Original Article

A Review On: Lumpy Skin Disease In Cattle

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Abstract

The geographical distribution of lumpy skin disease (LSD), an economically important cattle disease caused by a capripoxvirus, has reached an unprecedented extent. It is caused by Lumpy skin disease virus (LSDV), which belongs to the family Poxviridae, with the Neethling strain the prototype. LSDV belongs to the genus Capripoxvirus that includes sheep pox virus and goat pox virus. The original foci of LSD are from Zambia in 1929. LSD is considered as an endemic disease in the African continent. However, the disease has been moved beyond Africa in 1984.Vaccination is the only way to prevent the spread of the infection in endemic and newly affected regions. In the event of an outbreak, selection of the best vaccine is a major challenge for veterinary authorities and farmers. Decision makers need sound scientific information to support their decisions and subsequent actions. The available vaccine products vary in terms of quality, efficacy, safety, side effects, and price. The aim of the present study was to develop a universal real-time PCR assay using man chemistry to cover field, vaccine, and recombinant strains of lumpy skin disease virus isolates.

Keywords: Neethling, vaccination, milk loss, mortality rate, adverse effects, field-controlled, survival analysis, lumpy skin disease.

INTRODUCTION

LDS is viral infection caused by the lumpy skin disease virus (LSDV) that belongs to the capripoxvirus genus of the poxviridae family.[1]The virus affects cattle and spreads by blood- feeding insects including mosquitoes, flies, and lice. It can also transmit from contaminated fodder and water. According to European Food Safety Authority (EFSA), LSD leads to fever and nodules on the skin. The chances of casualties are higher in the case of animals who have not been exposed to the virus previously.[1,2]

LDS is viral infection caused by the lumpy skin disease virus (LSDV) that belongs to the capripoxvirus genus of the poxviridae family.[4] The virus affects cattle and spreads by blood- feeding insects including mosquitoes, flies, and lice. It can also transmit from contaminated fodder and water. According to European Food Safety Authority, LSD leads to fever and nodules on the skin. The chances of casualties are higher in the case of animals who have not been exposed to the virus previously.[3]

Jaipur Dairy Federation, the biggest milk cooperative in Rajasthan, told NDTV that milk collection has reduced by 15-18 per cent and is now 12 lakh litres, down from the normal 14 lakh litres"Before Lumpy struck, we used to get 14 lakh litres of milk daily at the cooperative, but now it's down to 12 lakh litres. Though there has been no disruption in milk supply, we are worried over animal deaths as the figures in reality are definitely more than what is being stated officially. If this continues, there could be a crisis – worse than what we faced during.[13]

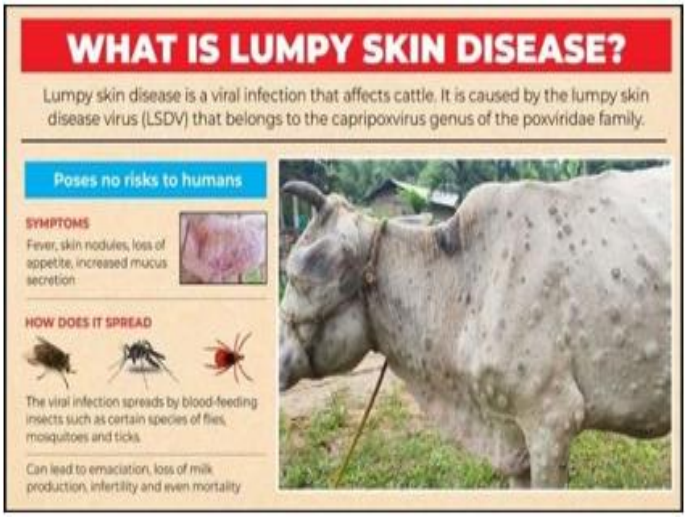

Fig.1 Spreading Lds

Lumpy skin disease virus (LSDV), together with sheeppox virus (SPPV) and goatpox virus (GTPV), belongs to the genus Capripoxvirus of the family Poxviridae .Capripox viruses in general are described as the most serious poxvirus diseases of domestic and production animals[2,3] LSDV, which naturally infects cattle and water buffalo [4,5] is mainly transmitted mechanically via blood-feeding insects[6] ,and possibly via hard ticks [10,11,12]. The clinical course of lumpy skin disease (LSD) ranges from subclinical through mild to acute[13] .

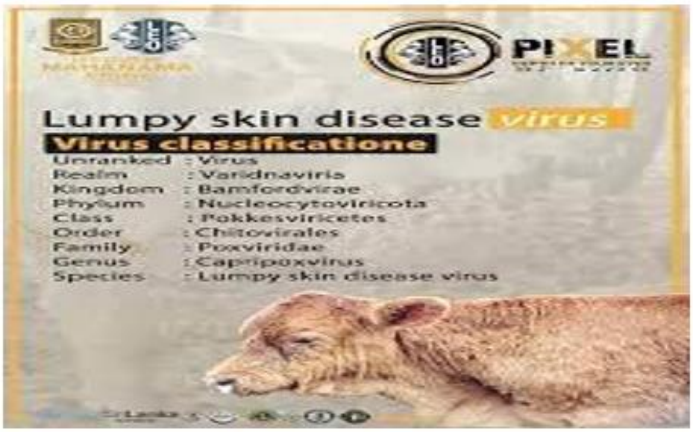

Fig. 2 Lumpy Skin Disease

Study Population

The dairy farms in Israel are divided mainly into two types: cooperative farms (kibbutz) and family farms. In 2018, 58% of the milk was produced by cooperative farms, 41% was produced by family farms, and 1% by agriculture school farms. The average size of the cooperative farms in 2018 was 474 cows, with an average annual milk production of 5,826,000 kg/farm.[24] The average size of the family farms at that year was 119 cows, and the average annual milk production was 1,361,000 kg/farm. All cows in the study were vaccinated by the veterinarians of the "Hachaklait" organization, which provides veterinary medicine services to more than 80% of the Israeli dairy cattle.[47,21]

Live Attenuated Homologous Vaccines

Homologous vaccines provide good protection for cattle against virulent field strains. LSDV vaccines either contain the well-known South African Neethling strain or, despite their confusing names, the KSGP O-240 and O-180 strains.[45] The Neethling strain was isolated from the first LSD outbreaks in South Africa and the vaccine strain was attenuated from the virulent strain by 61 serial passages in lamb kidney (LK) cells, followed by 20 passages in the chorioallantoic membrane of embryonated chicken eggs and three passages in LK cells [31,32] Another example of attenuation of a virulent field strain is the Madagascan LSD strain, which required 101 passages in rabbit kidney and five in fatal calf kidney cells [31]. Both of these examples demonstrate that a high number of passages are required to attenuate a highly virulent LSDV field strain for the safe to use in cattle. Still, homologous vaccines are known to cause side effects when cattle are immunized for the first time.[33]

Lumpy Skin Disease Virus Species

According to experts, lumpy disease is spreading in animals through a virus. It is also called 'Lumpy Skin Disease Virus' (LSDV). There are three species of this virus. In this, animals get fever. Along with this, weight loss, salivation, runny eyes and nose, milk starts decreasing. Different types of nodules start appearing on the body of animals. There are knots in their body. Female cattle can also suffer infertility, miscarriage, pneumonia and lameness due to this disease.[6,5,4] although the minimum protective dose is $\log_{10}$ 2.0 $TCID_{50}$. Capripoxvirus is highly susceptible to inactivation by sunlight and allowances should be made for loss of activity in the field.[28]

1. Capripox Speciesvirus :-

Fig. 3.1 Capripox Virus

1. Capripoxviruses represent a genus of the poxviridae family under the subfamily chordopoxviriniae; the genus includes three animal virus species that have a devastating impact on sheep, goats, and cattle in Africa, Asia, and most recently Eastern Europe.[45]

2. The viruses in the genus are sheeppox virus (SPPV), goatpox virus (GTPV), and lumpy skin disease virus (LSDV) which affect sheep, goats, and cattle, respectively ,Capripoxviruses share 98% sequence similarity between all three species; 147 putative genes are shared between goatpox and sheeppox while lumpy skin disease virus has nine additional genes which are not functional in SPPV and GTP.[3]

3. It is believed that SPPV was first reported in the second century in central Asia before spreading to surrounding countries and Europe.[3]

4. SPPV/GTPV are endemic in a large portion of the world [North and central Africa, the Middle East, Indian subcontinent, Southwest and central Asia.[4]

5. Outbreaks of sheep and goatpox can occur in new regions bordering endemic regions as illustrated by outbreaks in Mongolia and Vietnam.[4]

6. The transmission of sheep and goatpox can occur via aerosol, contact with contaminated material such as bedding, direct contact between infected animals.[3,5]

7. Historically LSDV is a relatively new.[45]

In this, animals get fever. Along with this, weight loss, salivation, runny eyes and nose, milk starts decreasing. Different types of nodules start appearing on the body of animals knots in.[,5,4]

Currently used vaccine for control of caprivirues

Fig. 3.2 Lumpivax Vaccine

The most effective and widdly used vaccine againt capripox viruses are attenuated vaccine.These live attenuated vaccine are generated by passaging field isolated viruses serially in tissue culture and or eggs unit attenuation is achieved.an example of a commonly used vaccine used vaccine is one developed in 1997 by precaustaet.

- which is a Romanian SPPV vaccine developed through passaging in lamb kidney cells 30 times until attenuated.This vaccine demonstrated protection against disease and generation of neutralizing serum antibodies.
- The vaccine is a freeze-dried vaccine without an adjuvant and can be stored for 2 years at 6 degrees allowing for flexibility in storage and production.[13]

2. Sheeppox Species

Sheep pox is a highly contagious disease of sheep caused by a poxvirus different from the benign orf. This virus is in the family Poxviridae and genus Capripoxvirus.

Rank: Species
Genus: Capripoxvirus Family: Poxviridae Order: Chitovirales
Phylum: Nucleocytoviricota Species: Sheeppox virus. [(3,2,4)]
Several SPPV based vaccines have been used in cattle against LSD with varying success in Turkey, the Russian Federation, parts of the Middle East, and the Caucasus region. The attenuated Yugoslavian SPPV RM65 strain vaccine was used in cattle in Israel and Jordan, while the Romanian SPPV strain in Egypt and Saudi Arabia.

Fig. 4.1 Sheeppox Virus

Sheep are the moving banks of shepherds and their economic contribution in terms of meat, wool and skin/hide is immense.[23,45] The causative agent, sheep pox virus (SPV), is antigenically and genetically closely related to goat pox virus (GPV) and lumpy skin disease virus (LSDV), the other members of the genus capripox virus. In some countries, SPV and GPV are cross infective to small ruminants posing problem in diagnosis and epidemiology. Prophylaxis using attenuated vaccines is the choice of control measure as the immunity is long lasting. Detailed information on isolation, identification, pathology, epidemiology, diagnosis and prophylaxis would not only help in updating the knowledge of scientific fraternity but will be useful to the policy makers in order to formulate appropriate measures for control and eradication of the disease. [22,23,]

Currently Used Vaccine For Control Of Sheeppox

Fig. 4.2 Sheeppox Vaccine

Sheep vaccinated with LSDV vaccine (G4) showed a slight increase in temperature between D2 and D4 pv and a limited local reaction was observed in 5 out of 8 animals from D3 pv until D12 pv. Cattle vaccinated with LSDV Neethling (G5) did not show hyperthermia except a slight rise at D7 pv for one cow. [4,7]

3. Gotpox Virus –

This chapter discusses the goatpox virus, which belongs to the Poxviridae family. The virus causes generalized pocks on mucos and on the skin of goats. Goats, sheep, and man are susceptible to the virus.(47,49.50) There are no reports of the goatpox virus from the Western Hemisphere that are unequivocal. Although there is cross-protection between goatpox and sheep pox, there is a difference in the pathogenesis. The goatpox virus in Kenya is not as host- specific as in the Middle East and India. In 2015, the safety, immunogenicity, and efficacy of a commercially available Gorgan goatpox strain vaccine was, for the first time, evaluated against LSD in Ethiopian cattle, using a combination of a vaccine challenge experiment and the monitoring of the immune responses in vaccinated animals in the field.[46]

Fig. 5.1 Gotpox Virus

Currently Used Vaccine For Conyrol Of Gotpoxvirus

Fig. 5.2 Varilrix Vaccine

India has about 150 million goat this disease is endemic in many parts of Asia, Africa and Middle East. Goat Pox is highly contagious and spreads through aerosol, contact and also through vectors such as flies. Goats of all ages and breeds are affected but disease is very severe in young, old and lactating animals.[8]

Vaccine Preparation

An inactivated antigen based on the LSDV-Serbia field strain [47] was prepared by Zoetis (Olot, Spain) and tested according to inactivation and sterility. The titer of antigen stock before inactivation was 10^6 cell culture infectious dose$_{50}$ CCID$_{50}$)/mL on the BHK-21 cell line.[36,44] The inactivated LSDV antigen preparation was then sent to the Friedrich-Loeffler-Institut on dry ice. There, the antigen dilutions were prepared, and the adjuvant was added. The antigen was used undiluted or diluted 1:10 (calculated titer before inactivation 10^5 CCID$_{50}$/mL on BHK-21 cell line) and 1:100 (calculated titer before inactivation 10^4 CCID$_{50}$/mL on BHK-21 cell line) in TE buffer at pH 8.0, and 10% Polygene (lot no. P10061; MVP Adjuvants®, Omaha, NE, USA) was added directly before the first immunization. Using real-time qPCR, the viral genome load of all three vaccine preparations was defined semi-quantitatively. For the undiluted vaccine preparation, Cq values of 14.2 and 15.0 before and after adding the adjuvant were ascertained.

The Role of Vaccination in LSD Prevention and Control

1. Strategic Considerations in LSD Vaccination

Vaccination represents the core tool in efforts to prevent and control LSD, yet its application varies greatly around the globe, not only due to the different epidemiological settings but also due to the socio-economic background and the pursued strategic goals in its implementation. A feasible vaccination approach depends on the epidemiological perspective, whether the country is facing an epidemic of LSD or the disease is already endemic.[36]

2. Vaccination-Oriented Risk Assessment

For maximum impact, vaccination against LSD should be embedded into existing disease control programs and risk-based surveillance, rather than stunting potential vaccine efficacy by treating it as a stand-alone measure.[10] The design of such disease control programs must consider the decision to vaccinate, economic effects of vaccination, the choice and availability of vaccine types, the timing and spatial extent of vaccination, the monitoring of the disease and vaccination progress, as well as the synergistic combination with additional, locally feasible control measures.[12]

Risk assessments and control of the risk factors for LSD offer valuable support in scenarios where LSD vaccination is not desired or possible for regulatory, economical, or infrastructural reasons, thus shifting from vaccination-cantered disease control programs to strengthening LSD biosecurity, awareness, relevant movement regulations, and risk-based surveillance. In summary, risk assessments guide LSD vaccination and control strategies by integrating current knowledge of disease control strategies, epidemiology, risk factors, and transmission dynamics. However, to date, no country has been able to eliminate the disease from its territory without vaccination.[31,22]

Experimental Design and Sample Collection

Cattle in group A were vaccinated with the undiluted antigen vaccine, cattle in group B received the antigen diluted 1:10, and cattle in group C were immunized with the antigen diluted 1:100. Cattle in group D served as the control group and were inoculated with PBS.[45,12] All animals were inoculated intramuscularly in the neck with 2 mL of the respective vaccine. mmunization was performed at day 0 of the animal trial, followed by secondary immunization 21 days post vaccination. Challenge infection was performed intravenously with 2 mL of the highly virulent LSDV-Macedonia2016 field strain 42 days post primary immunization (42 dpv ≅ 0 days post challenge. Back-titration of the challenge virus on MDBK cells revealed a titer of 106·6 CCID50/mL.33,45

Multidisciplinary Digital Publishing Institute (MDPI)

Lumpy skin disease virus (LSDV) belongs to the genus Capripoxvirus of the family Poxviridae.[9] Infected animals typically show fever, poor general body conditions, reduced feed and water uptake, lowered milk production, enlarged lymph nodes, and characteristic skin nodules.[2,8] The number of the lesions may vary from a few in mild cases,

to multiple lesions, covering the entire body in severely infected individuals. In addition, necrotic plaques may appear in the mucous membranes of the oral and nasal cavities, causing purulent or mucopurulent nasal discharge and excessive salivation. Moreover, ulcerative lesions may appear in the cornea of one or both eyes,[13,11] leading to restricted vision, and even to blindness. Severe cases may show characteristic lesions throughout the entire digestive and respiratory tracts and on the surface of almost any internal organ.[10,11]

LSD is a vector-borne disease, mechanically transmitted by blood-feeding mosquitos, biting flies [14,15] and some tick species.[18,26.30] The mechanical transmission mode (transmission of the virus does not depend on the capability of the virus to multiply inside vectors) is likely to allow the successful spread of the virus by any biting arthropod species if it prefers cattle or domestic buffalos, feeds frequently, and changes the host between the blood meals. Direct contact [19] and seminal transmission have been demonstrated experimentally, along with intrauterine transmission in the field. In almost all currently affected regions, the restriction of cattle or domestic buffalo movements face serious challenges, particularly in regions that lack the census data of cattle and buffalo populations, individual animal identification systems, and associated central record keeping, including movements of bovines. Farmers constitute the first line of defines against this highly contagious transboundary disease. Small-scale cattle and buffalo trade.[21,24]

Production, Quality, Transport, Storage, and Handling of the LSD Vaccines

Currently, most commercially available vaccines against LSD are live attenuated vaccines based on a LSDV strain, sheeppox virus, or goatpox viruss. The first inactivated vaccine has recently entered the market. The protection provided by a vaccine against LSDV depends on the seed virus, the level of attenuation, the volume of the dosage, and the titre of the attenuated vaccine virus in the final product. The quality of a vaccine product is of major importance to farmers and the welfare of cattle. Therefore, vaccines should be produced according to the good manufacturing practices. The guidelines for the production and control of immunological veterinary medicinal products have been published, for example by the European Medicines Agency.[38]

Most commonly used vaccines registered for use in cattle against lumpy skin disease (LSD). A good-quality vaccine, as well as its seed lots of virus, continuous cell lines, or primary cell culture batches and biologicals used for virus growth, must be free of extraneous viruses, mycoplasmas, other bacteria, fungi, protozoa, and rickettsia.[26,27]
The vaccine seed virus must be characterized using molecular tools and the origin and passage history should be well documented. LSDV is known to be very stable, and, for example, an experimental study has shown that a virulent LSDV kept in phosphate buffered saline (PBS) solution for 35 days at 28 °C was still infective with only some minor loss of titer.[32] More studies are warranted to investigate how long after dissolving the freeze-dried vaccine with a diluent the vaccine solution can be used without losing its efficacy.[30]

The costs of the vaccination are, therefore, covered by farmers themselves. Understandably, smallholders who own only a few animals cannot afford or do not want to buy vaccines in vials that contain more doses than they need. The strict requirement to use the vaccine within six hours after the reconstitution limits the possibility to share the vaccine vials between the farmers. The freeze-dried vaccine is stored at a refrigerator temperature, and for transport, the vaccine vials need to be kept at a stable temperature of 4 to 8 °C. During vaccination field campaigns, it must be considered that all capri poxvirus vaccines are believed to be sensitive to direct sunlight. The prices of the vaccines vary between different products and depend on the number of ordered dosages.[33]

Live Attenuated Homologous Vaccines

Homologous vaccines provide good protection for cattle against virulent field strains. LSDV vaccines either contain the well-known South African Neethling strain or, despite their confusing names, the KSGP O-240 and O-180 strains. The Neethling strain was isolated from the first LSD outbreaks in South Africa and the vaccine strain was attenuated from the virulent strain by 61 serial passages in lamb kidney cells, followed by 20 passages in the chorioallantoic membrane of embryonated chicken eggs and three passages in LK cells.[33.31]This can include local skin reaction at the vaccination site or generalized small-size skin nodules and a temporal reduction of the milk yield.[13,34,] often referred to as “Neethling disease” or “Neethling response”. The good field efficacy of the live attenuated vaccines was demonstrated between 2016 and 2017 when LSD outbreaks in Southeastern Europe were successfully eliminated by coordinated mass vaccination using homologous Neethling strain vaccines.[7]

Two so-called KSGP strains have been used in cattle against LSD in several countries, such as in Ethiopia,[36] Israel,[37] and Egypt.[38] Although the name of the strains refers to SPPV and GTPV, the real identity of the Kenyan sheep and goat pox (KSGP) and KS-1 strains has been revealed to be an LSDV strain.[29,41]. Capripoxvirus is highly susceptible to inactivation by sunlight and allowances shoul be made for loss of activity in the field.[28] According to the manufacturers, all currently available homologous and heterologous vaccines should be administered via subcutaneous route.[48] Two so-called KSGP strains have been used in cattle against LSD in several countries, such as in Ethiopia,[36] Israel,[37] and Egypt.[38] Although the name of the strains refers to SPPV and GTPV, the real identity of the Kenyan sheep and goat pox (KSGP) and KS- 1 strains has been revealed to be an LSDV strain.[29,41] although the minimum protective dose is $\log_{10}$ 2.0 $TCID_{50}$. Capripoxvirus is highly susceptible to inactivation by sunlight and allowances should be made for loss of activity in the field.[28]

Inactivated Vaccines

Nactivated vaccines provide both advantages and disadvantages compared to live attenuated ones. The most important benefit is the safety of inactivated vaccines. Their non-replicative characteristics prevent transmission of the vaccine virus to naïve animals, a reversion to virulence, and recombination with virulent virus strains.[36] Inactivated vaccines could provide a safe prophylactic vaccine alternative in disease-free at-risk countries, provided that a robust cattle identification and vaccination/health record system would be in place. In recent decades, several attempts have been made to generate inactivated vaccines, particularly against SPPV and GTPV, raising hopes for the successful development of inactivated capripoxvirus vaccines. As early as 1982, Solyom and co-authors published promising results regarding an inactivated SPPV vaccine.[22]

When comparing all three studies, conclusions can be drawn regarding the factors that are essential for the successful development of inactivated vaccines against LSDV. Since three different cell culture systems were used, primary cells, a bovine cell line, and a non-bovine cell line, and no differences could be observed between these systems, the influence of the cell culture system on the attenuation process can be considered minor. The choice of the adjuvant seems to be of major importance.[10,11]

Seroconversion and Duration of Immunity after Vaccination with LSD Vaccines

Immunity against poxviruses is both humoral and cell mediated.[17] Animals that recovered from natural LSDV infection developed antibodies capable of neutralizing up to three-log $TCID_{50}$/mL of the virus and were resistant to reinfection.[11] Antibodies are believed to play an important role during the early stages post-infection. Yet, the susceptibility of previously infected or vaccinated animals cannot be directly related to serum levels of neutralizing antibodies. It is known that not all vaccinated animals seroconvert, although they are fully protected against LSD.[28,30] Measuring anti-LSD antibodies alone may, therefore, not provide sufficient data on the protection status of the vaccinated animals, which must be considered when the effectiveness of the vaccination campaigns are evaluated in vaccinated herds.[50,45] . All capripoxviruses cross-react serologically and serology does not provide tools to differentiate if the animals are vaccinated using LSDV, SPPV, or GTPV strain vaccines. Recently, a commercially available ELISA by ID Innovative Diagnostics (Montpellier, France) has been demonstrated to be suitable for the detection of antibodies in serum and individual and bulk milk samples.[42]

Experimental Evaluation of the Efficacy of a Vaccine and Vaccination Effectiveness Studies

A challenge model for the evaluation of the efficacy of a vaccine against LSD has been described previously [35] Experiences obtained from previous animal experiments indicate that in order to produce visible clinical disease in half of the susceptible experimental cattle, the titter of the challenge virus needs to be between $10^{4.0}$ to $10^{6.5}$ $TCID_{50}$. Several different cells can be used to grow the virulent field strain. In addition, biopsies from the typical skin nodules can be tested with polymerase chain reaction (PCR) and used for the virus isolation purpose. Molecular tools have been described to differentiate a vaccine from a field virus [16,22]

Serological surveys after vaccination campaigns are complicated by the fact that some vaccinated animals, and those individuals showing a mild disease, may develop only low antibody levels although they are fully protected [11] The unclear meaning of seronegative animals decreases the value of sero-surveillance as a sole method. Seronegative animals in a vaccinated herd may or may not be protected by the vaccine or they may have been missed during the vaccination campaign.[14,15]

The most reliable results are obtained when the serum samples are collected not earlier than one month and not later than five months after vaccination .[37] Commercially available pan- capripoxvirus ELISA is available for large-scale testing, allowing easier monitoring of the duration of humoral responses in vaccinated herds than using a serum neutralization method.[18]

Vaccine Side Effects and Safety

The safety of live homologous vaccines in previously LSD-free countries is often of major concern. According to vaccine producers, the development of protective immunity takes approximately two to three weeks post-vaccination. During this time, animals can still show clinical signs if they become infected by a wild-type LSD virus. Usually, adverse reactions appear about one to two weeks after vaccination and often comprise a local reaction at the vaccination site and, more rarely, generalized skin lesions, known as a “Neethling response” [35] A temporary decrease in milk production may occur in vaccinated animals [13]. The level of attenuation of the vaccine product has a major effect on the appearance of fever and local or generalized skin reactions after vaccination with homologous vaccines. The skin lesions caused by the vaccine strain are clearly smaller and can easily be differentiated from those caused by virulent field strains [34]. [49]. Field experience obtained on the use of LSDV vaccines in the Balkan region and elsewhere indicated that the homologous vaccines caused side effects only when used for the first time in a previously disease-free country. The booster vaccination does not inflict reverse reactions, even if the initially used vaccine was a heterologous vaccine [34]

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