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Review Article

Lumpy Skin Disease: A Fast Growing Transboundary Disease in Many Countries of Different Continents Including Pakistan

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Abstract | The lumpy skin disease is a viral infection in which many nodules are appeared on skin and other parts of body in animals. This virus, lump skin disease virus (LSDV) belongs to capripox virus genus is the main cause of lumpy skin disease (LSD). It is an acute or sub-acute systemic viral disorder of buffalo and cattle. It is recently discovered disease of cattle which is putting a negative impact on economy of dairy industry in Asia. The rounded Nodules on skin is the early symptom of LSD in clinical investigation. The nodules in the mucous membranes of nose and mouth, subcutaneous edema, emaciation, and exaggerated lymphadenopathy are additional clinical symptoms of this disease. Mortality rates is about 3 % in endemic regions of Asia while the morbidity is upto10%. The LSDV is transmitted through the entry of blood from outsource by biting of arthropods including mosquitoes and flies from infected animal to healthy one. To control the dispersal of LSDV, infected animals should be quarantined, restricted its movement and place them in a place of no entry of vectors, arthropods. The recent review investigated new knowledge on several facets of the disorder, including its distribution, transmission, origin, pathophysiology, host vulnerability, diagnosis, preventiand therapeutic approaches. Lumpy skin disease virus belongs to *Poxviridae* family and genus, *Capripoxvirus*. It cause acute to fatal infection in cattle. Lumpy skin disease results in loss of weight, infertility, abortion in cows and reduction in milk production. In this way this disease has a serious threat to economy of Middle East, European and African countries due to loss of meat and dairy products. LSD is becoming a global threat mainly in region of Middle East and Europe due to trading patterns and climate change as well. LSDV is spreading from one to another through vectors like flies and insects which bite these infected animal and suck blood from their skin and transfer the causative agent from infected animals to healthy one. There are number of factors upon which the spreading of LSDV depends including, environment, humidity, temperature and regions where vectors of its dispersal are more. This disease is spreading at its high at the end of summer season when there is more humidity in air and autumn. Its control is done by vaccination and quarantine of infected animal to prevent its contact with the healthy animals.

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1. Introduction

Lumpy skin disease LSD also known as Neethling virus disease, Pseudo-utricaria, knopvelsiekte, and Exanthema nodularis bovis. Morris (1930) initially conducted experiments on lumpy skin disease by employing several medications in Northern Rhodesia in 1929 (Salib and Osman, 2011). LSD is the host specific that only affects ruminants such as water buffaloes and cattle. It is vector borne, non-zoonotic, contagious and transboundary disorder (Gupta *et al*., 2020). LSDV, a DNA virus belonging to the family *Poxviridea*, and the genus *Capripoxvirus*, is the main culprit behind lumpy skin disease (Magori-Cohen *et al*., 2012). The first instance of lumpy skin disease was certified in 1929 in Zambia, after which it transmitted across Southern Africa up to Sudan. In 1989, Israel was the country other than Africa to record a case, and in the years that followed, instances were also noted in Kuwait, Oman, Lebanon, Jordan, Bahrain, and Yemen (Zeynalova *et al*., 2016). LSD is now more likely to enter Western Europe, Central Eastern Europe, and Central Asia (Lafar *et al*., 2020).

Generalized lymphadenopathy, extensive cutaneous and internal pox lesions, pyrexia, mastitis, and orchitis are the hallmarks of the acute illness. Its symptoms are fever, emaciation, development of distinctive nodules on skin and significant financial loss (Gamal *et al*., 2021). Furthermore, bulls may also exhibit temporary and permanent infertility, abortions, declined milk production, as well as slowed development (Möller *et al*., 2019). While it has been shown that the respiratory system or skin are the main entry site for the poxviruses. It is thought that an ineffective way of LSDV to infect a host is direct association between susceptible and infected animals. Almost 50% of experimentally affected animals are more susceptible to exhibit clinical symptoms. The virus can be found in an infected animal's semen, ocular, nasal and semen secretions. As a result, the main reservoir of infection might include food or water contamination and artificial impregnation (Tuppurainen *et al*., 2011). Abortions and temporary and permanent sterility in both female and male population also happens (Tuppurainen *et al*., 2013).

The main route of the transmission of LSDV is directly linked with milk, nasal secretions, semen, saliva, and skin abrasions from the affected animals. However, arthropods play an important role as vector for its dispersal. The morbidity rate of this disease fluctuates between 5% and 45% and based upon the susceptibility of risk animals, their breeding, and the number of vectors (Jalali *et al*., 2017). World Organization for Animal Health (OIE) has also recognized LSDV as a reportable disorder because of an outbreak inducing a remarkable financial impact. The subsequent bacterial mastitis and high fever are considered as clinical symptoms of this viral infection are more severe in cows in terms of lactation which results in rapid decline in milk production (Tuppurainen *et al*., 2012).

Due to LSD, market sales value of meat and milk products have dropped up to 70% in Karachi, Pakistan. Due to the influence of LSD the significantly reduction of milk production from 10% to 85% is done (Khan *et al*., 2021). For viral identification the electron microscopy of inoculated eggs and cell culture can use. The Polymerase Chain Reaction (PCR) is the more advanced technique of identification of infectious agent from infected site on animal (Yimer and Advances, 2021).

The main purpose of this review article is to provide a detailed information about the Lumpy skin and its causative agent LSDV that how it discovers and become a transboundary disease. This review will explain about the epidemiology, mode of transmission of LSDV, diagnosis methodologies, preventive measures and treatment of affected animal.

1.1 History of LSDV

According to Morris (1930), the LSDV originated in Zambia in 1929, and arthropods were thought to be the primary disease vector. Thereafter, from 1943 to1945, the virus was discovered in South Africa, Zimbabwe, and Botswana. About eight million cattle were infected, and the disorder persisted until 1949 (Das *et al*., 2021). LSDV was discovered in Kenya, East Africa in 1957. The ailment was first noted in West Africa in 1974 and Sudan in 1972. In 1983, it was encroaching on Somalia (Al-Salihi and Animals, 2014). In the past 70 years, the virus that causes the lumpy skin disease has migrated to both North and South from its Sub-Saharan African origin. There is a genuine risk that LSDV might spread from Africa (Egypt) to Middle East, Europe and Asia (Babiuk *et al*., 2008). Till 1989, LSD was limited to Africa then this disease was moved to Madagascar and Middle East and reported a serious economic crisis in dairy

industry in these regions due to this disease (Al-Salihi, 2014).

First time in Viet Nam, Cambodia and Southeast Asia the LSDV was introduced in domestic cattle life in October 2020, May 2021 and June 2021, respectively. Near the end of 2021, Thailand reported number of cases of endangered species of animals infected with LSDV which raised the concern of wild life community to save such endangered species. These animals were banteng (*Bos javanicus*) and gaur (*Bos gaurus*). The community network of the region were utilized to save biodiversity (Pruvot *et al.*, 2023).

1.2 Epidemiology

One of the top ten most serious ailments affecting cattle worldwide is lumpy skin disease (Adedeji *et al.*, 2017) As an epidemic in Zambia in 1929, LSDV was first separated and discovered in cattle there. Since then, it has moved throughout Africa and harmed livestock, including outbreaks in the Egyptian governorates of Suez and Ismailia in 1989 (Abd El-Hamed and Ali, 2017). The Lumpy skin disease poses an inevitable warning to Asia, Europe, and all over the world. It is growing in several regions of the Middle East and is indigenous to several areas of Africa (Abutarbush *et al.*, 2015). The first case of LSDV was first recorded in 1983 in the Southwest of Lake Tana in Ethiopia's Western region. Nearly all of the areas and agroecological regions have already experienced its proliferation (Gari *et al.*, 2010). Documentation from epidemiology suggests that insects bite spread the LSDV (Chihota *et al.*, 2001).

1.3 Etiology

A DNA containing the virus from the family Poxviridae, Capripoxvirus genus is the main cause of lumpy skin disorder. Three viruses make up the capripoxvirus genus: it includes lumpy skin disease (LSDV), goat pox (GTPV), and sheep pox (SPPV) (Orynbayev *et al.*, 2021). It is brick or oval shaped, pleomorphic, double strand enveloped DNA virus. An LSDV has a molecular weight of 73 to 91 (Kilodalton) KDa, the molecular size of 350×300 (nanometer), and genome sequence ranges from 145 to 152 (Gammada et al., 2022). Two infectious forms of LSDV found: Enveloped virions (EVs) and mature virions (MVs) having an extra membrane and a single outer membrane respectively. These membranes are designed for cell-to-cell transmission (Kresic et al., 2020). Recently the exact causes of the wide variations in mortality are still unspecified but, a number of contributing factors involving secondary bacterial infections, virus isolation, breed of cattle, the animal's health and type of insect vector are involved in the spread of this disease (Babiuk *et al.*, 2008). The virus may survive for several months in disastrous environmental climate like polluted animal shelters, but it is susceptible to detergents having lipid solvents and sunlight (Mulatu and Feyisa, 2018). LSDV can be stored at -80°C for 10 years and may be extracted from skin nodules. LSDV is vulnerable to 65°C for 30 minutes and 55°C for two hours (Gerilovych *et al.*, 2016).

1.4 Transmission

The distribution of lumpy skin disease heavily depends upon environmental factors. It considerably affected the interactions between the vectors, agent and host. These influencing determinants play a remarkable role in spread of the virus to vulnerable animals and in the upkeep of the arthropod vectors (Hailu *et al.*, 2015). A number of blood feeding insects serves as mechanical vectors are believed to have a substantial impact on LSDV transmission (Issimov *et al.*, 2020). Through infected Aedes aegypti, LSDV can be transferred to vulnerable animals as it has already been documented (Chihota *et al.*, 2003). Vectors including Arthropods such as ticks including Rhipicephalus decoloratus, Amblyomma hebraeum, and Rhipicephalus appendiculatus, mosquitoes (*Aedes aegypti*), and biting flies are the major carrier agents of LSDV. Without actually replicating inside the arthropod tissue or cells, the virus can disseminate through mouth parts of infected vector (Kayesh *et al.*, 2020). Non-vectored LSD transfer occurs, when an unwell animal come in contact with infected items, regardless of involvement of mechanical or biological carriers, however it is ineffectual (Das *et al.*, 2021). Saliva, blood, lachrymal, milk, and nasal discharge are the indirect routes of transmission (Hasan, 2021).

1.5 Clinical manifestations

There are number of types of LSD includes acute and subclinical types as well as number of types of vectors for its transmission like insects that is why the mortality and morbidity of LSD fluctuates. (Ayelet *et al.*, 2013). The primary symptoms include nasal secretion and lachrymation, which are initially noticed. The high fever (> 40.5 °C) that may last about a week, rapid decline in milk production, enlargement of the subcapsular and prefemoral lymph nodes

and mastitis are further complexities can be seen in variety of LSD infected animals. In infected animal the development of distinctive nodular skin abrasions may spread throughout the body with the diameter of about 10 to 50mm, as well as painful ulcerative lesions occasionally form in one or both eyes, resulting in blindness. Pox lesions can also develop on nearly any internal organ surface as well as the entire respiratory tract and digestive system in infected animal (Gelaye and Lamien, 2019).

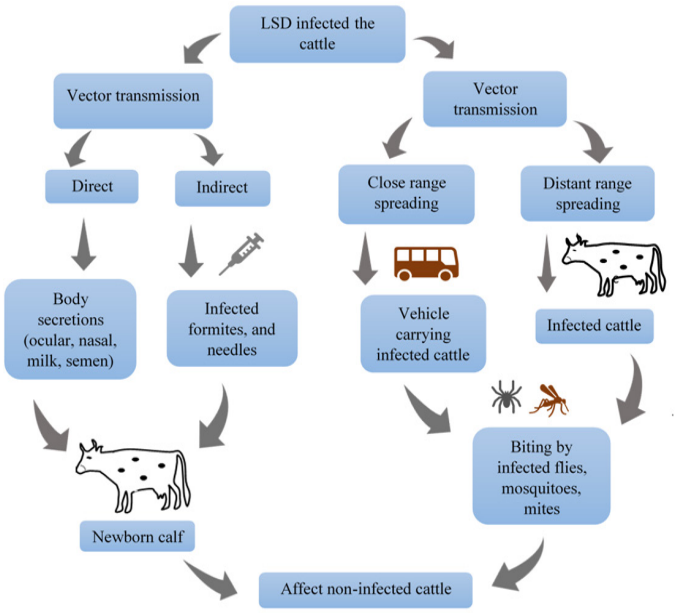

Figure 1: Transmission modes of LSDV from infected cattle to transmitting vector, flies or insects like mosquitoes and mites, then to healthy cattle to make it infected (Khan et al., 2022).

The nodules of greyish to white color are appeared on each layer of epidermis in case animal. A reddish yellow oedema exhibits on rejoin of several lesions of subcutaneous tissues (Davies, 1991). The mortality rate is typically mild and varying from 1% to 3%, but it can go as high as 20%. The rate of morbidity fluctuates from 3% to 85% due to certain reasons as described earlier. The severity of the disorder varies from normal illness to mortality depending on the age, virus strain, race, and immunological condition of cattle (Vidanović *et al.*, 2016). The condition may become worse if there is mastitis or secondary bacterial infection. It can take several months to recover from LSD. Typically, the incubation phase lasts for three to four weeks (Fenin et al., 2022).

1.6 Pathogenesis

The four steps of the pathogenesis consist of incubation, fever, exanthema, regression of nodules (Aiel and Ovine, 2009). There have been few studies on the pathophysiology of this illness. Viral inoculation at the site of entry, cell multiplication, propagation to the target organs, and diffusion into the neighboring environment are all component of a pathogenic pathway (Al-Sabawy *et al.*, 2020). The entrance of infected animals, transmission of vectors through the wind, and the migration of flying vectors conducting the LSDV from an infected animal to the target animal make up the mechanism for the introduction of LSD (Khafagi *et al.*, 2022). Viral particles move through the blood and cause systemic lymphadenitis. Following the first febrile state viremia lasts for about 4 days. Lesions develop in such areas as a result of virus replication in specific cells including pericytes, fibroblasts, endothelial cells of blood arteries and lymphatic vessels (Das *et al.*, 2021). When cattle are intradermally or subcutaneously inoculated with LSDV, a localized swelling and enlargement of lymph nodes occur four to seven days after the inoculation. The widespread eruption of skin nodules typically happens seven to nineteen days later (Yimer and Advances, 2021).

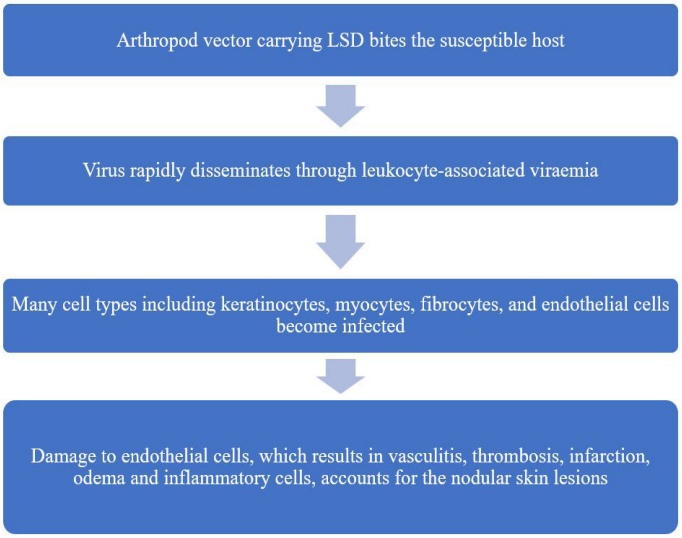

Figure 2: Pathogenesis of Lumpy skin disease virus entry to endothelial cells of susceptible host to induce skin lesions (Fenin et al., 2022).

1.7 Host susceptibility

The LSDV is transmitted to susceptible host animals from infected one by direct or indirect contact of vectors and owners of that infected animals secretion and contaminants from other associated objects including vehicle and equipment (Roche *et al.*, 2021). The host range of LSDV is constrained, and non-ruminant hosts do not allow for the completion of the replication cycle (Elhaig *et al.*, 2017). The lumpy

skin disease virus infects cattle and can result in mild to severe illness. The mortality and rate of mortality of LSD is different for different susceptible host which differing in age, strains and host immune response (Ratyotha *et al.*, 2022).

Although cattle of all ages were afflicted, young calves were most severely afflicted. The host vulnerability, insect densities, and inoculum dosage are all factors that affect disease severity as indicated by an appearance of lumps and the occurrence of complexity (Salib and Osman, 2011). The virus has a very limited number of hosts. According to researches, it exclusively affected cattle and buffalo (Choudhari *et al.*, 2020).

Bos taurus the strain of European cattle is more susceptible to LSD than Indian strain (*Bos indicus*). The domestic strain of buffalo in Southeast Asia (*Bubalus bubalis*) has shown lower susceptibility toward LSD (Tuppurainen *et al.*, 2017). The variety of genome can detect from nodules, ulceration and secretions from the infected body and arthropods near these animals (Tuppurainen *et al.*, 2015, 2017).

The disease primarily affects cows, though it can also attack buffalo, giraffes, and impalas (Neamat-Allah and Mahmoud, 2019). However as compared to cattle strain, *Bos indicus* cattle the *Bos taurus* strain has shown somewhat higher propensity to acquire LSD. Calves and animals with an impaired immune system are much more assailable to this infection, but animals of all ages are equally susceptible to infection. The prevalence of feral and wild animals are thought to play a little role in transfer of this virus (Khan *et al.*, 2021).

1.8 Viral stability

LSDV viral particles lose viability when exposed to direct sunlight but can withstand desiccation and high temperature. According to the reports, the virus takes 30 minutes to become inactive at 65°C or when it comes into direct exposure with lipophilic detergents, compared to 2 hours at 55°C. Many antiseptic agents are very efficient against LSDV including quaternary ammonium compounds, sodium hypochlorite, formalin, chloroform, ether, and phenol (Jamil *et al.*, 2022). With regard to LSDV stability, it is prone to acidic pH and highly alkaline pH, but stabilized at pH 6.6 to 8.6 for five days at 37°C (Khafagi *et al.*, 2022).

1.9 Economic losses

Lumpy skin disease (LSD) is a transboundary disease, which is now again affecting buffalo and cattle, and has a significant financial impact (Acharya *et al.*, 2020). Pakistan is a country which heavily depends upon agriculture and has the second largest cattle population in the world, it would be disastrous if LSD emerges here (Khan *et al.*, 2021). The economic damages brought on by LSD eruption are greater, despite its low mortality rate (1-3%).

Because of declined milk yield, miscarriage, infertility, damaged hides, and weight fluctuation, it causes a significant reduction in the economy. Furthermore, this disorder also hinders international trade as it is a significant contagious disease (Mulatu and Feyisa, 2018). The leather business has remarkably impacted by permanently spoiled of hide and skin. As a consequence, it prevents the export of cattle internationally and results in long-term economic losses (Tadesse Degu and Fesseha, 2020).

1.10 Prevention and control

LSDV is transmitted from animal to animal by a vector, arthropods under suitable environmental conditions (which enhance the growth and development of vectors). In the absence of vectors and unfavorable environmental condition for vector growth reduce the risk of spreading of LSDV. Milk and semen from infected animal would be a cause transmission of LSDV to health animals. To prevent this transmission source, milk from such animals can be pasteurized and transported through proper contamination free and closed containers. Raw material of such farms where infected animals are living can be contaminated with the viral load so proper treatment of such materials should be done before its storage to avoid spreading of LSDV (Tuppurainen and Galon, 2016). It is to be reported in 2016 that LSD is not a zoonotic disease so LSDV cannot affect humans (FAO, 2017).

It is challenging to successfully manage and prevent LSDV infection with a single strategy. In order to prevent and manage the LSDV infection, many strategies must be used. These strategies include disinfecting infected animals, screening, quarantining, controlling vectors, immunization, limiting mobility, and treating sick animals to avoid subsequent bacterial infection (Kayesh *et al.*, 2020). Stamping out and a combination of the following tactics are policies for limiting and eliminating LSD in the situation of

incursion:

- Disposal of tainted animal products and dead animals in a hygienic manner to stop the spread of disease.
- Prevent the spread of disease by mobility restrictions on animals, possibly contaminated objects, goods, and quarantine.
- Identification the point of infection, scope of infection, and to establish disease free status by surveillance and tracing.
- Inhibiting the virus from transmitting to other animals and buildings, and to get rid of pests disinfecting of tools, buildings and other objects is crucial (Kreindel *et al.*, 2016).

The LSD infected countries are relying on vaccines prepared by live and attenuated viruses for immunization. There are many genetically modified strains of LSDV were attenuated for vaccine preparation and designing including LSDV Neethling, LSDV-WB005KO and KSGP O-240 were used as prevention and control of LSDV (Li *et al.*, 2022).

Annual vaccination is recommended from its manufacturer because of pure immunity results of control after one time vaccination. About 1 mL to 2mL vaccine doses were prescribed for good result of immunization, while it depends upon type of vaccine as well. Calves can be vaccinated at any age. It is recommended that every animal should be vaccinated during spring to inhibit the spread of LSDV (FAO, 2017). Without vaccination, the prevention of LSDV is infamously difficult, but not impossible. To have any hope of managing the disorder through the eradication of in-contact and infected animals, an early discovery of index cases is necessary (Tuppurainen and Oura, 2014).

1.11 Diagnosis

LSD is frequently diagnosed using recognizable clinical indicators. Anyhow, rapid and precise laboratory testing is needed to establish the diagnosis in moderate and subclinical types (El-Nahas *et al.*, 2011). It is essential to undertake adequate outbreak control measures as soon as the virus is detected. Veterinary professionals depend on the existence of the LSD specific clinical symptoms (Shalaby *et al.*, 2016). LSD is merely symptomatic. It is treated with a mixture of anti-inflammatory, anti-microbial, anti-septic, and supportive diagnosis with the goal of preventing further bacterial infection (Namazi *et al.*, 2021). In recently impacted and endemic areas, vaccination is the only method of halting the infection's spread. However, choosing the appropriate vaccination in the case of an outbreak poses a significant problem to veterinary farmers and authorities (Tuppurainen *et al.*, 2021). Although intravenous fluid delivery might not be feasible in the field, but it could be advantageous.

To prevent disease propagation, there is a requirement for employing useful vaccination due to inadequacy of available treatments for LSDV (Babiuk, 2018). The most popular ways to diagnose LSD includes utilizing molecular testing, serology based diagnostic procedures to look for antibodies in LSD virus, and polymerized chain reaction (PCR) to identify virus DNA. For efficient eradication and appropriate management of LSD in endemic and non-endemic countries, quick diagnostic confirmation of the preliminary field diagnosis is essential (Gumbe, 2018). LSD can also be diagnosed and treated by serological testing procedure like western blotting, agar gel immune-diffusion test, indirect fluorescent antibody test (IFAT), and indirect enzyme linked immunosorbent assay (ELISA) (Zewdie, 2022).

1.12 Laboratory diagnosis

(i) Indirect fluorescent antibody test (IFAT): The serum antibody against LSD was estimated by IFAT. Following the onset of clinical indications, capripoxvirus antibodies are distinguishable beginning on day 2 and lasts for approximately 7 months. Yet a large spike in titer is usually observed in days ranging from 21 to 42 days (Gari *et al.*, 2008).

(ii) Virus neutralization test: Recognized antibodies that can stop the replication of viruses.

(iii) Polymerase chain reaction (PCR): It is the easiest and reliable method to find LSDV. An appropriate sample for the identification of LSDV are saliva, nasal discharge, blood, and skin nodules (Choudhari *et al.*, 2020). Even though gel-based PCR requires time and work than real time PCR, it is a reliable and affordable approach, making it beneficial in nations with a few numbers of resources (Tuppurainen *et al.*, 2012).

1.13 Treatment

The treatment strategies include following: Meloxicam 100mg bolus (0.5mg per kg body weight twice daily), Chlorpheniramine 4mg tablets (0.3mg per kg of body weight once daily), and Enrofloxacin 1500mg

bolus (10mg per kg of body weight twice daily). These doses are administered for a week (Xavier *et al*, 2020). For quick healing, particularly recommended Himax TM ointment was used on lesions that had appeared (Islam *et al*., 2021). Applying an antiseptic cream with fly repellent qualities like (Neem paste/oil, or turmeric) to the eroding skin sores can help. Three days therapy was given. When supervising animals, the shed was routinely sanitized and cleaned, and farmer employees were informed to use gloves. Skin lesions of animal had healed perfectly with improved appetite, and the animal had entirely recovered from lumpy skin disease (Vinothraj *et al*., 2020).

1.14 Future directions

Immunological characterization of lumpy skin disease virus (LSDV) is still needed in vaccine designing to prevent its future pandemic. The natural medicinal products isolated from plants may also useful in its treatment as well. There might be chances of becoming this LSDV as zoonotic in near future. So, early preventive measures and disease management would be done to prevent its exposure to humans. Although the trade of dairy products and cattle across the world is considered as viral transmission so, it would be done under medical examination and quality control to prevent its spreading.

Conclusions and Recommendations

Lumpy skin disease virus LSDV has become a major transboundary disease. It recently outbreak in disease free countries like Pakistan. There is a need to implement real time effective measures to control its spread. First of all, veterinary authorities should ban the illegal movements of cattle in border areas and make sure the proper testing of animals during import and export. In endemic areas, government should train the veterinary workers to timely and accurately diagnose the disease. Awareness of farmers is most important that how to deal with an LSDV affected animal. A vector control program for LSDV and vaccination campaign at national level are most efficient ways to restrain the transmission of this viral disease.

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Novelty Statement

LSD is an emerging disease and its outbreak in Pakistan clearly effect the livestock and economy as well as to control its spread there is a need of drug developing and proper management through awareness is still needed to eradicate such diseases to save animal and livestock community. This study will certainly help researcher communities to develop innovative measurements to control upcoming pandemics like LSD.

Author's Contribution

KJ, MA, conceived the idea, WF developed the manuscript and proof read it, MR supervised and correspond the manuscript write up, FY, SR, SuH and JA participated in data analysing and these all authors participated in writing the article.

Conflict of interest

The authors have declared no conflict of interest.

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