Emergence and transboundary spread of lumpy skin disease in South Asia

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ABSTRACT

Lumpy skin disease (LSD) is an OIE notifiable, transboundary pox viral disease of livestock. LSD is an emerging disease severely affecting livestock economics. The zoonotic potential of the LSD virus has not been extensively studied and reported. In approximately 90 years, the virus dispersed to numerous world locations after its first emergence in Zambia. LSD virus emergence in South Asia prevailed among livestock (cattle and water buffalo) owners due to economic/financial losses. The estimate of the economic impact of LSD in the southern, eastern and southeastern countries suggested direct losses of livestock and production of approximately USD 1.45 billion. In 2019, nearly the same time, the disease was reported for the first time from many bordering countries, such as India, Nepal, China, and Bangladesh. In 2020, the LSD was also recorded in Bhutan, Sri Lanka, Bangladesh, Vietnam and Southeast China. In 2021, it further spread to new countries such as Thailand, Malaysia and Cambodia. Cattle affected with LSD show a characteristic nodular lesion or skin lump over the whole body and may occasionally be associated with systemic signs. Hematophagous arthropod-borne mechanical transmission is considered primary and the most common route; however, other transmission routes related to illegal animal trade have played a role in the emergence of LSD in countries otherwise/earlier free from it. Among serological diagnostic tests, OIE recommends virus neutralization as the standard gold test. Diagnosis in LSD-free countries requires virus isolation and further sequencing of the isolate. Control of LSD is possible by most of the measures applied for rapidly transmitting viral infection, including vaccination. LSD virus-specific vaccines are considered suitable to confer protection to cattle and buffalo over heterologous vaccines. In countries such as India, the lack of a specific policy for LSD at the time of the first onset of this disease, the high density of susceptible unvaccinated populations, unawareness among farmers, veterinarians and prevailing laws of no slaughter of cattle created a favourable situation of its spread to many states. Amid COVID-19, the whole world is in turmoil; the emergence of diseases such as LSD is further lowering the economy, and hence must be reviewed to save and sustain the backbone of the developing country's economy in Southeast Asia.

Keywords: Asia, Bovine, Emergence, India, LSD, Vector

Lumpy skin disease (LSD) is an Office International des Epizooties (OIE) notifiable poxviral disease of livestock. LSD is also called knopvelsiekte, pseudourticaria, exanthema nodularis bovis and Neethling virus disease (Abutarbush 2017, CFSPH 2008, MacDonald 1931). In developing tropical countries of South-Asia, most farmers belong to marginal and small categories and rear livestock for an additional sustainable source of income. Furthermore, milk, as well as dung fuel obtained from livestock and draughts, contributes to the health and prosperity of farmers. The livestock sector plays a crucial role in curtailing poverty, enhancing resilience, and withstanding food insecurity and malnutrition (Enahoro *et al.* 2019). LSD virus emergence in South Asian countries has prevailed a concern amongst livestock owners due to production losses, loss of draught power, reduced feed intake, disease management, trade restriction, and long-term convalescence.

LSD is mainly limited to cattle and buffaloes. Animals affected with LSD show a characteristic nodular lesion or skin lump over the whole body and may occasionally be associated with systemic signs (Gupta *et al.* 2020). In a short span of approximately 90 years, the virus dispersed in numerous world locations after its first emergence in Zambia, Africa, in 1929 (MacDonald 1931). The spread to new countries free from this disease has been relatively rapid. The first report of LSD from the Middle East came in 1988 from Egypt and in 2005 from Bahrain and remained restricted to Middle East countries (Western Asia) until 2018 (OIE 2021, Stram *et al.* 2008). Later, the LSD virus was reported from South Asian countries such as China, Bangladesh, India and Nepal in 2019 (Hasib *et al.* 2021,

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OIE 2021). In India, the first outbreak of LSD was recorded in Odisha and later swept many states of the country within its grip (EFSA *et al.* 2020). In 2020, the LSD was recorded in India, Nepal, Sri Lanka, Bhutan, Bangladesh, Vietnam, and Southeast China (Acharya and Subedi 2020, Roche *et al.* 2020, Tran *et al.* 2021). In 2021, LSD spread further and was recorded for the first time in Malaysia, Thailand and Cambodia (OIE 2021). India has the most extensive inventory of cattle globally and cattle are considered the most susceptible animal to the LSD virus. Until 2019, the LSD virus was not present in this region and, therefore, did not have any government control plan or contingency for LSD. India has specific laws that restrict cattle slaughter, unawareness about this disease among stakeholders and no vaccination policy against LSD. With this background, there was a need to review this disease more precisely concerning its emergence in recent times and possible strategies.

LSD virus

The LSD virus belongs to the genus Capripox, subfamily Chordopoxvirinae (poxviruses of vertebrates) within the family Poxviridae. LSD virus is an enveloped double-stranded DNA virus that has a genome of approximately 151-kilobase pairs (Kbps) with a central coding region of 156 putative genes (Tulman *et al.* 2001). LSD virus shares antigenic similarity with sheeppox virus (SPPV) and goatpox virus (GTPV), causing devastating disease in sheep and goats, respectively (Abutarbush and Tuppurainen 2018). Genomic analysis revealed 98% sequence similarity between all 3 species of Capripoxviruses (CaPVs) (Gershon 1988, Tulman *et al.* 2002). Genomic similarity provides an opportunity to use GTPV and SPPV vaccines as prophylaxis to control this disease where the LSD vaccine is not licensed to practice. SPPV and GTPV strains can cause infection in sheep and goats, respectively, both experimentally and naturally.

On the other hand, with the LSD virus, the host sheep and goat can only be experimentally infected, underscoring the LSD virus to be host-specific and restricted (El-Kenawy and El-Tholoth 2010). The virus is considered stable for long periods and can endure in contaminated animal sheds, especially when devoid of sunlight. Likewise, steady persistence of the LSD virus has been recorded in dried scabs, necrotic skin nodules and desiccated crusts for almost up to a month or more at ambient temperature. For chemical control measures, the virus was susceptible to ether (20%), chloroform, formalin (1%), phenol (2% for 15 min), sodium hypochlorite (2–3%), iodine compounds (1:33 dilution) and quaternary ammonium compounds (0.5%). In contrast, the virus was remarkably stable, surviving for longer periods at ambient temperature (OIE 2013).

Disease emergence in India and South Asian countries

LSD is presently endemic in most African countries, a few Middle East countries and Turkey. The LSD outbreak timeline and its spread (Fig. 1) have been recently reviewed (Kayesh *et al.* 2020). LSD was identified for the first time

in Zambia in 1929 (MacDonald 1931). After that, Kenya reported the LSD prevalence at a farm concurrently with the SPPV outbreak (Burdin 1959). Outside of Africa, Israel documented the outbreak of LSD in 1989 (Zeynalova *et al.* 2016), reaching Egypt, which is considered a country linking northeast Africa with the Middle East, where the disease was first reported in 1988 (House *et al.* 1990). The outbreak season of LSD is in the summer and autumn, a favourable breeding time of vectors and is usually indicated to halt in the winter (EFSA *et al.* 2020).

Nonetheless, reports of an outbreak in June, July, October and November in 2015 from Azerbaijan (OIE 2013) and recent appearance from India in August 2019 and unconfirmed cases reported during most months from different parts of India, in July to December from Bangladesh, June to September in Nepal indicated that LSD may initiate as the outbreak in the newer area during the hot and humid period of the year. Nevertheless, after that, it spreads irrespective of the season. The chronology of disease outbreaks in China, Bangladesh, India, and recent reports from Nepal, Bhutan, Malaysia, suggested possible transboundary spread (Burdin 1959, Acharya and Subedi 2020, EFSA. *et al.* 2020, Roche *et al.* 2020). The disease spread may be equitable to an unofficial animal movement for trade and trafficking or transmitted by vectors from outbreak areas. In agreement, the LSD outbreak in Nepal has possibly been implicated due to informal crossborder movements of cattle from India bordering districts such as Bihar to Nepal (Acharya and Subedi 2020). However, to date, official confirmation of the LSD outbreak in Bihar has not been documented. Recent outbreaks in India have been ascertained by Odisha and Jharkhand (Kumar *et al.* 2021a, Sudhakar *et al.* 2020). In addition, numerous unconfirmed cases of LSD have been suspected from 14 states of India (Vora and Kulkarni 2020, Kumar *et al.* 2021a). In general, LSD has been documented to have high morbidity (2–45%) and low mortality (10%) (Tuppurainen *et al.* 2017a). In Odisha, the LSD morbidity was reported to be 7.1% with no mortality (Sudhakar *et al.* 2020). The LSD outbreak in China reports 6.6–100% morbidity and 0–16.7% mortality in 2 independent outbreaks (Lu *et al.* 2020). Similarly, in Bangladesh, the morbidity of LSD ranged from 0.01 to 8.26%, with a mortality of 1.0–2.0% (Kayesh *et al.* 2020).

Susceptible host

Primarily, cattle are the natural host for the LSD virus (Tuppurainen *et al.* 2015). Higher host specificity of the LSD virus prevents the virus from producing clinical disease in domesticated species such as sheep, goats, pigs and horses. However, other domestic animals, such as water buffaloes and yaks, may also be affected (USDA 2016). Asian water buffaloes (*Bubalus bubalis*) are recounted to have limited susceptibility to LSD; nevertheless, few clinical cases have been reported (Neamat-Allah and Mahmoud 2019). No correlation was recorded in the prevalence of LSD in cattle concerning age and sex (Elhaig
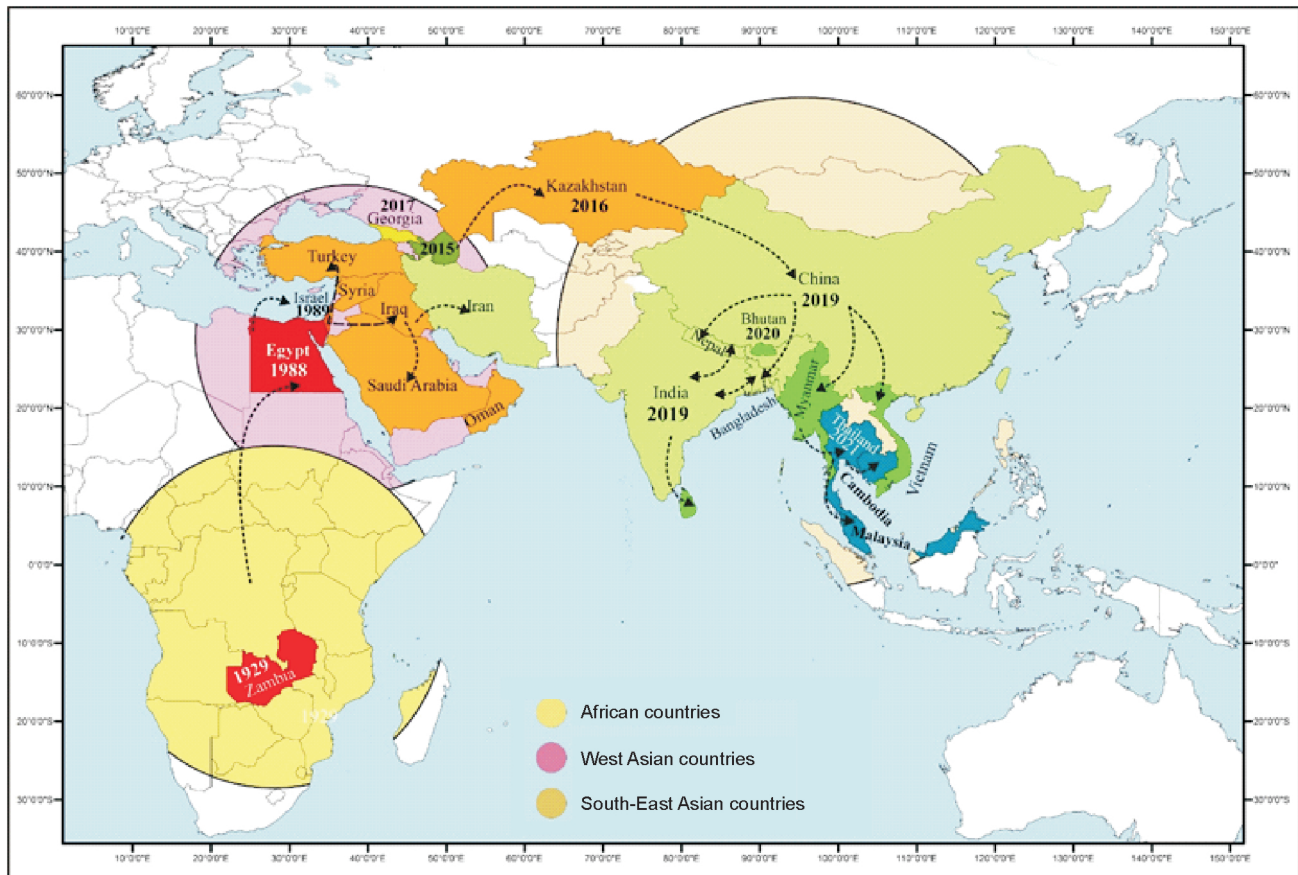
Fig. 1. LSD disease reporting from various countries year wise. Red indicates important milestone countries (Zambia in Africa and Egypt, Israel for Asian countries)**.** The most recent reports from Malaysia, Cambodia and Thailand in 2021 are marked in dark blue. Arrows indicate a possible path followed by the LSD virus. Source: OIE. World Animal Health Information Database World Organization for Animal Health (2021).

et al. 2017); however, differences are reported on breed type. Exotic and crossbred cattle are comparatively more susceptible than indigenous cattle and buffaloes (Kiplagat *et al*. 2020). Young calves (early age group), lactating cows, and malnourished animals appear to naturally acquire more severe disease (Carn 1995, Mulatu and Feyisa 2018). It may be due to impaired humoral immunity. In addition, Kenyan African buffalo (*Synercus caffer*) may act as reservoir hosts. Infected buffaloes had no clinical signs of LSD, but the antibody titre for the virus was detected (Davies 1991, Gibbs 2013).

Clinical LSD has been reported to be acquired by a few wildlife species, including an Arabian oryx (*Oryx leucoryx*) and springbok (*Antidorcas marsupialis*), experimental infection in impala (*Aepyceros melampus*) and giraffe (*Giraffa camelopardalis*) (Tuppurainen *et al*. 2018) and Thomson's gazelle (*Eudorcas thomsonii*) (Davies 1991). Additionally, blue wildebeest (*Connochaetes taurinus*), black wildebeest (*Connochaetes gnou*), springbok, and eland (*Taurotragus oryx*) and African buffalo (*Syncerus caffer*) tested positive for LSD antibodies in South Africa. The possible role of wildlife in disease epidemiology is still unknown due to incomplete access to the wild population for clinical examination, diagnosis and monitoring.

To date, LSD virus zoonotic potential has not been reported by OIE. In contrast, Kamal reported sporadic and anthroponotic transmission of the LSD virus to humans following the widespread outbreak of LSD in cattle in Cairo and Egypt during 2018–2019 (Kamal 2019). The report suggested that the LSD virus can infect humans probably by inhalation and by direct contact with fomites, infected persons, and an occupational hazard. In humans, the symptoms are similar to the formation of skin nodules but do not resemble an abscess on limbs in cattle and may sometimes lead to death. LSD virus infection is associated with herpesvirus infection in humans and cattle (Kamal 2019). Infection with herpesvirus infection in humans may act as a helpful factor for poxvirus disease.

Disease transmission

LSD is a transboundary disease. LSD virus detection in India and neighboring countries where this disease was nonexistent signifies the importance of comprehending its transmission mode. LSD virus-like poxvirus can be transmitted by both direct and indirect means from an infected host (Fig. 2). LSD virus epidemiology and possible routes of transmission have been reported by Carn and Kitching (Carn 1995) and elegantly reviewed by Sprygin and coworkers (Sprygin *et al*. 2019).
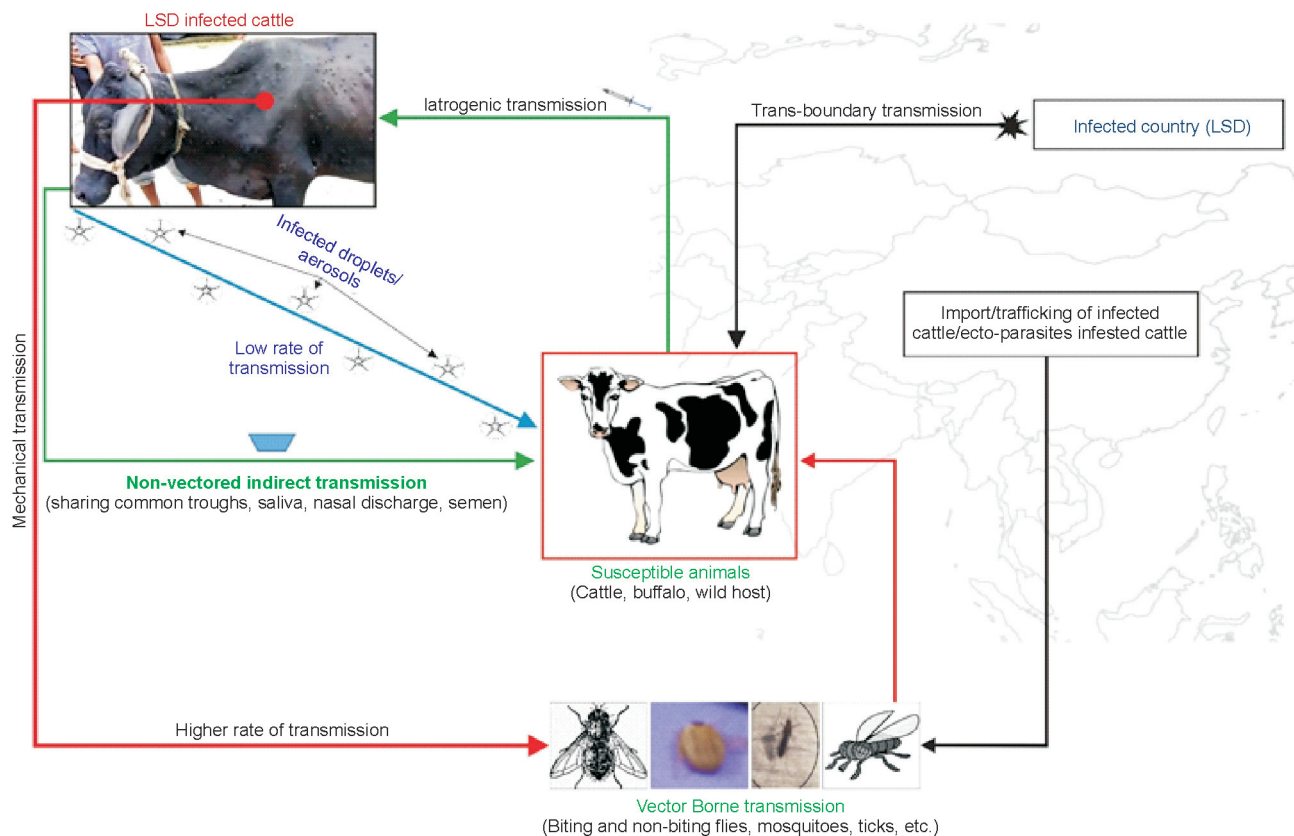
Fig. 2. LSD virus and its routes of transmission in susceptible cattle. Redline: Vector (*Stomoxys calcitrans* (Sandfly), mosquitoes, ticks, house fly, fleas, etc.) borne transmission (possible within the country and transboundary); Green line: non-vector borne transmission (including iatrogenic); Blue line. Droplet or aerosol; Blackline. Possible routes of transboundary spread of the virus.

The current COVID-19 pandemic, along with climate change, has brought unprecedented transformations in biodiversity and ecosystem patterns. Such transformation has contributed to the flaring up of the vectors and their associated emerging diseases. Hematophagous arthropod-borne mechanical transmission is considered the significant and common mode for LSD transmission; however, experimental evidence of disease transmission is restricted (Sohier *et al*. 2019, Weiss 1968). Ixodid ticks (*Rhipicephalus decoloratus*) can transmit this virus by trans-stadial and transovarial routes, while *Rhipicephalus appendiculatus* and *Amblyomma hebraeum* transmit the virus mechanically (Lubinga *et al*. 2014, Tuppurainen *et al*. 2011). Vector-borne transmission may also cause LSD infection in the same cattle and be complicated with other hemoparasitic conditions. The Indian cattle population suffers from tick-transmitted hemoparasitic infection (Kumari *et al*. 2019, Roy 2021) and is sometimes mixed infected (Kumar *et al*. 2021b). Recent reports provide experimental evidence of LSD virus mechanical transmission by *Stomoxys calcitrans* and *Haematopota* spp. in bulls (Sohier *et al*. 2019). Despite the complete restriction of animal movement, the spread of the LSD virus in Israel from Egypt proposes the likelihood of aerial transmission by the associated vectors (CFSPH 2008). Infected vectors can travel and transfer this virus in the range of approximately 300 kilometres (Australia 2009). LSD virus

was also reported to be transmitted by the intrauterine route (Rouby and Aboulsoud 2016). Calves have been delivered with skin lesions by LSD-infected pregnant cows. Secretions (blood, nasal and lachrymal secretions, semen and saliva) from the infected animal may act as the source of transmission.

Similarly, ulcerated LSD virus nodules on the mucous membranes of the eyes, nose, mouth, rectum, udder and genitalia are also an important source of transmission (Babiuk *et al*. 2008). LSD-infected bulls exhibiting clinical signs can ejaculate virus in semen for up to 22 days and at least 12 days in bulls with subclinical infection (Weiss 1968). Seminal transfer of LSD and artificial insemination are conceivable biosecurity risks (Annandale *et al*. 2014). Intravenous and intradermal routes of virus transmission have been demonstrated (Carn 1995). The probable occurrence of iatrogenic intra- or inter-herd transmission via contaminated needles during vaccination or other injections due to using the same needles between animals or herds is another known means of transmission of LSD (Tuppurainen *et al*. 2017b). The role of wild and migrating birds in mechanical transmission has been speculated, but no evidence has been documented.

Vector associated co-infections.

The mechanical transmission of the LSD virus by the vectors is considered the primary route of LSD spread.

However, it may also result in the transmission of other associated pathogens with these vectors. Coinfection can complicate the clinical condition and the eventual consequence of the disease. Ticks and flies are the primary vectors for the transmission of hemoparasitic diseases. This may result in the possibility of coinfection of LSD virus and hemoparasites, especially in tropical and subtropical countries. In Iraq, cows infected with the LSD virus have been reported to have mixed infections (babesiosis, theileriosis and anaplasmosis) of blood parasites (Jameel 2016). The available literature and analysis on vector-associated transmission of other pathogens as coinfections are limited. Further research is required to provide insight into the possible role of the immunocompromised state of hosts coinfected with hemoparasites and the clinical manifestation of LSD. Coinfection may also prolong the disease course, case fatality rate and production losses.

Pathogenesis and clinical findings

Arthropod vectors during feeding on host inoculate LSD virus into the skin of the animal. The virus then enters the bloodstream of the susceptible host. Tropism of LSD virus for keratinocytes causes hyperplasia and ballooning degeneration of the epithelium (Coetzer 2004). The OIE Terrestrial Animal Health Code gives a maximum incubation period of 28 days for regulatory purposes. However, experimentally, the virus has a shorter incubation period of 5 days (Woods 1990), and in the natural infection, the incubation period of this virus ranges between 4 and 28 days (Barnard *et al*. 1994). Susceptible animals of all age groups can become infected, and cases are expected in immunocompromised animals and young age groups.

The first clinical sign observed postincubation in cattle is high fever (103–106°F). Fever is observed for 1–3 days, or it may persist for a more extended period when coinfected with other tick-transmitted pathogens. The febrile phase may accompany symptoms such as lacrimation, nasal discharge, anorexia, reduced milk production, and apathy to the surroundings. These manifested signs result from the inflammation of different tissues by viremia in infected animals (El-Mandrawy and Alam 2018). It accompanies or follows the spontaneous eruption of skin nodules. Skin nodules up to 5 cm may initiate as localized forms at the head, neck, perineum, legs, udder, or be generalized, enclosing the whole body. These skin nodules are circumscribed, firm, round and raised and involve the skin, subcutaneous tissue and occasionally even the underlying muscles (OIE 2013). Experimental inoculation of LSD virus suspension by both intravenous and intradermal routes in calves resulted in the development of a firm, well-circumscribed, raised cutaneous nodule at each inoculation site that was approximately 4–8 cm in diameter by 7 days postinoculation and moderately to markedly enlarged prescapular lymph nodes at 5 days postinoculation (Sanz-Bernardo *et al*. 2020). Experimental infection in calves exhibited a febrile response 7–9 days postinoculation. In 2–3 weeks, large nodules on the affected animal skin may become necrotic (*sitfast*) and eventually fibrotic. These fibrotic marks may persist for several months or disappear with time (OIE 2019). Typical ring-like lesions may develop on the muzzle in the nares and the oropharynx, enlarging regional lymph nodes (Davies 1991). Myiasis and mastitis are reported to be associated complications of LSD in some infected cattle (Al Salihi and Hassan 2015). In the acute phase of LSD virus infection in pregnant cattle, there are reports of abortion with LSD skin lesions (Brenner *et al*. 2006). Infected bulls and cows may become permanently or temporarily infertile (Sohier *et al*. 2019, Tuppurainen and Oura 2012). Nasal discharge and inflammation of the lung may result in pneumonia. Extensive lesions of LSD and swelling of the limb may cause the animal to exhibit signs of lameness. LSD-infected cattle may show characteristic clinical signs, which are very useful in suspecting the disease. However, LSD-infected water buffaloes may not show any clinical symptoms due to limited susceptibility to the LSD virus (Mulatu and Feyisa 2018). Even susceptible cattle infected with the LSD virus may not show any clinical signs.

LSD virus is reported to cause major vascular changes in skin lesions, including vasculitis, by histopathological assessment in natural and experimental infections (Prozesky and Barnard 1982, Tageldin *et al*. 2014, Sanz-Bernardo *et al*. 2020). These modifications are reported only in the CaPV family, not in other poxviruses. Postmortem findings may reveal vesicles, erosions, ulcers in the mucous membranes of the mouth, abomasum, trachea and lungs. Throughout the internal organs, lung congestion and nodules were observed during necropsies carried out in 33 dead cattle of Azerbaijan (Zeynalova *et al*. 2016).

Diagnosis

The presumptive diagnosis of LSD can be banked to a large extent based on characteristic skin lesions and associated clinical signs. However, clinical-based diagnosis has a limitation in mild and asymptomatic disease, which requires laboratory methods for confirmation. Confirmation requires molecular and serological testing apart from virus isolation. Confirmation is also needed to differentiate LSD from other diseases of similar clinical signs, such as pseudolumpy skin disease, bovine papular stomatitis, pseudopox, foot and mouth disease demodicosis, tick bites, insect bites, photosensitization, urticaria, and other dermal disorders (Gupta *et al*. 2020, OIE 2013).

OIE recommends virus neutralization as the standard gold test among serological diagnostic tests, although the technique is labour intensive and time consuming (Krešiæ *et al*. 2020). Kresic and coworkers (Krešiæ *et al*. 2020) reported a modified virus neutralization test by employing Madin-Darby bovine kidney (MDBK) cells. They were suitable for detecting LSD virus-specific neutralizing antibodies and strongly correlated with the results obtained from commercial ELISA. Serological assays are recommended as convenient methods to investigate relatively recent outbreaks. Virus isolation can be performed

from blood, scab, skin nodules, and biopsy skin tissues (Kumar *et al*. 2021a). Virus isolation is required for confirmation of LSD diagnosis. It is a sensitive and reliable diagnostic test but requires a lengthy procedure to obtain the results (Tuppurainen *et al*. 2005).

Molecular techniques based on PCR and quantitative real-time methods have been described as faster and more sensitive, and the virus could be detected for a longer period (Tuppurainen *et al*. 2005, Balinsky *et al*. 2008, Kumar *et al*. 2021a). Detection by PCR is based on primers targeted to similar sequences found in sheep pox and LSD viruses due to the highly conserved nature of its genomic sequence of the capripox virus genome (Kara *et al*. 2003, Tuppurainen *et al*. 2005). PCR has been documented to detect viral nucleic acids in skin lesions 53 days longer than virus isolation (Tuppurainen *et al*. 2005). Phylogenetic analysis of the LSD virus was performed to determine the phenetic relationship with other isolates and CaPVs. However, such relationship analysis requires sequencing of the amplification product of PCR (Ochwo *et al*. 2020, Kumar *et al*. 2021a). A published study on phylogenetic analyses of circulating Indian LSD virus strains from Odisha and Jharkhand states suggested the highest similarity to Kenyan LSD virus strains (Kumar *et al*. 2021a, Sudhakar *et al*. 2020).

Nucleic acid sequencing has shown that nearly all CaPVs can be grouped according to their host origins (Le Goff *et al*. 2009). LSD virus genes targeted for PCR amplification include the one that encodes the G-protein-coupled chemokine receptor (GPCR), ankyrin repeat (ANK), RNA polymerase subunit (RPO30), and envelope protein p32 (Ireland, 1998, Kumar *et al*. 2021a, Mafirakureva *et al*. 2017, Salnikov *et al*. 2018, Stram *et al*. 2008, Sudhakar *et al*. 2020).

Treatment

There is no specific treatment to prevent and eliminate the LSD virus. Extensively, the treatment provided to the affected animals is supportive and aims to reduce the severity of virus pathogenesis and secondary complications associated with the disease (Al-Salihi 2014). The use of antiparasitic drugs and supportive therapies is justified based on reports of coinfection of hemoparasite (Jameel 2016). Supportive treatment aims to restore appetite by reducing inflammation, associated pain, and fever (Capstick *et al*. 1959). The use of anti-inflammatory and antipyretic drugs and antibiotics to prevent secondary bacterial complications has been reported (Woods 1988, Abdulqa *et al*. 2016). A common complication associated with LSD, which requires veterinary attention, is skin wound-associated myiasis, mastitis, pneumonia, lameness, corneal opacity, and coinfection with hemoparasitic diseases (Salib and Osman 2011). Combination therapy of dexamethasone (0.2 mg/kg/day) for 3 consecutive days and 10% oxytetracycline (10 mg/kg/day) for 5 successive days showed beneficial effects in LSD-infected bulls (Feyisa 2018, Biswas *et al*. 2020). In Ethiopia, a survey analysis of

LSD diagnosis and medication per affected animal costs USD 5 (Molla *et al*. 2017).

Economic impact of LSD

Diseases associated with CaPVs (GTPV, SPPV and LSD virus) are of considerable economic significance. LSD is characterized by high morbidity and low mortality. LSD has vast implications for livestock production and economics with its spread to new geographical areas. The losses are direct and indirect, depending on the farmer or the local/central government agencies. Direct losses to farmers may include milk reduction, abortion, diminished body growth, mortality, hidden damage, etc. Indirect losses may consider losses to farmers due to loss of opportunity, decreased lifetime productivity of infected animals, treatment cost and extra bearing on management. The government's direct losses are related to vaccination and control measures covering trade restriction, vector control, disease surveillance programs, awareness programs, etc. Multiple factors associated with production losses and mortality related to LSD epidemiology, LSD virus pathogenesis, breed of cattle, livestock trade, and control measures have been reported (Gari *et al*. 2011, Molla *et al*. 2017, Casal *et al*. 2018, Kiplagat *et al*. 2020). In countries where mass vaccination using an attenuated homologous LSD vaccine is undertaken, indicated a drop in milk yield after seven days of vaccination up to 6–8 kg/week (Morgenstern and Klement 2020). However, it did not significantly affect milk production during the one-month postvaccination period. An estimate by Molla *et al.* (2017) from Ethiopia suggested that at the herd level, the most significant component of the economic loss is due to mortality (USD 1000), while production loss due to milk alone may be approximately USD 120. Kiplagat *et al*. (2020) reported economic and production losses due to LSD in Ethiopia with variability related to indigenous versus exotic sources of cattle replacement and herd size. In indigenous breed farms, they estimated that the mean farm-level losses were comparatively higher due to milk yield (97 USD) than mortality (31 USD). This finding was contrary to reports of Molla *et al*. (2017). The estimate for indirect losses towards treatments and vaccinations was higher in exotic breed farms than in indigenous cattle farms (Kiplagat *et al*. 2020). Gari *et al*. (2011) estimated that the mean financial cost in infected herds of Ethiopia was higher in Holstein-Friesian/crossbred cattle (approximately USD 58) than that in native breeds (6.43/head). In Balkan countries, the reports and estimates of losses vary with the affected countries. The cost per animal in the affected herds was USD 648.51, 176.87 and 310.42 in Albania, Bulgaria and the Former Yugoslav Republic of Macedonia, respectively (Casal *et al*. 2018). Economic and production loss studies related to lumpy skin disease from Bangladesh, China and India have not been conducted due to its introduction in 2019. However, a recent paper by the Food and Agriculture Organization (FAO) reports the economic impact of LSD on southern, eastern and southeastern

countries. The estimated direct losses of livestock and production might be approximately USD 1.45 billion (Roche *et al*. 2020). The introduction of LSD in 2019 may have severe repercussions in Asian countries in the livestock trade. An estimate of 2017 indicated that Asian countries accounted for USD 5.5 billion associated with exports of live cattle and buffalo meat and meat products, dairy products and hides (Roche *et al*. 2020). According to data from the APEDA (Agricultural and Processed Food Products Export Development Authority), India's alone was 3,694.29 USD million with a major component of buffalo meat amounting to 3175.09 USD millions (APEDA 2021). In general, the variability in the estimate is related to factors considered in the study and policy of the country for disease control and surveillance and livestock rearing systems.

Prevention and control

The prevention and control measures for LSD are similar to those for most viral diseases. These can be covered under isolation and movement restrictions of affected animals, sanitary measures, vector control and vaccination. In countries such as India, stamping-out policy for the management and control of animal disease is not followed due to specific laws against cattle slaughter. These countries also do not have a policy for prophylactic vaccination using recommended vaccines. The control program should strictly revolve around adopting adequate sanitary measures, isolation and movement and trade restriction of infected animals, providing insect-proofed quarantine facilities, avoiding communal grazing, disease surveillance and vector control programmes. The different policies of the countries related to the killing and destruction of affected animals may significantly affect the total costs of the control program (Casal *et al*. 2018). The efficacy of movement restrictions in the LSD control program is limited because there is less than a week time between infection and viremia, during which time there is practically no way to detect infected animals.

Vaccination is the only practical and manageable method in controlling LSD in endemic places and countries with limited resources. It prevents the clinical manifestations of the presenting disease and further prevents other infections from superseding, reducing the financial burden on farmers due to LSD. Vaccines of homologous (Neethling LSD virus strain) and heterologous (SPVV or GTPV) types have been used to provide protection against LSD virus owing to cross-reactivity of CaPVs within the genus (Abutarbush and Tuppurainen 2018, Kitching 2003, OIE, 2013, Tuppurainen *et al*. 2014). SPPV- or GTPV-based vaccines for controlling LSD are used in countries where both viruses exist; otherwise, the vaccine could act as a source of newer infection. It has been reported that vaccination reduces the financial costs due to LSD by 17%/head in local zebu herds and 31%/head in Holstein-Friesian or crossbred herds (Mulatu and Feyisa 2018). Commercially available CPV vaccine strains include the LSD virus Neethling strain, Kenyan SPVV and GTPV (KSGPV) O-240 and O-180 strains, Yugoslavian RM65 sheeppox (SPP) strain, Romanian SPP, and Gorgan goatpox (GTP) strains (Abutarbush, 2017). Vaccination failure using different vaccine strains for LSD prevention and control from various countries is listed in Table 1.

Sheep and goatpox vaccine given to LSD infected cattle with a 10-fold increased dose is reported with lower incidence in some studies (Ben-Gera *et al*. 2015, Tuppurainen *et al*. 2017b). On the other hand, 2 independent reports suggest that the GTPV (Gorgan strain and G20-LKV) vaccine strain elicits a robust protective response and provides full equal protection in cattle against LSD (Gari *et al*. 2011, Zhugunissov *et al*. 2020). Most phylogenetic studies suggested that the goatpox virus is more closely related to the LSD virus than SPPV (Le Goff *et al*. 2009, Lamien *et al*. 2011).

Vaccines for sheeppox and goatpox can also be utilized to prevent spread to other susceptible animals. Cross-protection within the CaPV genus and SPPV vaccines have been widely used for cattle against LSD virus (Tuppurainen *et al*. 2014). Kitching reported that all strains of CaPVs are antigenically similar, and recovery from infection with one strain provides immunity against all other strains. Therefore, it is possible to use a single vaccine strain to protect cattle, sheep and goats (Kitching 2003). However, a recent study suggested that these SPPV and GTPV vaccines are not suitable to protect against the LSD virus. Mikhael *et al*. (2017) stressed the use of homologous strains against LSD over the Romania SPPV vaccine and/or a combination of SPPV and GTPV. The latter vaccines did not provide sufficient protection, and the serological response was not detected against LSD. Similarly, recent reports by Hamdi *et al*. (2020) also showed that the Romania SPPV vaccine

Table 1. Vaccination failure with different CaPV strains reported in various countries

Vaccine strain	Remarks	Reference
Heterologous vaccine	Israel (vaccinated 11% cattle became infected)	(Brenner *et al*. 2009)
Kenyan 67 sheep and goat pox vaccine	Continuous LSD outbreak for > three months in a vaccinated cattle herd in Oman.	(Ayelet *et al*. 2013)
KS1 O-180 virus strain vaccine	23.8% morbidity in the cattle population in Ethiopia after vaccination.	(Ayelet *et al*. 2013)
Heterologous vaccine	Jordon (LSD morbidity of 4.7% in cattle vaccinated against it)	(Abutarbush 2014)
SPPV Bakirkoy strain	Vaccination failure	(Şevik *et al*. 2016)
Romania vaccine	Cases of infected cattle emerging from a vaccinated herd in Egypt	(Abdallah *et al*. 2018, Zeedan *et al*. 2019)

gave only partial cross-protection to cattle against LSD, while the LSD virus protects cattle against LSD, which suggests that vaccination against LSD virus should be carried out with the homologous strain.

The commercially available LumpyVax® (MSD Animal Health-Intervet, South Africa) is a freeze-dried live attenuated virus (SIS Neethling-type) vaccine for LSD that uses field virus isolates. Live vaccines are the most common in the field, and their proper usage in target species is known to confer solid immunity. The recommended dose is 1 ml given by the subcutaneous route and considered safe for cattle of all ages and physiological status. The other 2 commercial vaccines contain cell-adapted strains of the original LSD virus Neethling strain and are produced by Onderstepoort Biological Products; OBP, South Africa (Lumpy Skin Disease vaccine for Cattle) and Bovivax LSD-N® (freeze-dried), MCI Santè Animale, Morocco (Morgenstern and Klement 2020). The recommended dose of both of these vaccines is 2 ml/animal given by the subcutaneous route. The first dose should be given to calves at 6 months of age and booster at the annual interval. Topical application of insecticides to infected cattle has been reported to have no apparent benefit in controlling disease transmission (Davies 1991).

Moreover, the implementation of practical and cost-effective vector control will reduce the impact, inhibit the further spread of the disease into new areas and reduce the expense of the vector control program. LSD control costs were the minor contributor to herd-level losses indicated by a questionnaire-based survey in Ethiopia (Molla *et al.* 2017, Kiplagat *et al.* 2020). The monetary analysis by Molla *et al.* (2017) showed a positive net profit of USD 136 (USD 56 for subsistence farm herds and USD 283 for commercial herds) per herd due to LSD vaccine undertaking. A recent study undertaken in 77 dairy farms of Israel suggested that this vaccine has negligible adverse effects due to vaccination on production parameters (Morgenstern and Klement 2020).

Restricted farm visits and awareness campaigns on LSD virus spread targeting those directly or indirectly dealing with the cattle population, including veterinarians, farmers, truck drivers, etc., will help in the early notification, detection and timely action of the authorities for this devastating disease. Religious constraints in India lead to the presence of the affected cattle as a source of infection in the population for a prolonged period, as there are no DIVA vaccines against LSD to detect the same. Active monitoring will be of paramount importance in limiting the spread of this disease.

Among countries where LSD was reported, the latter could eradicate diseases, including Israel and Southeastern Europe. Israel could successfully irradicate LSD by following the strict slaughter of all infected and in-contact cattle and ring vaccination program using sheep pox virus vaccine (SPVV) (Stram *et al.* 2008). However, LSD remerged in Israel in 2019, attributed to voluntary vaccination policy against LSD and circulating viruses in the region (EFSA *et al.* 2020). Efforts in southeastern

Europe focused more on mass vaccination with LSD homologous vaccine than other measures to restrict entry (EFSA *et al.* 2020).

CONCLUSION

In the current pandemic, livestock services are being hampered to some extent; climate change favours the expansion of vectors in different newer regions. All these factors make LSD a critical emerging disease likely to spread continually. Research efforts into this rapidly emerging pathogen are currently needed in developing countries such as India. Special efforts should focus on better understanding the role of vectors present among nations and their potential role in disease transmission.

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