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Emergence of Lumpy Pox Virus and Their Preventive Measures: A Global Livestock Threat

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Abstract

In the last few years viral disease not only affect the human but also the other life on this planet and result epidemic condition at global level. The highly transmissible viral disease called Lumpy skin disease (LSD) spread in sequential manner at worldwide level affecting the cattle or dairy animals of caprine, ovine and bovine family. The highly mutational efficiency of this viral strains affects the large-scale population and still no effective cure for it. Different vaccines designed at national and international level as a preventive measure to overcome the reoccurrence of this virus e.g., Bovivax-LSD™, Lumpivax™, Poxvac™, Lumpi-ProVac^{Ind}. However, still the mortality of LSD are low, not affect humans but emergence of the mutational variants demands novel vaccines.

Keywords: *Virus, Skin, Lumpy, Infection, Cattle, Vaccine*

1. INTRODUCTION

Lumpy skin disease virus (LSDV) belonging to family *Poxviridae* and genus *Capripoxvirus* is known for causing an infectious, limited host range, acute, sub-acute or inapparent disease known as Lumpy skin disease. LSD is a vector borne and non-zoonotic disease generally affecting cattle and water buffaloes causes due the biting flies, ticks and mosquitoes as across trans boundary LSD vectors. In some cases skin lesions are reported in sheep, goat, giraffe, Giant gazalles, impalas post experimental infection, however natural infection cases are rare **[1].** High morbidity and low mortality rates are observed in various outbreaks of LSD. The incubation period of LSDV varies from 1–4 weeks, and the clinical symptoms consist of fever (40–41°C), nasal discharge, edema, motion reluctance, excessive salivation, loss of appetite, lacrimation, infertility and enlargement of the subscapular and pre-crural superficial lymph nodes **[2].** The classic manifestations of LSD are skin nodules that vary in number and size. Overall, it has an impact on the economical worth of the animal because it affects hide quality, meat and milk productivity, draft power, and reproductive efficacy. The initial outbreaks of LSD was observed in Zambia in 1929 **[3],** and thereafter from other countries in southern and northern Africa and later spread to Israel, Kuwait, Oman, and Yemen **[4].** LSD is generally endemic in African nations however in past few years it has spread to new regions across the globe especially in South East Asian countries. It is now well established in Southeast Asian countries, posing a challenge to the livestock management in these regions and an immense hazard to food security.

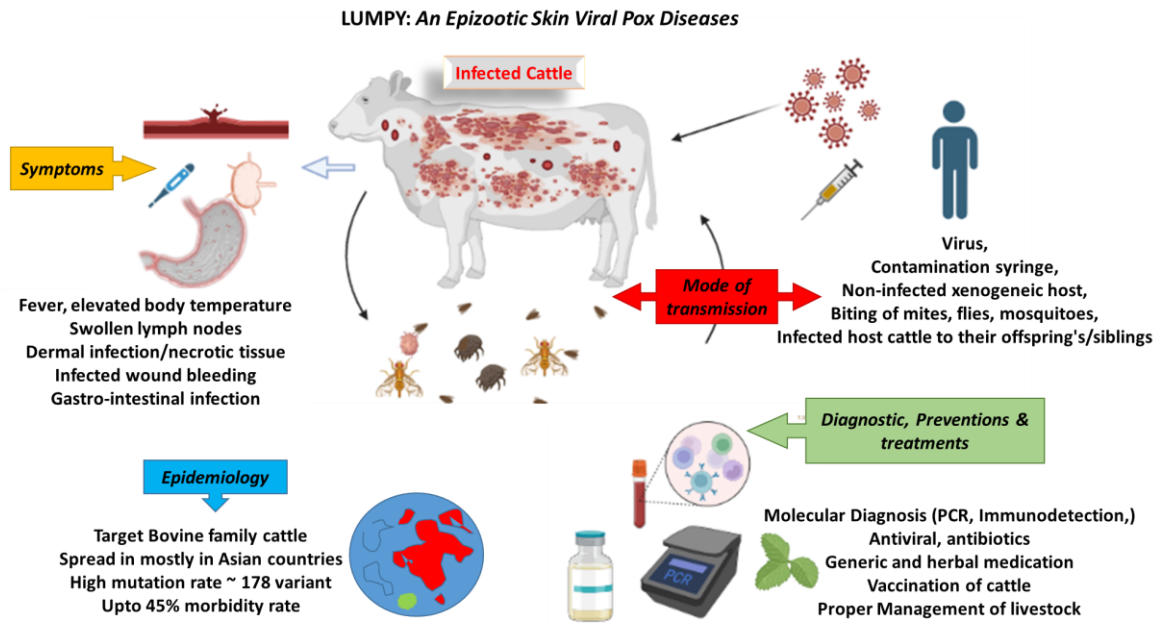

Figure 1: *Schematic representation of the LSD causes, symptoms, diagnostic, prevention, treatment and epidemiology at a global level.*

Etiology

The *Capripoxvirus* genus consists of Sheeppox, goatpox and lumpy skin disease virus which infect sheep, goat, and cattle, respectively **[1].** LSDV is a brick-shaped enveloped virus having size 320 × 260 nm. It has complex symmetry double stranded DNA as the genetic material that replicates inside the host cytoplasm. The LSDV genome is 151 kbp in size, with 156 putative genes and a central coding region surrounded on both sides by 2.4 kbp-inverted terminal repeats. The genome of LSDV encodes 30 structural and non-structural genes having 97% homology to sheep pox and goat pox viruses. The terminal regions of the LSDV genome codes for N2L, IL-1 receptor, K7 L, vaccinia virus F11L and myxomavirus M003.2 and M004.1genes. A unique gene LSDV132 encoding for virulence factors and host specificity is interrupted by accumulated mutations both in sheep pox and goat pox virus **[1].** In accordance to recent research the application of homologous live attenuated vaccines influence the LSDV to undergo mutations due to recombination. Between 2017 and 2019, multiple vaccine-like recombinant strains of LSDV were reported from Kazakhstan and neighbouring Russia and China **[5]**. Prior to 2020, the isolated recombinant strains of LSDV were made up of distinct combinations of open reading frames. Post 2020 all the reported strains in Russia and Southeast Asia belong to a single lineage that spread throughout the region **[5].** The vaccine-like recombinant strains have been categorized into four groups on the basis of distinct breakpoint pattern resulted due to different recombinations in accordance to **[6].** The latest upsurge of vaccine-like LSDV strains in different regions of Southeast Asia is most probably the outcomes of spread from Lumpivax vaccinated cattles. Additionally, it was reported a recombinant LSDV vaccine strain in Thailand possessing a mosaic hybrid genome consisting of vaccine viral DNA as the major one and a field strain DNA as the minor donor previously found in China and Vietnam**[7]**.

Transmission

Most endemic countries, such as Egypt, Sub-Saharan Africa and Ethiopia, observe an increase in disease incidences with the arrival of summer and seasonal rains, which coincides to the maximal active period of the vectors **[8].** LSDV is mechanically transmitted by blood-feeding vectors, primarily biting flies (*Biomyia fasciata* and *Stomoxy calictrans*), mosquitos (*Culex mirificens* and *Aedes natrionus*) and ticks (*Amblyomma hebraeum, Rhipicephalus decoloratus* and *Rhipicephalus appendiculatus*). LSDV has been reported from saliva of ticks feeding of infected cattle thus signifying their role in LSDV transmission. Transovarian and transstadial spread is also reported from ticks **[1].** The presence of LSDV in cattle semen for an extended period, also in asymptomatic cattle, suggested the venereal transmission of LSDV. In addition transmission via artificial insemination and intrauterine route (milk and skin abrasions) has also been affirmed **[2].** Iatrogenic virus spread occurs on using single needle for mass vaccination acquiring LSDV from skin scabs or crusts **[1].** According to recent reports, contact spread of the virus has been found in exclusion of insect vectors. A LSDV strain formed due to recombination between a live-attenuated vaccine and a field strain (Saratov/2017) was injected in cattle's and spread of this strain to in-contact cattle in an insect-proof space was reported **[9].** LSDV is present in milk, lachrymal, nasal and saliva discharges and blood making them an indirect transmission source amongst animals that share feeds and watering troughs **[1].**

Epidemiology

Incidence of infection in animals

Cattle (*Bos indicus* and *Bos taurus*) and buffalo (*Bubalus bubalis*) are the natural host of LSDV. *Bos taurus* is most susceptive amongst the native cattle breeds. The young animals are highly susceptive and lesions occur within 24 to 48 hours **([1].** Lesions due to experimental infection are found in wild animals such as; Arabian oryx, Giraffe, Impala, Springbok, and Thomson's gazelle, however they resist LSDV in natural environments **[1].** Most of the affected animals' show pathological alterations such cow mastitis, cardiac damage, disseminated vasculitis, lymphadenitis, necrotic hepatitis and orchitis. A limited percentage of cattle also show myocardial damage, tracheitis other pathological alterations and these changes might cause varying levels of injury induction in the infected individuals, making LSDV more harmful to the body. No infections are observed in humans and thus they are resistant **[10].**

Susceptibility and mortality rate

LSD outbreaks vary enormously in terms of death and morbidity which depend on factors such as; geographical location, climate, breed, nutritional and immune status of the animal, population levels, distribution of presumed vectors in different environments and virus virulence. LSD has a morbidity rate ranging from 5 to 45%, but the rates of 1 to 5% are considered more common. High morbidity rates have been observed in epizootics in Southern, West, and East Africa, as well as Sudan. Furthermore, high morbidity and mortality rates of 30-45% and 12%, respectively, were recorded in Oman in 2009 in Holstein cattle **[4]**. In the recent outbreaks in Southeast Asian countries very low mortality rates in range of 0-0.24% and morbidity rates of 8.48-14.52% were recorded **[2].**

Early cases and Ecological Distribution

Historical Cases

Long before the aetiology of LSD was documented, a cattle skin disease known as "pseudo-urticaria" was discovered in an area of Northern Rhodesia in 1929. The clinical lesions in the infected animals were assumed to be due insect bites at the time **[3].** The disease persisted in successive years and was also attributed to plant poisoning. Von Backstrom **[11]** for the first time identified LSD as an infectious disease following an outbreak in Ngamiland in 1943. The disease first appeared in the Transvaal near the end of 1944 **[12]** and then transmitted speedily across South African region over the next few years, in spite of strict regulations and control measures. In 1988, LSDV infection occurred in Egypt owing to the transfer of diseased animals from affected nations. Similarly in 2006 again, the disease was reported from African region due to unrestricted cattle movement **[1].**

Recent Scenario

LSD is an emerging disease threat as a result of the impact of global climate change and changes in animal and their product trading behaviour. Civil conflict in the Middle East and Asia, which impedes veterinary services and disrupts livestock movement behaviour, contributes to the enhanced transmission of the LSDV. Various LSD outbreaks, which were once restricted to the African region, have occurred sporadically outside of Africa. In past few years, LSD was documented for the first time in Bangladesh, Bhutan, Cambodia, China, India, Laos, Nepal, Malaysia, Myanmar, Sri Lanka, Thailand and Vietnam **(Table 1),** primarily infecting Asian cattle (*Bos indicus*) and Asiatic (water) buffaloes (*Bubalus bubalis*), though *Bos taurus* breeds were also infected in Nepal.

Table 1*: Recent Epidemiology of LSDV and Temporal distribution of LSD virus in Asian countries from 2019 to 2021 (Data source: OIE disease record)* [2]

Year of Occurrence	Country (Region)	No. of Cases
July 2019	Bangladesh (Chittagong)	66 (Mortality: 0%)
August 2019	China (Xinjiang)	65 (Mortality: 0%)
August 2019 (3 outbreaks)	India(Orissa)	88 (Morbidity: 8.48%; Mortality: 0%)
October 2019	Bangladesh (Dhaka)	16 (Mortality: 0%)
March 2020	Bangladesh (Khulna, Rajshahi)	93 (Mortality: 0%)
June-August2020 (8 outbreaks)	Nepal (Koshi, Narayani, Bagmati, Gandaki)	2420 (24 deaths) (Morbidity: 14.52%, Mortality: 0.14%)
July 2020 (8 outbreaks)	Seven Chinese provinces	156 (7 deaths)
September 2020 (6 outbreaks)	Sri Lanka (Northern Province)	83 (Mortality: 0%)
September 2020 (7 outbreaks)	Bhutan	147 (3 deaths) (Morbidity: 11.86%; Mortality: 0.24%)
November 2020	Myanmar (Sagaing Region)	6 (Morbidity: 9.52%; Mortality: 0%)
March 2021	Vietnam	137 (2 deaths)
April 2021	Thailand (Roi Et Province)	10 (Mortality: 0%)

May 2021 (23 outbreaks)	Malaysia (Perak, Kedah, Pahang, Perlis, Melaka and Terebgganu)	54 (Mortality: 0%)
May 2021 (9 outbreaks)	Loas (Savannakhet and Vientiane)	369 (Mortality: 0%)
May 2021	Cambodia (Preah Vihear Province)	103 (Mortality: 0%)

Diagnostics

The clinical symptoms are frequently used in the on-site diagnosis of LSD to identify whether the cattle are infected. A quick and effective tool for LSDV field infection diagnostic is the PCR method. Recombinase polymerase amplification assay is a portable, easy, and quick method for LSDV genome field detection **[13]**. Loop-mediated isothermal amplification (LAMP) is another unique technique for the detection of LSDV and it targets the poly (A) polymerase small subunit (VP39) gene with increased detection rate and sensitivity **[13].** In order to detect LSDV antibodies early in vaccination and disease infection, Haegeman et al. **[14]** designed a unique highly specific and sensitive assay the Immunoperoxidase Monolayer Assay. This technique may be processed in a typical biosafety level laboratory and is highly safe for use in simple and crude environmental detection. Immunohistochemical (IHC) techniques can be used to diagnose the pathological sections taken from skin lesions, and particular anti-LSDV antibodies can be used to identify the distribution of pathogenic antigens. Recombinase polymerase amplification assay (RPA) in combination with CRISPR-Cas12a-based fluorescence test is a novel diagnosis method for LSDV-ORF068 gene targeting. It has great sensitivity and accuracy in the detection of trace quantities and doesn't show cross-reaction with other common bovine viruses **[15].** Two monoclonal antibodies directed against various epitopes of P32 structural protein of LSDV and gold nanoparticles were used to develop a quick diagnostic tool for colorimetric sandwich-type lateral flow immunoassay **[13]**. The sensitivity of this method is comparable to that of ELISA, however its specificity must be evaluated post clinical trials because it has not been widely employed in clinical diagnosis yet. Korthase et al. **[16]** devised a novel process by extracting nucleic acid without electricity, namely Triple*E*, which can extract nucleic acid from 8 samples within 10 min and ensure sensitivity. It may be employed in locations without ideal experimental conditions for diagnosis.

Treatment and preventive measure

The initial diagnosis of the infected host based on the pre-examination such as body temperature, pastures, physical examination, and if any sign of infection shown than the pathological testing have to be done at molecular level to confirm the pathogenicity as per the standard guidelines **[17]**. However, the cattle bulk vaccination, slaughter campaigns, management strategies, and movement control (quarantine) are the four methods to control and prevent lumpy skin disease **[18]**. Besides that few basic preventive measure to overcome the diseases transmission is to check the hygiene, prevent the contamination of feed, fodder, grazing areas, water, feed yards, and water bodies by infected animals. Among the all the strategies, immunization with the LSD pox vaccine and their homology vaccines (Sheep pox virus vaccine, Goat pox virus vaccine) e.g., Lumpyvax™, Bovivax-LSD™, LumpyShield-N™, Lumpivax™, Penpox-M™, Poxvac™, Lumpyvac™ Poxdoll™, LSD-NDOLL Sheep Pox, Cultyral Dry™, encompassing of the specific viral gene recommended by the veterinary guidelines at national and international level such ICMR, FAO **[19,20].** Since the heterologous vaccine strains can produce some local reactions, it is not advisable to use them in places where sheep pox and goat pox are prevalent because they may infect susceptible populations. Live attenuated Gorgan goat pox strain offers effective side-effect-free protection for cattle **[1]**. The LSDV possess a complex immune response and thus currently there are no safe and effective vaccinations available for this illness. Since the vaccines against sheep pox virus and goat pox virus exhibit antigenic similarity and cross protection with LSDV, thus they can be used to prevent LSD. The two vaccinations mentioned above are live-attenuated vaccines developed from strains identified in the field; therefore they unavoidably carry certain potent risk factors and are thus not advised in places disease free areas. Using a strain CIRAD AF262936 and the Neethling strain (ID: AF409138), Safini et al. **[21]** developed a bivalent vaccination that can cause inoculated cattle to produce high-level neutralizing antibodies against the two diseases without causing clinical side effects. There is no challenge with virulent strains, nevertheless, and the direction of future tests should go toward confirming the protection following the challenge of virulent strains. It is suggested to carry out immunization of new animals prior to their transport to the infected farm. Three to four months old calves should be immunized and breeding bulls and pregnant cows must be vaccinated annually **[1].**

In addition to nonsteroidal anti-inflammatory drugs (NSAIDs), antibiotics may also be used when necessary to treat subordinate infections on the skin. The commercial vaccine for the immunization of cattle are the live attenuated vaccines having adverse effect on host body after vaccination i.e., minor inflammation, decrease of mammary gland expression and Neethling disease (skin lumps) **[17].** Therefore, recommended the use of inactivated and DIVA (Differentiation of infected from vaccinated animals) vaccine rise up as prevention in the virus free-zone countries and their reoccurrence in live-stocks **[22]**. In India Ministry of Agriculture &

Farmers Welfare on 10 August 2022 released local vaccine Lumpi-ProVac^{Ind} developed by the research team of National Equine Research Center, Hisar (Haryana) and Indian Veterinary Research Institute, Izzatnagar (Bareilly) for immunization of livestocks **[23]**. In a recent study the effective immunological outcomes reported in the field trail adjuvant based vaccinations of inactivated pox vaccine to provide complete prevention against this challenging virulent strain **[22]**. At the global level to improve the efficiency of the vaccine and the chances of reoccurrence of infection in the livestocks, the molecular and immunology factors considers to design multi-epitope protein, viral subunit (LSDV031, LSDV090, LSDV103, and LSDV109), adjuvants vaccine, and generic vaccine against this pathogen **[24]**.

Table 2: *Different types of vaccine developed for LSDV and their shortcomoings*

Strain	Type & Virulence	Shortcomings	Reference
South Africa Neethling (Onderstepoort Biological Products SOC Ltd.)	Live attenuated; Low	12% of livestock showed lumps at the inoculating site and the viral load was observed in the milk	**25**
Lumpyvax (MSD Intervet South Africa (Pty) Ltd., Spartan, RSA, attenuated SIS type virus)	Live attenuated; Low	Viral load observed in milk	**26**
Onderstepoort (Biological Products OBP; South Africa; batch 442)	Live attenuated; Low & 100% protection	86% of livestock developed hypothermia post immunization	**14**
Lumpyvax (MSD-Animal Health; South-Africa; batch BNDM07)	Live attenuated; Low & 100% protection	All the vaccinated livestock developed hypothermia post immunization	**14**
Kenyavac (Jordan Bioindustries Center Jovac; Jordan; batch 220,115–04)	Live attenuated; Low & 100% protection	71% of the livestock developed hypothermia post immunization	**14**
Herbivac LS (Deltamune; South-Africa)	Live attenuated; Low & 100% protection	Vaccinated livestock exhibited enlarged prethoracic lymph nodes; 57% of the livestock developed hypothermia post immunization	**14**
Vaccine LSD Neethling O vivant (MCI Santé Animal; Morocco, batch 17BLSDN001)	Live attenuated; Low & 100% protection	43% of immunized cows had severe swelling>10 cm in diameter at the inoculating site; 57% of livestock developed hypothermia post immunization	**14**
RM65 (Abic Ltd. Netania, Isral)	Live attenuated; Low	11.1% of the livestock exhibited general symptoms of LSD	**14**
combined Mmm/LSDV vaccine	Live attenuated; Low	No side effects	**21**
South Africa “Neethling”	Inactive vaccine; Low & 100% protection	No side effects	**22**
LSDV-BTV4	Inactive vaccine; Low & 100% protection	No side effects	**27**
LSDV- “Neethling Vaccine”	Inactive vaccine; Low & 100% protection		**28**

Conclusion

The success of LSD eradication depends greatly on the vaccination strategy applied in countries surrounding LDS-infected regions. A growing threat to the bovine production chain has made LSD an essential threat, which requires adequate and effective solutions at the earliest opportunity. At present, only live attenuated vaccines are available to the public. In many areas, live vaccines are contributing to the control of disease as they generate a strong and long-lasting immune response. There are many advantages to inactivated vaccines, including their safety, stability in the tropics, and ability to combine them with other antigens to make polyvalent vaccines. Vaccines made with inactivated DNA are safe, stable, and can be used in disease-free countries without losing their freedom. Inactivated vaccines do not revert to virulence or transmit the virus between vaccine recipients and their co-habitants, although they are very expensive. As part of an overall strategy that utilizes live vaccines first to reduce the prevalence of LSD, inactivated vaccines can also be used to decrease LSD prevalence in countries at risk of LSD introduction with large cattle populations. Hence, the modernized tool and techniques provide sustainable treatment to cure livestock on a global scale.

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Highlights:

1. *Worldwide LSD is the root cause of significant economic losses.*
2. *Epidemiological assessment of LSD outbreaks identifies the key risk factors and transmission patterns of disease's expansion.*
3. *Revealing imperative, the pathogenesis assist in the theragnostic approaches provide preventive strategies e.g., vaccination, biosecurity protocols, and surveillance systems.*

Comprehensive outline could be the Global precautionary actions to effectively limit the spread of virus across worldwide.

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