



A Review on: Lumpy Skin Disease: Enhance Awareness on the Epidemiological situation and Diagnosis; Prevention and Control Measures in Ethiopia

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Review Article

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Abstract

Lumpy skin disease (LSD) is an economically significant viral disease of cattle and caused by lumpy skin disease virus (LSDV). The virus is belonging to the genus *Capri poxvirus* (CaPV) of the family *Poxviridae*. Recently, the disease has been rapidly spreading to the Middle East, South east Europe and parts of Russian federation. The disease causes significant economic loss due to hide damage, loss of milk production, mastitis, infertility and death. Clinically, LSD is characterized by circumscribed skin nodules, fever, and abortions in females and sterility in males. LSD damages hides and causes death due to secondary bacterial infections. LSD is principally transmitted by blood-feeding arthropod vectors. However, transmission of the disease between animals is inefficient. Diagnosis is mainly based on observation of clinical signs and identification of the agent using conventional and real-time PCR methods, electron microscopy, and isolation of the virus in cell cultures, and using conventional serological tests. In endemic countries, vaccination is the only effective method to control the disease using live attenuated vaccines derived from Kenyan sheep and goat pox virus (KSGP) strains. However, there are reports of insufficient protection of the existing vaccines. Therefore; there is a need for more extensive data from the field and for larger-scale clinical trials to ensure the efficacy and safety of the current vaccines.

Keywords: Cattle; CAPV; KSGP; Lumpy skin disease; LSDV; Outbreak; Vaccine

Introduction

Lumpy skin disease (LSD) is an emerging viral disease of cattle caused by LSD virus (LSDV), belongs to the genus *Capri poxvirus* (CaPV) in the family *Poxviridae* which can lead to significant economic losses [1,2]. The disease is characterized by circumscribed firm skin nodules covering all parts of the body, lesions in the mouth, pharynx, respiratory tract, pyrexia, enlarged lymph nodes [3,4].

Until 1989, Lumpy skin disease is limited to African continent where the disease imposes serious constraints on livestock production and it is rapidly spreading throughout the Middle East regions and causes serious economic loss to the livestock industry [5-8]. Furthermore, currently the

disease has become a risk for European and Asian countries by moving beyond its usual territory [2]. LSD hinders cattle industry due to reduced milk production, mastitis, infertility, abortion, damaged hides, and sometimes death because of secondary bacterial infections [9,10].

Severity of clinical signs depends on the strain of the virus and breed of infected cattle [3]. Impacts of the global climate changes were considered to have the potential risk factor to establish the disease outside Africa. In Ethiopia, LSD was first observed in the North-west part of the country in 1983 [11]. Now the disease has been spreading to almost all the regions and agro-ecological zones of the country [12,13]. Ethiopia has the largest livestock population in Africa. The country has 60.39 million cattle, 31.3 million sheep and

32.74 million goat population [14].

Livestock industry plays an important role in the overall development of the country's economy but, the country is facing serious economic losses from viral diseases of cattle. Major epidemic outbreaks of LSD have been reported in between 2000 and 2007 in different regional states of Ethiopia; Amhara, Oromiya, Southern Nations, Nationalities and Peoples regions, Tigray, et al. [12]. Similar outbreak eruption had also been reported in all major parts of the country between 2000 and 2015 [13].

Vaccination is the only effective method to control the disease in endemic areas. A movement restriction of infected and exposed animals alone is usually not effective [15]. Live attenuated Kenyan sheep and goat pox (KSGP) vaccines produced in Ethiopia, at National Veterinary Institute (NVI), and the most commonly used [16]. However, outbreaks were reported after animals have been vaccinated against LSD from different countries [17].

Moreover, sheep pox virus based vaccines have also elicited incomplete protection against LSDV [18]. Given that, LSD is economically important trans-boundary livestock disease and/or major constraints for livestock development in Ethiopia. Therefore, the objectives of this review article are:

- To enhance awareness on the epidemiology, diagnosis, prevention and control measures of Lumpy skin disease
- To recommend the development of new effective vaccines by characterizing LSDV circulating in the field

Literature Review

a. Epidemiology

i. Historical Background of Lumpy Skin Disease: Lumpy skin disease was first recorded in Zambia in 1929. Soon after, the disease spread to other African countries causing severe outbreaks in the horn of Africa [19]. In 1970, it spread north into the Sudan and between 1981 and 1986 reached to Tanzania, Kenya, Zimbabwe, Somalia and Cameroon [20]. The disease is now enzootic throughout sub-Saharan African countries [19].

LSD was first diagnosed outside of Africa in Israel in 1989 and in subsequent years, cases were reported in Bahrain, Kuwait, Oman, Yemen, Lebanon, and Jordan. In 2006, the disease was re-introduced into Egypt through imported cattle from East Africa, and subsequently emerged throughout the Middle East. Since 2015 widespread LSDV outbreaks have occurred across several eastern European countries (Russia, Turkey, Greece, Albania, Bulgaria, Montenegro, Serbia, and Macedonia) [2,21,22].

b. Etiology

Lumpy skin disease (LSD) is caused by lumpy skin disease virus (LSDV), belongs to the family *Poxviridae*, genus *Capri poxvirus*. This virus is closely related to sheep pox (SPPV) and Goat pox virus (GTPV) [23]. Serologically, it is difficult to differentiate *CaPVs*. Thus, LSDV is antigenically related to SPPV and GTPV [24]. The members of this family are among the largest of all viruses, enveloped, linear ovoid shape with a molecular brick shaped or ovoid virion measuring 220-450nm by 140-266nm (Figure 1). LSDV is susceptible to sun light and detergents containing lipid solvents. The virus could be inactivated after heating for 1 hour at 55°C [25].

However, it withstands drying, pH changes if not an extreme pH and can remain viable for months in dark room such as infected animal shade off its host. LSDV can persist in skin plugs for about 42 days. It is likely that the viral type inclusion body protein in infected cells may protect the virion after the scab has disintegrated, although not yet proven [1].

c. Viral Genome

LSDV has double-stranded DNA genome of about 151kb. The full-genome sequencing of LSDV consists of a central coding region bounded by identical 2.4 kbp-inverted terminal repeats and contains 156 putative genes [26]. These genes encode several pox viral proteins known to be structural or involved in virion morphogenesis and assembly. The terminal genomic sequences contain a unique complement of at least 34 genes which are responsible in virulence, host range and/or immune evasion [27,28].

The *CaPVs* homolog of G-protein-coupled chemokine receptor (GPCR) gene is one of the variable genes within the *CaPVs* and used for genetic differentiation between members of *CaPV* [26,29].

Capri poxvirus nucleotide sequences are highly conserved and there is more than 95% homology amongst LSDV, SPPV and GTPV, LSDV is genetically and antigenically closely related to a strain of sheep and goat pox virus [28,30]. LSDV has an additional nine genes that are non-functional in sheep pox and goat poxviruses, some of which are likely responsible for their ability to infect cattle [26].

Comparative sequence analysis of the two field isolates of LSDV with the genome of the South African Onderstepoort vaccine strain suggests that *Capri poxvirus* virulence are linked to a number of genes putatively involved in host immune-modulation [28]. Lumpy skin disease viruses have complement of genes such as IL-10, (IF- γ) receptor; IL-1R, IFN- α/β binding protein and IL-18 (binding protein) are secreted and responsible for modulation or evasion of host immune response, inhibition of host cell apoptosis and in cell

or tissue tropism. Entrance of the virion particles in to the host cell membrane undergoes penetration and uncoating to

carry out its replication independently to the host nucleus [31,32].

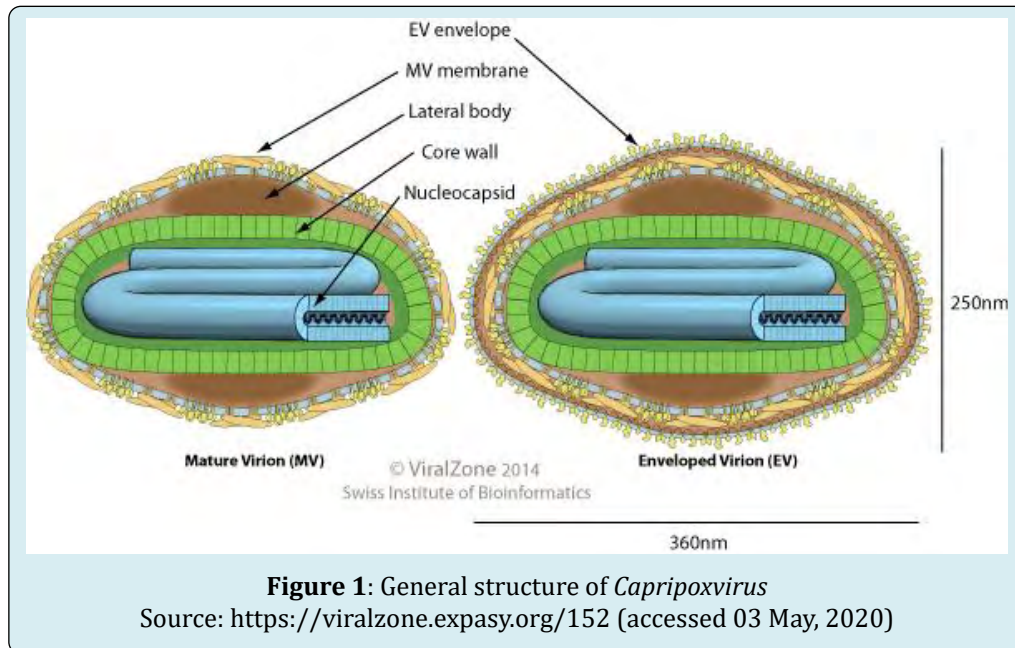


Figure 1: General structure of *Capripoxvirus*

Source: <https://viralzone.expasy.org/152> (accessed 03 May, 2020)

d. Viral Replication

Poxviruses carry out both replication and transcription their genome within the cytoplasm of infected cells and encode most of the proteins required for the synthesis of viral macro-molecules. After fusion of the virion with the plasma membrane or via endocytosis, the viral core has released into the cytoplasm. Transcriptase released from the core of the virion facilitates formation of mRNA within minutes after infection [33]. The polypeptides produced by translation of these mRNAs complete the uncoating of the core before the actual viral DNA synthesis begins 1.5 to 6 hours of infection. Two forms of virion have released from the infected cells (virion with one membrane, and virion with two membranes) and both types are infectious [34].

e. Host Range

LSDV mainly affects cattle but also observed in domestic Asian water buffaloes [35,36]. The European breed (*Bos Taurus*) is usually more susceptible than Zebu or Sub-Saharan Africa breed (*Bos indicus*). LSD-like lesions have been observed in intra-dermally inoculated with LSD [37]. Moreover, giraffe and impala has experimentally infected with LSDV. Domesticated buffaloes are more susceptible to LSDV than wild buffaloes [38]. LSD clinical signs have also been observed in a two year female Arabian Oryx [39].

f. Transmission

The principal means of transmission is believed to be mechanically by biting and blood-feeding arthropods. Under experimental condition, female mosquitoes such as

Aedes aegypti have been also involved in the transmission of LSDV [10,40]. Experimentally the virus was recovered from *Stomoxys*, *Biomyia*, *Musca*, *Culicoides* and *Glossina* species that may have a potential to transmit LSD, as all feed voraciously upon domestic cattle [41].

Three common African hard tick species, such as, brown tick (*Rhipicephalus appendiculatus*), the bont tick (*Amblyomma hebraeum*) and the African blue tick (*Rhipicephalus (Boophilus) decoloratus*) have been recorded in the transmission and epidemiology of LSD [2,42]. Direct transmission of LSD by contact between animals is inefficient [3].

However, husbandry practices such as communal grazing and watering troughs, introduction of new animals to the herd might contribute towards the spread of the disease [43]. Secretions of infected animals include milk of lactating cows, blood, nasal and lachrymal, semen and saliva may be sources for the transmission of LSDV when nodules on the mucous membranes of the eyes, nose, mouth, rectum, udder and genitalia are ulcerated [1].

Experimentally, LSDV has been isolated from infected semen [43]. Similarly, transmission of LSDV to heifers via semen has been clearly demonstrated [44]. In most of Sub-Saharan Africa, LSD has been observed following the rainy seasons. LSD outbreaks are associated with the rainy season due to the abundance of arthropod vectors [45]. However,

the incidence drops during the dry and cold weather seasons. In Ethiopia, higher prevalence of LSD has been related with risk factors like warm, humid agro-climate and abundance of vector population [12].

g. Morbidity and Mortality Rates

In outbreaks of the disease, morbidity and mortality of the disease varies extremely depending on the ages, breeds, geographic location, and climatic condition, and virus virulence, immunological status of the host and the abundance of arthropod vectors [19]. Naturally, *Bos Taurus* (European breed) is more susceptible than *Bos Indicus* (local Zebu) and cows at peak lactations are usually the most severely affected [46].

The morbidity can reach as high as 100% in natural outbreaks while mortality rate rarely exceeds 5% [1]. In Ethiopia, the highest morbidity (15.1%) and mortality (5.37%) of LSD were recorded in vaccinated feedlot cattle [16]. Moreover, morbidity and mortality rates of 22.9% and 2.31% respectively reported in vaccinated cattle [47].

h. Geographic Distribution of Lumpy Skin Disease

In the past, LSD was endemic throughout the entire continent of Africa, except Libya, Algeria, Morocco and Tunisia [19]. Now a days, the disease has been moved beyond Africa and sporadic LSDV outbreaks were reported in the Middle East region; such as Israel, Bahrain, Kuwait, Oman, Yemen and the West Bank (Figure 2) [8].



Figure 2: Geographical distribution of LSD, OIE Data [2]. https://www.researchgate.net/figure/Geographical-distribution-of-lumpy-skin-disease_fig1_283791807 [accessed 27 Jul, 2020].

Similarly, in recent times, new cases of LSDV have been reported in Iran, Azerbaijan, Iraq, Greece, and Cyprus between 2014 and 2015 [21,46]. Between 2015 and 2016, the first incursion of LSDV was reported in the European Union territory and in the northern Caucasus region of Russia [21,46]. Lebanon and Jordan joined LSD-affected countries in 2012 and 2013. Moreover, the armed Conflicts in Syria may allow the disease to spread into LSDV free European countries using Turkey as a portal of introduction [2].

i. Status of Lumpy Skin Disease in Ethiopia

Currently LSD has been recorded to almost all the regions and agro-ecological zones of Ethiopia [11,12]. However, according to the country's outbreak report database, at least one LSD outbreak was occurred from the period 2000-2009. As a result, Amhara and West Oromiya in 2000/2001, Oromiya and SNNP regions in 2003/2004, Tigray, Amhara and Benishangul regions in 2006/2007 and the outbreak numbers were progressively increased in central parts of Oromiya region in 2007/2009 [12].

LSD epidemic reoccurs after an interval of 5-6 years cycle in unvaccinated cattle population [30]. This also supports which stated that, outbreak occurs in epidemics several years apart. In Ethiopia, the national disease outbreak report during these 10 years has showed that the disease spreads almost too all the regional states of the country and in different agro- climatic zones [12,48].

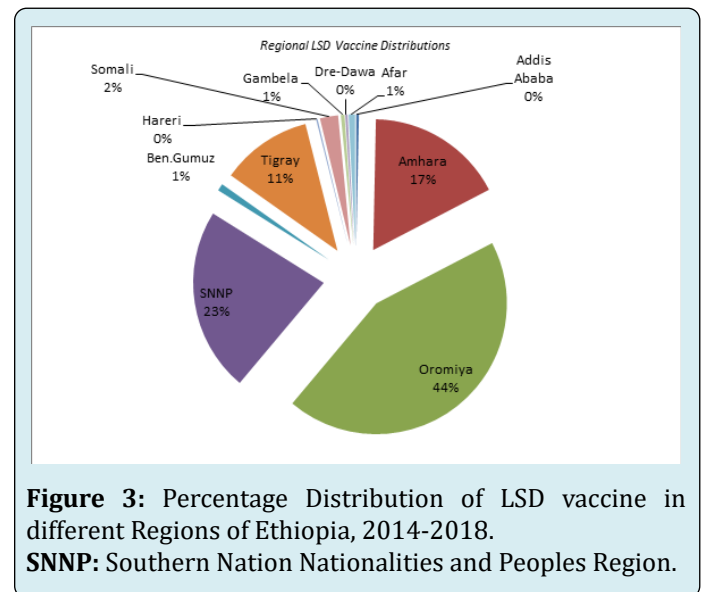


Figure 3: Percentage Distribution of LSD vaccine in different Regions of Ethiopia, 2014-2018.

SNNP: Southern Nation Nationalities and Peoples Region.

Based on outbreak reports, KS-1 vaccine distributions were carried out from the period 2014 to 2018 (Table 1) in different regional states of Ethiopian to prevent cattle against LSD. The regional delivery of the vaccines indicates that, the greatest number of live attenuated KS-1 vaccines

was distributed in Oromiya (44%), SNNP (23%), Amhara (17%) and Tigray regional states (11%) to vaccinate cattle against LSD (Figure 3). For the period 2014-2016, the

vaccine sales in National Veterinary Institute (NVI) revealed that the number of LSD outbreak was increased (personal communication from vaccine sales directorate).

Regions	2014	2015	2016	2017	2018	Total
Addis Ababa	93,200	194,840	110,800	2,800	8,600	410,240
Amhara	4,481,000	5,335,000	662,150	3,861,500	6,809,800	21,149,450
Oromiya	11,301,400	9,352,860	13,921,340	8,653,500	11,061,800	54,290,900
SNNP	2,281,100	6,787,400	8,142,690	3,000,700	8,032,500	28,244,390
Ben.Gumuz	204,200		280,300	340,000	278,200	1,102,700
Tigray	2,700,000	2,900,000	771,290	3,600,000	4,000,000	13,971,290
Hareri	-	-	205,000	25,000	-	230,000
Somali	-	-	1,477,500	1,000,000	300,000	2,777,500
Gambela	-	560,300	-	-	-	560,300
Dre-Dawa	50,000	100,000	100,400	100,000	300	350,700
Afar	-	200	243,550	240,000	501,600	985,350.00
Grand Total	21,110,900	25,230,600	25,915,020	20,823,500	30,992,800	123,662,580

Table 1: Yearly distribution of LSDV vaccines from 2014-2018.
Source: National Veterinary Institute's Sales Directorate.

Annually, LSD vaccine distributions were increasing (except in 2017) from the period 2014 to 2018 (Figure 4). In 2018, the highest number of LSD vaccines (13%) was distributed within the country to control the disease; this trend has showed that LSD outbreaks are dramatically increasing in Oromiya, SNNP, and Amhara and Tigray regions

in every year. Most of the LSD vaccine sales in Ethiopia have been carried out consistently associated with outbreaks of the livestock diseases; because mainly reactive vaccination campaigns have been practiced using KS-1 vaccine following outbreak reports (also applies for other animal diseases in Ethiopia).

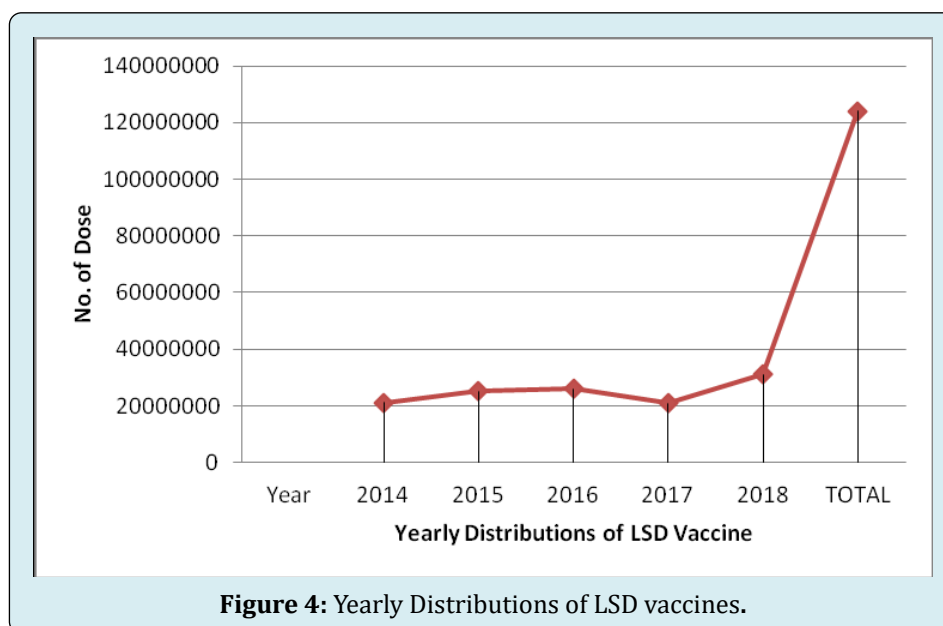


Figure 4: Yearly Distributions of LSD vaccines.

However; timely diagnosis of susceptible animals are important to implement LSD control measures. Disease

prevention should be implemented via vaccination with sheep pox and attenuated LSDV based vaccines [48]. In 2014,

field visits were carried out in some districts of Ethiopia such as; Debre-Zeit, Addis Ababa, Ambo, Ginchi, Holeta and Selale based on LSD outbreak reports to NVI. I was conducted interview with cattle owners and veterinarians about the prevalence of the disease and their vaccination strategy to control the disease. Some owners started vaccinating animals when the disease is already circulating in the area. Among the vaccinated group some animals developed clinical sign three to six days following vaccination with live attenuated KSGP vaccines.

However, animals will develop protective immunity from 10 to 21 days post vaccination, and then require an annual booster dose [49]. Some cattle owners also did not vaccinate their animals for the last 5-6 years and this could be an indication of lack of sufficient herd immunity. Some owners were not willing to vaccinate lactating cows and beef cattle due to lack of awareness. The storage temperature was not maintained as manufacturer's labeled (-20°C). Healthy and incubating animals were vaccinated with the same needles. A few number of dairy farms followed regular vaccination programs are protected from LSD. Therefore this will be the reason of detecting clinical signs in vaccinated animals with KSGP.

j. Economic Importance of the Disease

Due to its rapid spread of the virus in susceptible cattle populations and its economic consequences on the global cattle industry, LSD is categorized as a modifiable disease by the World Organization for Animal Health (OIE) [19].

The economic importance of LSD is reflected with loss of milk production, temporary or permanent sterility in bulls and cows, damage to hides and death due to secondary bacterial infections, costly control and eradication measures and enforced animal movement restrictions [19,20,50]. Moreover, LSD is one of the trans-boundary diseases extending beyond its traditional boundaries. Hence, movement restriction of live animals and animal products can significantly affect the global trade [2].

In Ethiopia, the financial losses estimated based on milk, beef, draught power, mortality, treatment and vaccination costs for individual head of local zebu to be 6.43 USD and for the Holstein Friesian 58 USD [12] and the total loss of USD 667,786 in feedlots in and around Adama due to mortality and rejection [50]. Furthermore, total losses of 51,590 USD from death of 108 cattle had been calculated in central Ethiopia [16].

Diagnosis

Diagnosis of LSD is often based on characteristic clinical signs and clinical diagnosis. In naturally infected animals,

the following Clinical manifestations have been observed: such as; Lachrymation, nasal discharge, enlarged lymph nodes, high fever ($>40.50^{\circ}\text{C}$), drop in milk yield, generalized skin nodules (Figure 5), necrotic pox lesions around muzzle (Figure 6), Skin lesions in the legs and secondary bacterial infections, deep scab formations (sit-fast) (Figure 7), and mastitis [51].

Milder forms of LSD could be confused with other diseases causing skin lesions such as pseudo-lumpy skin disease (bovine herpesvirus-2 infection), insect bites, demodocosis, and dermatophilosis. Moreover, diseases causing mucosal lesions, such as Rinder pest, bovine viral diarrhoea/mucosal disease, and bovine malignant catarrhal fever, also makes field diagnosis complex [49].



Figure 5: Generalized skin nodules.

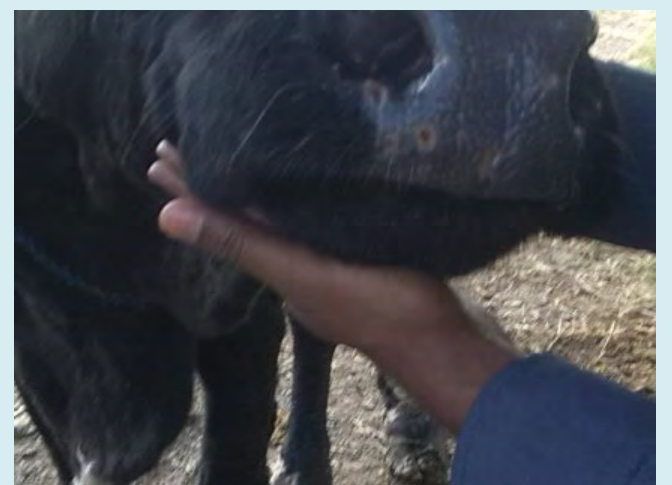


Figure 6: Necrotic pox lesions appear in the muzzle.



Figure 7: Necrotic nodules and deep scab formation (sit-fast).

Source: Author, 2014 (figures 5, 6 and 7)

Effective control or eradication of LSD in endemic and non-endemic areas requires rapid and accurate diagnostic methods to confirm a presumptive diagnosis [52]. However, mild and subclinical forms require rapid and reliable laboratory testing to confirm diagnosis [53]. Most commonly used methods of diagnosing LSD are detecting LSDV DNA which is most rapidly done by using the polymerase chain reaction method (PCR) [54].

A variety of molecular tests using Capripoxvirus-specific primers are considered sensitive and specific for LSDV identification [29,55]. Electron microscopy can be used to identify the classic poxvirus virion but cannot differentiate to genus or species level [49], and virus isolation using cell culture followed by PCR is important to confirm the virus identity [56]. Virus isolation on primary or secondary bovine dermis cells or lamb testis cells is considered to be the most sensitive. All *CaPVs* share a common major antigen for neutralizing antibodies, therefore; it is not possible to distinguish strains of *CaPVs* using serology-based diagnostic techniques [49].

Virus neutralization tests and electron microscopy examination are widely used as gold standard methods for the detection of *CaPV* infection [56]. Serological assay methods such as indirect enzyme linked immuno-sorbent assay (iELISA), western blotting, agar gel immuno-diffusion test and the indirect fluorescent antibody test are also used to diagnose LSD. However, Serological assessment of antibodies to a *CaPVs* may sometimes be difficult due to the cross-reactivity encountered with other poxviruses as well as to the low antibody titers elicited in some animals following mild infection or vaccination. Therefore, PCR was

the test of choice for rapid detection and identification of the LSD outbreak causative agents [49].

k. Treatment, Prevention and Control

Unfortunately there are no specific antiviral drugs available for the treatment of lumpy skin disease. However, Sick animals may be removed from the herd and given supportive treatment such as antibiotics, anti-inflammatory drugs, and vitamin injections to treat secondary bacterial infections or to improve the animal's appetite [57]. LSD thought to be transmitted primarily by blood-feeding insects; hence quarantine and movement restriction alone are not very effective to control LSD unless supported by mass vaccination [57]. Therefore, efficient insect control may reduce the rate of LSDV transmission [58]. All strains of *CaPVs* from cattle, sheep and goat origin, share a common major antigen that makes it possible to use sheep pox or goat pox vaccine against LSDV infection in cattle [59].

In endemic countries, vaccination against LSD with live attenuated vaccines are the only effective method to control and prevent the disease [60]. Because immunity to *CaPVs* is mainly cell mediated and is better stimulated by the use of live vaccines. *CaPV* vaccine strains include LSDV Neethling, Kenyan sheep and goat pox virus (KSGPV) O-240 and O-180 strains, Yugoslavian RM65 sheep pox (SPP) strain, Romanian SPP, and Gorgan goat pox (GTP) strains have been used for the control of LSD [5,18,59]. Homologous live attenuated (Neethling strain) LSD vaccines are more successful than vaccines based on attenuated sheep pox viruses. Heterologous live attenuated virus vaccine may cause local and sometimes severe reactions [57].

Partial sequences of (KSGPV) O-240 strain has shown to be LSDV and not SPPV or GTPV [61]. Soon after, the complete genome sequences of the strain KSGP O-240 was confirmed to be LSDV [62]. In 2006, the use of live attenuated KSGP O-240 vaccine strain in Egypt [63] and RM65 SPP vaccine to cattle from 2006 and 2007 did not provide complete protection against LSDV in Israel [18]. Similar phenomenon has also been reported in Egypt in 2016 [64]. In Ethiopia, the KS-1vaccine did not provide complete protection against LSDV. Then, challenge experiments has to be carried out to measure cellular and humoral immune responses [16]. However, field report in Kenya has showed that the KSGP strain is safe and protective [65]. Thus, vaccines with demonstrated safety and efficacy in challenge experiments have been recommended to solve these disagreements [66].

Conclusion

In conclusion, the present review has shown that LSDV is prevalent to almost all the regions and agro-ecological zones of Ethiopia and the disease poses considerable economic

losses to cattle populations. Transmission commonly is by blood-feeding arthropods and direct contact is considered to be relatively ineffective. Although vaccination with KSGP is a realistic approach to control the disease in endemic countries, but several reasons were forwarded to defend the efficacy or effectiveness of KSGP vaccines. Hence, the occurrence of LSD after vaccination with KSGP strain will be suggestive of insufficient protection. Therefore, in order to come across these disagreements between these results, the following recommendations are forwarded:

- Detailed epidemiological investigations should be done to fully establish mode of LSD transmission;
- Full genome sequencing should be done to design a safe vaccines with good protection
- Further molecular characterization should be done on the existing vaccines;
- Vaccine efficacy should be measured in large-scale challenge studies;
- To create sufficient herd immunity, regular Vaccination campaigns should be implemented by effective and potent vaccine.

Ethical Statements

This article did not include animal experiments

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Competing Interests

The author declares that there is no conflict of interest regarding the publication of this article.

Additional Information

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