



EPIDEMIOLOGY, DIAGNOSIS AND CONTROL OF LUMPY SKIN DISEASE IN EGYPTIAN RUMINANTS

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Summary

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Lumpy skin disease (LSD) is one of the most important diseases causing great economic losses in live animals stock industry of affected countries. It is an infectious vector borne viral illness considered one of major trans-boundary animal diseases affecting cattle and Asian domestic buffaloes (*Bubalus bubalis*). The aim of the current review is to clarify the current status of LSD epidemiology and to throw light on the methods of LSD diagnosis, prevention, treatment and control. LSD is rarely fatal, characterised by nodules on the entire skin of the affected animals, and has a high morbidity rate. The disease has severe direct adverse effects on cattle production, milk yields and animal body condition from damage of hides, abortions, infertility and other indirect effects resulted from restriction of animal movements and trade. The first recorded outbreak was in Zambia in 1929. It is considered an endemic disease in African continent. First report of LSD in Egypt was in Suez Canal governorate in 1988. Diagnosis of LSD virus depends on the highly characteristic clinical signs in severely infected cases. In mild cases the diagnosis depends on the detection and isolation of the virus on different cell lines and on chorio-allantoic membranes of embryonated chicken eggs. Viral nucleic acid detection by molecular techniques as real time PCR is considered the test of priority because it is rapid, sensitive and quantitative. Prevention of the disease depends mainly on vaccination programmes for the entire cattle and buffalo populations, restriction of animals' movement inside the country and through country borders, controlling insect vectors, in addition to symptomatic treatment of infected animals.

Key words: control, diagnosis, epidemiology, lumpy skin disease, ruminants

INTRODUCTION

Lumpy skin disease (*Pseudo-urticaria*, *Neethling disease*, *exanthema nodularis bovis*, and *knopvesiekte*) are multiple names for one of the vector borne diseases of cattle and Asian water buffaloes. Affected animals suffer from fever, multiple

firm well circumscribed deep-seated skin nodules and necrotic plaques in the mucous membranes of the oral cavity and upper respiratory tract, mastitis, and orchitis with generalised lymphadenopathy (Sprygin *et al.*, 2019b). Although LSD is

of low mortality rate, the disease is of major economic importance due to production losses from severe emaciation, drop in milk production, abortions, secondary mastitis, loss of fertility, and hides damage (Gari *et al.*, 2011). It was first reported in Northern Rhodesia in 1929 (Morris, 1930) and it was suggested that the skin lesions resulted from insect bites or plant poisoning. LSD was firstly described as an infectious disease in 1943 after an epizootic in Northern Botswana (Von Backstrom & Ngamiland, 1944). LSDV is one of the capripoxviruses which include lumpy skin disease virus (LSDV), sheep pox virus (SPPV) and goat pox virus (GPPV), in subfamily Chordopoxvirinae, family Poxviridae. Those capripoxviruses are responsible for great economic losses of domestic ruminants in Africa and Asia (Tuppurainen *et al.*, 2017a). From Central and East Africa, the disease rapidly spread in Africa and was first recorded in Ethiopia in 1983 (Mebratu *et al.*, 1984). LSD was reported as an endemic disease in Africa. The first report of LSD in Egypt was in 1988 after starting the importation of cattle from African countries (House *et al.*, 1990). It was reintroduced in Egypt during 2006 and many outbreaks were recorded after that in 2011, 2014, 2017, and 2018 (Salib & Osman, 2011; Abdallah *et al.*, 2018). Although LSDV is transmitted mechanically or biologically by arthropod vectors, transmission can also occur through consumption of contaminated food or water, direct contact, contaminated semen in natural mating and artificial insemination (Abdulqa *et al.*, 2016; Alkhamis & VanderWaal, 2016). Severe cases of LSD have characteristic clinical signs, but early and mild cases of the disease need laboratory confirmation (Tuppurainen *et al.*, 2018). Real time PCR is the test of choice

for the viral nucleic acid detection, as it is rapid, quantitative, simple, specific and sensitive and can be used in large scale testing (Sprygin *et al.*, 2019a). LSD is considered a major transboundary animal disease due to its economic impact on animal production, it is rapidly spread across national borders resulting in international trade restrictions. Thus, regional cooperation in prevention, control and eradication including regular vaccination, restricted animal movement and quarantine, slaughter of infected animals, proper disposal of contaminated materials and disinfection of contaminated premises are necessary (Gumbe, 2018). Therefore, this review will throw light on LSD recent situation updates raising concerns about biology of lumpy skin disease virus, mechanism of the disease spreading, clinical and laboratory diagnosis and measures for control and/or eradication.

BIOLOGY OF LSDV

Agent characteristics

LSD virus is a member of family Poxviridae that includes the biggest viruses causing disease naturally in most domestic animals except in dogs. It composed of two subfamilies; Chordopoxvirinae, Poxviruses of vertebrates and Entomopoxvirinae, Poxviruses of insects (Haegeman *et al.*, 2021). All capripoxviruses are growing slowly on cell cultures and may need several passages on cells of bovine and ovine origin. Intra-cytoplasmic eosinophilic inclusion bodies can be seen microscopically after staining the infected monolayer cells with haematoxylin and eosin (Prozesky & Barnard, 1982). The virus causes macroscopic pox lesions when propagated onto the chorio-allantoic membranes of embryonated chicken eggs (Hala *et al.*, 2021).

Phylogenetics

The family Poxviridae is characterised by its large and complex genome containing single, linear molecule of double-stranded DNA (dsDNA) coding for about 200 proteins. DNA molecule is continuous without free ends because the dsDNA are ligated to each other (Toplak *et al.*, 2017). Poxviruses are the only DNA viruses that complete their replication cycle in the cytoplasm. In the cytoplasm, the produced mRNA is translated to proteins and then to copies of genome for progeny virions. The new progeny virions are released from the cell by budding. The Poxviridae family has at least ten major antigens with a common nucleoprotein antigen which causes the cross-reactivity among species. Ten viral enzymes are present within the virus particles. Their function is to promote nucleic acid metabolism and genome replication (Tulman *et al.*, 2001; King *et al.*, 2012). Capripoxviruses include LSDV, SPPV and GPPV. Their dsDNA have around 150 kilo base pairs (Kbp) and are relatively large in size (230–260 nm). Their capsid containing the genome and lateral bodies is brick or oval shaped. There is extensive DNA cross hybridisation between species responsible for serological cross reaction and cross protection between their members (King *et al.*, 2012; Calistri *et al.*, 2019). They are sharing about 97% sequence identity (Tulman *et al.*, 2002). Molecular studies indicated that LSDV is phylogenetically distinct from SPPV and GPPV as it has two unique genes not present in sheep pox or goat pox viruses (Tulman *et al.*, 2002). All available data suggest that there is only one serotype of LSDV (Neethling strain) as complete genome sequencing of recent isolates of LSDV show 99.5% and 99.8% homology, respectively with the field LSDV isolated in South Africa that

is ensuring genetic stability of LSDV and indicate that the virus is a single serotype (Toplak *et al.*, 2017). The phylogenetic analysis of G-protein coupled chemokine receptors (GPCR) genes of LSD in cattle and buffaloes in Egypt during the summer in 2011 revealed that GPCR genes were genetically closely interrelated showing the ability of transmission of cattle LSDV to water buffaloes (El-Tholoth & El-Kenawy, 2016).

Virulence

So far, researches have not found differences in the virulence between different LSDV isolates. The severity of the disease is attributed mainly to the immune status, breed, production stage and age of the affected animals (Badhy *et al.*, 2021).

Resistance and survival of the virus

LSDV is highly stable for long periods at room temperature especially in air dried hides. It is recovered for about 18 days, 33 days or longer and persists in necrotic skin nodules, while in desiccated crusts the virus remains viable up to 35 days. The virus persists for several months in contaminated animal sheds. Inactivation of the virus can occur at temperature of 55 °C for two hours and 65 °C for 30 minutes. Also, it is stable at skin nodules at –80 °C for 10 years and in infected tissue culture fluid at 4 °C for 6 months. Concerning the stability of LSDV, it is susceptible to high alkaline pH or acid pH and stable at pH 6.6–8.6 for 5 days at 37 °C. The virus is greatly susceptible to ether (20%), chloroform, formalin (1%), phenol (2%) for 15 min, sodium hypochlorite (2–3%), iodine compounds (1:33 dilution) and quaternary ammonium compounds (0.5%) (OIE, 2017).

EPIDEMIOLOGY

Geographical distribution

LSD virus is causative agent of an endemic windy spread disease in Africa except Algeria, Morocco, Tunisia and Libya. The Americas and Australia are free from all capripoxvirus infections (FAO, 2017). In 2013, it was recorded in Turkey (Timurkan *et al.*, 2016) and now it is endemic in this country, its spread causing many outbreaks in European countries since 2014.

African first LSD report was in Zambia, 1929 (Gari *et al.*, 2011). In 1989, LSD was recorded outside Africa through Israel to Palestine, Jordan, Lebanon, Kuwait, Saudi Arabia, Iraq, Oman, Yemen, United Arab Emirates and Bahrain (Abutarbush *et al.*, 2015; Al-Salihi & Hassan, 2015; Sameea *et al.*, 2017). It was reported in the middle and east of Europe in 2014 (Tageldin *et al.*, 2014; Sameea *et al.*, 2017). In 2016, LSD was confirmed in South East Europe – in the Balkans and Caucasus (OIE, 2017).

In Egypt, LSD was reported in 1988 after importation of cattle from Ethiopia and other African countries where it was clinically demonstrated in Suez Canal governorates in the summer season of the same year. The infection was not recorded in the winter season (Ahmed *et al.*, 2021). In 1989, reoccurrence of LSD in a period of five to six months was recorded within 22 of the 26 Egyptian governorates. In summer of 2006, other outbreaks reoccurred in many of the Egyptian governorates (Abdallah *et al.*, 2018). The reoccurrence of the disease in Egypt after its absence for 17 years was attributed to a combination of the uncontrolled animal movements, immune status of the animals, wind and rains which are the most important influences on the vector population

density and strengthen the transmission rates (Al-sabawy *et al.*, 2020). This was followed by other outbreaks in 2011, 2014 and 2017 which may have occurred as a result of the endemic status of the disease when the virus finds its way to the non-immune cattle herds. In 2017, the outbreaks of LSD occurred through the importation of cattle from Ethiopia as a result of the unlimited movement of animals at country borders which is the major threat for LSD (Zeedan *et al.*, 2019). It was followed by another outbreak in 2018-2019 that occurred mainly in the Nile delta and the western region.

Host range

Cattle and Asian water buffaloes (*Bubals bubalis*) are the main natural host to LSDV with all ages and sexes susceptible to infection, while calves develop severe lesions 24–48 hours earlier than their dams (Elhaig *et al.*, 2017). More severe disease signs were recorded in thin skin breeds as Friesians and in cow's peak lactation (Şevik & Doğan, 2017). No epidemiological data on the role of small ruminants as a reservoir for LSDV have been recorded although mixed herds of cattle, buffaloes, sheep and goats are more commonly encountered (Elhaig *et al.*, 2017). In Egypt, the LSDV is causing unapparent to severe disease in native breeds of all ages affected but severe cases were found in young calves and foreign breeds (Salib & Osman, 2011). Also, isolation of LSDV from naturally infected water buffaloes has a great role in the appearance of disease outbreaks (Elhaig *et al.*, 2017; Sharawi & Abd EL-Rahim, 2011). Although in another study buffaloes were in contact with clinically infected cattle confirmed by virus isolation and PCR, none of buffaloes were positive for LSDV by virus isolation and

PCR, despite little increase in antibodies levels against LSDV in their sera (Elhaig *et al.*, 2017). Clinical signs of LSD have been reported in Arabian Oryx (*Oryx leucoryx*) and spring box (*Antidorcas marsupialis*). Also giraffe (*Giraffa camelopardalis*) and impala (*Aepyceros melampus*) have been experimentally infected, but wildlife has no significant role in the epidemiology of the disease (Gortázar *et al.*, 2021). Experimental infection of sheep and goats with LSDV can occur, but there is no natural infection with the virus (Wolff *et al.*, 2020). LSD is not a zoonotic disease (Şevik & Doğan, 2017).

Morbidity and mortality

Morbidity rates range from 10 to 20% (OIE, 2021), but under certain conditions may reach 80–90% while mortality rate is from 1 to 5% (Kiplagat *et al.*, 2020). In Egypt, morbidity rate recorded during LSD outbreaks may attain up to 100%, while mortality rates and case fatality in Egyptian cattle: 1.8% and 1.8%, respectively. The morbidity rate is high as a result of the exposure of cattle at the same time to the infection with FMDV, which has an immune suppressive effect and theoretically could occur (OIE, 2017).

Transmission

Source of infections

The main source of LSDV infection to healthy animals are clinically ill animals whereas skin lesions are source of the virus for a long period of time (Şevik & Doğan, 2017). LSDV was also detected in blood, nasal and conjunctival secretions, saliva, semen and milk. In affected ruminants, nodular lesions on different mucous membranes (eye, nose, mouth, rectum, udder and genitalia) may ulcerate and act as a source of the virus (Tuppurainen *et al.*, 2015; Abdulqā *et al.*, 2016). Viraemic

animals act as a source of infection as viraemia may extend for up to two weeks (Gari *et al.*, 2011; Tuppurainen *et al.*, 2017a). The susceptible ruminants get infected by blood feeding arthropods (biting flies, mosquitoes and ticks), through direct contact or contaminated feed and water in seldom cases. Intrauterine transmission can occur at late gestation and infected cows deliver calves exhibiting skin lesions all over their bodies with immature developed signs, they may die within few hours after birth (Rouby & Aboulsoud 2016). Calves are infected either through LSDV-contaminated milk or from teats lesions (Sprygin *et al.*, 2019b). Accidental transmission may happen during mass vaccination with a single syringe, in this case the needle spreads virus from skin lesions or viraemic animals to healthy ones (Tuppurainen *et al.*, 2017b).

Route of transmission

Direct transmission. Direct contact does not have an efficient role in LSDV transmission (Sprygin *et al.*, 2019b), but sometimes it may have a respective role in LSDV transmission as outbreaks of the disease are reported in absence of the insect vectors (Sprygin *et al.*, 2019b). Transmission via semen is experimentally reported (Abdulqā *et al.*, 2016). During experimental infection, live LSDV was isolated from semen 42 days post infection (dpi) and specific viral DNA was demonstrated using PCR 159 dpi from bulls that showed no clinical signs (Irons *et al.*, 2005). Vaccinated bulls with Neethling LSDV strain didn't shed vaccine virus in their semen (Osuagwuh *et al.*, 2007).

Indirect transmission. Earlier studies suggested that LSDV transmission between naive (non-immune animals) and infected animals kept together failed in

transmission of the virus (Sprygin *et al.*, 2019b), but recent experimental studies suggested that 50% of these animals present clinical signs and others are only viraemic (Sohier *et al.*, 2019; Wolff *et al.*, 2020). Further studies are required for clarifying the LSDV transmission mechanisms. Recent data about the occurrence of LSD in Russia found infected cases 800 km away from the centre of the outbreak which was attributed to the use of the same vehicles that transport infected animals (Sprygin *et al.*, 2019b).

Role of vectors

It has been ensured that large populations of arthropod vectors have a good chance to carry and transmit the virus. These vectors vary according to geographical regions (Alkhamis & VanderWaal, 2016). There are no biological arthropods vectors for LSDV, mechanical role of transmission only occurs. High density of biting arthropods affect the disease prevalence, in the presence of warm and humid weather conditions (Şevik & Doğan, 2017; Gumbe, 2018). There is a higher prevalence of LSD recorded in wet summer and fall months in South Africa (Gari *et al.*, 2012). In Egypt, LSD outbreaks were reported in summer and fall seasons in the presence of insect vectors that have a main role in virus transmission and which are abundant in these seasons, while the disappearance of cases were seen in winter (Salib & Osman, 2011). Transmission between different herds that keep long distance between each other and the presence of quarantine measures suggests that the infection is vector-mediated as the disease outbreaks at different governorates of Egypt in summer 1989 occurred despite restrictions of animal movements (Fayez & Ahmed, 2011). Also, high morbidities are observed where

mosquito population is abundant. Mechanical transmission through contaminated mouth parts of vectors is also possible (Sprygin *et al.*, 2019b). Recently, some researches concentrated on the role of ticks carried by migratory birds in transmission of LSDV (Sprygin *et al.*, 2019b). Molecular studies showed trans-ovarian transmission of LSDV by *Phipicephlus decoloates* ticks, *Phipicephlus appendiculates* and *Amblyomma hebraicum* ticks (Lubinga *et al.*, 2014). *Aedes aegypti* has been involved in airborne transmission over long distance in free areas of disease which complicates the control measures by animal movement restriction (Sprygin *et al.*, 2019b). The virus has been also detected in *Stomoxys*, *Biomyia*, *Musca*, *Culicoides* and *Glossina* species which potentially transmit LSDV (Issimov *et al.*, 2020). A significant role of *Culicoides* species was reported in the transmission of LSDV during 2014–2015 in Turkey (Şevik & Doğan, 2017). The wind currents play an important role in the spreading of virus by female *Culicoides* and mosquitoes (Issimov *et al.*, 2020). Severe climatic changes in the three months before the epidemic outbreak have a role in the spread of the disease, as happened in Egypt in 1989 and 2006. In 1989, Occupied Palestine was attacked by LSD outbreak and the source of the virus was from the Egyptian Domiatia and Port Said governorates (El-Sherif *et al.*, 2010). Another outbreak occurred in Nile delta, Suez Canal and North Sinai in 2006 due to importation of cattle from Ethiopia. The disease spread to Occupied Palestine and Saudi Arabia at the same time. Stable flies were recorded to have a role in the wind transmission of LSDV from Egypt to Occupied Palestine (Calistri *et al.*, 2018). All these studies confirmed that infected vectors have a great role in the transboundary

transmission of vector borne diseases in the Middle East and Europe, as Middle East is present in an area which joins Europe, Africa, and Asia (Sprygin *et al.*, 2019b).

Pathway of the disease

The movement of animals is the main risk factor to introduce infectious diseases into disease-free areas. The pathway of LSD introduction comprises introduction of infected animals, movement of flying vectors and the windborne transmission of vectors carrying the LSDV in blood meal from an infected animal (Şevik & Doğan, 2017). In 2014, epidemiological investigations of LSD outbreaks in Egypt, Palestine, Iran and Azerbaijan revealed that the legal and illegal animal movements are the pathway for LSDV introduction (OIE, 2017). The biggest movements of live cattle in Muslim countries reach a peak on Eid El-Adha which enhances the animal trade of high numbers of animals. Such movements of high numbers of animals over a short period of time may have resulted in poor regulation and increased risk of introduction of the transboundary animal diseases (Sprygin *et al.*, 2019b).

DIAGNOSIS

Clinical diagnosis

Clinical signs

LSD incubation period in natural infection ranges from 2 to 5 weeks, while in experimental infection: between 4–7 days (Wolff *et al.*, 2020). There are mild and severe forms depending on the number of nodules, susceptibility of the host, insect population and occurrence of complications. LSD can be diagnosed clinically depending on its highly characteristic signs but mild and asymptomatic disease

is difficult to be demonstrated and rapid laboratory techniques are needed to confirm the diagnosis (Tuppurainen *et al.*, 2005; Calistri *et al.*, 2018). The signs begin with fever over than 40.5 °C for about one week with depression, anorexia and sharp drop in milk production in dairy cattle and lactating buffaloes (FAO, 2017; Tuppurainen *et al.*, 2017b). The characteristic lumps (nodules) appear after 2 days of fever. Their diameters range from 1 to 7 cm, they are uniform in size, painful, inflamed and may be scattered all over the animal body especially on muzzle, genitalia, udder, eyelids, ears, nasal and oral mucosa where they may persist for 12 days. Hundreds of nodules can cover the entire animal body involving all skin layers reaching the muscular layer. Then nodules became moist, necrotic and ulcerated (Sanz-Bernardo *et al.*, 2020). After persisting for a long time, the lesion ulcerates and scabs are formed on its top. The lesions may involve large areas, aggregating to form a hole through all skin thickness which is called “Set Fast” (Abutarbush *et al.*, 2015). Affected animals demonstrate salivation, lacrimation, nasal discharge and enlargement of superficial lymph nodes (ten times their original sizes). Complicated clinical signs lead to mastitis, temporal or permanent sterility in bulls and cows due to lesions on genital organs, severe lameness caused by lesions above the joints of the limbs. Keratitis is also reported (bilateral or unilateral). Lesions in the respiratory tract are followed by pneumonia (Babiuk *et al.*, 2008). In Egypt, mild form of LSD was recorded in native breeds of cattle but severe form was reported in foreign breeds (Salib & Osman, 2011). During the LSD outbreak in 2006 in Egypt, about 95% of caws had no ovarian activity, no signs of estrus and the ovarian size was smaller than normal

as detected by transrectal ultrasonography examination (Ahmed & Zaher, 2008). Recovery from infection is slow, the necrotic skin area exposed to fly strike are shed giving rise to deep holes in the hide (OIE, 2017).

Post mortem findings

At the slaughterhouse skinned infected animals show subcutaneous lesions. LSD lesions are found in respiratory and digestive tracts and on most of the internal organs. Necrotic areas about 1–2 cm in diameter are found, then scar formation occurs weeks after acute stage (Sanz-Bernardo *et al.*, 2020).

Histopathological findings

Acute histopathological lesions include epidermal vascular changes with intracytoplasmic inclusion bodies and vasculitis, and chronic histopathological lesions showing fibrosis (Sanz-Bernardo *et al.*, 2020). Histopathological findings of LSD provide the basis of diagnosis. Ballooning degeneration was found in the cell layers of skin nodules and eosinophilic intracytoplasmic inclusion bodies specific for LSD virus infections. Epidermal layer of skin exhibits necrosis and large number of neutrophils, lymphocytes and macrophages. The dermal layer is infiltrated with inflammatory cells and the muscular layer is necrotic. Aggregation of inflammatory cells around the blood vessels is recorded (Salib & Osman, 2011; Constable *et al.*, 2017).

Haematological and biochemical changes

There is an alteration in biochemical analysis results due to liver and kidney failure and severe inflammatory changes which occurred due to disease complications as anorexia and decreased muscular mass during LSD infection (Abutarbush *et*

al., 2015; Neamat-Allah, 2015; Şevik *et al.*, 2016). Macrocytic hypochromic anaemia, leukopaenia, lymphopaenia, thrombocytopaenia, hyperfibrinogenaemia, decreased creatinine concentrations, hyperchloremia, hyperkalemia, decreased total protein and albumin, increased globulins were detected in sera of naturally infected cattle (Abutarbush *et al.*, 2015). Serum biochemical analysis indicates increased activity of aminotransferases, alkaline phosphatase, globulins and creatinine concentrations (Şevik *et al.*, 2016; El-Mandrawy & Alam, 2018).

Differential diagnosis

Severe cases of LSD give characteristic clinical signs, but early and mild cases of the disease need laboratory confirmation (Tuppurainen *et al.*, 2017b). Sometimes the condition may be confused with foot and mouth disease and bovine and malignant catarrhal fever (Constable *et al.*, 2017).

Laboratory diagnosis techniques

Post-mortem examination is not commonly carried out in the field, by reason of the highly characteristic clinical signs in severely infected cases of LSD and the fact that mild infected cases don't show internal lesions. So it is preferred to take samples from live animals for laboratory diagnosis (FAO, 2017). The most suitable samples from live animals are skin nodules, scabs, saliva, nasal secretions, and blood for virus isolation, PCR detection of LSDV and electron microscopy (FAO, 2017).

Virus detection (live virus or viral nucleic acid)

- Virus isolation
Live virus can be propagated on different bovine and ovine cell lines (primary

lung, kidney or testicle cultures). LSD grows slowly on cell culture and needs many passages to enhance its growing as on VERO cell line and Baby Hamster kidney cell line (Babiuk *et al.*, 2008). Egyptian isolates are able to replicate directly on chorio-allantoic membranes (CAMs) of specific pathogenic free-embryonated chicken eggs (SPF-ECE) inducing small white foci spread on the CAM, and also may result in their thickening and congestion (El-Kenawy & El-Tholoth, 2010; El-Nahas *et al.*, 2011; Hodhod *et al.*, 2020).

- The general CaPV real time PCR methods

Molecular assays, gel-based PCR and real-time PCR are very sensitive, well validated and mainly used in detection of the presence of capripoxviruses nucleic acid (CaPV DNA) (Vidanovic *et al.*, 2016; Chibssa *et al.*, 2018). The real time PCR method used for detection of CaPV has greater sensitivity than conventional gel-based PCR assays; no cross reaction with related poxviruses and no false positive results are reported. Real-time PCR is rapid, quantitative, simple, specific and sensitive. It can be used in large scale testing (Sprygin *et al.*, 2019a). CaPV gel based PCR is good choice if real time PCR is not available as it is cheap and of good sensitivity and specificity, but not a quantitative technique (Chibssa *et al.*, 2018). Conventional PCR can also differentiate between SPPV and GTPV (Gnanavel *et al.*, 2012; Mahmoud & Khafagi, 2016; Zeedan *et al.*, 2021).

- Species-specific real time PCR methods

Species-specific real time PCR methods are used for differentiation of capripoxviruses (SPPV, GTPV and LSD); they can detect and differentiate these viruses in EDTA blood, scabs, ocular and nasal

lesions, saliva and semen samples. The species specific PCR assay recorded differences in melting point temperature between probe and its target which will result in different melting temperature for SPPV, GTPV, and LSD detected after fluorescence melting curve analysis (Chibssa *et al.*, 2018).

- Portable pen side PCR

Portable pen side PCR is a field test showing result within one hour and there is no need for cold chain. Its reagent is freeze dried, quick confirmation enhances efficacy of the control measures (Armson *et al.*, 2017). Also rapid recombinase polymerase amplification (RPA) is 100% sensitive when compared with real-time PCR results which can be used in field or at quarantine stations for LSD identification (Cabada *et al.*, 2017).

- Loop-mediated isothermal amplification assays (LAMP)

It is a molecular test that uses the loop-mediated isothermal amplification for identification of capripoxviruses genomes recording the same sensitivity and specificity like real-time PCR, but the latter is more simple and of low cost (OIE, 2017). Interpretation of LAMP results depends on colour changes, its sensitivity ranges from 70–100% and the specificity ranged within 92.3–100% (Mwanandota *et al.*, 2018).

- Gene sequencing

Sequencing of host range genes requires well trained staff and expensive equipment but it can detect the virus (Sprygin *et al.*, 2019b). It is considered as an important technique in molecular epidemiology analysis of the LSD for differentiation of virulent isolates which are highly conserved compared with vaccinal isolates by complete genome sequencing (Menasherow *et al.*, 2014; Gelaye *et al.*,

2015; Saltykov *et al.*, 2021) or by RP030 phylogenetic analysis of different isolates (Molini *et al.*, 2018).

- Electron microscopy

It needs expensive specialised and trained staff and cannot even differentiate *Capripox* from *Orthopox* virus members (Sprygin *et al.*, 2019b).

Detection of antibodies against LSDV

LSDV host immunity depends on cell mediated immunity rather than on humoral immunity. Low antibody titres in mild infection and/or vaccinated animals cannot be sensitively detected (Gari *et al.*, 2011; Tuppurainen *et al.*, 2017b).

- Serum virus neutralisation test

It is the gold standard serological technique yet it cannot detect low antibody titres in LSD infected animals. Its sensitivity ranges from 70–96% and the specificity may reach 100% (Babiuk *et al.*, 2008).

- Indirect fluorescent antibody test (IFAT)

The capacity of the assay permits testing larger number of samples than the neutralisation test. It can be used to evaluate immune status against LSDV in epidemiological studies (Gari *et al.*, 2008; 2011).

- Agar gel immune diffusion test (AGID)

AGID is a simple test of low sensitivity, its results must be confirmed with another test (Sprygin *et al.*, 2019a).

- Enzyme linked immunosorbent assay (ELISA)

ELISA IDVet was the first validated ELISA assay. It is commercially available, and facilitates large-scale serosurveillance for LSD. While the VNT is labour intensive and needs more time, it is the test recommended by the OIE (Krešić *et al.*,

2020). VNT has a higher specificity than ELISA (Samojlović *et al.*, 2019).

- Western blotting

Western blotting used in detection of antibodies in sera against capripoxvirus infected cell lysate is considered a specific and sensitive system for detection of capripoxviruses structure protein antibody, but is expensive and labourous (OIE, 2017). Its difficulty is due to requirement for pure antigens, also it is not easy to perform. Western blotting is used mainly as a confirmatory test to verify SNT and ELISA positive results (Sprygin *et al.*, 2019b).

CONTROL OF LSD IN ENDEMIC COUNTRIES

Egypt had recent outbreaks due to several factors including its geographical position between three continents: Africa, Asia and Europe, political events with adverse impact on regional cooperation, the great differences in climatic conditions between different regions, the uncontrolled animal movement, import of animals and animal products, routes of migratory birds between Africa and Europe, increasing human population and water resources limitation. All these factor badly affect LSD control plans (Shimshony & Economides, 2006). For minimising LSD losses, controlling measures include regular vaccination (Wallace *et al.*, 2020), restricted animal movement and quarantine, discarding of affected animals, proper disposal of contaminated materials and disinfection of contaminated premises (Şevik & Doğan, 2017). Finally, prevention in endemic countries with LSDV infection as Egypt and most of the African countries, depends mainly on vaccination and supportive symptomatic treatment of infected animals (Wallace *et al.*, 2020).

Prevention

Controlled vaccination programmes to the entire cattle and buffalo population should be implemented, restricted movement of ruminants inside the country and across country borders as movement must be authorised. Vaccinated animals movement must be restricted until full immunity reached (28 day after vaccination). Insect repellents and insecticides should be regularly used to reduce the vector-borne transmission of the disease and the risk of disease spreading by this route of transmission (FAO, 2017). Cleaning and disinfection on infected farm premises with removal of dirt and manure should be practiced (FAO, 2017). Vaccination is the only effective method to control the disease in endemic areas as movement restrictions and removal of affected animal alone are usually not effective (Tuppurainen *et al.*, 2017b; Mulatu & Feyisa 2018; Namazi & Tafti 2021). In addition, rapid confirmation of a clinical diagnosis is essential so that eradication measures such as quarantine, slaughter-out of affected and in-contact animals, proper disposal of carcasses, cleaning and disinfection of the premises and insect control can be implemented as soon as possible during eruption, moreover rigorous import restrictions on livestock are important (Constable *et al.*, 2017; Tuppurainen *et al.*, 2017a).

Immune response

Capripoxviruses (CaPVs) differ from other enveloped viruses, because the most predominant immunity type produced in infected animals is cell mediated immunity (Hamdi *et al.*, 2021). Naturally this occurs as a result of the nature of CaPV which remain inside infected cells. They spread from cell to cell (Tuppurainen *et al.*, 2021) so the immune status of previ-

ously infected or vaccinated animals should not be estimated by the level of serum neutralising antibodies (Kitching & Smale 1986). All CaPV are sharing common antigens and thus these viruses exhibit immunological cross reaction (Gelaye *et al.*, 2015; Molini *et al.*, 2018). Apparent or unapparent natural infection with LSD gives up to 3 log of neutralising antibodies against the virus. This level of immunity protects well the animal from reinfection for its whole life (Milovanović *et al.*, 2019). Vaccinated animals develop low antibody titres against LSDV, beginning within 15 days post vaccination and reaching peak level after 30 days (Samojlović *et al.*, 2019). Some vaccinated animals are fully protected without seroconversion occurring (Smith & Kotwa, 2002; Ayelet *et al.*, 2013).

Vaccination strategy

LSD control is depending mainly on vaccination which is the main effective method for control as restriction of movements and culling of affected animals are not effective alone to control the disease. Objective of vaccination in endemic areas is rather clinical protection than elimination of the virus circulation (Calistri *et al.*, 2018; 2019). Vaccination of susceptible cattle and buffaloes should be done annually. Stopping of vaccination in the inter epidemics periods is the greatest problem facing the control of LSD recurrent outbreaks (OIE, 2017; Mulatu & Feyisa, 2018). Only live vaccines against LSD which are authorised for use in ruminants in Africa to reduce the economic losses from LSD are now available. Eighty percent vaccination coverage in cattle helps to cut the virus transmission cycle and gives good protection from recurrent outbreaks (Tuppurainen *et al.*, 2017a). Recurrent outbreaks recorded in

Turkish animals resulted from insufficient vaccination coverage (Calistri *et al.*, 2019). Calves from non-immunised dams can be vaccinated at any age, while calves from infected or vaccinated dams should receive the vaccine at 3–6 months of age. Regional vaccination should be done before animals' movement (OIE, 2017).

Available LSD vaccines

Commercially available live attenuated strains of capripoxviruses are used for vaccination in order to control LSD (OIE, 2017).

- Attenuated sheep pox and goat pox vaccines

These vaccines are used in countries where LSDV, SPPV and GTPV are present. Kenyan sheep and goat pox viruses by 18 passages in lamb testis (LT) cells or foetal calf muscle cells, Yugoslavian RM65 sheep pox strains and Romanian sheep pox strain used in vaccination of susceptible animals in Egypt are prepared by 60 passages on Lamb kidney cells and 20 times passages on chorioallantoic membrane of embryonated chicken eggs (Hamdi *et al.*, 2021). The vaccine dose (0.5 mL by intradermal route in the tail fold of cattle over 6 month of age) could give a 3-year protection. Insufficient protection from sheep and goat pox based vaccine was recorded in Turkish animals especially when the dose of the vaccine was less than 10 times the amount given to sheep (Calistri *et al.*, 2019). The partial protection from these vaccines against LSD will be effective if there is full vaccination coverage and restricted movement control measures (Tuppurainen *et al.*, 2017b). Partial protection of the vaccine in vaccinated animals was noticed in Egypt in summer 2016 and 2017, where LSD symptoms were seen in 5% of cattle previously vaccinated with the Romanian

SPPV vaccine, previously noticed in outbreaks of LSD in Ethiopia among cattle vaccinated with sheep and goat pox vaccine (Kenya Strain KS) due to lack of LSDV antibodies protection and lack of cross protection (Lubinga *et al.*, 2015; Zeedan *et al.*, 2019). Evaluation of the vaccine efficacy under field condition must be qualified (Abdallah *et al.*, 2018).

- Homologous live attenuated LSDV vaccine (Neethling strain)

It is effective in prevention of infection about four times more than the 10-fold dose of Romanian strain sheep pox vaccine (RM. 65 SPPV) (Ben-Gera *et al.*, 2015; Sprygin *et al.*, 2019b). This vaccine is allowed for use by the Egyptian veterinary authorities for vaccination of cattle and buffaloes livestock in Egypt since 2019, and now is produced by Sera and Vaccine Research Institute, Egypt and seems to give a complete protection against LSDV infection for about 3 years in cattle, including small calves and pregnant cows.

- Adverse reactions of available vaccines

Mild adverse reactions may be showed in 0.09% of the vaccinated animals with attenuated LSDV vaccines, called Neethling disease (Ben-Gera *et al.*, 2015), which including fever, low drop in milk production and superficial small lesions may appear at 7-17 days post vaccination. These signs disappeared within 2–3 weeks without any complications into necrotic scabs or ulcers (Tasioudi *et al.*, 2016; Agianniotaki *et al.*, 2017; Abutarbush *et al.*, 2015 and (Tuppurainen *et al.*, 2017a; Katsoulos *et al.*, 2018). Full protection is occurred about three weeks post vaccination. During these three weeks vaccinated animals may be infected by field virus and show clear clinical signs. Others may be in incubation period at the time of

vaccination and thus give rise to clinical signs less than ten days after vaccination (FAO, 2017).

Animal movement control

The movement of unvaccinated animals during LSD outbreaks is an important risk factor. Strict regulation on the movement must be applied by veterinary authorities. Cattle must be vaccinated before moving for at least 28 days, also unvaccinated animals should not allowed to move during outbreaks. Open transport vehicles give time to insect vectors to transmit the virus from cattle moving to slaughterhouses which must be in restricted zones (FAO, 2017; OIE, 2017). The OIE guidelines advised 3 km protection ring zone from infected herd or village, 20 km zone for surveillance and at least 50 km restriction zone around the outbreaks area (OIE, 2017). Recent reports allow vaccination zone of at least 50 km in radius around infected area and at least 90% vaccination coverage (FAO, 2017).

In many countries in Africa there are no quarantine measures, there is no clearance between these countries and an international organisation for control and prevention of infectious diseases (Shimshony & Economides, 2006). The lack of information and notification about the diseases to prevent the effect on the international trade, lack of laboratory capacity which affects the early reporting of disease, are problems faced by us in controlling and preventing infectious diseases including LSD (Abutarbush *et al.*, 2015).

Treatment

The treatment strategy depends on the enhancement of the animal immunity. This can be achieved by use of plant-derived compounds such as curcumin, resveratrol, epigallocatechol-3-gallate, qu-

ercetin, colchicine, capsaicin, andrographolide and genistein (Jantan *et al.*, 2015). The second step of the treatment is the antimicrobial treatment in animals with clinical signs of LSD and complications to overcome the secondary bacterial infections and save the animal life. Terramycin® long acting oxytetracycline could be used by the intramuscular route at a dose of 1 mL/ 10 kg body weight. In addition, subcutaneous injection with 10 mL levamisole per animal acts as immunostimulant drug. Intravenous injection of metamizole (Novacid®) at 20 mL/animal twice daily until recovery from fever and once daily intramuscularly after that may be applied. Diclofenac sodium can be administered for fever resolution (Salib & Osman, 2011).

CONCLUSION

LSD is an infectious disease of cattle and buffaloes, causing great losses in non-immune and young animals from reduction in weight and milk production, generalised skin lesions and loss of hide, infertility, abortion and mortalities. LSDV remains viable for 15 day post infection in ocular and nasal discharges, in scabs for 6 months and in air dried hides for about 18 days. Arthropod vectors have an important role in LSDV transmission between susceptible animals by mechanical route. Direct and indirect contact are possible routes for LSDV transmission. The movement of diseased animals and arthropods vectors is the main possible pathway for LSD introduction, windborne transmission of vectors (after blood meal from infected animals) represents an important route of LSD introduction into a country. Movement of animals across boundaries of countries should be restricted and authorised.

Rapid reliable laboratory confirmation is important for early diagnosis and control of disease spread. Real time PCR is the method of choice for diagnosis of LSDV infection. Only live attenuated vaccines against LSD are commercially available. Romanian strain of sheep pox vaccine cannot give effective protection against LSD. Neethling attenuated LSDV vaccine should be taken annually and not neglected between outbreaks periods.

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