimmu.2025.1624290)
- Cook C, 2022. *Stomoxys calcitrans* influence the outcome of lumpy skin disease virus inoculation in bovine experimental models. Doctoral dissertation, University of Oxford.
- Coradduzza E, Fiori PL, Contini C, Carcangiu L and Lai A, 2024. The global evolutionary history of Orf virus in sheep and goats revealed by whole genomes data. *Viruses* 16(1): 158. DOI: [10.3390/v16010158](https://doi.org/10.3390/v16010158)
- Davis AD, Messenger S and Moore SM, 2024. History of rabies in the United States. *History of Rabies in the Americas: From the Pre-Columbian to the Present 2*: 27–78. Springer International Publishing, Cham.
- Ding Y, Jiang X, Sun L, Sha Y, Xu Z, Sohail A and Liu G, 2023. Multiple-pathway synergy alters steroidogenesis and spermatogenesis in response to an immunocastration vaccine in goat. *Cells* 13(1): 6. DOI: [10.3390/cells13010006](https://doi.org/10.3390/cells13010006)
- Endale H, Aliye S and Mathewos M, 2022. Vaccine epidemiology, evaluation, and constraints of vaccine effectiveness – a review. *Veterinary Vaccine* 1(1): 100004. <https://doi.org/10.1016/j.vetvac.2022.100004>
- Espinosa-Hernández FA, Moreno-Vargas AD, Díaz-Villaseñor A, Mata-Torres G, Samario-Román J and Andrade-Cetto A, 2025. Tissue-specific enhancement of insulin function and restoration of glucose-stimulated insulin secretion by *Croton guatemalensis* Lotsy and *Eryngium cymosum* F. Delarocche. *Pharmaceuticals* 18(10): 1433. DOI: [10.3390/ph18101433](https://doi.org/10.3390/ph18101433)
- Ewies SS, Tamam SM, Abdel-Moneim AS and Roubay SR, 2024. Contagious ecthyma in Egypt: clinical, virological and molecular explorations. *Virology* 589: 109924. DOI: [10.1016/j.virol.2023.109924](https://doi.org/10.1016/j.virol.2023.109924)
- Gülyaz V, Saraç F, Hasöksüz M and Uzar S, 2020. The use of rabbits in studies of immunity and safety of contagious ecthyma (CE) vaccine. *Etlik Veteriner Mikrobiyoloji Dergisi* 31(1): 75–81.
- Helmold M and Amann R, 2025. Advancing ORFV-based therapeutics to the clinical stage. *Reviews in Medical Virology* 35(3): e70038.
- Hussain I, Khan MUR, Aslam A, Rabbani M, Masood S and Anjum A, 2023. Identification, molecular characterization, and pathological features of Orf virus in sheep and goats in Punjab province, Pakistan. *Tropical Animal Health and Production* 55(1): 24.
- Joseph S, Kinne J, Nagy P, Juhász J, Barua R, Patteril NAG, Hoffmann D, Pfaff F, Hoffmann B and Wernery U, 2021. Outbreak of a systemic form of camelpox in a dromedary herd (*Camelus dromedarius*) in the United Arab Emirates. *Viruses* 13(10): 1940.
- Kamboj A, Dumka S, Saxena MK, Singh Y, Kaur BP, da Silva SJR and Kumar S, 2024. A comprehensive review of our understanding and challenges of viral vaccines against swine pathogens. *Viruses* 16(6): 833.
- Kassa T, 2021. A review on human orf: a neglected viral zoonosis. *Research and Reports in Tropical Medicine* 12: 153–172.
- Knipe DM, Prichard A, Sharma S and Pogliano J, 2022. Replication compartments of eukaryotic and bacterial DNA viruses: common themes between different domains of host cells. *Annual Review of Virology* 9: 307–327.
- Lacasta D, Pérez M, Villalba R, Ruiz H and Ferrer LM, 2021. Effect of a topical formulation on infective viral load in lambs naturally infected with orf virus. *Veterinary Medicine: Research and Reports* 12: 149–158.
- Lacasta D, Reina R, Ruiz de Arcaute M, Ferrer LM, Benito AA, Tejedor MT, Echeverria I, Ruiz H, Martinez Cardenas S and Windsor PA, 2021. Effect of a topical formulation on infective viral load in lambs naturally infected with orf virus. *Veterinary Medicine: Research and Reports* 12: 149–158.
- Lacasta D, Ríos M, Ruiz de Arcaute M, Ortín A, Ramos JJ, Villanueva-Saz S, Tejedor MT, Ruiz H, Borobia M, Reina R and Gómez A, 2023. Use of a local anaesthetic/antiseptic formulation for the treatment of lambs experimentally infected with Orf virus. *Animals* 13(18): 2962.
- Lawan Z, Bala JA, Bukar AM, Balakrishnan KN, Mangga HK, Abdullah FFJ, Noordin MM and Mohd-Azmi ML, 2021. Contagious ecthyma: how serious is the disease worldwide? *Animal Health Research Reviews* 22(1): 40–55.

- Li S, Zhang Y, Chen W, Liu H and Wang X, 2023. Genetic analysis of Orf virus (ORFV) strains isolated from goats in China: insights into epidemiological characteristics and evolutionary patterns. *Virus Research* 334: 199160.
- Lu X, Liu X, Song Q, Wang X, Hu S and Liu X, 2022. Amino acid mutations in hemagglutinin-neuraminidase enhance the virulence and pathogenicity of the genotype III Newcastle disease vaccine strain after intravenous inoculation. *Frontiers in Veterinary Science* 9: 890657.
- Mansoor MK, Iqbal K, Hassan A, Saqib M, Zohaib A and Masood S, 2025. Comparative homology and complete B2L gene-based sequence analysis of ORF virus from sheep and goats in Pakistan. *Asian Journal of Agriculture and Biology*.
- Mao L, Li W, Hao F, Yang L, Li J, Sun M, Zhang W, Liu M, Luo X and Cheng Z, 2022. Research progress on emerging viral pathogens of small ruminants in China during the last decade. *Viruses* 14(6): 1288.
- Martins M, Duarte M, Silva J, Costa A and Oliveira P, 2021. Orf virus ORFV112, ORFV117 and ORFV127 contribute to ORFV IA82 virulence in sheep. *Veterinary Microbiology* 257: 109066.
- Müller M, Reguzova A, Löffler MW and Amann R, 2022. Orf virus-based vectors preferentially target professional antigen-presenting cells, activate the STING pathway and induce strong antigen-specific T cell responses. *Frontiers in Immunology* 13: 873351.
- Mungmunpantipantip R and Wiwanitkit V, 2024. Orf, a human parapoxvirus infection. *Poxviruses* 171–181.
- Nashiruddullah N, Pathak DC, Barman NN, Ahmed JA, Begum SS and Roychoudhury P, 2022. Natural infection of goats with orf (contagious ecthyma) and its diagnosis. *Indian Journal of Animal Research* 56(2).
- Patil MR and Bihari A, 2022. A comprehensive study of p53 protein. *Journal of Cellular Biochemistry* 123(12): 1891–1937.
- Peralta A, Gomez L, Rojas M, Fernandez P and Silva R, 2023. Identification and molecular characterization of Orfvirus infection in occupationally exposed women in South America. *Revista Argentina de Microbiología* 55(2): 4–4.
- Petkar KC, Patil SM, Chavhan SS, Kaneko K, Sawant KK, Kunda NK and Saleem IY, 2021. An overview of nanocarrier-based adjuvants for vaccine delivery. *Pharmaceutics* 13(4): 455.
- Poulinlu G, 2022. Whole genome sequencing of vaccine strain and evaluation of diagnostic potential of Baculovirus expressed immunogenic proteins of Orf virus. Doctoral dissertation, Indian Veterinary Research Institute.
- Prasad RD, Sonawane KD, Prasad RS, Prasad SR, Prasad N, Shrivastav RK, Shrivastav OP, Charmode N, Vaidya AK, Desai CB and Patil VN, 2024. A review on livestock viral disease and their management. *ES General* 5: 1227.
- Ravikumar R, Chan J and Prabakaran M, 2022. Vaccines against major poultry viral diseases: strategies to improve the breadth and protective efficacy. *Viruses* 14(6): 1195.
- Reichen C, Beirão BCB and Monteiro ALG, 2025. Contagious ecthyma in small ruminants: from etiology to vaccine challenges a review. *Veterinary Research Communications* 49(2): 115.
- Shehata AA, El-Nahas EM, Abo Hatab EM, Sharawi SS and Ahmed HA, 2021. The genetic identification of camel contagious ecthyma virus as the causative agent of contagious ecthyma in dromedary camels (*Camelus dromedarius*) in Qatar. *Tropical Animal Health and Production* 53(2): 332.
- Shehata AA, Elsheitik HA and Abd-Elfatah EB, 2022. Molecular detection and characterization of Orf virus from goats in Egypt. *Open Veterinary Journal* 12(2): 273–280.
- Siddique A and Terrill TH, 2025. Orf (Parapoxvirus Orf Virus). *The One Health Model as Applied to Zoonotic Diseases* 283–288.
- Sohaimi NM and Clifford UC, 2023. The importance and challenges of primary chicken embryo liver cells in studies of poultry viral diseases: a review. *Journal of World's Poultry Research* 13(4): 364–372.
- Spunde K, Korotkaja K and Zajakina A, 2022. Recombinant viral vectors for therapeutic programming of tumour microenvironment: advantages and limitations. *Biomedicines* 10(9):2142.
- Stricker E, Peckham-Gregory EC and Scheurer ME, 2023. HERVs and cancer—a comprehensive review of the relationship of human endogenous retroviruses and human cancers. *Biomedicines* 11(3):936.
- Sun S, Zhao K, Lu H, Liu X, Li Y, Li Q, Song D, Lan Y, He W, Gao F and Li Z, 2022. Establishment of a sheep immortalization cell line for generating and amplifying Orf virus recombinants. *Frontiers in Veterinary Science* 9: 1062908.
- Tang YD, Li Y, Cai XH and Yin X, 2025. Viral live-attenuated vaccines (LAVs): past and future directions. *Advanced Science* 12(3): 2407241.
- Thompson HJ, Harview CL, Swick B and Powers JG, 2022. Orf virus in humans: case series and clinical review. *Cutis* 110(1): 48–52.
- Umizhanov M, Sansyzbai AR, Makhmutov AK, Turebekov OT and Bakirov NZ, 2024. Sustainable development and conservation of ecosystems: epizootic situation of contagious ecthyma of sheep and goats in Kazakhstan and neighbouring countries. *AIP Conference Proceedings* 3033(1).
- Wang Y, Liu H, Chen X, Zhang Z, et al. 2022. Evaluation of the immune response afforded by combined immunization with orf virus DNA and subunit vaccine in mice. *Vaccines* 10(9): 1499.
- Yattoo MI, Parray OR, Ul Haq RI and Mushtaq M, 2023. Diagnostic techniques in goats. In: *Principles of Goat Disease and Prevention*. 237–249.
- Zhang J, Ma H, Ai J, Qi T, Kang M, Li J and Sun Y, 2022. Serological analysis of IgG and IgM antibodies against *Anaplasma* spp. in various animal species of the Qinghai-Tibetan Plateau. *Animals* 12(19): 2723.
- Zhang S, 2021. Progress in the study of live vector vaccine for swine fever virus E2 gene. *World Scientific Research Journal* 7(11): 26–34.
- Zheng W, Zhang Y, Gu Q, Liang Q, Long Y, Wu Q and Xian S, 2024. Development of an indirect ELISA against Orf virus using two recombinant antigens, partial B2L and F1L. *Journal of Virological Methods* 326: 114891.
- Zhu Z, Qu G, Du J, Wang C, Chen Y, Shen Z, Zhou Z, Yin C and Chen X, 2022. Construction and characterization of a contagious ecthyma virus double-gene deletion strain and evaluation of its potential as a live-attenuated vaccine in goat. *Frontiers in Immunology* 13: 961287.