The Pharma Innovation Journal 2023; 12(7): 3543-3549

www.ThePharmaJournal.com

The Pharma Innovation

ISSN (E): 2277-7695
ISSN (P): 2349-8242
NAAS Rating: 5.23
TPI 2023; 12(7): 3543-3549

www.thepharmajournal.com
Received: 22-05-2023
Accepted: 26-06-2023

Deepak Kumar Pankaj
Ph.D., Scholar Division of Pathology, ICAR-Indian Veterinary Research Institute, Izatnagar, Uttar Pradesh, India

Arpita Sain
Ph.D., Scholar, Department of Veterinary Microbiology, Indian Veterinary Research Institute, Izatnagar, Bareilly, Uttar Pradesh, India

Rahul Kumar
M.V.Sc. Scholar Department of Veterinary Medicine, Nanaji Deshmukh Veterinary Science University, Jabalpur, Madhya Pradesh, India

Neeraj Kumar
Ph.D., Scholar Division of Pathology, ICAR-Indian Veterinary Research Institute, Izatnagar, Uttar Pradesh, India

Pushpendra Kumar
NAMDEO SRF, ICAR-Indian Veterinary Research Institute, Izatnagar, Uttar Pradesh, India

Corresponding Author:
Deepak Kumar Pankaj
Ph.D., Scholar Division of Pathology, ICAR-Indian Veterinary Research Institute, Izatnagar, Uttar Pradesh, India

Lumpy skin disease in India: A comprehensive review

Deepak Kumar Pankaj, Arpita Sain, Rahul Kumar, Neeraj Kumar and Pushpendra Kumar

Abstract
Lumpy skin disease (LSD) is a viral infection of cattle and buffaloes that is caused by a LSD virus, genus capripoxvirus and transmitted by biting insects. It is a transboundary disease that has recently emerged in India and spread rapidly across the country. LSD causes skin nodules, fever, reduced milk production, infertility, and sometimes death in affected animals. It has significant economic and social impacts on the livestock sector and rural livelihoods. This review provides an overview of the current knowledge on the epidemiology, host range, gross and histopathological findings, diagnosis, prevention and control of LSD in India.

Keywords: Lumpy skin disease, LSD, capripoxvirus, emerging disease, LSD virus

Introduction
An emerging disease is defined as "a novel infection that originates from an evolution or change of an existing pathogenic agent, an established infection spreading to a new geographic area or population, or a previously unrecognised disease detected for the first time and which has significant consequences on animal or public health" (WHO, 2014). An arthropod-borne viral disease that affects cattle and buffaloes the throughout the globe is known as lumpy skin disease (LSD). Exanthema nodularis bovis, LSD, Neethling virus disease, pseudo-urticaria, and knopvelsiekte are all names for the infectious condition lumpy skin disease. The Capripoxvirus genus of the Poxviridae family of viruses is responsible for its development. In Europe, the Middle East and Southeast Asia right now, the disease has become a deadly threat. The disease has significant economic consequences because morbidity (5%–45%) rather than mortality (often under 10%) is high (Tuppurainen *et al*., 2017) [54]. According to Gumbe (2018) [26], the estimation of the loss in Ethiopia is 6.43 USD per head for zebu and 58 USD per head for Holstein Friesian. Because of the potential for transboundary spread and the threat that it poses as an agroterrorism disease, the WOAH has designated Lumpy skin disease as an officially notifiable outbreak.

Aetiology
LSD virus from the Poxviridae family causes lumpy skin disease. This family of viruses has two branches: Chordopoxvirinae, which infects animals with backbones (vertebrates), and Entomopoxvirinae, which infects animals without backbones (invertebrates) (Quinn *et al*., 2016) [44]. The Chordopoxvirinae branch has 10 groups, and one of them is Capripoxvirus. This group has three kinds of viruses that infect different kinds of livestock: SPPV for sheep, GTPV for goats, and LSDV for cattle (King *et al*., 2012) [29]. LSDV is a virus with a complex shape and a double stranded DNA inside. It has a cover and shape looks like a brick. It is 320 × 260 nanometres in size. It makes copies of itself in the cytoplasm part of the cell.
LSDV is a virus that can survive high temperatures and dryness. It can still infect animals for many days (18–35 days) even after they die and their skin becomes dry and hard. But the virus dies quickly when it is in the sun or when it touches soap-like substances. The virus also dies in 2 hours at 55 °C or in 30 minutes at 65 °C. The virus does not like very high or very low pH levels. It can only live in a pH range of 6.6 to 8.6 at 37 °C for five days without losing its strength. Some chemicals can kill the virus very well, such as iodine (1:33), formalin (1%), ammonium (0.5%), 2% phenol (for 15 minutes), ether (20%), chloroform and bleach (2–3%). LSDV can last for a long time if it is stored well. Some studies have shown that the virus can be grown from skin samples that were frozen at – 80 °C for 10 years. Even at 4 °C, the virus can be grown from skin samples for 6 months (WOAH, 2023) [56].

Epidemiology

In 1929, a new skin disease in cattle, known as 'pseudo urticaria,' was first reported in Northern Rhodesia (now Zambia) (MacDonald, 1931) [36]. From there, the disease spread to other southern African countries by the 1940s. Over the following decades, the disease slowly spread northward and is now present throughout Africa, including Madagascar. Only Morocco, Algeria, and Tunisia Libya are still considered free of the disease. It has been suggested that as the virus expanded its geographical distribution, it also increased in pathogenicity, causing extensive epidemics and pandemics on the African continent with sporadic cases occurring during interepidemic years. The first outbreak of the disease in Egypt was reported in May 1988, but the origin of the outbreak could not be traced with certainty by the Egyptian veterinary authorities. A higher incidence of LSD was associated with greater insect population densities in some parts of the country (Ali *et al*., 1990; Gupta *et al*., 2020; Tuppurainen and Oura, 2012; European Food Safety Authority *et al*., 2020) [27, 23]

In August 1989, the disease spread outside of Africa for the first time, reaching Israel (Yeruham *et al*., 1994) [57]. It was suspected that the stable fly (Stomoxys calcitrans) transmitted the disease from Egypt via wind-borne transmission. This assumption was based on several factors: no new animals were introduced into the infected herds, LSDV had previously been isolated from stable flies that had fed on infected animals, stable flies had been shown to transmit capripoxvirus between susceptible and infected animals, and Stomoxys spp. were more widespread than other insects that feed on blood in Israel (Yeruham *et al*., 1994; Weiss, 1968) [57, 55]. After a 17-year absence, LSD reappeared in Egypt in 2006, introduced by infected cattle imported from the African Horn countries. Despite an extensive vaccination campaign, the disease spread rapidly throughout the country. In June 2006, cases of LSD were reported again in Israel, and authorities speculated that It's possible that LSDV was already in circulation in other Middle Eastern nations. (Ali *et al*., 1990).

Since 1990, There have been reports of LSD outbreaks in several Middle Eastern countries, including Kuwait in 1991, Yemen in 1995, Lebanon in 1993, Bahrain in 2003, Israel in 2006-2007, the United Arab Emirates in 2000, and Oman in 2010. The presence of LSDV in Saudi Arabia, reported in 1992, was never confirmed with certainty. The Middle East has become a significant importer of live cattle, frozen meat, and animal feed from Europe, Asia, and Africa to feed its rapidly growing population. Without strict testing of imported live animals and sufficient control during quarantine, large-scale importation of live animals and animal products can easily introduce infectious diseases. The cattle farming industry in the region is limited by a lack of suitable fertile land, leading to dense cattle populations in small areas located mainly on river deltas and basins. High temperatures, heavy seasonal rains, and the presence of watercourses increase populations of blood-feeding arthropods, enhancing the likelihood of transmission of vector-borne diseases such as LSD (El-Kholy *et al*., 2008; Brenner *et al*., 2009) [22, 10].

The disease's initial outbreak in India was discovered in the state of Odisha (August 2019) and reported to the OIE on 18 November 2019. India faced three primary outbreaks of LSD in Odisha. The first event occurred on August 12, 2019, on a farm where 9 cases (a total of 135 animals) were reported in the Mayurbhanj districts of Orissa. The second outbreak was discovered at Patalipura, where a farm contained 20 cases (441 animals). On August 20, 2019, a third case outbreak was reported in Bhadrak, where 50 cases (356 animals) were found in a farm (Choudhari *et al*., 2020) [16].

The first LSD outbreaks in India were recorded in the coastal districts of Odisha state. The origin and source of LSDV in India are not yet clear, but there are several possibilities, including uncontrolled or illegal transferring sick animals, animal products, or fomites through the porous Indo-Bangladesh border, or movement of blood-sucking insect vectors by wind or vehicular transport. The reasons for the disease's spread to Odisha have yet to be identified. Odisha is a state that is highly susceptible to natural disasters such as cyclones and floods. In May 2019, the state was hit by a cyclone with exceptional severity, "FANI," which caused serious loss of livelihood and livestock in the coastal districts. After the storm, animals in the coastal districts began to show signs of a nodular skin disease similar to LSD. This may have been due to movements of livestock outside of national borders or movements of vectors from neighboring countries. LSD has been recorded in neighboring countries such as China and Bangladesh in recent years. Identifying the the prevalence or epidemiology of exotic infections is important for planning successful disease control in a timely manner (Sudhakar *et al*., 2020; Gupta *et al*., 2020) [50, 27].

Table 1: Epidemiology in India

Year	Area	Reported By
Aug, 2019	Chhotanagpur plateau region which covers parts of Orissa, Jharkhand, West Bengal and Chhattisgarh	Sudhakar *et al.*, 2020 [50]
Aug, 2019	Khairbani, Betnoti, Mayurbhanj of Orissa	Choudhari, 2020 [16]
Jan, 2020	Palakkad, Thrissur and Malappuram districts of Kerela	The Hindu, Choudhari, 2020 [16]
Sep, 2020	Chittoor district, Andhra Pradesh and 15 states	The Hindu, Choudhari, 2020 [16]
Sep, 2020	Beed district, Maharashtra	Karyarambh newspaper

Table 2: Current situation in India

Year	No. of animals	Area	Reported By
19 May, 2022	120 cattle died	Jaisalmer district of Rajasthan	The Times of India
24 May, 2022	10 cattle died, 517 infected	Jamnagar and Dwarka, Gujarat	Ahmadabadmirror.com
31 May, 2022	120 cattle died	Jalore, Rajasthan	Dainik Bhaskar

Hosts

The virus that causes lumpy skin disease (LSDV) can infect both cattle and buffalo, but it affects them differently. Cattle from the Bos taurus breed are more likely to get sick than native cattle breeds. Calves are also more prone to the disease and show symptoms within a day or two of infection (Al-

Salihi 2014) [4]. Most wild animals are not affected by the virus in nature, but some experiments have shown that it can cause lesions in certain species of giraffes, antelopes, and gazelles (Davies 1991; Padilla *et al*., 2005) [19, 41]. However, wildlife does not play a significant role in spreading or maintaining the virus. LSDV does not affect humans (WOAH, 2023) [56].

Transmission

LSD is a viral infection that affects cattle and buffalo. The primary mode of transmission of the disease is through mechanical vectors, such as flies and mosquitoes, that transfer the virus from infected animals to susceptible ones through their bites. The disease incidence varies according to the activity of the vectors and seasonality. The disease is more prevalent in rainy and summer seasons, when the vector population is high, and less prevalent in winter seasons, when the vector population is low. These observations have been confirmed by several studies and reports (AU-IBAR, 2013; Mulatu and Feyisa, 2018) [7, 39].

Some of the insect vectors that have been reported as mechanical vectors and reservoirs of the virus are *Rhipicephalus decoloratus, Amblyomma hebraeum* and *Rhipicephalus appendiculatus* (Ali and Obeid, 1977; Lubinga *et al*., 2013a, 2013b; Lubinga, 2014) [1, 34, 33]. Seasonality and vector activity have an impact on LSD incidence. Indirect or direct contact between animals, which are regarded as ineffective pathways for disease transmission, is less likely to do so. (Weiss, 1968; Carn and Kitching, 1995; Nawathe *et al*., 1982; Magori-Cohen *et al*., 2012; Gumbe, 2018; Kondela *et al*., 1984) [55, 26, 14, 40, 30, 37].

Secretions from infected animals, such as nasal secretions, milk, blood, saliva and lachrymal secretions, that are shared by other animals through watering and feeding troughs (Ali *et al*., 2012) [3]. Intrauterine route, where the virus can pass from an infected mother to her calf (Rouby and Aboulsoud, 2016) [48]. Semen, where the LSD virus can persist and survive for up to 42 days after infection and can be transmitted through mating or artificial insemination (Irons *et al*., 2005; Annandale *et al*., 2013) [28, 6]. Iatrogenic pathway, in which a single needle used for mass vaccination that can take up the virus from the skin crusts or scabs of sick animals and transmit the disease (Mulatu and Feyisa, 2018) [39]. Quarantine alone cannot stop the spread of LSDV, as insect vectors, such as flies and mosquitoes, can also carry the virus from one animal to another (WOAH, 2023) [56].

Pathogenesis

The disease, referred to as a generalized epitheliotrophic disease, it can cause localized and systemic reactions leading to vasculitis and lymphadenitis. This is then often followed by serious symptoms such as edema and necrosis. In some cases, thrombosis and infarction may also occur. The skin may become grey-pink in color and have an irregular nodular texture with caseous necrotic cores. There may also be ulcerated, circumscribed necrotic lesions referred to as 'sit-fasts'. The lymph nodes may be enlarged, and secondary bacterial infections are quite common in the necrotic cores. Multiple virus-encoded factors are produced during infection, which can also affect the pathogenesis and the course of the disease. Research suggests that the combined effect of these factors can be responsible for the occurrence, severity, and progression of the disease (Moudgil *et al*., 2023; Tuppurainen *et al*., 2017; Sukoco *et al*., 2023; Ren *et al*., 2023) [38, 51, 54, 47]. It is therefore important to treat this disease early to decrease the severity and chances of further complications.

Clinical signs

LSD is an infectious disease that predominantly affects sheep and goats. LSD is characterized by two febrile phases that follow an incubation period of 4-12 days, usually 7 days. During the first phase, infected animals experience a fever of 40-41.5°C that can last for 6-72 hours, or even up to 10 days in rare cases. Additionally, the animals may exhibit lacrimation, pharyngeal secretions and increased nasal, a disinclination to move, general depression, dysgalactia, and anorexia. Age or gender have little bearing on how severe the initial clinical signs are; instead, it depends on the herd's management strategy. Following the fever, multiple firm, circumscribed nodules appear on the skin, usually on the neck, head, genitalia, perineum, udder, and limbs. These nodules typically measure 5-50 mm in diameter and appear as raised areas of skin covered in erect hair. The skin surrounding the lesions is hyperaemic, and in some cases beads of serum may be exuded from them. These lesions may be widespread or restricted to just a few areas. The regional lymph nodes may also be enlarged and easily palpable, and lumps may be felt in the subcutaneous tissue throughout the body (Diesel 1949; Datten *et al*., 2023; Ratyotha *et al*., 2022; Liang *et al*., 2022) [21, 17, 32, 46].

Fig 1, 2 and 3: Showing gross skin nodular lesion on facial head abdomen, hind quarters and emaciated body of cattle.

Pathology

Gross pathological findings

The gross pathological findings of LSD are important for diagnosing the disease and assessing its severity and impact on animal health and trade. LSD can cause significant economic losses and affect animal welfare and production.

LSD causes characteristic lesions on the skin and mucous membranes of the infected animals. The lesions are usually

round, firm, and raised nodules that are uniform in size, but sometimes they can merge into large and irregular plaques. The nodules have a reddish-gray color and contain a reddish-gray fluid and edema in the subcutaneous layer. The lesions can heal and leave hard scars, called "sitfasts", or they can break down and form deep ulcers. The lesions can also be found on the mouth, nose, throat, lungs, stomach, reproductive organs, and udder of the animals (Ali *et al*., 1990; Sanz-Bernardo *et al*., 2020) [1, 49].

The infection also affects the lymph nodes of the animals, which become swollen, oedematous, and filled with pus. The lymph nodes can be three to five times their normal size and show signs of inflammation and infection. The infection can also spread to the muscle tissue and the fascia over the limb muscles, where it causes grey-white nodules surrounded by red tissue. The lesions are caused by the infiltration of large epithelioid cells, called "celles claveleuses", that are typical of poxvirus infections. These cells separate the necrotic tissue from the healthy tissue and cause inflammation and tissue damage. The necrotic tissue eventually falls off and leaves an ulcer that heals slowly (Moudgil, *et al*., 2023; Parvin *et al*., 2022) [38, 42].

The lesions can affect various organs and systems of the animals, such as: The kidney: The nodules can be found throughout the kidney and measure about 10-30 mm in diameter. They can cause kidney damage and impair renal function. The lungs: The nodules can be scattered in the lungs and measure about 10-20 mm in diameter. They can cause interstitial or bronchopneumonia, which is a type of lung infection that affects the alveoli and the bronchi. They can also cause respiratory distress and difficulty breathing. Animals with severe infections may display secondary bacterial pneumonia, tracheal stenosis, acute and chronic orchitis, secondary bacterial infection of mastitis, and similar lesions in the female reproductive system (El-Neweshy *et al*., 2012; Davies *et al*., 1971; Kumar 2011) [18, 31].

Histopathological findings

The histopathological findings of LSD disease are very distinctive and can help confirm the diagnosis. The lesions show different features depending on their stage of development. In the early stage of the disease, the lesions mainly consist of inflammation, clotting, and death of the blood vessels and the surrounding tissues. The infected areas are filled with immune cells, such as macrophages, lymphocytes, and eosinophils. Some cells, such as keratinocytes, macrophages, endothelial cells, and pericytes, have abnormal structures inside their cytoplasm that stain pink with eosin. These structures are called intracytoplasmic eosinophilic inclusions and indicate viral infection. The outermost and middle layers of the skin, called epidermis and dermis, are swollen and infiltrated with large epithelioid macrophages. These are specialized cells that engulf and destroy foreign particles. They are also characteristic of sheep pox infection. In the early lesions, these macrophages are accompanied by plasma cells and lymphocytes, which produce antibodies against the virus.

In the older lesions, they are accompanied by fibroblasts and polymorphonuclear leukocytes with some red blood cells, which are involved in tissue repair and inflammation. The blood vessels in the dermis and subcutis show signs of proliferation of the endothelial cells that line them, as well as accumulation of lymphocytes around them. This leads to clotting and necrosis of the blood vessels and the tissues they supply. Specific intracytoplasmic inclusions can also be found in various epithelial elements, such as sebaceous glands and hair follicles. These inclusions are mostly eosinophilic-purple and appear to have a clear halo around them, which may be an artifact of the processing method. The lesions are similar throughout the body (El-Neweshy *et al*., 2012; Burdin 1959; Ali *et al*., 1990; Body *et al*., 2012; Badr *et al*., 2022; Gharban *et al*., 2019; Trinh *et al*., 2022) [1, 8, 9, 11, 25, 52]

Diagnosis

It is necessary to isolate and identify the virus in order to confirm lumpy skin disease in a new location. Before neutralising antibodies develop, samples for virus isolation need to be taken within the first week of the onset of clinical symptoms (Datten *et al*., 2023) [17]. Early lesions (those without necrosis) on the skin can be biopsied to obtain samples for viral isolation and electron microscopic examination. Additionally, during the viraemic stage of LSD, blood samples taken into EDTA or heparin can be used to isolate the LSD virus from buffy coat. At least three different animals should be used for the samples. For viral isolation, samples collected from swollen lymph nodes can also be employed. In tissue cultures of bovine, ovine, or caprine origin, the LSD virus multiplies. The most vulnerable cells are thought to be ovine dermis cells or lamb testis (LT) cells (secondary or primary culture) (Amin *et al*., 2021; Liang *et al*., 2022) [5, 32]. According to the WOAH Terrestrial Manual (2023), LSD capripoxvirus has also been modified to grow on the chorioallantoic membrane of embryonated chicken eggs and Vero cells, which is not advised for primary isolation.

Electron microscopy: Within a few hours after receiving the samples, a transmission electron microscopy (TEM) diagnosis of LSD can be made. In biopsy samples taken from afflicted skin or mucous membranes, the virus was visible using TEM in negatively stained preparations. Orthopox virions have a much rounder profile and smaller lateral bodies than mature capripox virions, which have an average dimension of 320 × 260 nanometers (WOAH, Terrestrial Manual, 2023) [56].

Fluorescent antibody tests: Using fluorescent antibody tests, we can detect the presence of Capripoxvirus antigen on the cover-slips or tissue culture slides that have been infected with the virus.

Agar gel immunodiffusion (AGID): This technique can be used to identify the precipitating antigen of capripoxvirus, however it has the drawback of also detecting parapoxvirus (Liang *et al*., 2022) [32].

Enzyme-linked immunosorbent assay: In order to create P32 monospecific polyclonal antibodies and monoclonal antibodies (MAbs), expressed recombinant antigen is used (Carn, *et al*., 1994) [15].

Differential diagnosis

Lumpy skin disease can be confused with other diseases such as Bovine papular stomatitis (Parapoxvirus), Pseudocowpox (Parapoxvirus), Bovine herpes mammillitis (bovine herpesvirus 2), Vaccinia virus and Cowpox virus (Orthopoxviruses), dermatophilosis, demodicosis, insect or tick bites, besnoitiosis, *hypoderma bovis* infection,

photosensitisation, urticaria, cutaneous tuberculosis, onchocercosis and rinderpest (Sudhakar *et al*., 2020; Ratyotha *et al*., 2022) [50, 46].

Prevention

There is no effective cure for LSD yet. The only treatment available is to use anti-inflammatory and antibiotics to ease the symptoms. To prevent the disease from spreading across borders, some control and prevention measures are necessary, such as:

a) **Limiting animal movement:** Animals infected with LSD should not be allowed to move to other areas. They should be isolated and checked for signs of the disease. This can help stop the disease from spreading quickly within a country.
b) **Limiting vector movement:** Vectors can carry the disease through the wind. To prevent this, vector control methods such as using vector traps or insecticides can be applied.
c) **Vaccination:** For LSD, a live attenuated vaccination is available. Companies developed vaccinations based on several LSD virus strains. It is either based on the SIS Neethling type (Lumpyvax, MSD Animal Health-Intervet, South Africa) or the Neethling strain, such as the Lumpy Skin Disease Vaccine for Cattle (Onderstepoort Biological Products; OBP, South Africa) or Bovivax (MCI Sante Animale, Morocco).

Since the virus that causes sheeppox and goatpox is closely related to LSD, the vaccination for both diseases can be used to treat LSD (Tuppurainen *et al*., 2017) [54]. According to OIE, many viral strains can be used as vaccine strains. homologous virus causing lumpy skin disease Three years of protection are provided by the South African Neethling strain, which is passed through 60 times in lamb kidney cells and 20 times on the chorioallantoic membrane of embryonated chicken eggs. Kenyan sheeppox virus passaged 18 times in lamb testis (LT) cells or foetal calf muscle cells, Yugoslavian RM 65 sheep pox strain, and Romanian sheep pox strain are among the sheeppox strains utilised as vaccinations against LSD.

The strains used in the heterologous vaccines trigger certain local responses. As these vaccinations may act as a source of infection for a vulnerable population of sheep and goats, they are not recommended in locations where sheeppox and goatpox are prevalent. Cattle have effective protection against the live attenuated Gorgan goatpox strain with almost no negative side effects (Gari *et al*., 2015; Brenner *et al*., 2009; Capstick and Coakley 1961 and 1962; Carn *et al*., 1994) [24, 10, 61, 62, 14].

Since the LSD virus is stable and lasts a long time in the environment, long-term immunisation with 100% coverage should be made mandatory for disease control and prevention. It is advisable to immunise fresh animals before bringing them to the affected farm. At the age of 3 to 4 months, calves who have been nursed by mothers who have had vaccinations or are infected naturally should be immunised. Breeding bulls and pregnant cows can both receive yearly vaccinations (Tupprainen *et al*., 2017) [54].

Since sheep and goat poxviruses and the LSD virus are closely related, vaccinations for both of these viruses can also be used to prevent LSD. At the age of three to four months, calves should receive their first vaccination. Annual vaccinations are recommended for adult animals. The ICAR-IVRI produced the live attenuated sheep pox vaccine using an indigenous strain (SPPV Srin 38/00), and the technology was then given to Hester Biosciences. The technology for the live attenuated Raksha Goat Pox vaccine (Uttarkashi strain) was provided to Indian Immunologicals Ltd (IIL) by ICAR-IVRI. Live-attenuated LSD Neethling strain.

Lumpi-ProVacind is a homologous live-attenuated LSD vaccine. In addition to offering 100% protection against a fatal LSDV challenge, Lumpi-ProVacind is safe for animals and triggers an LSDV-specific antibody and cell-mediated immune response. Animals are vaccinated against Lumpy Skin Disease as a preventative measure using Lumpi-ProVacind, which provides immunity for roughly a year. The live-attenuated LSDV (Ranchi strain) vaccine contains $10^{3.5}$ TCID50 per dose. At 4 °C, the vaccination is kept safe. After reconstitution, the vaccine must be used within a few hours and must be sent on ice. The ICAR has submitted a patent application for the technique (PIB, 2022) [43].

Conclusion

The disease was endemic in Africa until the 19th century, but it has since spread rapidly to the Middle East, Eastern Europe, Russia, and, most recently, south-east Asia. As a result, it is imperative that emergency preparations be made in order to prevent this transboundary disease from spreading significantly further. Vector control, movement restrictions, rigorous quarantines, improved immunisation programmes, appropriate veterinarian care, and overall farm sanitary management should all receive special attention.

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