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A short review on transmission of lumpy skin disease

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Abstract
Lumpy skin disease (LSD) is a viral transboundary disease caused by lumpy skin disease virus (LSDV), a member of *Capripoxvirus* genus of *Poxviridae* family. This disease was known to be once endemic in Saharan regions of Africa but later, reported in central Asian and neighbouring countries like Pakistan, India, Iran and China. This disease continuously spreading from region to region before vaccination campaigns took their full effect, mainly showing seasonal patterns despite implementing control and eradication measures. Within a short period of time this disease spreads to several hundred kilometers away from initial outbreak sites. LSDV spreads to long distance by the movement of infected animals, but different seasonal patterns indicating that an arthropod-borne transmission is most likely responsible for aggressive short-distance spread of the disease. Due to this reasons scientific interest is renewed resulting in the initiation of novel research into broad aspects of the disease, including epidemiology, modes of transmission and associated risk factors. It is a vector borne disease with high morbidity and low mortality. Arthropod-borne mechanical transmission is considered primary and the most common route. The virus is transmitted to susceptible hosts by blood-sucking arthropods such as stable flies (*Stomoxys calcitrans*), mosquitoes (*Aedes aegypti*), and hard ticks (*Rhipicephalus* and *Amblyomma species*). Insects can be transstadial and transovarial. Illegal animal trade considered as other route of transmission, which have played a role in the emergence of LSD in countries which is earlier free from it. Exploring the mechanisms of transmission of LSDV will enable the development of effective actions for containment and eradication of the virus. From the new evidence it is suggested that synanthropic house fly, *Musca domestica*, may also play a role in LSDV transmission, but this has not yet been tested in a clinical setting. The objective of this review is to discuss earlier as well as the most recent research data on LSDV transmission

Keywords: LSDV, transboundary spread, non-vector transmission, arthropod transmission, tick transmission

Introduction
Lumpy skin disease (LSD) is a trans-boundary disease. Earlier LSD was restricted to Sub-Saharan regions of Africa and few other countries, but now this disease spread into climatically new regions. So, that it is important to focus an in-depth understanding of the transmission mechanisms of the virus, contributing towards improved control and prevention of the disease. Thorough understanding of the different transmission routes, enable safer methods to decrease the prevalence of the disease (Sprygin *et al.* 2018c) [44].

LSD disease was first observed in Sahara regions of Africa until 1989 and later transboundary spread of the disease was observed in the Middle East Asia (House *et al.* 1990) [19]. For the first time the LSD outbreak was reported during 2019 in Bangladesh, India, China, and also re-emerged in Israel (Yeruham *et al.* 1995; Tuppurainen & Oura, 2012 and OIE, 2017) [61, 52, 34]. In India the disease might have emerged from its neighbouring countries and reported for the first time in 2019 (Sudhakar *et al.* 2019 and Kumar *et al.* 2021) [46, 24].

LSD is caused by the lumpy skin disease virus (LSDV) that belongs to the *Capripox virus* genus, subfamily *Chordopoxvirinae*, family *Poxviridae*. LSD is known by various names such as knopvelsiekte, pseudourticaria, exanthema nodularis bovis and Neethling virus disease (Al-Salihi, 2014 and Tuppurainen *et al.* 2017) [3, 56]. LSDV is a brick shaped, enveloped, double stranded DNA virus with complex symmetry. The LSDV genome is 151 kbp in length (Tulman *et al.* 2001 and Lojkic *et al.* 2018) [49, 25]. This virus contains 30 structural and non-structural genes, shares antigenic similarity with two other *Capri poxviruses*, *Sheeppox virus* (SPV) and *Goatpox virus* (GPV) which cause devastating disease in sheep and goats respectively (Abutarbush & Tuppurainen, 2018) [1].

LSD is mainly limited to Cattle (*Bos indicus* and *Bos taurus*) and buffalo (*Bubalus bubalis*). Indigenous cattle breeds were resistant compared to *Bos taurus*.

All age group animals were susceptible but calves are more susceptible and they develop lesions within 24 to 48 h of infection (Al-Salihi, 2014) [3]. Wild animals are resistant to infection under natural conditions, but experimental infection produced clinical lesions in Giraffe and impala, Arabian oryx, springbok and Thomson's gazelle (Davies, 1991 and Padilla *et al*.2005) [11, 36]. The incubation period of LSD is 4–12 days and clinical signs start with fever (40–41.5 °C) which lasts for 1–3 days (Woods, 1998) [60]. This is followed by increased nasal and pharyngeal secretions, lachrymation, Enlargement of lymph nodes, anorexia, dysgalactia and disinclination to move (Tasioudi *et al.* 2015) [47]. Animals affected with LSD show a characteristic nodular lesion and they may occasionally be associated with systemic signs (Gupta *et al.* 2020) [18].

LSDV is known for their ability to use various direct or indirect means to infect their susceptible hosts, such as through direct contact, via exposure to aerosols produced by infected hosts, through semen or via intrauterine infection. Transmission of this virus can also occur indirectly via a contaminated environment, fomites, or vectors. Transmission pathways may vary between different genera of the *Poxviridae* family and also within a genus, as exemplified by *Capripoxviruses* (Sprygin *et al.* 2019) [45].

LSDV seasonal outbreaks increased suspicions, that local dissemination of virus is associated with the activity and abundance of vectors (Weiss, 1968) [58]. Slow reporting of the disease by farmers facilitated the rapid spread of the virus, which in turn delays the implementation of control measures (Ince *et al.* 2016) [20]. From the recent epidemiological study of LSD outbreaks in Russia, three cases were identified which occurred more than 800 km away from the outbreak Epicenter, thus suggests vehicle-assisted transport of infected animals (Sprygin *et al*. 2018a) [42].

When infected animal introduced into a new region, the virus needs effective dissemination to the susceptible cattle in nearby farms or environments for an outbreak to initiate and manifest. The data collected during LSD outbreaks in the Balkan indicate that short-distance spread which is approximately 7.3 km per week, and is associated with cattle movements and presence of vectors (Mercier *et al.* 2018) [33].

Strict quarantine of newly introduced animals, control of vector and prophylactic vaccine are effective strategies for limiting the risk factors of the disease. Future studies would be directed towards determining the true burden of LSD on livestock. The objective of this review is to summarize the current knowledge on transmission of LSDV obtained from the field and experimental studies and also identify areas in which further research is still required.

Non-vector transmission

LSD is a transboundary disease. Animals infected with the LSDV can spread it directly or indirectly. Detection of this virus in India and neighbouring countries where this disease was non-existent signifies the importance of understanding its transmission mode. Epidemiology of LSD virus and its possible routes of transmission have been documented by Carn and Kitching, 1995 [9] and Sprygin and co-workers reviewed these findings (Sprygin *et al.* 2019) [45].

Transmission of LSDV through direct contact shown to be an ineffective route of transmission, but correct experimental reports were less. Early experimental work and field observations in South Africa led to the conclusion that direct contact transmission of LSDV occurs at low rates and efficiency (Weiss, 1968 and Diesel, 1949) [58, 12]. This is supported by observations of LSD outbreaks occur outside the window of optimal insect activity temperatures (WAHID, 2018) [59]. However, risk of LSD outbreaks increases after introduction of new animals into a herd and sharing of water sources (MacOwan, 1959) [31]. Although these early observations are accurate, they are mainly based on clinical signs. Diagnostic methods available in earlier days were of relatively less sensitivity compared to modern molecular techniques available today. Mathematical model was used by the researchers to investigate different modes of transmission of LSDV, during an outbreak on a dairy farm in Israel in 2006 (Magori-Cohen *et al.* 2012) [32] and concluded that direct contact of animals did not play a significant role in transmission because no positive correlation was found between cattle density and infection rates. Whereas the observed pattern of spread was explainable by indirect transmission, probably by bloodsucking insects (Magori-Cohen *et al.* 2012) [32].

For the members of the *Capripoxvirus* genus, *Sheeppox* (SPP) and *Goatpox* (GTP) viruses, direct contact with virus-containing droplets and aerosols is an important route of virus dissemination (Carn and Kitching, 1995) [9]. Indirect LSDV transmission might occur when infected animals share feed or water troughs contaminated by nasal discharge or sailva with healthy animals (Weiss, 1968 and Ali *et al.* 2012) [58, 4]. Babiuk and co-workers reported that low levels of virus in oral and nasal secretions, 12–18 days post-infection. However, high virus loads were found in the mucous membranes of the mouth and nose comparable to those of skin lesions (Babiuk *et al*. 2008) [6].

Prozesky and Barnard demonstrated several lesions in the mouth, nostrils, pharynx, larynx, and trachea characterized by erosion and ulceration in severely infected animals (Prozesky and Bernard, 1982) [38]. These erosions and ulcerations are virus sources into the saliva and nasal discharge of severely infected animal and infectious viruses are likely to persist in aerosols and droplets originating from these animals. However, saliva and nasal swabs are good sampling materials, equal to those obtained from the skin (Dietze *et al.* 2018) [13]. Nasal or other discharges with low virus titres are indeed likely to lower the risk of contact transmission, so there is a need to re-investigate the direct mode of transmission as it pertains to spread of LSDV.

Recently Rouby and Aboulsoud, 2016 documented intrauterine transmission of LSDV (Rouby and Aboulsoud, 2016) [39]. Tuppurainen and coworkers, 2017 reported LSDV transmission from mother to calf via contaminated milk or skin lesions on the mother's udder and teats are also likely to occur but there is a need to experimentally confirm this assumption (Tuppurainen *et al.* 2017) [56].

Weiss, 1968 isolated LSDV from the semen of experimentally-infected bulls 22 days post-infection (dpi) (Weiss, 1968) [58]. Recent study detected the persistence of live virus and viral DNA in bovine semen for up to 42 dpi, and 159 dpi (Irons *et al.* 2005) [21]. Experimentally demonstrated that the transmission of virus via contaminated bovine semen (Annandale *et al.* 2014) [5]. Artificial insemination or natural mating should be considered as risk factors for transmission during an outbreak. Vaccination using a homologous vaccine eliminate the virus from semen, and the vaccine virus was also not detected in semen samples (Osuagwuh *et al.* 2007) [35].

Intradermal inoculation trials of LSDV in cattle was performed by Carn and Kitching and found that less than 20% of cases show generalized disease, whereas the remaining

animals exhibited only localized disease. In contrast, the intravenous route of LSDV inoculation produced 70% of animals with generalized disease. Infection was not achieved through the conjunctival sac, in a trial conducted on only two experimental animals (Carn and Kitching, 1995) [9]. These findings suggests that a successful infection cycle requires after inoculation into the bloodstream, which is a typical route in insects feeding from the lumen of a blood vessel. During vaccination programmes transmission of LSDV by contaminated needles is a potential mechanism for the spread of infection within the herd (Tuppurainen *et al.* 2017) [56]. When a vaccine virus is inoculated into an already infected animal, the natural infection even becomes worse.

After observing these reports further transmission studies are required to understand the role of direct contact and also for detecting subclinical infections. Sensitive molecular methods for detecting viral antigens, highly virulent field strain LSDV, duration of the experiment and sufficient numbers of experimental animals are required to make those studies relevant.

Arthropod transmission

Mechanical transmission by arthropod vectors have been reported for several *Poxviruses*, such as *Fowl pox* (Brody, 1936) [7], myxoma (Fenner *et al.* 1952) [14], and *Swinepox viruses* (Tripathy *et al.* 1981) [48]. Rabbit fibroma virus is transmitted mechanically by mosquitoes, fleas and other biting arthropods (Kilham and Dalmat, 1955) [23]. Transmission of virus in all these cases associated with the arthropod's mouthparts and head region, but not its body.

The competence of vector depends on, but is not limited to the frequency of biting habits, vector abundance, and host availability (Kahana-Sutin *et al.* 2017) [22]. In cattle after inoculation of virulent virus at high titres via both intravenous and intradermal routes, only 70% of the animals typically develop a severe clinical disease, (Carn and Kitching, 1995 and Tuppurainen *et al.* 2005) [9, 50]. Successful mechanical transmission probably requires tens or hundreds of bites from blood-feeding vectors, to pass on the virus contained in their contaminated mouthparts.

A general prerequisite for an arthropod, as a mechanical vector is its presence in high numbers at an outbreak site (Kahana-Sutin *et al.* 2017) [22]. Insects which feeds directly from blood vessels, the level of viremia in LSD infected host is usually low, and viraemic stage lasts for less than 12 days (Tuppurainen *et al.* 2005) [50]. These insects inoculate the virus directly into the blood stream increasing their infectivity. Mosquitoes were present in high numbers where the first European LSD outbreaks were detected in 2015 (Tasioudi *et al.* 2015) [47], however outbreaks also reported other than the vector prevalence period (May to August), arguing for another yet overlooked means of transmission (WAHID, 2018) [59]. Skin lesions of severely infected animals contain high titres of virus which act as a source of contamination for blood sucking arthropods vector (Babiuk *et al.* 2008) [6].

The most widely suspected vector species for LSDV spread is stable fly (*S. calcitrans*) (Yeruham *et al.* 1995; Prozesky and Bernard, 1982; Dietze *et al.* 2018 and Aboulsoud, 2016) [13, 38, 61]. Stable flies are persistent feeders and aggressive, feeding is often interrupted by the host, due to their painful bites requiring flies to continue feeding on another host. Due to this, stable flies usually require three to five feeding attempts to achieve satiety (Irons *et al.* 2005 and Schofield and Torr, 2002) [21, 41]. Isolation and identification of live virus using PCR from stable flies either directly or 24 h post-feeding on infected cattle (Weiss, 1968 and Annandale *et al.* 2014) [58, 5], and still the actual transmission of LSDV by this vector remains to be conclusively demonstrated in an experimental setting.

The LSD outbreak in Peduyim, Israel, in 1989, suggested that the infection originated from a concurrent outbreak in Ismailiya, which is located over 85 kms away or in northern Sinai, Egypt. It was suspected that the virus was introduced by contaminated stable flies, carried by prevailing winds or inside cattle transport vehicles (Yeruham *et al.* 1995) [61].

In another study from Israeli, LSD outbreaks on dairy farms correlated with a high relative abundance of stable flies in November-January and March-April 2012–2013 (Rouby and Aboulsoud, 2016) [39]. Even though the numbers of *S. calcitrans* dropped between October and November, LSD was detected in adjacent beef herds. Other vectors, such as a horn fly, *Haematobia irritans*, could have played a role in transmitting the virus. This suggestion was based on the observation of abundant fly populations in areas where beef cattle were being kept (Rouby and Aboulsoud, 2016) [39]. Thus, the role of horn flies in the mechanical transmission of LSDV should also be examined in an experimental setting.

The *Musca domestica*, house fly seems to be capable in transmission of numerous viral and bacterial pathogens of livestock (Pitkin *et al.* 2009) [37]. The proboscises of non-biting flies gets contaminated after feeding on well-developed skin lesions in myxomatosis-affected rabbits, these insects are able to transfer the disease-causing pathogen (Fenner *et al.*1952) [14]. Non-biting flies could also act as vectors by feeding on the carcasses of cattle which have recently died of LSD or were culled due to LSD, thereby taking up the virus from open skin lesions or body fluids containing high virus titres (Sprygin *et al.* 2018b) [43]. *Biomya fasciata*, a non-biting fly, has been implicated as a one of the vector for LSDV. This virus was isolated from flies collected from infected cattle in the field, as well as three days after being artificially fed virus-spiked blood (Weiss, 1968) [58]. *M. domestica* ubiquitous, synanthropic houseflies, tested positive for the presence of vaccine-like LSDV genomic DNA during an LSD outbreak in Russia in 2017 (Sprygin *et al*. 2018a) [42].

Mechanical transmission of the LSDV by *Aedes aegypti* mosquitoes (Chihota *et al.* 2001) [10] and some African hard tick species has been reported (Tuppurainen *et al.* 2011) [51]. Recently, there is an evidence on the potential role of non-biting flies has been presented (Sprygin *et al.* 2018b) [43]. Mosquitoes were suspected to play a role in LSD transmission, Burdin reported, that a high incidence of *Aedes natronius* and *Culex mirificus* mosquitoes were associated with LSD outbreaks in Kenya (Burdin, 1959) [8]. *Culex quinquefasciatus* and *Anopheles stephensi Liston* mosquitoes failed to transmit the virus experimentally but had tested positive for LSDV using PCR, a few days after feeding on infected animals (Annandale *et al.* 2014) [5].

Mosquitoes and Sandflies can intravenously inject LSDV (Carn and Kitching, 1995) [9]. *Aedes aegypti* mosquitoes after feeding on LSDV-rich skin lesions, were shown to transfer the virus to susceptible cattle over a period of two to six days (Chihota *et al.* 2001) [10]. Regardless of the titre of the virus in the blood that mosquitoes imbibed, the efficiency of transmission differs among mosquito species (Gray and Banerjee, 1999) [17].

Friedberg reported that horse (*Tabanidae*), horn (*Haematobia*

irritans), and louse (*Hippoboscidae*) flies may act as potential vectors for several diseases in Israel, and LSD viral DNA has been isolated from *Tabanus spodopterus* females (Friedberg, 1985 and Alexandrov, 2016) [15, 2].

Systematic surveillance of the activity levels of suspected vector species would provide essential data for risk assessment. Currently several research projects investigating on potential vectors for LSDV, and next coming years these could lead to increase in our understanding of the vector transmission of LSDV.

Tick transmission

LSDV transmission from infected to naïve hosts experimentally demonstrated in male ticks of *Rhipicephalus appendiculatus* (Tuuppurainen *et al.* 2013a) [51] and *Amblyomma hebraeum* (Lubinga *et al.* 2013) [26]. Lubinga and coworkers in 2014 used immunohistochemical methods to detect LSD viral antigen in tick salivary glands, hemocytes, synganglia, ovaries, testes, fat bodies, and midgut (Lubinga *et al.* 2014a) [27]. LSDV demonstrated in tick saliva after feeding on infected cattle (Lubinga *et al.* 2013) [26], and transstadial transmission of the virus has also been reported (Lubinga *et al.* 2014b) [28]. Lifecycle of *Rhipicephalus decoloratus* occur on the same host as it is a one host tick. Females were able to transmit LSDV to the next generation of larvae, through their eggs after feeding on infected cattle which in turn were able to infect healthy cattle (Tuppurainen *et al.* 2013b) [54]. Further investigation is necessary to know the exact mechanism of transmission of LSDV as it is very stable (Tuppurainen *et al.* 2015) [55]. Transovarian transmission of LSDV in ticks following exposure to cold temperatures that imitate natural overwintering conditions (Lubinga *et al.* 2015 and Lubinga *et al.* 2014c) [30, 29].

Mouthparts of male gets contaminated with the virus after interrupted feeding on the skin of an infected animal. Since semen sack of male is placed into the females genital openings with its mouthparts it also contaminates the female during copulation (Varma, 1993) [57]. Rouby and coworkers reported similar type of transmission, engorged *R. annulatus* ticks were collected in the field from LSDV-infected cattle and females were allowed to oviposit. Then live virus was isolated from larvae on chorioallantoic membranes of embryonated hen eggs (Rouby *et al.* 2017) [40]. 13 species of *Ixodid ticks* were detected during the recent outbreaks of LSD in the northern hemisphere of the Republic of Dagestan and Kabardino-Balkaria in Russia, which belongs to six genera. Genome of the LSDV was frequently detected in *Ixodes ricinus* (16.3% of ticks tested), *Boophilus annulatus* (14.3%), *Dermacentor marginatus* (13.8), *Hyalomma marginatum* (11.6%) and *Haemaphysalis scupense* (8.1%). This data led to the conclusion that during 2015 outbreaks Ixodid ticks played role as vectors for LSDV, but more detailed studies were required to confirm these tentative findings (Gazimagomedov *et al.* 2017) [16]. In *Hyalomma marginatum* females and *Rhipicephalus bursa* males and females LSDV DNA was detected during surveillance in Bulgaria (Alexandrov, 2016) [2].

The outbreaks of LSD have led to an increase in research on potential arthropod vectors of LSDV. The vector capacity and potential role of ticks as reservoirs of LSDV were understood fully by further studies in an experimental environment.

Conclusion

Cattle and buffaloes are the most important domestic livestock group of animals contributing substantially to the world economy. Earlier LSD was known to be endemic in Saharan regions of Africa and few other countries. But the recent spread of this disease to previously disease-free region like India and other Asian countries, which is a matter of concern for the livestock rearing sector as most of these countries' economies were of agriculture-based. Now in developing countries like India, there is a demand for research on this quickly growing virus. Extra efforts should be made to know the function of vectors those responsible for spread of LSDV. To some extent livestock services are affected by recent pandemic and this climatic change favours the vectors to spread in fresh areas. Large-scale transboundary dissemination of LSDV can be prevented by detailed understanding of the various transmission mechanisms and role of local vector species. This would assist in limiting the spread of the disease at a very early stage. In case of an outbreak this data could help farmers to implement biosecurity measures to protect their livestock. Most of the literature suggests that arthropod transmission of LSDV is the effective strategy by which the virus spreads and climate change favours the expansion of vectors in different newer regions thus seasonality of outbreaks observed. Animal movements considered as one of the reason for the long distance spread of this virus. LSDV vectoring potential of abundant ticks, flies etc., associated with cattle should be evaluated. New vectors that harbours the virus to be discovered.

LSD outbreaks may also occur in areas with no vectors, this suggests that vector-borne transmission is not the only mode of LSDV transmission. No season considered as safe with respect to spread of LSD.

An in depth understanding of feeding habits, survival of virus in those vector could allow veterinary authorities to develop effective strategies for control and prevent spread of LSDV. Further science based investigation required to know the role of vector saliva, the survival time of LSDV in their mouthparts or salivary glands, duration of time in which mechanical vectors remain infective and the number of insects or biting flies required to transmit infection present among nations and their potential role in disease transmission. Strict vector control might be one of the method to control this disease.

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