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Review Article

# A Review on Lumpy Skin Disease: One of the Most Neglected Diseases of Cattle with an Unprecedented Incidence in Non-Endemic Countries

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## Abstract

Lumpy skin disease (LSD) of cattle is considered to be a neglected disease that mostly remains endemic in African countries. It is caused by a pox group of viruses. Presently the disease has crossed the fence and surfaced with an unprecedented incidence in Asian countries like India Bangladesh, Nepal and Bhutan. As per scientific reports, several arthropod species like biting flies, mosquitoes and ticks act as mechanical vectors for the transmission of the disease. Animal-to-animal contact may also disseminate the disease as well as long-distance man-made travel of the infected animal is the source of disease transmission. Cattle and buffalo of all age groups are susceptible to this virus. The disease is not zoonotic and morbidity may rise up to 40% yet mortality is too low. Among cattle breed Bos indicus is relatively less susceptible than Bos taurus. The LSD virus is an enveloped virus having 151 kbp double stranded DNA that remain enclosed by an outer protein coat. Genome sequencing of sheep pox virus (SPV), goat pox virus (GTPV) and LSDV has given an indication that all these three viruses have a common ancestral origin with antigenic relatedness. Due to antigenic sharing serological detection of antibody may not add accuracy in diagnosis of LSD. Easily identifiable firm raised skin nodules of 2-7 cm diameter spread throughout the body typically confined to neck, leg and back region extend to tail, are the cardinal sign of LSD that hardly goes unnoticed. Histopathology, serology, virus isolation and PCR techniques are used for laboratory diagnosis. As of now no specific treatment is recommended, but to prevent any secondary infection use of antibiotic is suggested. Several homologues and heterologous vaccines are available to control the disease severity in endemic regions. Most prevalent vaccine is cell culture adapted live attenuated vaccine derived from Neethling strain of LSD virus. To prevent the infection in disease free countries few items like semen, embryo and milk should not be imported from those countries where active cases persists. Complete eradication of the LSD in resource poor countries is not feasible yet reduction in disease incidence can be achieved either with ring vaccination or mass vaccination of healthy cattle at the disease endemic area.

**Keywords:** Arthropod Vector; Capripox; Homologous Vaccine; Lumpy Skin Disease; Mechanical Transmission; Neethling Strain; Skin Nodules; Vaccines

## Introduction

Geographical distribution pattern of infectious diseases affecting man and animal fluctuates with change of time. Several infectious diseases which were previously under control with very few sporadic appearances has surfaced out in the form of transboundary reemerging diseases. Nothing better than the catastrophes of monkeypox can be cited here which was once restricted to African countries is now a global threat [1]. As on date with no end of monkeypox infection, yet another pox group of animal virus the lumpy skin disease has aggressively invaded with its full potential causing devastation to cattle population across the countries once considered as neglected disease [2]. To describe the enormity of any disease, epidemiologists prefer to deep dive to probe the incidence and prevalence rate along with morbidity and mortality of the disease so that, strategic measure can be taken to curb the disease burden in future. Due to environmental changes and fast forward mobility of man and animal across the geographical boundaries the disease diffusion rate has worsened in an unprecedented manner. When we declare a disease in real sense, we do it once the disease is detected, diagnosed and registered as documental evidence so that it can be available in public domain for academic and scientific research. LSD is a viral disease mostly affects cattle with prominent nodular skin lesions evenly distributed covering the entire body including neck, leg, back, and genitals. In the year 1929 the disease was first reported from northern part of Zambia (South Africa) and Madagascar [3]. This disease has also been designated with different names such as "Pseudo-urticaria," "Neethling viral sickness," "exanthema nodularis bovis," and "knopvelsiekte"[3]. Since 2012 the geographical distribution of the LSD has further extended to China and Bangladesh [4]. At the time when we are submitting the manuscript the disease has already invaded neighbouring country Bangladesh since August 2019 [5] and laboratory confirmed cases of LSD from Indian state like Odisha has established transcontinental spread of the disease [6]. This is the first authenticated report of LSD outbreak from India [6]. The disease has already been recorded from eastern, western, southern and central part of India [7]. Presently Rajasthan a northern state of India is facing alarming level of infectivity. Interestingly the genome analysis of the LSD virus isolated from the state of Odisha (India) has shown nearly 100% (99.7-100%) genetic identity with Kenyan strain of LSD virus, but no mortality was recorded in this outbreak [8]. This piece of information has indicated that the origin of presently circulating LSD virus in India is from far of place but somehow it has crossed the fence as transboundary disease. According to FAO report from early July 2019 the LSD virus entered Bangladesh, China and India subsequently from June 2020 the disease has spread to neighbouring countries Nepal and Bhutan [4]. In the present discussion we are intended to focus on reemerging cases of LSD, presently circulating in Asian countries including India. Therefore, the message is clear; LSD one of the neglected diseases is on a moving path so to curb the disease we have to face the battle to save the cattle with track and crack strategy.

### Host specificity and breed susceptibility

LSDV can infect a narrow host range and replication of the virus takes place in ruminants like cattle and buffalo affecting all age groups. The causative virus, a member of capripoxvirus group, exhibit hosts specificity with restricted geographic distribution. Till date carrier state of animals for LSDV has not been reported but asymptomatic cattle maintaining the disease cycle is suspected to be the reason behind sporadic cases that appear all over the year in endemic areas [9]. The virus is species-specific infecting only cattle, buffalo and closely related wildlife. All breeds of either sex is equally susceptible to this virus. Within the cattle breed *Bos indicus* is relatively less susceptible than *Bos taurus* [10]. As of now a solitary case of natural infection of LSD in Arabian oryx (*Oryx leucoryx*, desert antelope) has been reported in Arabian zoo [11]. Due to breed susceptibility the morbidity and mortality rate varies and influenced by the type of cattle population existing in the affected area. With available information the LSD is considered as vector borne transboundary disease where mechanical transmission of the virus takes place due to blood feeding arthropods like biting flies, mosquitoes and ticks (Figure 1). Further the immune status of the animals, pathogenicity of the circulating virus, vector population prevailing at that locality are predisposing factor for the final outcome of the disease to be either mild or wild.

### Virus detail (from core to mantle)

The genomic content of LSDV being DNA, it is placed under DNA group of viruses assigned to family *Poxviridae*, subfamily *Chordopoxvirinae,* genus *Capripoxvirus.* To be precise there are eight genera under the subfamily *Chordopoxvirinae* out of it the Capripoxviruses are one among the eight genera. Under the genus *Capripoxvirus* the sheep pox and goat pox virus are two other members that can infect sheep and goat respectively; however sheep and goats are not naturally infected with LSDV unless experimentally infected [12]. The architecture of LSDV having a central core comprised of double stranded DNA, surrounded by protein coat (Figure 2). The core and lateral body are enclosed by capsid. The electron microscopic image has detected presence of two lateral bodies, located in the concave region between the membrane and inner core wall of the virus. Structurally lateral bodies are amorphous in nature. The function of lateral bodies is unknown yet lateral bodies may have some role in host pathogen interaction thereby virus

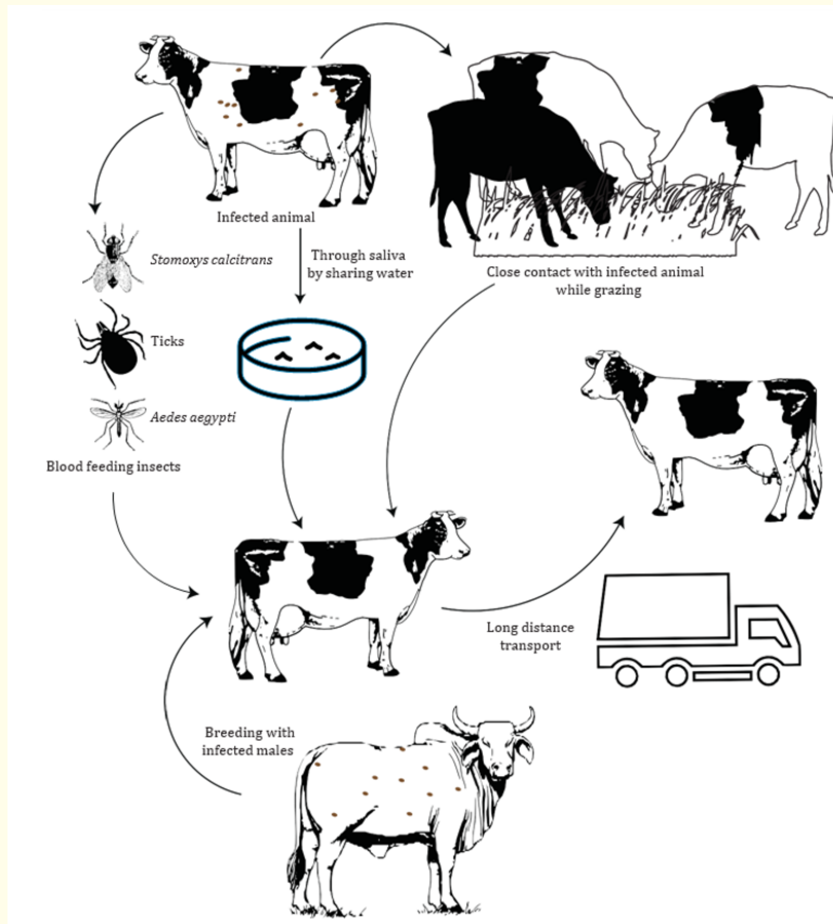


**Figure 1:** Modes of transmission of Lumpy Skin Disease Virus (LSDV). LSDV can be transmitted to the uninfected animals through (a) blood feeding insects, (b) infected semen from diseased males, (c) saliva while sharing common water trough and pastureland with the infected animals and (d) long distance transport of infected animals to disease free area.

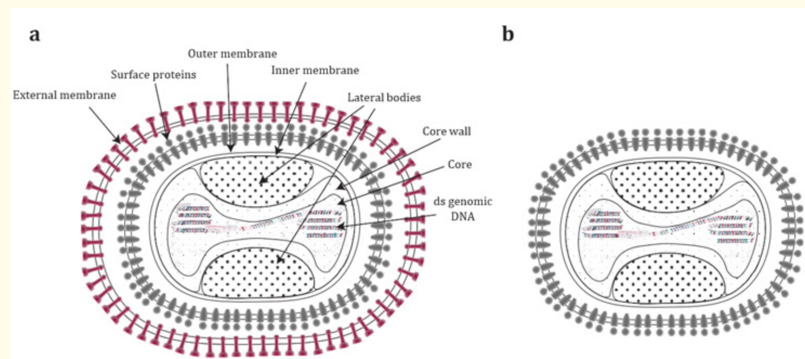


**Figure 2:** Schematic structure of LSDV. (a) External enveloped LSDV. (b) Internal mature LSDV.

can evade innate immune-response of the host is predicted [13]. LSDV is an enveloped virus; under electron microscope it appears to be brick shape measuring 320 X 260 nm in size [14]. Analysis of LSDV genome indicated that overall genome size of 151 kbp is conserved among sheep pox and goat pox viruses. Further the 151 kbp genome of LSDV having nucleotide identity towards sheep pox and goat pox virus is already validated. Gene sequence data indicated that the LSD viral gnome has preserved majority of pox viral gene as conserved gene to an extent of 97% homology, accountable for viral replication. Whole genome sequencing of sheep pox virus (SPV) goat pox virus (GTPV) and LSDV has given a clue that all these three viruses have an ancestral viral origin relates to LSDV, further 30 structural proteins of LSDV have revealed homology to poxvirus [14]. All the members under *Capripoxvirus* share a common antigen generating virus neutralizing antibodies as protecting antibodies to prevent infection. Circulation of several field vaccines strains has given an opportunity to generate recombinant strain of LSDV carrying genetic units resembling mosaic of DNA fragments derived from both LSDV and sheep pox and goat pox virus strain. The first genetic evidence of multiple introductions of LSDV has been reported from Russia [15]. Differentiation of capripox viruses from LSDV either morphologically or serologically is an erroneous approach; rather targeting specific nucleotide polymorphism sequence is more reliable yet few dark points remain there to discriminate closely related recombinant strains. Complete genome sequence data adapting high throughput sequencing is the only choice for strain differentiation policy.

Physical properties of virus indicate its susceptibility to sunlight yet in the dried scab it remains viable at ambient temperature for near about one month. The dried scab is the prime source of infection; similarly, virus can persist in skin and hide up to 18 days in carcass [12]. Inactivation of the virus can take place once exposed to 55$^{o}$C for 2 hours or 65$^{o}$C for half an hour. At low temperature (-80$^{o}$C) the viability of the virus is preserved and can be revived after 10 years of storage. Being enveloped virus it is susceptible to lipid solvent like ether (20% concentration) chloroform and detergent like sodium dodecyl sulphate. Formalin is an effective inactivating agent for LSDV. Exposure to chemical agent like phenol at 2% for 15 minutes, sodium hypochlorite (2-3% solution) and iodine compound at 1:33 dilution as well quaternary ammonium compounds at 0.5% concentration is quite effective for complete inactivation of the virus. Virus infectivity is not reduced at acidic pH. More detail in this aspect is available in FAO report [4].

### Nodular mark as diagnostic track

Animals infected with LSDV hardly go unnoticed due to prominent skin lesions. During physical examination the animals are invariably having pyrexia, loss of appetite, with cardinal sign of firm raised skin nodules of variable size ranging from 2-7 cm in diameter (Figure 3 and 4). The skin nodules may be localised or generalised evenly spread throughout the body typically confined to neck, leg and back region extend to tail, that can be easily noticed [16]. The nodules usually contain creamy or yellowish mass of necrotic tissue. Secondary bacterial infection may occur in those nodules with suppuration and animal become emaciated. Due to disease progression the nodules may appear on the skin of muzzle, nostrils, eyelids, scrotum and perineum as well as on nasal and oral mucosa. Nasal discharge, drooling and lacrimation as associated clinical symptoms due to replication of virus in the epithelial cells of nostril, oral cavity and eyelids are invariably observed in affected animals. In experimentally infected animal virus replication takes place within cytoplasm of fibroblast, macrophages, pericytes and endothelial cells resulting vasculitis and lymphangitis in nearby affected tissues [17].

The disease progression in experimentally produced cases varies that depends upon several factors like, number of live viruses present in the inoculum, route of inoculation and the genetic susceptibility of the animals. Rise of temperature along with lymphadenopathy in the prescapular and subscapular lymph node is generally observed in affected cases [16]. In a recent outbreak at the time of observation most of the affected animals were febrile with excessive salivation, nasal and ocular discharge enlargement of prescapular and prefemoral lymph nodes along with typical small (1-2 cm) to large (7-8cm) skin nodules on entire body surface including udder and teats of affected cattle. Due to disease severity corneal opacity, hind limb oedema and pneumonia were recorded in some cases. In the affected bulls oligospermia and azoospermia were noted along with skin lesions on scrotum [6]. Skin nodules may extend deep below to subcutaneous even underlying muscles. Nodules persists for several months and may invite secondary bacterial infection. On several cases during post-mortem pox lesions may be there on almost all internal organs [16].

Initially the skin lesions appeared as macules subsequently

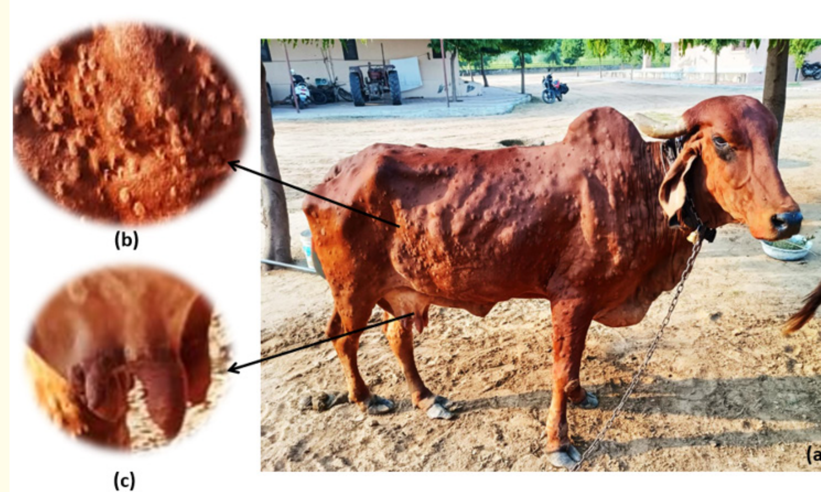


**Figure 3:** (a) Gir breed of cattle from Mahipura, Rajasthan, India, infected with Lumpy Skin Disease Virus showing generalized skin lesions spread throughout body including teats. (b) Enlarged view of skin nodules on body and (c) Enlarged view of skin nodules on teats.

nodules gradually turn in to papules. The papules may change to either hard nodules or it may turn to vesicles and finally ends with pustules. Once skin nodules dried up to form scab it sloughed from the skin, the virus laden scab is the prime source of infection to susceptible animals. In critical cases, the respiratory and gastrointestinal tract may also be affected with necrotic lesions [18]. Denuded skin lesion is prone to screwworm infestation (*Cochliomyia hominivorax,* fly larvae maggots) that leads to myiasis along with secondary bacterial infection and septicaemia [18]. Clinicians are of view that many a times the cases with skin nodules might be confused with severe form of dermatophilosis. According to a present report, the LSD can be differentiated from other diseases showing similar kind of skin lesions in the following manner: if the scabs/lumps are easily detachable then it may be dermatophilosis, if hard to detach then case of LSD is suspected, If pus appear from the hair follicle on pressing the nodules, then more likely case of demodex mange [19]. Dermatophilosis and demodectic mange is easy to diagnose in lab than LSD, yet differential diagnosis remains problematic [19]. In several other infectious diseases of cattle such as pseudo lumpy skin disease/bovine herpes mammillitis (bovine herpes virus 2), pseudo cowpox, bovine papular stomatitis (Parapoxvirus), onchocerciasis, skin nodules having resemblance with LSD lesions which needs differential diagnosis. In case of bovine herpes virus 2, the disease span is relatively short with superficial mild form of nodules, in pseudo cowpox the lesions are restricted to teats, for bovine papular stomatitis the lesions are only on mouth, for onchocerciasis lesions most likely at ventral midline. Invariably diagnosis of LSD is based on typical skin lesions and observation of associated clinical signs in affected animals. Histopathology and virus isolation add the diagnostic accuracy. Many times virus isolation takes enough time or may be unsuccessful therefore confirmatory diagnosis rely on PCR technique.

## Experiment detail in ruminant model

In several occasion clinical manifestation of experimentally produced LSD differs from natural cases. In field condition the incubation period for the disease onset require 4 weeks' time. In an experimental setting, the incubation period is nearly the same that varies from 6 to 26 days, therefore quarantine period for LSD should not be less than 28 days for disease free herd [20]. Near about 50% of the cattle developed clinical infection with characteristic skin lesions on experimental inoculation of virus [16]. Every minute detail of clinical signs exhibited by British cattle in response to experimental inoculation of LSDV (Neethling strain) was recorded from day one up to 3 weeks of post inoculation. Findings indicated rise of body temperature (peak 41$^{o}$C) but pyrexia was not definite sign for all the animals. Intradermal inoculation caused early disease setting with detectable skin lesions as early as 2 days of post inoculation (pi) and within 9-14 days generalised lesions surfaced out.  Only few animals (2 out of 11) were viraemic for a

transitory period and virus could not be isolated from the secretion of any of these animals [21]. As per published report wild animals like impala (*Aepyceros melampus*) Thomson's gazelle (*Eudorcas thomsonii)* and giraffe (*Giraffa camelopardalis*) never suffer from LSD in their natural habitat however experimentally disease has been produced in these animals [16]. Very often experimental production of disease in natural and unnatural host is very much essential not for scientific curiosity rather to be ascertain the pathogenicity of the virus in susceptible host as well to be sure whether wild animals can act as reservoir of the specific disease or not. As per available information wild animals are not act as reservoir or a carrier of LSD virus so there is remote chance of disease spill over from these wild animals.

## Laboratory diagnosis

Frank clinical cases with characteristic skin nodules on affected animals can be easily diagnosed by smart veterinarians, but subclinical and in apparent cases needs further confirmation using laboratory test procedures. For laboratory diagnosis invariably either biopsy or necropsy samples of skin nodules, fluid from skin nodules, skin scab, skin scrapping, lymph nodes, lesions on internal organs and even blood samples are collected for isolation of virus or virus specific nucleic acid detection to confirm the disease. In conjunction with clinical signs an early excretion of virus from infected animals in their oral, ocular and nasal discharge can be collected without invasive procedure as a rich source of virus for confirmatory diagnosis [22]. Skin lesions are preferably collected from the infected animals during active illness to conduct histopathology, immune histochemistry and for virus isolation. Virus can be isolated from blood during viraemic stage, yet it has limitation as viraemic stage persists only for a short duration of 4-11 days and all possibilities are there to skip the window of opportunity [23], therefore, skin lesions are the best choice for virus isolation.

## Virus isolation and diagnostic relation

Earlier in 1900 alternative to original host the laboratory animals and embryonated eggs were used for isolation of virus. Isolation of virus in cell culture and further identification through transmission electron microscopy having highest credential. Initially isolation of Neethling strain of LSD was achieved in primary lamb and calf kidney cell culture. Several cell cultures derived from lambs, calves, rabbit, monkeys and hamster are reported to be susceptible for LSDV. Foetal bovine muscle and foetal bovine skin cells are equally susceptible for LSD but less sensitive than lamb testis cells [24]. Preferably bovine dermis cell lines are used for isolation showing typical CPE within 7-8 days of incubation [23]. LSDV is equally infective to Madin-Darby bovine kidney (MDBK) resulting multifocal areas of hyperplastic cells as characteristic CPE. In an outbreak study, all effort was made to isolate the virus in various cell cultures such as primary goat testis, primary goat kidney (PGK) and primary lamb testis with or without success. Out of all PGK cells were most sensitive with characteristic cytopathic effect (CPE) rounding ballooning and degeneration of cells, but PGT was refractile. Primary cell culture amplified virus was successfully adapted in Vero cell but isolation of field virus in Vero cell was too cumbersome until 3$^{rd}$ blind passages to adapt the virus in Vero cell with detectable CPE as mentioned in a recent literature [7]. Embryonated chicken egg and Vero cells are not suitable for primary isolation, however cell culture amplified virus can be adapted in these already mentioned in OIE manual [25].

## Antibody as diagnostic buddy

Detection of virus specific antibody in the serum/plasma substantiates the diagnostic conformity. Among the serological tests due to high sensitivity ELISA has been popularised for seroprevalence of LSD in endemic zone [26]. Available commercial ELISA kit marketed in the form of ID Screen® Capripox double antigen multi-species ELISA is the choice of few labs. As per lab reports this kit can detect antibodies against LSD, sheep pox and goat pox with specificity of 99.7% without showing cross reactivity with parapox viruses [26]. Alternative tests like virus neutralisation, immunoperoxidase monolayer assay [27] and indirect fluorescence antibody test also have diagnostic prominence for LSD. As per OIE manual serum/virus neutralisation test has been considered as gold standard test for disease diagnosis. Adaptation of virus and detection of cytopathic effect (CPE) in cell culture is the major limitation of the neutralization test. A recent literature has discussed about the use of several peptides, recombinant protein as well as inactivated whole virus as test antigen used by several workers in the ELISA format without declaring satisfactory validation data. In that report, author has implemented a new immunoperoxidase monolayer assay and have claimed to detect antibody at lower dilution (1:50) as well as in higher dilution (1:3500) much earlier than the application of virus neutralization test and ELISA procedure [27]. Due to specificity and sensitivity detection of virus specific nucleotide sequence using PCR technique is universally accepted

as bench-mark with legitimacy for the detection and differentiation of LSD from other members of capripox viruses. Further PCR based on PRO-30 gene provides swift differentiation between LSDV and sheep pox virus without error [28]. Confirmation of LSD through virus isolation may not always yield success yet *in vitro* adaptation of virus in various cell culture systems with or without showing cytopathic effect is one of the diagnostic protocols preferred by many workers [7].

### Histology as diagnostic biology

Virus isolation may not be always successful, but on histopathology intracytoplasmic eosinophilic inclusion bodies on epidermal cells represent the viral infection. Invariably hydropic degeneration of keratinocytes and infiltration of mononuclear cells in the subepidermal layer are commonly observed in tissue samples collected from LSD infected animals. Profuse infiltration of lymphocytes, plasma cells and macrophages but few neutrophils in the superficial and deep dermis was recorded in a recent report [5]. Very often presence of intracytoplasmic inclusion bodies (so-called sheep pox cells (SPCs) is observed whereas absent of such inclusion but acanthosis and orthokeratotic hyperkeratosis of skin nodules was prominent in their findings [5]. Case to case variation in histopathological lesions showing either proliferation of epidermis with ridge formation, and even necrosis of epidermis to a great extent in other cases are being reported. On immunoperoxidase staining golden-brown patchy area within cytoplasm of epidermal cells and prickle cells indicates the presence of viral antigen; considered to be more specific for LSD diagnosis [29].

### Insect source and disease course

Literature survey has identified blood feeding arthropod vectors is a major risk factor for transmission of LSD. Due to lack of evidence arthropod vectors are never been considered as amplifying host, rather act as mechanical vector is authenticated. It has been observed that majority of LSD outbreaks coincides with warm and humid climate when population density of insects is at high supports the above proposition. The seasonal pattern of spreading of disease with high incidence preferably during hot humid weather is already on record. Exact mode of disease transmission is poorly understood, yet human assisted animal movement escalates the disease dissemination has been suggested. The low incidence of LSD outbreaks during cold spell signifies the role of insect's population as insects` activity in cold is stalled. Weather restriction is not too absolute rather outbreaks during winter and dry season have been recorded from past to present [2]. Landmark climate report published in 2021 indicates that the earth`s global surface temperature has increased by around 1.1°C compared with the average in 1850-1900 [30], therefore it has been predicted that due to global warming, the microclimate of some regions is altering in favour of arthropod vectors thereby it is likely that the incidence of LSD will continue further. Several arthropod species including biting flies, midges, mosquitoes and ticks are found to be the vector for LSDV transmission. From late sixty the LSD virus was successfully isolated from *Stomoxys calcitrans* and *Biomyia fasciata* flies after induced feeding on infected cattle in experimental trial. Involvement of blood feeding insects such as mosquitoes and sand flies play prime role as mechanical carrier for virus transmission during viremia of animals to susceptible population has been verified [31]. An experimental finding has suggested that out of four insect's species (*Aedes aegypti*, *Culex quinquefasciatus*, *Stomoxys calcitrans* and *Culicoides nubeculosus*) all the species were able to collect virus from LSD infected animals at the same intensity but the virus was retained for a longer period up to 8 days in case of *Aedes aegypti* and *Stomoxys calcitrans*. Replication of virus inside the insects was not observed therefore the insects are considered to be mechanical transmitting agent rather than biological amplifier. Due to limited virus acquisition during preclinical stage the probability of virus transmission is relatively low as compare to clinical stage of the animals. The biological character of insects such as reproduction number also determines the incidence burden. Among all the four species the reproduction number was highest for *Stomoxys calcitrans*, followed by *Culicoides nubeculosus* and *Aedes aegypti,* so all these three species are considered as potential transmitting agents of LSDV [32]. Possibilities of contact mode of diseases distribution has not been ruled out but animal to animal contact is considered to be less effective as compare to arthropod mediated mechanical transfer of virus. Copious amount of virus in saliva and nasal secretion are rich source of infection through feed and water to other animals thus mass grazing facilitates the disease transmission due to proximity of animals and insect movement has already been reported [33]. Detection of LSD specific viral DNA in semen for nearly 5 months and isolation of live virus up to 42 days in some infected bull is considered to be a hidden source of disease dissemination remains unnoticed [34]. Presence of viral DNA in frozen semen samples through PCR has been recovered from the stockpiled samples retrieved from frozen semen bank. Out of 17 cryopreserved semen samples, 17% were positive for viral DNA.

The presence of viral DNA in semen correlated with clinical lesions in the affected bull in a recent outbreak in India. Possibly this is the first report of virus shedding in semen of naturally infected animals as suggested by the authors [6].

## Treatment

As of now any antiviral drug against LSD has not been formulated so no specific treatment is recommended, but to prevent secondary infection use of antibiotic with supportive therapy is suggested. The choice of antibiotics and supportive therapy may vary from case to case with judicial decision of the clinician. To reduce the respiratory distress in an experimentally produced case of LSD, intravenous administration of sulfatrimetoprim and phenylbutazone has been tried to save the animal. In a recent report use of gentamycin for 5 days and chlorpheniramine maleate for three consecutive days, along with meloxicam for two days was given to a calf to recover from the disease severity [35]. Although the disease appearance is sporadic yet a large mass of animals suffers at the same time for which mass treatment is a daunting task for clinicians. For resource poor countries treatment of animals is a costly subject. Medicinal cost compounded with visiting charges of clinicians along with maintenance of non-productive animal during illness and post recovery period is great financial burden to farmer. Test and cull policy is not applicable to many countries due to religious bias and prohibiting law of the land. Undoubtedly, reduction in occurrence of LSD is possible but eradication of disease in those countries where already incidence of disease has been reported is not practically feasible. Success depends upon the extent of vaccination coverage and the type of vaccine used in the susceptible species. Vaccination is the only alternative yet to vaccinate all the animals is beyond the scope for farmers due to low affordability, unless otherwise provided by the respective governments as free service to farmers.

## Vaccination for prevention

Vaccination is considered to be the most acceptable method for controlling LSD in endemic zone while non-endemic zone is not routinely covered. Infected animals should not be vaccinated or else there are all possibilities to develop recombination of vaccine and field strain virus [15]. Homologous vaccine is considered to be the best choice however heterologous vaccine derived from sheep pox and/or goat pox virus works well. Types of vaccine, whether live or inactivated vaccine to be used is mostly decided with regional approach, considering the gravity of the situation and assessing the risk of disease and availability of vaccine at that point of time. Usually, with quality vaccine the protecting antibody is mostly developed on 3rd week of vaccination so a window of opportunity for infection always remains open within that period. In this regard widely used live attenuated vaccine against LSD is Neethling strain of LSDV of South African origin [36]. After serially passaging 61 times in lamb kidney cell culture followed by 21 passaging in chicken embryo through chorioallantoic membrane Neethling strain of virus has been tamed down with sufficient reduction in its virulency [37]. In other reports it has been described that the above-mentioned cell culture adapted Neethling strain has been further propagated 10 times more on Madin Darby Bovine Kidney (MDBK) cells, followed by additional passaging five times in primary bovine testis cell culture arrangement for its attenuation [38]. Besides Neethling strain, one more pathogenic strain of LSDV isolated from Madagascar (Africa) has been modified in rabbit kidney by serial passaging up to 101 times subsequently five times propagation in foetal calf kidney cell culture has made it usable for vaccination against LSD [37]. Adaptation of virus either in homologous and/or heterologous cell culture system or unnatural host require adequate number of unceasing replication cycle to reduce its virulency to original host. The attenuated live vaccine strain can induce local skin reaction at the site of inoculation known as "Neethling response" due to local amplification of virus representing the viability and replication efficiency of vaccine virus. Experimental findings from European Union LSD reference laboratory (Sciensano in Belgium) have authenticated the efficacy of Neethling strain vaccine with satisfactory challenge results [39]. The extent of attenuation in Neethling strain vaccine induces protective immune-response but very often it can cause local reaction with minor adverse effect. In absence of homologous (LSDV strain) vaccine or during shortage of desired vaccine, heterologous vaccine (SPV and/or GTPV) are preferably used for mass vaccination due to antigenic sharing among capripox viruses. In several reports it has been observed that both GTPV based vaccine and LSDV vaccine are equally protective against lumpy skin disease [40]. Within homologous vaccination regime, in several occasions the Kenyan sheep pox and goat pox (KSGP O/240) strain has been used to protect sheep pox and goat pox in respective species in East Africa. The KSGP0/240 virus isolated from sheep and goat from Kenya has been attenuated by propagating the virus in bovine foetal muscle cells cultures up to 20th passage level; virus at 18th passage level has been used as safe vaccine for cattle against LSD [38]. Another

pox virus the KSGP-180 strain after 18-time serial propagation in muscle cells was made to diminish its virulence, however further detail is not mentioned by the author [38]. The KSGP O/240 vaccine is safe for *Bos indicus* but occasionally cause mild generalised reaction in *Bos taurus* breeds [41]. Many a time the KSGP vaccine strain was found to be the genuine offender for clinical illness in the vaccinated animal [42]. Recently in 2019 a virulent LSD virus (LSDV/*Bos taurus*-tc/India/2019/Ranchi) isolated from an outbreak in Ranchi (India) has been adapted in Vero cell culture for vaccine preparation [7]. Further serial passaging of Ranchi strain in the virus has lost its virulency and its safety and potency have been tested at 50th passage level in laboratory setting. Afterwards, in August 2022 this cell culture adapted virus (LSDV/*Bos taurus*-tc/India/2019/Ranchi) has been released as live attenuated vaccine for emergency use against lumpy skin disease by Indian Council of Agricultural Research in the name of Lumpi-ProVac[Ind] to control the on-going outbreaks of LSD in India as per media report [43]. Relevant information about LSD vaccines produced by different manufacturers have been retrieved from the respective web sites up to 3rd September 2022 for compilation (Table 1). In summary all these vaccines are cell culture adapted live attenuated vaccine derived either from Neethling strain and/or field isolates of LSD; or capripox (sheep/goat) virus.

| Name of product | Virus strain | Virus titter | Species | Dose | Manufactured by |
|---|---|---|---|---|---|
| Lumpy skin disease vaccine | Neethling strain | Not mentioned | Cattle | 2ml S/C | Onderstepoort Biological Products (OBP)<br><br>South Africa |
| Lumpyvax | Neethling strain | $10^4$ TCID $_{50}$ | Cattle | 1ml S/C | Intervet (Pty) South Africa/MSD Animal Health |
| Bovivax LSD | Neethling strain | $10^{3.5}$ TCID $_{50}$ | Cattle | 2ml S/C | MCI Santé Animale Morocco |
| Lumpy Shield N | Neethling strain | $10^4$ TCID $_{50}$ | Cattle | 1ml S/C | Jordan Bio-Industries Center (JOVAC)<br><br>Jordan |
| MEVAC LSD | Neethling strain | Not mentioned | Cattle | 1ml S/C | Middle East for Vaccines (MEVAC)<br><br>Egypt |
| Lumpy skin disease vaccine | Capripox vaccine | $10^3$ TCID $_{50}$ | Cattle | 2ml S/C | National Veterinary Institute (NVI)<br><br>Ethiopia |
| Lumpivax TM | Neethling strain | Not mentioned | Cattle | 2ml S/C | Kenya Veterinary Vaccines Production<br><br>Institute (KEVEVAPI |
| Lumpivac | Neethling strain | $10^{3.5}$ TCID $_{50}$ | Cattle | 2ml S/C | Vetal animal health product Turkey |
| Lumpy Doll | KSGP 0240 | $10^{3.5}$ TCID $_{50}$ | Cattle | 1ml S/C | Dolvet Turkey |
| Pox doll | SPV BK<br><br>(SPV Bakirkoy strain) | $10^{2.5}$ DKID $_{50}$ | Cattle | 3ml S/C | Dolvet Turkey |
| Lumpi-ProVac* | LSD (LSDV/*Bostaurus*-tc/India/2019/Ranchi strain) Vero cell adapted at 50th passage | $10^{3.5}$ TCID $_{50}$ | Cattle | 3ml S/C | Released on August 2022 by Indian Council of Agricultural Research – New Delhi. India |

# Retrieved from Product catalogue and manufacturers website assessed on 3rd September 2022

* Experimental vaccine for emergency used not for sale (compiled information as available on the product literature)

**Table 1:** Commonly available vaccine against LSD produced by different manufacturers[#].

In absence of live attenuated vaccine inactivated vaccines are used to prevent infectious disease is common practice. In this regard at one point of time due to lack of attenuated live goat pox vaccine, cell culture adapted pathogenic goat pox virus with adequate inactivation has been tested for its emergency use [44]. The small pox vaccine generally induces strong immune response that persists for a longer duration up to decades but same is not true for LSD vaccine, therefore annual vaccination is recommended. Several reports of vaccine breakdown with LSD vaccine, has been reported but the reason may not be always linked with vaccine efficacy. Reinfection in vaccinated animals and morbidity with mortality in fully vaccinated herd in Ethiopia has raised doubt about the efficacy of LSD vaccines so currently the efficacy of available LSD Vaccine is not too clear.

### Vaccine type and immunity hype

No matter whatever quality vaccines used in field, all the animals may not respond equally yet near about 80% protection was observed during mass vaccination, whereas assessment of individual immune-response may yield unrealistic scenario [37]. In a candid experimental finding immunereponse against two different capripox virus vaccines (Romanian strain and Gorgan strain) was equally detectable with similar magnitude in Holsten calves as early as one weak of post immunization. Detectable CMI response quantified with lymphocyte stimulation index and IL-4 cytokine level was at escalated level up to 3rd weeks of post immunization in both the vaccinated groups. Comparatively goat pox vaccine strain was better inducer of INFγ than sheep pox vaccinated group [45]. In a comparative study live attenuated Neethling strain was found to be more protective with higher serum neutralization titre over live sheep pox vaccine against LSD. At 21days of post immunization the humoral immune-response detected through ELISA Kit was in favour of homologous vaccine rather than heterologous sheep pox vaccine strain [46]. The LSD specific antibody in post vaccinated animal never persists more than 40 weeks. Repeated vaccinations of cows with LSD vaccine have shown persisting antibody up to 46-47 weeks detectable through VNT, IFAT and ELISA test. Passive transfer of antibody from mother to offspring was detectable at 14 days post birth [47]. In one of the experimental trial due to colostrum feeding LSD specific neutralizing antibodies were detected up to 3 months of age in 16 out of 18 calves (nearly 89%) born to cows immunized with Neethling strain of vaccine, subsequently, maternal antibodies declined despondently to an undetectable level at 5 months age [48]. For quality assessment of LSD vaccines in a designed experiment, five different LSD vaccines viz. (1) Lumpy Skin Disease Vaccine (Onderstepoort Biological Products OBP; South-Africa) (2) Lumpyvax (MSD-Animal Health; South-Africa) (3) Kenyavac (Jordan Bioindustries Center Jovac; Jordan) (4) Herbivac LS (Deltamune; South-Africa) (5) Vaccine LSD Neethling O vivant (MCI Santé Animale; Morocco) have been used to probe the extent of seroconversion in the recipient animal groups. The onset of seroconversion detected through immunoperoxidase monolayer assay varies between 6 (OBP) to 13 (Herbivac) among different vaccine groups. At 3rd week of post vaccination, the seroconversion rate varies from 71% to 100% but the difference was statistically insignificant, whereas complete seroconversion was never observed within any of the vaccine groups during the trial period [39]. Many a time the heterologous vaccine used to protect LSD may not yield seropositivity in vaccinated animal, yet protection level is found to be satisfactory, possible role of CMI is projected [49]. It has also been observed that immunomodulatory substance given in systemic route can activate ovine neutrophil without inducing virus specific neutralising antibody thereby to a certain extent it can protect against sheep pox in absence of humoral immuneresponse [50]. A blended vaccine comprising of contagious bovine pleuropneumonia (CBPP) and LSD as well as monovalent vaccine has been given to animal in one shot to detect what extent and how early these vaccines can induce detectable immuneresponse against each of the antigenic component in bovine model. According to their findings LSD specific neutralizing antibodies were detectable as early as day 7 of post vaccination in combined vaccine groups while initiation of immune response was delayed up to 14 days in case of monovalent vaccine. On the other hand, due to antigenic exposure for a longer duration after 35 days of post vaccination the seroconversion was 100% for monovalent LSD vaccine and 90% for combined vaccine. It could be concluded that combined vaccine of LSD/CBPP as well as monovalent vaccine are equally immunogenic without interfering in immune-response to each of the antigenic components [51]. As LSD and rift valley fever is more prevalent in African countries, therefore in a novel approach LSD virus-vectored recombinant rift valley fever vaccine was evaluated in cattle with end result indicated the vaccine to be immunogenic and equally protective against both the diseases. In the experiment proper all the five animals were found to be seropositive for LSD on day 17 of post vaccination and two out five exhibited virus neutralising antibody as early as day 11 of immunization [52]. As on date whatever vaccines are available (either live or inactivated)

for protecting cattle from LSD none of them is marker assisted and can't differentiate infected from vaccinated animals. Due to availability of several heterologous and homologous vaccines with variable efficacy, as of now no consensus has been developed amongst researchers for use of any specific vaccine or uniform vaccination strategy against LSD.

### Import restriction for disease suppression

As per OIE the LSD should be declared when any of these is detected: (i) animal is showing clinical symptoms (ii) LSD specific antibody is detected in animals (iii) virus is isolated from samples or virus specific nucleic acid is detected in sample. Incubation period is 28 days to be considered for LSD as precautionary measure. For importing animal origin products like meat, gelatine, collagen, tallows, hooves and horns no special care is needed to detect LSD from these commodities of products. Import should be banned on semen, embryos and milk from infected country when active cases are reported and once the disease subsides the import should be initiated as per the guidelines of OIE [53].

## Conclusion

Among viral diseases of cattle, lumpy skin disease is a neglected nasty disease caused by pox group of viruses. The disease appears sporadically and mostly remain restricted in African countries however, it has crossed the boundaries and has caused devastation in Asian countries including India, Bangladesh, Nepal and Bhutan. The disease is mechanically transmitted through blood feeding insects. The disease is characterised by typical firm raised skin nodules spread throughout the body including genitalia. Invariably pyrexia, viremia and inappetence are most commonly observed as associated clinical signs of infected animals. The disease mortality is low yet large number of animals suffers at a time. The disease is self-limiting and not a zoonotic disease. The causative agent is relatively thermostable virus and remain viable in the dried scab for a quite long period and the major source of infection to other animals. No specific treatment is recommended except antibiotic therapy to prevent secondary infection of skin nodules. Several live attenuated live vaccines are commercially available for mass vaccination. Recently a cell culture adapted live attenuated vaccine derived from Indian isolates has been released by Government of India for emergency use. Insect control is not practically feasible. Restriction on animal movement from affected region to disease free location along with import ban from countries with active cases are two major guidelines to reduce the disease occurrence. No uniform policy or guidelines can be formulated for the use of any specific vaccine or vaccination strategy against LSD as situation differs enormously from one country to another. Unless free service is provided, treatment cost and maintenance of animal with low productivity during illness as well as post recovery period is great financial burden for resource poor farmers. Control of arthropod may reduce the disease spread yet complete eradication is practically not feasible for many countries. To save the cattle we have to face the battle with scientific approach.

## Conflict of Interest

The authors declare no conflict of interest, financial or otherwise.

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