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ENTOMOLOGICAL ASPECTS
OF LUMPY SKIN DISEASE EPIZOOTOLOGY (REVIEW)

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SUMMARY

Lumpy skin disease (LSD) is a serious threat to the global cattle farming, including that in the Russian Federation where the first outbreak was reported in 2015. Since the disease occurred for the first time, it has continued to spread in this country; however, virus transmission mechanisms have not yet been studied. Transmission through insect bites is considered to be the most likely mechanism of virus short-range transmission. At present, such arthropod species as stable fly (*Stomoxys calcitrans*), *Aedes aegypti* mosquitoes, as well as *Amblyomma hebraeum* and *Rhipicephalus appendiculatus* ticks are regarded as potential vectors. Viral DNA has also been detected on the exoskeletons of house flies (*Musca domestica*). The available literature describes the results of many studies on the role of arthropods in LSD virus spread, but the data presented are inconsistent and do not provide an unambiguous answer concerning the level of significance of potential LSD virus vectors in the progression of the field epizootic. These papers investigate the ability of gadflies, flies and ticks to act as mechanical vectors. Currently, there is no unequivocal viewpoint with respect to the proved LSD vector. This paper reviews the entomological papers aimed at studying possible LSD virus transmission by arthropods.

Key words: lumpy skin disease, insects, transmission.

Lumpy skin disease (LSD) is a disease of cattle and buffalo characterized by fever, lymphatic system lesions, oedema of subcutaneous tissue and internal organs, development of skin nodules (lumps), eye lesions, lesions in the mucous membranes of respiratory organs and gastrointestinal tract. The disease is characterized by high morbidity and low lethality [9].

The agent of LSD is an enveloped DNA virus of the genus *Capripoxvirus* (also comprising SPPV – sheep pox virus and GTPV – goat pox virus) within the family *Poxviridae* [12]. The LSDV genome consists of double-stranded DNA [15].

Lumpy skin disease is a highly dangerous animal disease that can cause epidemics and inflict significant economic damage. It is included in the list of diseases notifiable to the OIE. In 2018, the infection outbreaks were reported in Albania, Bulgaria, Greece, Serbia, Turkey, the Russian Federation and other countries (according to the OIE data).

There are two routes of LSDV spread outside the outbreak area. Firstly, it is through infected animals and animals during the incubation period that are active producers of the virus in inapparent form. It is believed that cattle may carry the latent virus without developing skin lesions. In this case, subclinically infected animals are likely to be an active source of infection, as well as a significant factor for the long distance spread of the virus; this is mostly related to cattle drive or illegal transportation by vehicles. It is important to note that LSD causes major economic losses due to sharp decrease in milk yields and milk and hide quality, mass loss, abortions, sterility in bulls and fertility decline in cows, as well as because of restrictions imposed on trade in animal products [25].

Secondly, it is suggested at present that insects and ticks play an important role in LSD spread [21, 22]. Besides, it has been found that warm humid climate, joint grazing/watering and introduction of new animals to the herd are potential risk factors [1, 19].

Epidemiological data show that there is a correlation between LSD outbreaks and the presence of a large number of blood-sucking arthropod populations acting as mechanical vectors [17]. The outbreaks of lumpy skin disease occur mainly in summer, when favourable environmental conditions, especially high rainfall and temperatures, have an impact on the activity of insects [6, 10]. Unfortunately, the available literature lacks information on how the virus survives in the inter-season, when the activity of vectors is minimal or entirely absent.

The causative agent of LSD is predominantly transmitted by blood-sucking arthropods. Direct or indirect contacts between infected and susceptible animals are deemed to play no significant role in the epidemics, at least at the early stages of the disease. This point of view was proposed by V. M. Carn et al. who demonstrated that susceptible animals housed in close contact with infected ones remained healthy during a month-long experiment [5].

Indirect LSDV transmission is of high relevance. Experimental infection of animals by intravenous injection did not produce generalized infection in contrast to intravenous inoculation [5]. A mathematical model created while studying an LSD outbreak on a dairy farm in Ein-Tzurim (Israel, 2006) confirms these findings and demonstrates the significance of indirect virus transmission (presumably, by a vector) [20]. The hypothesis that LSDV transmission is ineffective without the involvement of blood-sucking arthropods is in agreement with the experimental findings of K. E. Weiss who reported impossibility of virus spread between infected and healthy animals in the absence of mechanical vectors [33]. It is also consistent with the papers reporting that LSD outbreaks continued in the presence of even small populations of biting flies, and the number of new outbreaks diminished with the onset of the dry season and the reduction in the number of blood-sucking insects [4].

It should be noted that the efficient control of LSD spread requires studying the role of various arthropod species in LSDV transmission in different geographical regions.

The abundance of insects at the time of the outbreak is the first prerequisite for them to be considered a vector [24]. Therefore, determination of seasonal dynamics in potential vector population, in addition to vector competence (i. e. the ability of a vector to transmit the virus), is very important for accurate understanding of epidemiological characteristics of transmissible diseases. The potential of a vector for transmitting the virus is also determined by the probability of getting bitten by it, the number of bites, insect population density and susceptibility of a host [17].

Formerly, the clinical signs of LSD were identified as manifestations of allergic reaction to insect bites. This hypothesis was based on increased number of LSD outbreaks after rains when the number of bites was the highest [32].

There is evidence that cold weather helps to sharply reduce virus transmission; much fewer or no LSD cases are reported. This is directly related to the decreased activity of insects and confirms their role in the transmission of the disease [7]. Most epidemiological data from Africa show that the direction of virus spread from outbreak areas, despite strong control, is associated with insect movement [16]. The analysis of LSD outbreaks in Israel also supports the finding that animals develop clinical signs following the air movement of infected insects. The virus was transmitted over distances from 70 to 300 kilometres. According to meteorological data, winds were registered that were able to carry infected insects from the Nile delta to the territory of the country [23].

Literature lacks experimental or epidemiological evidence of poxvirus ability to replicate in the body of an insect, possibly due to the size of the virion. At the same time, there are enough papers describing the mechanical transmission of poxviruses, for example, in myxomatosis [13], in particular, the experimental transmission of the virus by mosquitoes.

The results of epidemiological studies of LSD outbreak areas in Egypt provided a basis for the hypothesis that the virus could be mechanically introduced to the disease outbreak area by a contaminated vector, namely stable flies (*Stomoxys calcitrans*). The distance between active and emerging outbreaks was more than 85 kilometres [27]. It is well known that under natural conditions the flying range of most blood-sucking insects rarely exceeds 100 metres [2], but winds can significantly increase this range. However, this hypothesis is not supported by experimental data.

The distinctive feature of stable flies is intermittent feeding (3–5 meals for complete satiation). Bloodsucking can be interrupted due to the animal's defensive behaviour in response to the painful insect bite. The fly can continue feeding on the same host or find a new one. Such behavior confirms the possibility of mechanical transmission of the virus [26].

A laboratory experiment revealed that *St. calcitrans* are PCR-positive within 24 hours after bloodsucking, but at this stage they cannot be the source of virus transmission to susceptible animals. The attempt of scientists to demonstrate infection transmission by stable flies failed [3].

Virus transmission by insects 24 hours after bloodsucking was described by other researchers. Since stable flies are characterized by intermittent feeding and the virus is suspected to be transmitted mechanically, its transmission following such a long interval between sucking blood from an infected animal and finding a new host cannot guarantee 100% persistence of the virus under field conditions. However, these insects can transmit a different capripox virus similar to LSD virus [30]. Therefore, further studies of insects during shorter periods between biting infected and susceptible cattle are needed to determine the role of *St. calcitrans* as an LSD vector.

There is evidence that relative abundance of stable flies at the time of LSD outbreaks (late July – early September) was considerably higher than that of other dipterans during the same period. To validate these findings, I. Yeruham et al. (1995) used a stable fly population model based on meteorological parameters for infected areas (the model relied on data for several years) [27]. It was shown that the number of outbreaks correlated with *St. calcitrans* abundance. The model demonstrates that *St. calcitrans* population peaked in the months of LSD onset on the dairy farms where livestock tethering was practised. Besides, a lower abundance of stable flies was revealed during October and November, when the disease was reported on neighbouring farms where cattle grazed in the field. These findings suggest that *St. calcitrans* is a potential LSD vector on dairy farms and that another vector is possibly involved in LSDV transmission in grazing herds [17].

Hematophagous arthropods are the main suspected vectors for LSDV during outbreaks. To date, the only dipteran able to perform the full transmission of LSDV (this means that an infected insect is able to infect susceptible animals) is the *Stegomyia aegypti* (*Aedes aegypti*) mosquito (Diptera: *Culicidae*) [21]. These mosquitos can transmit the virus from infected cattle to susceptible ones during 6 days after bloodsucking. It is thought that the virus is located in particular regions of the insect's body. For example, in *Ae. aegypti* that had fed on myxomatous lesions of rabbits, the virus content in the mosquito's head was higher than that in other body parts [14].

Hematophagous feeding characteristic of mosquitos makes them ideal candidates for the mechanical transmission of LSDV. In support of this hypothesis, V. M. Carn and

R. P. Kitching demonstrated that intravenous inoculation of animals with the virus causes its mass dissemination within the animal body [5]. Therefore, it is quite likely that other mosquito species can be potential vectors; however, additional studies are required to examine the role of each particular species in the LSD epidemiology.

It is important to note that virus transmission by insects is only possible in case of interrupted feeding on an infected animal and further re-feeding on a susceptible one [3].

Non-bloodsucking flies have never been considered to be LSD vectors because it is believed that infection is mostly transmitted through the bites of blood-sucking insects [5]. During the 2017 LSD outbreak in the Russian Federation, the field trapping of house flies (*Musca domestica*) was carried out using fly strips. A study performed at the FGBI "ARRIAH" detected the viral DNA of the vaccine LSDV strain in the insects [8]. This appears to be due to the entry of the virus into the insect body in the process of feeding on nodular skin lesions containing high concentrations of the virus. An open nodule or wound is a potential blood meal source for house flies. Therefore, the epidemiological role of house flies in LSDV transmission requires further investigation. It is necessary to note that virus isolation in cell culture was not performed and, for this reason, it is unknown whether the flies transmitted the infectious virus or genome fragments. It was highly probable that it was the virus present on the exoskeleton of flies, and this is consistent with the findings of other studies, which have demonstrated that *M. domestica* can transmit swine and poultry pathogens [28].

Ticks of the genus *Amblyomma hebraeum* are distributed in South Africa [29]. The persistence of the virus at different stages in the life cycle of the tick makes it a potential reservoir for overwintering of LSD virus. J. C. Lubinga et al. demonstrated that *A. hebraeum* ticks are better suited to supporting virus persistence in winter months than stable flies since they can survive a long time off the host on stored nutrients from their previous blood meals. This may help explain where the LSD virus survives between the outbreaks. Nymphs become adult ticks in early summer; at that time, they transmit the virus mechanically through biting. The virus persists in epidermis, synganglion and reproductive organs of the adult tick that do not undergo histolysis during molting and might therefore serve as a source of virus spread in other organs, in particular salivary glands. Other studies performed by the authors demonstrated the mechanical transmission of the virus by male *A. hebraeum* ticks, though antibodies were absent and the level of viraemia was low [11, 22]. The experimental findings published by the authors in 2014 point out the presence of the viral nucleinic acid in *A. hebraeum* and *Rhipicephalus appendiculatus*. The presence of the virus was confirmed by immunohistochemical staining of different body parts of ticks, in particular midgut, salivary glands, testis and fat body. The studies also experimentally demonstrated the possibility of the transovarial transmission of the LSD agent by female *A. hebraeum*, *R. appendiculatus* and *R. decoloratus* to larvae and then to recipient animals [31].

Ticks of the genus *Rhipicephalus*, parasites of ungulates, are widespread in the south of Africa. Depending on climatic conditions, several generations of ticks may grow up during the year; the peak in the number of feeding male and female ticks is observed in summer [29]. Studies performed by E. S. Tuppurainen et al. presented the first evidence of the role of hard-bodied (ixodid) ticks (*Rhipicephalus decoloratus*, *Rhipicephalus appendiculatus*) in the transmission of LSD virus detected in adult ticks' tissues and saliva. Male ticks were fed on experimentally infected cattle, feeding was interrupted and they were transferred to feed on uninfected animals. The animals subsequently became viraemic and seroconverted. The ticks are able not only to transmit the virus but also to support its survival during their entire lifecycle without replication, i. e. they might be involved in the overwintering of the LSD agent. *R. decoloratus* is associated with transovarial transmission [22]. However, the life cycle of ticks, comprising a long period when the tick is attached to the host, does not explain the rapid occurrence of large-scale epidemics; it can therefore be assumed that these insects can only serve as potential reservoirs for the virus.

The survivability of the virus in tick tissues is probably more significant than the actual replication of the virus in cells which is absent in case of LSD virus according to experimental data. Nevertheless, summarized experience in the experimental studies of "virus-vector" associations, shows that all possible ways of survival and transmission of viral agents should be taken into account in case of their persistence in the arthropod population.

Intradermal inoculation of the virus, in contrast to intravenous route, is associated with local lesions and a low likelihood of generalized disease [5]. F. Fenner et al. reported that in myxomatosis, rabbits with generalized lesions were the most important in the transmission of the disease by mosquitos. The virus was transmitted when insects fed on the blood of viraemic animals [13]. V. M. Carn et al. [5] used animals with secondary lesions as the source of infection in the spread of capripoxvirus to other sheep and goats. Capripox viruses, including LSDV, produce multiple lesions, which are particularly attractive to blood-sucking and non-bloodsucking insects, and in which high titers of the virus may be present. Cattle with generalized lesions can therefore be assumed to be the most probable source with respect to the transmission of the virus.

Historically, it has been noted that livestock movement restrictions were inadequate to control the disease [24], whereas in certain outbreaks the spread of the disease was limited [18]. Intravenous inoculation of the virus through insect bites that produces generalized infection is of importance in LSD transmission. That is why the control of such potential vectors as stable flies (*Stomoxys calcitrans*), *Amblyomma hebraeum* and *Rhipicephalus appendiculatus* ticks, in the absence of vaccination, is a priority for reducing the consequences of the disease.

CONCLUSION

In spite of international efforts to eradicate lumpy skin disease, the outbreaks of the disease are occasionally reported in different previously free countries. The major obstacle to its complete eradication is lack of unambiguous data regarding the transmission of the virus. The conducted analysis of literature on the subject revealed that the most probable virus transmission mechanism is through insects, that was why the infection was categorized as a transboundary disease. The epidemiological studies demonstrate that the seasonality and frequency of outbreaks are correlated. However, the characteristics of mosquito and tick life cycle do not fully explain the rate of LSDV spread. Despite the availability of indirect evidence with respect to the role of insects, LSD outbreaks can occur sporadically in the absence of vectors but this does not exclude the possibility of contact transmission, in particular through skin lesions that serve as a long-term depot for the high concentrations of the virus, or other transmission mechanisms.

Conflict of interests. The authors declare that there is no conflict of interests.

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