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Review article

UPDATE OF LUMPY SKIN DISEASE: EMERGENCE IN ASIAN PART OF EURASIA

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Lumpy skin disease (LSD) is an infectious disease mostly of cattle. The typical clinical picture is usually characterized by the appearance of multiple nodules on the skin and internal organs. They can cover the entire body of the animal in the course of severe illness. This disease causes serious economic damage despite the fact that mortality of cattle with LSD is often low. Now LSD is a serious danger for cattle in the Asian part of Russia (part of the territory of the Russian Federation geographically belonging to Asia) and the Southeast Asia. Initially LSD was an endemic disease in many Sub-Saharan African countries, then it spread to Asia and Europe. In order to prevent the spread of the lumpy skin disease virus (LSDV), strict quarantine is introduced, vector control is carried out and various other LSD control measures are implemented. An effective vaccination campaign is required to significantly reduce the morbidity. However, the risk of spreading this transboundary disease to neighboring LSDV virus-free countries and regions of Asia, remains high enough. This article contains a summary of the available information about the spread of LSD in Asian part of Eurasia for the period of 1984 - February 2022. We are also discussing the latest available findings on the epidemiology of LSD and the methods currently used for the prevention and control of the LSDV.

Key words: Asia, cattle, LSD, lumpy skin disease virus, outbreaks

INTRODUCTION

Lumpy skin disease (LSD) is a transmissible viral disease which primarily affects cattle and water buffaloes. It is caused by a DNA-virus belonging to the *Poxviridae* family and genus *Capripoxvirus*. LSD is characterized by fever, specific nodes on the skin, lymphatic system and internal organs. Lumpy skin disease virus (LSDV) can be transmitted from infected animals to healthy individuals in the following major ways: (i) mechanically via blood-feeding arthropod vectors, (ii) by direct contact between animals as reported [1,2], (iii) through contaminated food and water. Animal transportation plays an important role in the long-distance spread of the virus [1,3]. It

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was previously reported that the transmission of the virus could occur during artificial insemination [4].

LSD was first registered on the African continent in Zambia in 1929. Gradually, the disease spread widely throughout Africa. In the subsequent years, studies have shown that the geographical spread of the infection is much wider and it is present not only in Africa, but also in Europe and Asia [3,5].

At present, LSD poses a destructive threat to large domestic ruminants in South, East and Southeast Asia, and the Asian part of Russia. While the disease persists, new outbreaks of LSD were registered in the countries of the above regions in 2021, according to the official data [6,7].

The disease is on the list of diseases to be registered by the World Organization for Animal Health (OIE). The disease has a significant socio-economic impact on world livestock, tanneries for leather production and agriculture in general. The disease has a negative impact on cattle meat and dairy production, causes abortions and leather damage. It also leads to economic losses due to necessary quarantine, diagnostic costs and eventually the death of heavily affected animals [1,8]. The economic cost of LSD can be as high as $1.45 billion in South, East and Southeast Asia (specified in the text of the document of the Food and Agriculture Organization of the United Nations (FAO) from 2020) [9].

The farmers also have to face the economic crisis incorporated by LSD (loss of livestock commodities, such as milk, meat, and the costs of veterinary services and vaccines used for prevention). Recurrent new outbreaks, the appearance of novel



Figure 1. Map showing the Asian part of Eurasia. The map was generated with Esri ArcGis Desktop 10.6.1 (www.esri.com (accessed on 28.02.2022)).

'vaccine-like' recombinant strains of the LSDV [10] and the re-appearance of the disease in various parts of the world highlighted the importance of further studies on the transmission of the virus in the environment, LSDV strains genetic diversity, and preventive control methods.

This study summarized the latest developments related to LSD, focusing on countries in the Asian part of Eurasia (Figure 1).

A comprehensive study of the recently published scientific literature was conducted through PubMed [11] and Web of Science databases [12]. The outbreak data used for the study were obtained from the Global Animal Disease Information System EMPRESS-i of FAO [6]. The system included all geographical locations and the start dates of LSD outbreaks in cattle populations, which were reported by Asian countries to the OIE [13].

The data were analyzed using the Esri ArcGis Desktop 10.6.1. [14].

DISTRIBUTION OF LSDV IN THE ASIAN PART OF EURASIA

LSD was considered endemic on the African continent until the 1980s. But the disease was transferred outside Africa to Southwest Asia. Cattle disease was reported in Oman and Kuwait from 1984 to 1988. According to alternative information, initially the disease spread from the African continent to Israel in August of 1989. Allegedly, it came from the very center of LSD outbreak in Egypt, through blood-feeding insects (*Stomoxys calcitrans*). Vaccination of cattle dairy herds, strict quarantine measures and slaughter of sick animals led to the successful eradication of the disease [5,15].

In the same year a case of LSD was reported in the *Oryx leucoryx* (Arabian oryx, Family Bovidae) in Saudi Arabia. Depression, fever, anorexia, more than 1000 skin nodules and then gradual recovery within 2 months were observed in an animal [16].

Some sources mentioned outbreaks of the disease in Bahrain and Lebanon (1993), Yemen (1995), United Arab Emirates (2000) [5,17,18]. According to the official data [6,7] the disease has come back many times to the some of the above-mentioned countries in the following years (Figure 2).

Syria and Iraq joined the countries affected by LSD in 2012-2013. Civil conflict or war and collapse of veterinary services in those countries promoted the spread of LSD to neighbouring countries of Southwest Asia [20]. The first cattle LSD outbreaks were registered in Iraq at the end of August in 2013. There was no specific antiviral treatment for infected animals. Therefore, only symptomatic therapy was administered. Some attempts were made to stop the spread of the disease by means of ring vaccination for animals, imposition of quarantine, animal carcass disposal, cleaning and disinfection of premises [20].

As most of the LSD outbreaks occurred in Turkey along the border with Syria and Iraq, this disease probably spread from these two countries. First LSD outbreaks in

cattle were registered in Turkey in August of 2013. Animals had not been vaccinated prior to these outbreaks. Initially, the vaccine was based on the strains of sheep and goat pox virus and was used only in affected areas. Mass animal immunization began in 2014 [19,21]. However, LSD outbreaks were regularly recorded between 2013 and 2019 [6,7] despite the extensive livestock vaccination campaign using a heterologous vaccine (Figure 2).

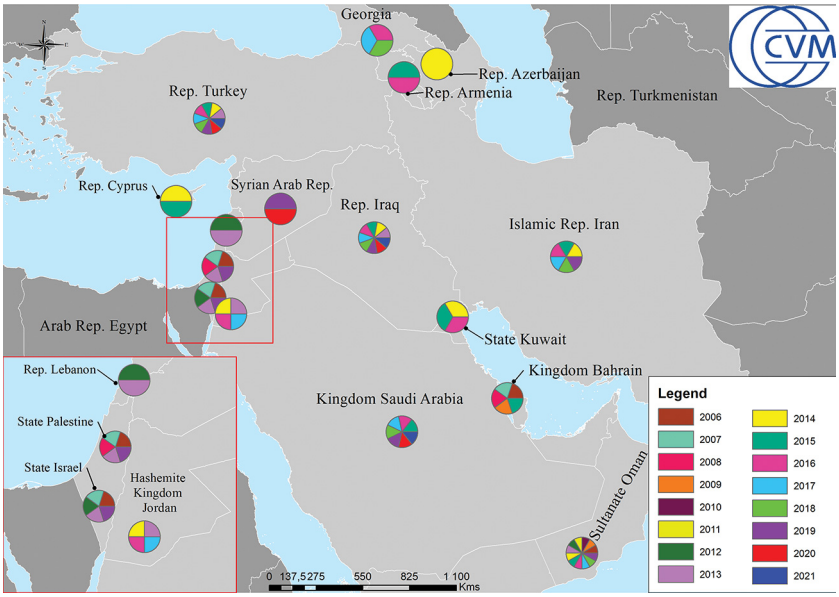

Figure 2. Geographic distribution of lumpy skin disease cases and outbreaks reported in cattle in the Southwest Asia from 2006 to 2021 [6,7] (accessed on 28.02.2022). The map was generated with Esri ArcGis Desktop 10.6.1 [14] (accessed on 28.02.2022).

Not previously reported LSD also appeared in Jordan in April in 2013. Clinical signs, indicating LSD, appeared in dairy cattle. PCR showed the presence of virus nucleic acid. The affected herds were mostly treated with broad-spectrum antibiotics and anti-inflammatory drugs [22].

In 2014 LSD outbreaks were recorded in Iran. The first case of LSD was detected in a sick dairy cow. It was discovered by a vaccination team during routine vaccination against foot-and-mouth disease. All affected animals were destroyed after laboratory confirmation of the disease [19].

In the same year some cattle with clinical signs which are characteristic of LSD were first discovered in Azerbaijan. The diagnosis was confirmed by laboratory testing. The samples from skin lesions more often were tested positive for PCR. They had higher virus concentrations than the internal organs and blood samples. Some preventive measures were adopted to slow down the spread of the disease. The measures included restrictions on the movement of cattle, vector control and livestock vaccination [23]. A long-range transmission of the disease from Iraq, Iran or Turkey to Azerbaijan is

likely to have occurred through animal movements (legal/illegal), but not through arthropod vectors [24].

Since the LSDV entered Turkey in 2013, the disease spread throughout the country and reached South-Eastern Continental Europe (Greece, Bulgaria, North Macedonia, Serbia with Kosovo, Albania, Montenegro) and also Armenia, Georgia, the Russian Federation and Kazakhstan from 2015 to 2016 [25,26].

A favourable LSD situation was reported in South-Eastern Europe at the 8th meeting of the Standing Group of Experts on LSD (SGE LSD8, Paris, 2019) [27]. A favourable LSD situation was observed from 2018 to 2020 because of mass immunization of animals with homologous vaccines, which began in 2015. According to the official data [6,7] new LSD outbreaks were not registered in the Balkan region until 28 February 2022.

Heterological vaccines for LSD immunization of cattle based on sheep and goat pox virus are widely used in the Russian Federation. Active mass vaccination of cattle has been provided since 2017 [10]. Despite it, LSD outbreaks continue to be reported every year, including February 2022 [6] (Figure 3).



Figure 3. Geographic distribution of lumpy skin disease outbreaks reported in cattle in Russia from 2015 to February 2022 [6] (accessed on 28.02.2022). The map was generated with Esri ArcGis Desktop 10.6.1 [14] (accessed on 28.02.2022).

Compared to 2018, the LSD epidemic in Russia spread from the south of the country along the border with the Republic of Kazakhstan. There the cattle have been vaccinated with a homologous vaccine based on Neethling strain since 2017 [3].

The Republic of Kazakhstan, as mentioned above, was the only country among the Central Asian countries south of the Russian Federation (Kazakhstan, Kyrgyzstan,

Tajikistan, Turkmenistan and Uzbekistan) that reported LSDV in 2016 [3]. According to available data [7], LSD outbreaks have not been reported in the bordering Republic of Kazakhstan in the last 5 years. Furthermore, it is important to note that the so-called 'vaccine-like' recombinant LSD strains have been detected in Russia since 2017 [10]. It is believed that specified variants of LSD appeared after the beginning of the vaccination campaign in 2017, where homologous vaccines were used in neighbouring countries of the Russian Federation [28].

DISTRIBUTION OF LSDV IN SOUTH, EAST AND SOUTHEAST ASIA

During 2019-2020, the disease spread to the South and East Asia (Bangladesh, China, India, Nepal, Bhutan, Sri Lanka), then the LSDV spread to Southeast Asia (Vietnam, Myanmar). Now the disease is well-established in Asia. It has become a problem for Asian livestock and a threat to food security. LSD outbreaks continued to be reported in 2021 in Mongolia, Taiwan, Thailand, Lao People's Democratic Republic, Cambodia, Malaysia, including Indonesia (February 2022) [6] (Figure 4).

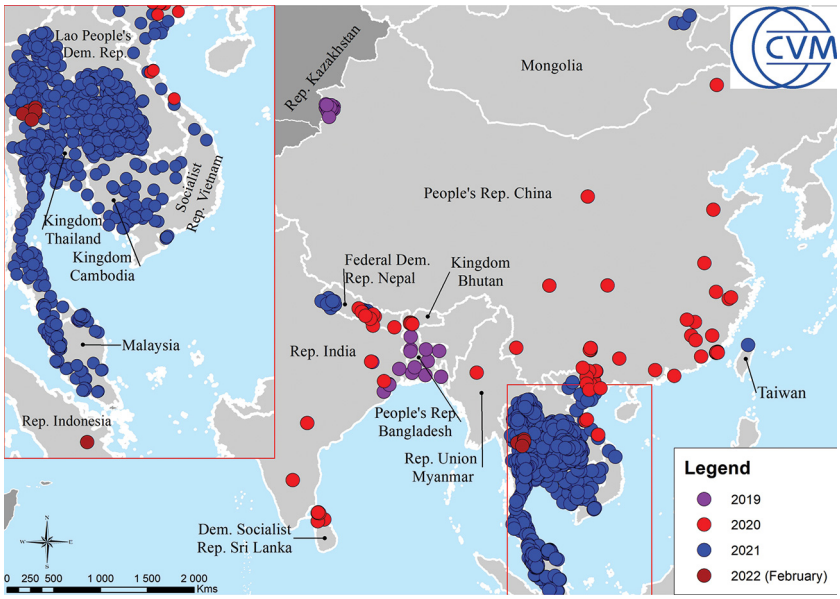

Figure 4. Geographic distribution of lumpy skin disease outbreaks reported in cattle in the South, East and Southeast Asia from 2019 to February 2022 [6] (accessed on 28.02.2022). The map was generated with Esri ArcGis Desktop 10.6.1 [14] (accessed on 28.02.2022).

The first LSD outbreaks in Bangladesh were recorded in July 2019. The samples from cattle with clinical signs of LSD tested positive in PCR/PCR real-time. The disease appeared in the south-east part of the country and then spread throughout the whole country. Animal deaths were not reported. It's worth mentioning that cattle in Bangladesh had not been vaccinated against the LSD before the outbreaks began.

The immunization of cattle started later. It was also discovered that the viruses which caused the outbreaks in Bangladesh were genetically different from LSD field strains circulating around the world, including the recombinant strains described between 2017 and 2019 in the Russian Federation [29,30].

The first LSD outbreak of cattle in China was reported in August 2019 in the north-west of the country about 20 km from the border with Kazakhstan and about 780 km from the border with Russia. The virus spread across the country from west to east within a year. Later it reached Taiwan Island outside of mainland China. It was reported that one of the isolated strains was 'vaccine-like', but it was different from Russian recombinant strains. At least 25 recombinations between the vaccine strain and the field strain, which could affect the virulence and transmissibility of the virus, were found in its genome [31,32]. Clinical signs that were characteristic of LSD emerged in wild cattle in Hong Kong in October 2020. Whole genome sequencing and phylogenetic analysis of the isolated strain showed that the strain was most similar to live-attenuated Neethling vaccine strains and more distantly related to wild field strains from Africa, Middle East and Europe [33].

The LSD outbreak in cattle also occurred in India in August 2019. The genetic material of the LSDV among the affected animals was more commonly found in scabs than in the blood and sperm of bulls. The molecular genetic analysis showed that the Indian strains of the LSDV were genetically closer to the South African NI2490/KSGP-like strains than those which had been found in Europe. Thus, it was established that field strains of the LSDV were involved in the LSD outbreaks in India [34].

The first LSD outbreak in cattle occurred in Nepal not far from the border with India in June 2020. Animal samples of the clinical material were examined by PCR real-time and they tested positive for the presence of the genetic material of the LSDV. The epidemiological investigation of LSD could not identify the source of the virus. However, there is a suspicion that the virus could have come into the country from India because of a weak quarantine system on the border between Nepal and India [35].

The first LSD outbreaks in Vietnam were reported in a province bordering China in October 2020 and was officially announced to OIE on 1 November 2020. The LSDV in cattle was confirmed with a conventional PCR and PCR real-time. Further molecular genetic analysis showed that the LSDV, isolated in the first outbreaks, was 100% identical to the virus isolated in China (2019) and was genetically similar to the virus isolated in Russia (2017) [36].

The first LSD outbreaks occurred in northeastern Thailand in March 2021. The official document about them was presented to OIE in April 2021. After that, the disease spread throughout the country. Typical clinical signs of LSD were detected in cattle. They included fever, reduced appetite, lymphadenitis and appearance of skin nodules which turned into multiple ulcerative necrotic nodules and deep ulcers. Laboratory results showed that the genetic material of the LSDV was found in the

clinical material from sick animals. It also turned out that the isolated strain of the LSDV was genetically similar to circulating strains from Russia (2019) and India (2019) [37].

The first LSD outbreaks occurred in Malaysia and Lao People's Democratic Republic in May 2021. That was reported at the 2nd Lumpy skin disease (LSD) coordination meeting for South-East Asia [38]. Malaysia uses homologous vaccines against LSD. Lao People's Democratic Republic did not use or import any vaccines against LSD. Laos focused on surveillance, movement control of animals and informing the areas affected by the LSDV.

PREVENTION AND CONTROL OF LSD

Nowadays, cattle and buffalo trade in Asia is very complicated. A significant number of regions, animals, vehicles and many trade routes are involved in it. This makes it difficult to control animal movement and veterinary inspections. Vaccination of cattle, timely diagnosis and implementation of quarantine measures are the main methods of LSD prevention and control.

Quarantine is the very first measure which must be quickly taken, especially at the first detection of LSD in a country or region. Awareness of veterinarians, farmers and other relevant stakeholders is essential for improving surveillance and early detection and control of LSD. Regular and thorough cleaning and disinfection of premises where cattle are kept are important general measures. In addition, it is necessary to clear or limit insect vectors breeding sites (standing water sources, manure, etc.) [9].

At present, there is no specific treatment for LSD. All currently available commercial vaccines are live and contain whole viruses which have been attenuated. These vaccines are based on the Neethling strain of LSDV (homologous vaccines) or based on sheep/goat pox virus strains (heterologous vaccines) [39]. Live attenuated *Capripoxvirus* vaccine strains used in vaccines are produced by repeated passages on different cell cultures [40] and/or chicken embryos [41]. However, full genome sequences have not been widely available yet for all commercial vaccine strains. Also, their level of attenuated virulence is not always fully described. Despite this, animals are immunized with live attenuated vaccines against LSD, sheep and goat pox in all endemic regions. It is important to conduct the vaccination to avoid iatrogenic transmission of the disease when vaccinating or treating animals according to professional and biosecurity standards. The quality and safety control of each batch of both homologous and heterologous vaccines must be ensured [9]. Additionally, the certain discrimination of the LSDV strains including the emergence of the so-called novel 'vaccine-like' recombinant variants [10] should be taken into account for the development of the next generation of vaccines against LSD.

Experience gained in the Balkan region (South-Eastern Europe) has shown that the spread of the LSDV can be successfully controlled through a well-organized animal

immunization campaign with sufficient livestock coverage and effective vaccines. Mass vaccination of cattle using live homologous vaccines against LSD is considered the most effective way to control the spread of LSDV and reducing direct and indirect economic losses [3,9].

Another important problem is the occurrence of clinical signs of LSD in some animals, vaccinated with homologous vaccines. They were accompanied by the detection of a direct LSDV in the animal. Moreover, it is clear that further work on assessing the prevalence of 'vaccine-like' recombinant strains in the world is necessary. It should be aimed at clarifying specific reconfigurations in the Capripoxvirus genome. At the same time, from a scientific point of view, it is necessary to note an important fact of the discovery of recombination in *Capripoxviruses*. It was first recorded in LSD strains isolated from cattle vaccinated with a heterologous vaccine in Saratov region (Russian Federation, 2017) [42].

Therefore, it is necessary to carry out a genetic characterization of novel strains of LSDV, including related strain vaccines. Also, virulent properties of LSD virus isolates circulating in different geographical territories should be studied. The determination of their molecular genetic characteristics will make it possible to assess their genetic diversity, which is necessary for analyzing the evolution and studying the propagation of the LSDV.

CONCLUSION

LSD is a severe ailment of cattle with far-reaching socio-economic consequences. The recent LSD outbreaks in the Asian part of Russia and Southeast Asian countries have raised concerns about the potential transboundary spread of the LSDV in the relevant regions and other neighboring LSDV virus-free countries. The evidence also suggests that LSD remains an urgent agricultural problem for Asian countries and world livestock in general. Attention should be paid on the exchange of expertise and resources that would be required to address this issue between affected and at-risk countries. The selection of the right vaccine should be based on analyzing the advantages and disadvantages of each vaccine and adapted to the specific situation in a certain country. It is necessary to focus on identifying the source of infection, molecular genetic characterization of the strains of the LSDV and the epidemiology of LSD worldwide, especially in the Asian part of Russia, South, East and Southeast Asia.

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Authors' contributions

YVS conceptualization, formal analysis, data curation, writing - original draft preparation. YVS and AAK software, investigation. YVS and VAF writing - review and editing. All authors have read and agreed to the published version of the manuscript.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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AŽURIRANJE PODATAKA O NODULARNOM (*LUMPY*) DERMATITISU: NOVA ŽARIŠTA U AZIJSKOM DELU EVROAZIJE

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Nodularni (*Lumpy*) dermatitis je infektivno oboljenje, pre svega goveda. Tipična klinička slika se obično karakteriše pojavom većeg broja nodula u koži i unutrašnjim organima. Ukoliko se radi o težim oblicima bolesti, noduli mogu da prekriju celu površinu tela. Nodularni (*Lumpy*) dermatitis izaziva značajne ekonomske štete uprkos činjenici

da je mortalitet relativno nizak. Danas nodularni dermatitis predstavlja ozbiljnu opasnost po zdravlje goveda u azijskom delu Rusije (geografski deo Ruske Federacije koji pripada Aziji) kao i u jugoistoku Azije. U početku, nodularni dermatitis je bila zarazna bolest koja bila enzootski prisutna u subsaharskim zemljama Afrike. Usledilo je širenje ka Aziji i Evropi. U cilju sprečavanja širenja virusa izazivača nodularnog dermatitisa, uvedene su striktne mere karantina, kontrole vektora kao i ostale mere kontrole. Da bi se postiglo značajno smanjenje morbiditeta, neophodno je da se obavi vakcinacija. Međutim i dalje postoji dovoljno visok nivo rizika od širenja ove zarazne bolesti na susedne države i regione u Aziji koji su slobodni od nodularnog dermatitisa. U okviru rada, prikazane su raspoložive informacije koje se odnose na širenje nodularnog dermatitisa u Azijskom delu Evroazije i to za period od 1984. do februara 2022. godine. Isto tako, u okviru diskusije, razmatraju se najnovije epizootiološke informacije u vezi nodularog dermatitisa kao i metode koje se danas koriste u cilju sprečavanja pojavljivanja i kontrole ove zarazne bolesti.