Research Article

Epidemiology and Diagnostic Insights into Orf Virus Infection in Palestinian Sheep and Goats: A Histopathological and Serological Study

Hazem Sawalha*, Mujahed Abu-Alrub, Bashar Abu-Alrub, Abdalsalam Kmail**

Faculty of Sciences, Arab American University Jenin, P. O. Box 240, Jenin, Palestine.

Abstract | Contagious ecthyma, known as Orf virus, is a prevalent disease in livestock, particularly affecting young sheep and goats, with significant implications for Palestinian agricultural economy and animal production. This investigation explores the incidence and impact of contagious ecthyma Orf virus in sheep and goats across various age groups in Jenin governorate, Palestine. Employing ELISA testing and histopathological examination, the study aims to provide a comprehensive understanding of the disease's manifestation and control. The disease presented with severe symptoms, notably in mucocutaneous areas, and was most prevalent in younger animals during colder months. Histopathological findings indicated pronounced tissue damage, including epithelial hyperplasia and necrosis. Infection rates were highest in newborn sheep (31.03% in January) and mortality peaked in newborn goats (25.4% in March). Control measures showed diclofen as the most effective treatment with an efficiency rate of 89.19%, followed by isolation rate of 84.3%. The study confirms the Orf virus's significant impact on livestock, with young animals being particularly vulnerable. Effective control measures are crucial, especially during peak infection periods. The results serve as a vital resource for developing strategic interventions to manage and mitigate the disease's effects on animal health and the agricultural economy.

Keywords | Orf virus, Livestock disease, Sheep, Goats, Histopathology, Diclofen treatment

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***Correspondence** | Hazem Sawalha, Abdalsalam Kmail, Faculty of Sciences, Arab American University Jenin, P. O. Box 240, Jenin, Palestine; **Email:** hazem.sawalha@aaup.edu, abdalsalam.kmail@aaup.edu
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INTRODUCTION

Contagious ecthyma, commonly known as Orf virus, is a significant viral skin disease that primarily affects sheep and goats, and occasionally humans (Lawan et al., 2021). The disease is caused by a parapoxvirus and is transmitted through contact, often resulting in lesions that progress from papules to pustules before crusting over (Zewdie et al., 2021). It is characterized by infectious dermatitis, primarily impacting the lips of young animals, and can be more severe in goats than in sheep (Lawan et al., 2021). All sheep and goats are susceptible, but young, suckling ones are particularly vulnerable, leading to a high mortality rate, whereas death is rare in adults (Hajkazemi et al., 2016).

The symptoms off contagious ecthyma include the appearance of blisters, red grains, and wounds covered with crusts at the onset, primarily around the mouth, throat, and sometimes extending to the nipples, udders, and between the hooves. The disease also manifests as small boils and scales on the face, and red spots, deformities, and scars near the mouth, causing swelling and difficulty in feeding due to pain, leading to fever and emaciation (Lawan et al., 2021). Orf virus is resilient to environmental conditions such as heat and drought, with the ability to reactivate when conditions are favorable. The infection cycle is completed when scales fall from the mouth of infected sheep to the ground, with an incubation period of two to three days (Gelaye et al., 2016; Kassa, 2021). The virus can also spread to humans, typically resulting in a single, red sore that heals spontaneously within 3-6 weeks (Karki, 2019). The virus can be present throughout the geographic distributions of its hosts, making it a challenge to distinguish specific ecological niches (Nair et al., 2024). Globally, Orf virus is recognized as a significant concern in animal husbandry, affecting the health and productivity of sheep and goats worldwide. Studies have reported varying incidence rates, such as 12% among screened sheep and goats in Northwest Ethiopia (Tedla et al., 2018), and approximately 40% of sheep and goat operations in the United States reported cases within three years (Thompson et al., 2022).

In the Palestinian territories, the livestock sector is a cornerstone of the agricultural economy, contributing significantly to family incomes, especially in rural areas, accounting for about 46% of the Palestinian agricultural income. The sectors of sheep, goats, cattle and poultry, in addition to beekeeping and fish, are among the main pillars of this sector. The number of sheep and goats on 01/10/2021, in the West Bank, reached 713330 and 231327, respectively (Palestinian Central Bureau of Statistics, 2021). Recently, many symptoms and deformities have appeared in the Palestinian areas that raise sheep in the mouth area, as well as signs of poor growth, especially in young sheep. However, the cause of this disease is a significant decrease in production and significant mortality in animals, especially newborns. In addition, the disease caused a significant increase in production costs, which in turn incurred huge losses for farmers, forcing some of them to leave their farms or switch to other agricultural activities of less importance than the previous agricultural activity (Coradduzza et al., 2024).

The purpose of this study is to examine the current state of animal production in Jenin governorate and to address the challenges posed by a specific disease affecting livestock. The research aims to provide insights into the conditions of animal husbandry and to develop interventions to alleviate the impact of this disease. Additionally, the study seeks to offer advice and guidance to local farmers to prevent or minimize the damage caused by this disease, which poses a risk of spreading to other areas within the Palestinian territories. Jenin governorate was selected for this study due to its significant contribution to the Palestinian food basket, particularly from the rural northern regions. The area is known for its fertility and ample water resources, which are favorable for agriculture and grazing. It also stands out as an important province for animal production, making it an ideal location for conducting this research (Palestinian Central Bureau of Statistics, 2021).

MATERIALS AND METHODS

Study Site

Sheep and goat pens were representatively and randomly selected for the study in the town of Al-Masiliya/Jenin governorate. The town is located 14 kilometers south the city of Genin. (32.48333 °N 35.3 °E). Samples were obtained in accordance with the international regulation and Arab American University guidelines. Proper permissions were obtained in compliance with local laws. Written informed consent was obtained from the owners of the animals for the collection of samples from their property and for the participation of their animals in this study. Research procedures adhere to the principles of humane treatment, ensuring the well-being of the animals involved. The study also prioritized reducing pain, distress and suffering using the least methods possible. In addition, informed consent was obtained from the animal owners, explaining the purpose, procedures, and potential risks of the study. Proper care and monitoring were provided after sample collection to ensure animal health. All relevant national and international and ethical regulations related to animal research were strictly followed.

Sample Diagnosis and Collection

Samples were taken from the mouths of adult, 30-day-old SHAMI goats and newborn, 7-day-old ASSAF sheep. For histological analysis, samples of infected tissue and sections of the hairy skin afflicted at the lip, eye, and foreskin mucosal junctions were gathered. The signs of red patches, edema, and anomalies in the mouth and lip area were used to characterize the condition tentatively. Samples were collected from hairy skin of lips, eyes, and foreskin mucosal junctions. In the same manner, samples from the mouths of healthy sheep and goats were also taken. After the material had been removed with sterilized scalpels and tweezers, it was placed into Falcon tubes containing formalin. Formalin, is widely used for preserving biological samples due to its ability to effectively fix and stabilize tissues. It penetrates tissues quickly, cross-linking proteins, which helps maintain cellular structure and prevents decay. This makes it ideal for long-term storage of specimens.

Enzyme Linked Immunosorbent Assay (ELISA)

The enzyme-linked immunosorbent assay (ELISA) was employed for the detection of Immunoglobulin G (IgG). The assay kit was provided by SunLong Biotech Co., LTD, and the procedure was conducted in accordance with the protocol established by Bala et al. (2018). Serum samples, both negative and positive controls, were dispensed at a volume of 50 µL into six designated wells of the ELISA plate. Concurrently, a mixture comprising 40 µL of the sample dilution buffer and 10 µL of the serum specimen was allocated to twenty wells. Following thorough admixture, the plate was sealed and incubated for 30 minutes at 37° C. The wells were washed 5 times at interval of 30 seconds each with a wash buffer. Thereafter, 50 μL of goat anti-rabbit (GAR)-conjugate reagent was added to each well, and incubated at 37° C for 60 minutes. Post-incubation, the wells were subjected to the aforementioned washing protocol, after which the chromogenic substrate was added. A lapse of 15 minutes permitted the development of the ELISA reaction, the results of which were ascertained via an automated ELISA-Reader. Absorbance was performed at a wavelength of 450 nm (Sawalha, 2009). Cut off (CO), threshold point, value = the average value of 2 negative controls. OD readings, values less than the CO value were considered as negative, whereas OD values higher than the CO value were interpreted as positive.

Histopathological Analysis

Histopathological studies were done in histotechnology laboratory/ Faculty of Allied Medical Science/ The Arab American University of Palestine (AAUP). The analysis was performed according to Kinley et al. (2013), with modifications mentioned below.

Tissue Processing

Tissue processing which includes fixation. Dehydration, clearing and embedding were done using an automated tissue processor (Leica Tp 1020 atomic tissue processor). Formalin 10% was used to fix the samples then dehydrated by dipping subsequently in 75 and 95% ethanol. The tissues were cleared and alcohol residues and fat were removed by dipping for an hour in absolute xylene. Imbedding was performed using liquid paraffin to fill the free spaces after lipid removal. The process was done using Tbs88 paraffin embedding system thermal unit. The tissues were cut into 5 nm thick stripes using an automated microtome device, then dipped in water bath for 20 seconds.

Tissue Staining

The tissues were stained using both hematoxylin and eosin. Tissues were dipped subsequently in xylene (3 minutes), absolute alcohol (3 minutes), 95% alcohol (3 minutes), tap water (1 minute), Hematoxylin stain (5 minutes), tap water (1 minute), 0.1 M HCl (1 minute), tap water (1 minute), eosin (1 minute), 95% alcohol (1 minute) and xylene (3 minute).

Microscopic Examination

The samples were examined with Leica ATC 2000 Microscope.

Disease Incidence

Over the course of a year, disease incidence was investigated by routinely visiting pens on a monthly basis and randomly collecting animal samples. Samples were collected from the lips and mouth regions of animals of various ages. A total of 300 samples were collected. ELISA, chosen for its sensitivity and specificity in detecting Orf virus, was used to test the samples, which were then transferred to The microbiology laboratory, Faculty of Science, AAUP.

Mortality Rate and Disease Control

Two methods were employed to study disease control and mortality. First, in-person interviews with sheep breeders were conducted to gather data and complete study forms. Second, regular visits to the sheep and goat pens were made throughout the year to count the number of deceased animals and observe the effectiveness of various control strategies. The mortality rate was calculated as a percentage of the total herd. Additionally, ELISA was used to investigate each dead animal to determine the cause of death.

Statistical Analysis

Statistical analysis of the data was done using the Two-Sample Tests of Proportions (TSTP) to compare treatments. The results were analyzed using a level of significance when α = 0.05. Calculation was done according to the following equations (Lind et al., 2005; Montgomery, 2008). Comparison was made between elements of the same treatment.

$$Z = \frac{\hat{P}_1 - \hat{P}_2)}{\sqrt{\hat{P}(1-\hat{P})(\frac{1}{n_1}+\frac{1}{n_2})}}$$

Two – Proportion Z- test, pooled for "$H_0: P_1 = P_2$"

$$\hat{P} = \frac{X_1 + X_2}{n_1 + n_2}$$

α, the probability of Type I error (rejecting a null hypothesis when it is in fact true)
n = sample size; n_1 = sample 1 size; n_2 = sample 2 size.

$$\hat{P} = \frac{X}{n} = sample\ proportion$$

P_0=hypothesized population proportion; P_1=proportion 1; P_2= proportion 2.

RESULTS AND DISCUSSION

Disease Diagnoses

In addition to the damaged hairy skin at the mucosal skin joints, lips, eyes, and foreskin, the disease's symptoms were identified in the field included the appearance of red spots, swelling, and deformities on the lips and mouth area (Figure 1). The disease has been confirmed to affect both goats and sheep of all ages, causing significant losses for livestock breeders.

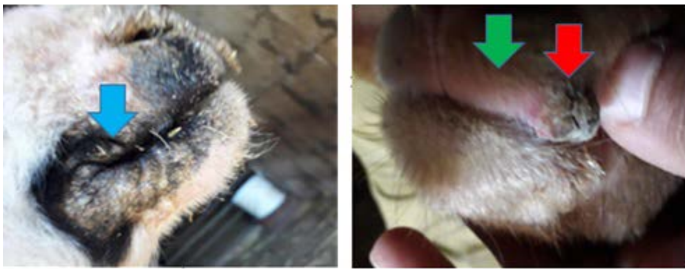

Figure 1: Orf-sick sheep. Symptoms appear clearly as swellings (red arrow), red spots (green arrow), and deformities (blue arrow) on the lips and mouth of Orf-sick sheep.

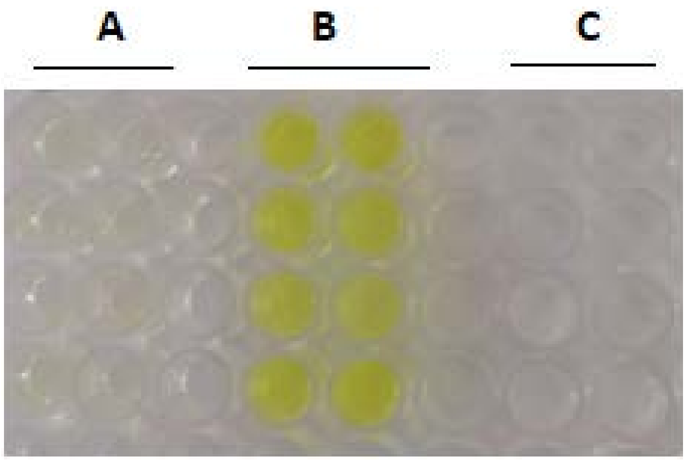

Figure 2: ELISA plate showing the antibody-antigen reaction of samples collected from the animal lips. Dark yellow wells are considered positive; A: Healthy animal; B: Diseased animal; C: Buffer sample.

Serological Detection

The results of the ELISA technique showed accurate identification of the virus when using the virus-specific-antiserum produced by specialized companies. The examination showed a clear distinction between infected and non-infected samples through the appearance of a dark yellow color in the wells containing the infected samples. The final soluble product of dark yellow was obtained from p-Nitrophenyl Phosphate, Disodium Salt, Hexahydrate substrate for alkaline phosphatase-based ELISA assay (Figure 2). On the other hand, an ELISA reader showed that the absorbance values of infected samples at 450 nm wavelength is at least twice (threshold point) the absorbance of samples prepared from healthy tissue (Figure 3).

Histopathological Analysis

Our study revealed that the Orf virus severely affect goat lip epithelial tissue. Hyperplasia, cell proliferation, and necrosis with inflammatory infiltrates within the tissue were observed. The virus also caused cytopathic effects, such as cell content malformation, cytoplasmic inclusion bodies, and cell lysis. Notably, the development of subcorneal vesicles and crusts was evident on the lip tissues (Figure 4). A dense presence of mononuclear macrophages (MPCs), intracytoplasmic inclusions, subcorneal vesicles, epithelial hyperplasia, and necrotic crusts were consistently observed, underscoring their role in the pathology of Orf virus infection.

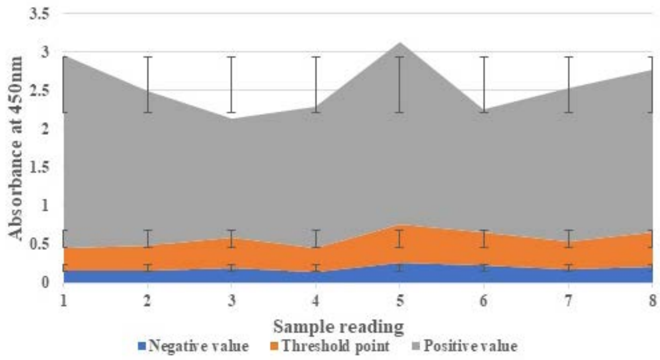

Figure 3: ELISA readings for positive and negative control. All readings above the threshold point are positive, while readings below such point are negative.

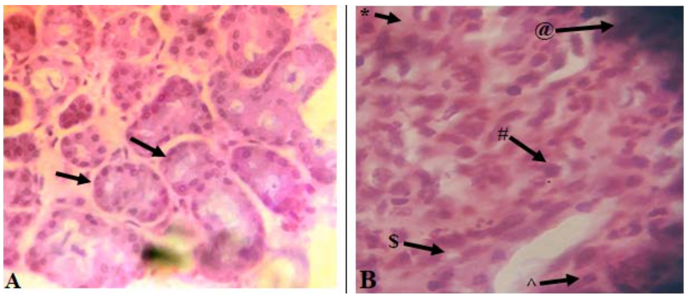

Figure 4: Microscopic images show a histological comparison between the lip tissues of an infected and a healthy sheep, where the former shows significant cellular and histological abnormalities with ulcerative and proliferative dermatitis; A: Healthy tissue with simple cuboidal epithelial forming the ducts of the salivary gland (black arrows); B: Infected tissue with a densely populated area of mononuclear phagocytic cells (personal communication with Dr. Khaled Qabaha, AAUP-Palestine) (Hash (#)), pale intracytoplasmic inclusion bodies (Caret (^)), subcorneal vesicles (Dollar Sine ($)), epithelial hyperplasia (Asterisk (*)), and necrotic crusts (At Sign (@)).

Disease Incidence

The study revealed that the virus infects sheep and goats of all ages in varying proportions. The highest infection rates were observed subsequentially in newborn sheep, followed by weaned sheep, newborn goats, weaned goats, mature sheep, and finally mature goats, which showed the least infection rates. The infection rates peaked between December and February, with the following percentages for each group: 31.03% in newborn sheep, 14.7% in weaned sheep, 8.07% in newborn goats, 4.8% in weaned goats, 2.5% in adult sheep, and 2.03% in adult goats (Figures 5 and 6). In terms of animal mortality, the highest rates were in newborn goats, followed by newborn sheep, weaned sheep, and weaned goats. No deaths were recorded among mature animals. The mortality rate for newborn goats was highest from January to April, peaking at 25.4% in March. For newborn sheep, the highest mortality rate was in December at 23.6%. Weaned sheep showed the highest mortality rate in January at 16.6%, while weaned goats peaked in December at 6.26% (Figures 7 and 8).

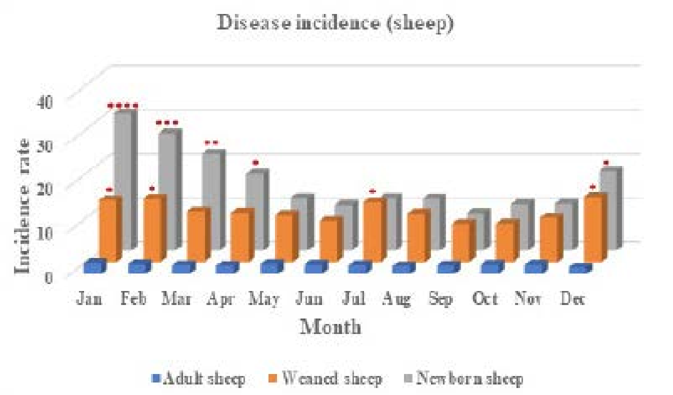

Figure 5: The disease incidence in adult, weaned, and newborn sheep throughout the year (January-December). Statistical analysis shows the significant differences between the treatments as indicated by asterisks.

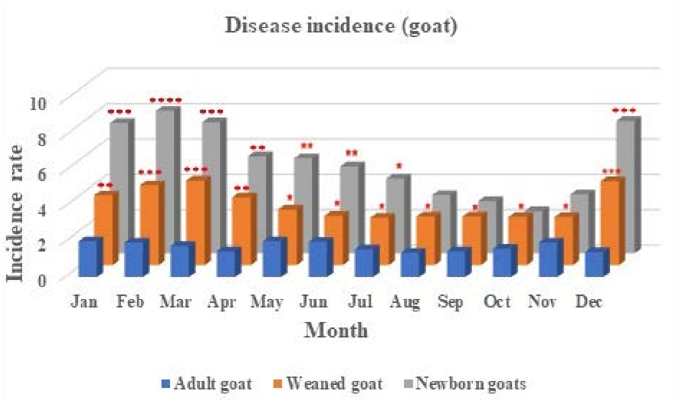

Figure 6: The disease incidence in adult, weaned, and newborn goats throughout the year (January-December). Statistical analysis shows the significant differences between the treatments as indicated by asterisks.

Disease Control

The control measures for the disease were assessed for their effectiveness, revealing that diclofen was the most effective treatment with an efficacy rate of 89.19%. The isolation method was the second most effective, with an efficiency of 84.3%, followed by the use of iodine at 58.61%, and penicillin at 55.88%. The least effective method was the avoidance of air exposure, with an efficiency of only 44.46%. Diclofen's effectiveness and widespread use among livestock farmers can be attributed to its availability and affordability (Figure 9). The isolation method also proved to be a strong contender in disease control, albeit requiring more effort and specific barn arrangements.

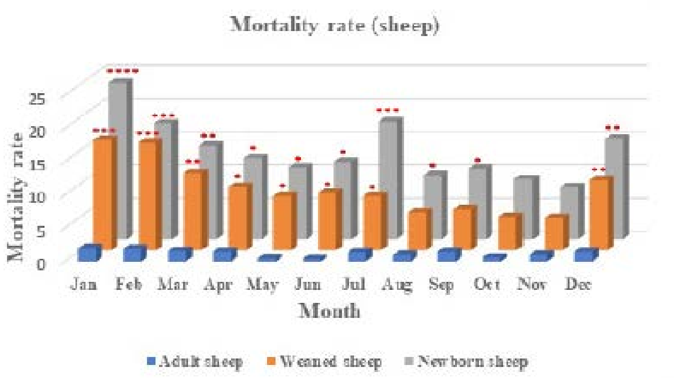

Figure 7: Mortality rate in adult, weaned, and newborn sheep throughout the year (January-December). Statistical analysis shows the significant differences between the treatments as indicated by asterisks.

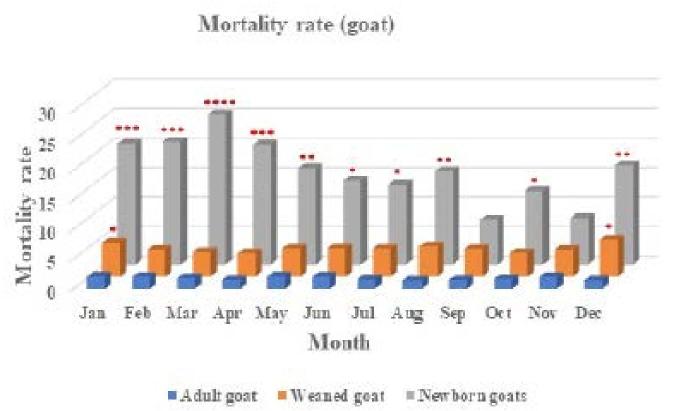

Figure 8: Mortality rate in adult, weaned, and newborn goats throughout the year (January-December). Statistical analysis shows the significant differences between the treatments as indicated by asterisks.

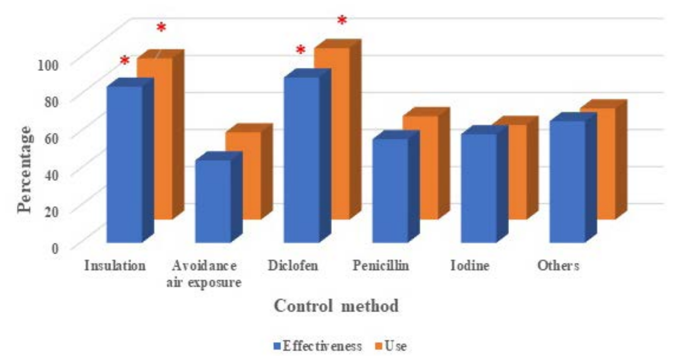

Figure 9: Methods of disease control, percentage of use and effectiveness. Statistical analysis shows the significant differences between the treatments as indicated by asterisks.

Orf virus infection has been confirmed to affect both goats and sheep of all ages, causing significant losses for livestock breeders. This is in line with findings that respiratory diseases and allergies are common in farmers working with livestock, which can also affect the animals themselves (Sigsgaard et al., 2020). The disease's symptoms that identified in the field are consistent with research from other regions. For instance, a study in the Republic of Panama observed a group of goats at the Paso Canoas quarantine station showing clear signs of infection by the 13th day of quarantine. Diagnosis involved collecting biopsies and crusts from the lips, nose, and corners of the eyelids (Magaña et al., 2014).

Our study's use of ELISA reflects these advancements, providing a sensitive and specific method for disease detection in Palestine. ELISA has proven to be a pivotal technology in animal pathology, as it provides a powerful and sensitive method for detecting virus-infected tissues, and has also proven effective in combating diseases. The test has provided a sensitive, specific and versatile method for detecting disease and provided analytical tools, which has greatly contributed to scientific discoveries and medical progress (Singla and Dhawan, 2022). A review by Pang and Long (2023), discusses various diagnostic methods for Orf virus, including conventional, serological, and molecular methods, highlighting the need for rapid and efficient diagnostic approaches.

Mononuclear phagocytic cells (MPCs) are crucial for immune homeostasis and response regulation, encompassing monocytes, macrophages, and dendritic cells. Originating from the monocyte-macrophage lineage, they contribute to both innate and adaptive immunity, acting as tissue sentinels to phagocytize foreign materials like virus particles and regulate immunity (Wynn et al., 2013). Intracytoplasmic inclusions within cells serve important functions and are involved in various pathological conditions. They can contain proteins, lipids, carbohydrates, and viral particles, providing diagnostic insights for identifying viral infections. For instance, eosinophilic globules in hepatocytes are indicative of alpha-1 antitrypsin deficiency (Perlmutter, 1999), while Negri bodies and viral inclusion bodies signal rabies and herpes simplex virus infections, respectively (Jackson et al., 1999; Roizman et al., 2013). These inclusions are also significant in neurodegenerative diseases, such as the tau protein tangles in Alzheimer's disease (Lee et al., 2001).

The Orf virus infection begins with subcorneal vesicles, progresses to epithelial hyperplasia due to keratinocyte proliferation, and culminates in necrotic crusts from viral-induced cell death and immune response (Mercer et al., 2006). The virus's ability to modulate the immune system allows it to persist in the host (Sharp et al., 1998). Recent studies have expanded our understanding of the Orf virus's pathological impact. A study conducted in Punjab, Pakistan, identified and characterized the Orf virus in sheep and goats, revealing significant histopathological features (Hussain et al., 2023). The research highlighted hyperplasia, anastomosing rete ridges formation, and degenerative changes such as spongiosis and vacuolation of epidermal cells. Understanding these mechanisms is vital for developing effective treatments and managing the disease's progression.

The observed infection and mortality rates may be attributed to the farming practices throughout the year. The disease spreads significantly in winter when farmers keep sheep in pens without taking them out, leading to close contact among the animals, which facilitates disease transmission. Newborns, seeking warmth from their mothers and each other, are particularly vulnerable. Unsanitary conditions in the barns, such as wet floors mixed with dung, contribute to the rapid spread of the disease. The prevalence of the disease on goats was 76.62%. When dividing the animals into different age groups from 0-2, 2-4, 4-6, and more than 8 months old, it was found that the highest prevalence rate of the disease was in the age group over 8 months, and a decrease in infection rates was observed in goats aged 2-4 months (Bora et al., 2016; Khalafalla et al., 2020). A study in Kars, Turkey, using ELISA tests, found that 52.81% of lamb serum samples and 5% of human samples were positive for Orf virus, indicating its prevalence in both lambs and humans in contact with sheep (Gokce et al., 2005). In Argentina, phylogenetic analysis identified different strains of Orf virus circulating in the country (Peralta et al., 2018).

In winter, the lack of heating and closed barns weakens the immune system of sheep, making them susceptible to diseases. Conversely, starting from spring, disease incidence and mortality rates decline significantly as farmers take animals out to graze, improving their immune system and reducing contact among them. The warm weather, varied diet, barn cleaning, separation of newborns, and vaccinations contribute to the low infection rates during this period. Similar practices continue into summer and early fall, maintaining low infection rates until temperatures drop and animals are returned to the pens. Recent epidemiological studies emphasize the critical role of farm management practices in the incidence and spread of infectious diseases among livestock. A comprehensive review on livestock health and disease economics underscored the need for understanding the burden of animal diseases and informed policy-making to promote safe consumption and efficient markets (Kappes et al., 2023). These insights align with the observed patterns in the study, where management practices, particularly during winter, significantly influenced disease incidence and mortality rates. The findings suggest that improved farm management, including adequate heating, ventilation, and regular cleaning, could substantially reduce the prevalence of infectious diseases and enhance animal welfare, ultimately leading to safer and more sustainable livestock production systems.

The results align with current trends in livestock disease management, which prioritize accessible and cost-effective treatments. A recent review on disease control in livestock emphasizes the importance of practical and affordable strategies for farmers, highlighting the role of good husbandry practices, including biosecurity and vaccination, in maintaining animal health (Islam et al., 2020). Another study demonstrated the significant impact of vaccinations in reducing the spread of diseases like bovine tuberculosis in dairy herds by up to 89%, mirroring the high efficacy rate of diclofen observed in the current study (Buchan et al., 2023). These findings suggest that the integration of cost-effective treatments like diclofen with robust biosecurity measures could enhance disease control in livestock.

CONCLUSIONS AND RECOMMENDATIONS

In conclusion, our comprehensive investigation into the Orf virus outbreak has elucidated its significant impact on both sheep and goat populations, affecting animals of all ages with a pronounced susceptibility in the young. The clinical manifestations, characterized by lesions at mucocutaneous junctions and notable deformities, coupled with the ELISA technique's efficacy in virus detection, have provided a clear diagnostic pathway. The ELISA's ability to differentiate between infected and non-infected samples through colorimetric analysis has proven invaluable, with a marked absorbance difference at 450 nm serving as a reliable indicator of infection. Histopathological examination has further revealed the virus's detrimental effects on epithelial tissues, with hyperplasia, necrosis, and cytopathic effects being prominent features. These findings are critical for understanding the pathogenesis of the disease and formulating targeted treatments. The infection and mortality rates, peaking during the colder months, underscore the need for heightened vigilance and proactive measures during this period. Our study's insights into the efficacy of various control measures have highlighted Diclofen's superior performance, followed by isolation methods, iodine application, and penicillin treatment. The suboptimal results of air exposure avoidance suggest that more robust strategies are necessary to mitigate the spread of the virus effectively. Overall, this research provides a foundational understanding of the Orf virus's behavior and impact, offering a strategic framework for disease management and control. It is imperative that these findings be leveraged to enhance the welfare of livestock and the economic stability of breeders, ensuring the sustainability of the industry. Future studies should focus on optimizing treatment protocols and preventive strategies to further reduce the incidence and severity of Orf virus infections.

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NOVELTY STATEMENT

This study has investigated the severe symptoms of Orf virus, especially in mucocutaneous areas, figured out the infection rates in newborn sheep and mortality peaks in newborn goats, and spots the strategic interventions crucial during peak infection periods.

AUTHORS' CONTRIBUTIONS

Hazem Sawalha and Abdalsalam Kmail: Conceptualization, Methodology, Writing- Reviewing and Editing. Mujtahed Abu-Alrub and Bashar Abu-Alrub: Field studies, Visualization, Investigation. All authors checked and approved the final version of the manuscript for publishing in the Journal of Animal and Health Production.

AUTHOR'S DECLEARATION

We hereby confirm that all the Figures in the manuscript are ours.

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Data Availability

Data supporting the findings of this study are available with the corresponding authors upon request.

Conflict of Interest

The authors declare that there is no conflict of interest.

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