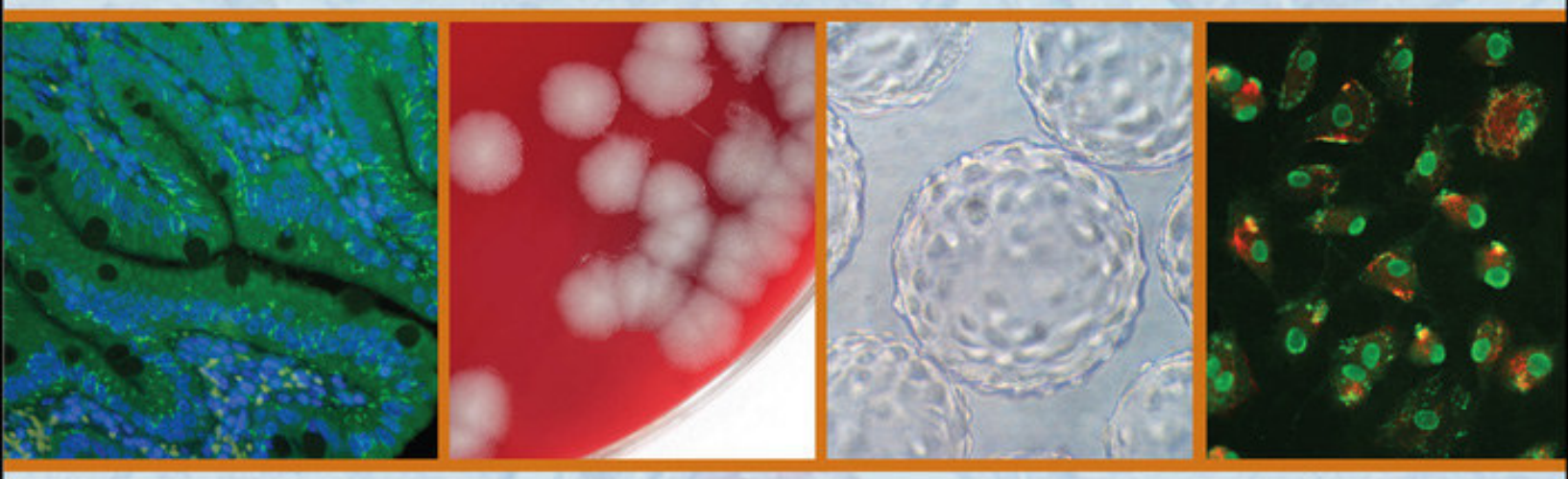

VETERINARY VACCINES

PRINCIPLES AND APPLICATIONS

FIRST EDITION

EDITED BY

SAMIA METWALLY | GERRIT VILJOEN

AHMED EL IDRISSI

Food and Agriculture Organization of the United Nations

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Capripox (Lumpy Skin Disease, Sheep Pox, and Goat Pox)

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28.1 Introduction

Lumpy skin disease (LSD), sheep pox (SPP), and goat pox (GTP) are economically important pox diseases of domestic ruminants caused by lumpy skin disease virus (LSDV), sheep pox virus (SPPV), and goat pox virus (GTPV). These three viruses compose the genus *Capripoxvirus* within the family Poxviridae. Due to the direct and indirect economic losses caused by capripoxvirus (CaPV) outbreaks, these are categorized as notifiable diseases by the World Organization for Animal Health (OIE) which provides recommendations for international trade standards in the LSD chapter (11.9) and SPP/GTP chapter (14.9) of the *Terrestrial Animal Health Code* (OIE 2018a) and for diagnostic assays and vaccines in the LSD chapter (3.4.12) and SPP/GTP chapter (3.7.12) of the *Manual of Diagnostic Tests and Vaccines for Terrestrial Animals* (OIE 2018b).

Currently, LSD is widespread throughout the African continent, excluding Morocco, Algeria, Tunisia, and Libya. Between 2012 and 2015, the disease spread across the Middle East and was reported by Israel, the Palestinian Autonomous Territories, Jordan, Lebanon, Kuwait, Saudi Arabia, Oman, Bahrain, Iran, and Iraq. Turkey was affected in 2013 and in late 2014, and the first cases were detected in the northern part of Cyprus from where it was swiftly eradicated by vaccination. In 2014, LSD spread to the Caucasus region, first to Azerbaijan, then to Georgia, south-western parts of the Russian Federation, Armenia, and Kazakhstan. Within south-east Europe, Greece was affected first in 2015, followed by Bulgaria, the Republic of North Macedonia, Kosovo region, Montenegro, Serbia, and Albania in 2016. In 2019, LSD outbreaks were reported in China, Bangladesh, and India.

In Africa, SPP and GTP occur from North Africa to Tanzania and the Democratic Republic of Congo. Their endemic zone is across the Middle East and the Indian subcontinent, Iran, Iraq, southern Russia, Kazakhstan, Kyrgyzstan, Afghanistan, Pakistan, Nepal, Mongolia, China, Bangladesh, Vietnam, and Chinese Taipei. SPP and GTP are widespread in Turkey and between 2013 and 2015, four outbreaks of SPP occurred in Bulgaria and several outbreaks were reported in Greece in 2014, and again in 2017.

28.1.1 Characteristic Clinical Signs

The incubation period of LSDV varies from 4 days to 5 weeks (Haig 1957) and is defined for official purposes as 28 days (OIE 2018a). About a week after infection, animals start to show ocular and nasal discharges and high fever. Highly characteristic skin lesions of 10–50 mm in diameter start to appear. The number of nodules varies from a few in mild cases to multiple nodules, covering the entire body, in severely affected animals. Enlarged subscapular and precrural lymph nodes can be detected at the onset of fever.

The incubation period for SPPV and GTPV is between 4 days and 2 weeks. Infection starts with nasal and ocular discharges and pyrexia (40–42 °C). Affected animals show laborious breathing, depression, and loss of appetite. Skin lesions develop first on the face, around the lips, nares, and on the eyelids. Skin nodules progress until a scab forms on top of the lesion. In severe cases, pox lesions may cover the whole body, but are more easily detected under the tail, on the belly, and on the mammary glands, where the hairless parts are.

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Typically, for all CaPV diseases, small necrotic plaques appear on the tongue and oral and nasal mucous membranes. Nasal discharges and saliva contain infectious virus. Lesions may also be found throughout the digestive and respiratory tracts and on the surface of almost any internal organ. LSDV may cause very painful ulcerative lesions in the cornea of one or both eyes, leading in some severe cases to blindness.

Pneumonia, caused by the virus itself or by secondary bacterial infection(s), is a common complication in severely affected cattle, sheep, and goats. Deep necrotic skin lesions in the legs and on top of the joints may become complicated with secondary bacterial infections, leading to lameness. Infected females often show mastitis and abortions. Fly strike may occur in skin ulcers.

28.1.2 Virulence and Host Specificity

For LSD, the morbidity rate varies between 5% and 45% and the mortality rate usually remains below 10%. However, both rates can be considerably higher (morbidity up to 100%) when an outbreak occurs for the first time in naïve European cattle breeds (Coetzer 2004). Highly infectious SPPV and GTPV may cause very high morbidity of 70–90% and mortality up to 50%. Young lambs and kids are especially susceptible and mortality among young animals may sometimes rise to 100% (Rao and Bandyopadhyay 2000). The virulence of different strains may vary to some extent, but the severity of the clinical disease depends more often on the host species, breed, age, immune status, and stage of production. European high-producing dairy cattle and sheep breeds, as well as animals in the peak of production, are often more severely affected.

In general, CaPVs are relatively host specific, causing clinical disease in either sheep, goats, or cattle. However, exceptions exist and some SPPV and GTPV strains can affect both sheep and goats. Interestingly, in a recent molecular study, GTPV was found to be solely responsible for all investigated outbreaks in both sheep and goats in Ethiopia (Gelaye et al. 2015). Recently, GTPV infection in wild ruminants, red serow (*Capricornis rubidus*), has been reported in Mizoram, India (Dutta et al. 2019).

Lumpy skin disease virus infects domestic cattle and Asian water buffalo (El-Nahas et al. 2011) while some strains may replicate in sheep and goats. The role of wildlife in the epidemiology of LSD is not well understood. Springbok (Lamien et al. 2011), impala, and giraffe (Young et al. 1970) are known to be susceptible and African buffaloes have been found to be seropositive (Davies 1982; Fagbo et al. 2014). In addition, antibodies have been detected in various wild ruminants, such as blue wildebeest, eland, giraffe, impala, and greater kudu (Barnard 1997).

28.1.3 Epidemiology

Transmission of LSDV is believed to occur mainly mechanically by blood-sucking insect and tick vectors, feeding frequently on cattle. The most important arthropod vector is likely to vary between affected regions, depending on the climate, season, environmental temperature, humidity, and vegetation, favorable for the biology of different insect and tick species.

The common stable fly (*Stomoxys calcitrans*) or other biting flies, mosquitoes, or midges have been the suspected vectors for spreading LSDV, although actual experimental evidence on the potential role of different blood-feeding insect species is still lacking. To date, only transmission of the virus by female *Aedes aegypti* mosquitoes has been experimentally demonstrated (Chihota et al. 2001). New studies are ongoing to investigate the vector capacity of different insects and more research data are expected to become available soon.

Tick vectors are likely to be of more importance in African environments than, for example, in the Middle East. Experimental evidence has been obtained on the role of the African brown ear tick (*Rhipicephalus appendiculatus*) (Tuppurainen et al. 2013a) and African bont tick (*Amblyomma hebraeum*) males (Tuppurainen et al. 2011; Lubinga et al. 2013) as well as African blue tick (*R.* [*Boophilus*] *decoloratus*) females (Tuppurainen et al. 2013b). Further proof on the transovarial mode of LSDV transmission by *R. annulatus* ticks has been reported by an Egyptian research group that collected engorged females from LSD-infected cattle, allowed females to oviposit, and were then able to isolate a live LSDV from subsequent larvae using chorioallantoic membranes of embryonated chicken eggs (Rouby et al. 2017). To date, no evidence on the actual multiplication of LSDV either in insect or tick vectors exists.

The efficiency of LSDV transmission by direct contact is believed to be relatively low. Infection can be transmitted through contaminated feed or water. LSDV is known to persist in semen of infected bulls and, therefore, natural mating or artificial insemination may be a source of infection for cows (Annandale et al. 2013). In the field, infected cows are known to give birth to calves with skin nodules (Rouby and Aboulsoud 2016). Iatrogenic transmission may happen when already infected herds are vaccinated or veterinary treatments are administrated without changing needles between animals.

Due to vector transmission, LSD spreads more easily during hot and humid seasons, although sporadic cases or outbreaks have also been reported during the vector-free season, such as during the most recent outbreaks in Georgia, Greece, and Albania. Typically, in endemic

regions, LSD outbreaks occur in epidemics, with several years between the outbreaks (Davies 1991). Reemergence of the disease is likely to be associated with uncontrolled animal movements, accumulation of sufficient numbers of naïve animals, and abundance of blood-feeding vectors, generating favorable conditions for viral spread. It is not known precisely if and where in the environment the infectious virus can survive between outbreaks. Recently, the potential role of air currents in long-distance transport of LSDV-contaminated insects was investigated by Israeli scientists (Klausner et al. 2015).

Sheep pox and GTP are highly contagious diseases and direct contact between infected and naïve animals is the main mode of transmission. Outbreaks of these diseases occur throughout the year. SPPV and GTPV spread via contaminated aerosols following inhalation, oral absorption, or through skin abrasions. They can also spread indirectly via fomites originating from infected premises and carried by personnel, equipment, or vehicles. Experimentally, stomoxys flies have been demonstrated to transmit the virus in sheep and goats (Kitching and Mellor 1986).

In all CaPV diseases, high titers of virus are known to persist in skin lesions and in scabs that develop on top of the lesion. Virus-containing dried scabs are shed by infected animals, contaminating the environment.

In cattle, natural resistance to LSDV is believed to occur and asymptomatic LSDV infections are common in the field (Weiss 1968). In addition, approximately one-third of experimentally infected animals show no clinical signs at all, although all became viremic (Tuppurainen et al. 2005; Osuagwuh et al. 2007; Annandale et al. 2013). Viremic animals without skin lesions may be capable of transmitting the virus via arthropod vectors, which complicates the control and eradication of LSDV in those countries where slaughter of all infected and in-contact animals is not feasible. Thus, killing only those animals showing LSD skin lesions is unlikely to limit the spread of the virus if a modified stamping-out method is used without vaccination.

28.1.4 Currently Available Diagnostic Tests

Capripoxviruses are large, enveloped, double-stranded DNA viruses. The size of the genome is approximately 151 kb, comprising at least 147 putative genes in the SPPV/GTPV and 156 in LSDV genomes. In general, they are closely related but phylogenetically distinct viruses. Comparison of the full genome sequences of several CaPV isolates showed 96% of similarity between LSDV, SPPV, and GTPV compared with over 99% for intraspecies similarity (Tulman et al. 2001, 2002).

Several conventional and real-time polymerase chain reaction (RT-PCR) methods have been developed and are widely used for the detection of CaPVs. PCR kits for all CaPVs are also commercially available.

Species-specific molecular assays utilizing the G-protein-coupled chemokine receptor (GPCR) or 30 kDa RNA polymerase subunit (RPO30) genes have been described (Le Goff et al. 2005, 2009; Lamien et al. 2011a,b). Molecular assays for the differentiation of virulent and vaccine strains are needed for epidemiological field investigations. The first assay based on the detection of a 27-nucleotide difference, in the gene for an extracellular enveloped virion protein, between virulent and attenuated LSDV has been published (Menasherow et al. 2014), followed by gel-based and RT-PCR methods for SPPV (Haegeman et al. 2016; Chibssa et al. 2018). Alternative methods have been developed by Serbian (Vidanovich et al. 2016) and Greek (Agianniotaki et al. 2017) scientists. Sequencing of the GPCR-gene provides an alternative means to differentiate between field and vaccine viruses (Gelaye et al. 2015).

There are no pen-side tests commercially available for the detection of CaPV in the field. Two loop-mediated isothermal amplification (LAMP) assays for the specific identification of CaPV have been developed (Das et al. 2012; Zhao et al. 2014). Such assays, with the possibility of naked-eye reading, have great potential for use in diagnostic laboratories with limited resources and even in the field. PCR methods suitable for portable thermocyclers (Armson et al. 2017) and other simple molecular methods for pen-side testing (Shalaby et al. 2016) have been described, and more assays are expected to become available in the near future.

All serological tests in use (serum/virus neutralization, enzyme-linked immunosorbent assay [ELISA], fluorescent antibody, indirect fluorescent antibody, and agar gel immunodiffusion tests) are for CaPV group diagnosis. Except ELISA, none of them is suitable for testing large numbers of samples. Indirect ELISAs based on killed whole virus, recombinant antigens, or synthetic peptides have been developed (Babiuk et al. 2009; Bhanot et al. 2009; Bowden et al. 2009; Tian et al. 2010). In 2017, the first ELISA kit (ID Screen® Capripox Double Antigen Multi-species, IDvet, France) became commercially available for the detection of antibodies against CaPV, enabling serological surveillance for CaPV.

28.1.5 Disinfection

In general, purified LSDV is sensitive to many commonly used disinfectants when used at appropriate concentrations. CaPV is stable between pH 6.6 and 8.6 but due to the lipid-containing surface structure, the virus can be inactivated by most common detergents. Phenol (2%), sodium hypochlorite (2–3%), strong iodine compounds (1:33

dilution), Virkon® (2%), and quaternary ammonium compounds (0.5%) can be used for the disinfection of equipment, facilities, and vehicles. The virus is chloroform and ether (20%) sensitive and can be inactivated at 56 °C in 2 hours or at 65 °C in 30 minutes (www.oie.int/fileadmin/Home/eng/Animal_Health_in_the_World/docs/pdf/Disease_cards/LUMPY_SKIN_DISEASE_FINAL.pdf). More detailed practical recommendations for proper decontamination of premises, equipment, and environment are provided by the Food and Agriculture Organization (FAO) in the *Animal Health Manual* (FAO 2001).

28.2 Types of Vaccines

To date, only live attenuated CaPV vaccines are commercially available and all of them require an authorization prior to use in nonendemic countries. In the Balkan countries, affected with LSD between 2015 and 2017, use of live attenuated LSDV vaccines was authorized if the specific conditions set by the European Commission and national competent authorities were fulfilled. The superiority of live attenuated vaccines compared with the killed ones is well known. It is believed that in order for a vaccine to provide a solid protective immunity against CaPV *in vivo*, replication of the agent is required to mimic the natural infection. However, in specific circumstances, inactivated vaccines against CaPVs would be advantageous, and these products are likely to enter the markets in the near future.

28.2.1 Vaccines Against Lumpy Skin Disease

Homologous live vaccines against LSDV are derived either from the South African LSDV Neethling strain or alternatively from an attenuated LSDV field strain. Both vaccine types were widely used during the LSD outbreaks in southeastern Europe. The efficacy of these vaccines against field LSDV is very good and when combined with high vaccination coverage, total or partial stamping-out policy, and movement restrictions, the spread of the disease can be effectively stopped within a short period of time. For example, in Bulgaria the vaccination effectiveness was 96% (EFSA 2018).

So-called "Kenyan sheep and goat pox virus" (KSGP) O-240 (also named KS1) and O-180 strains have been used in cattle against LSDV with varying success, for example in Egypt and Oman. As both these Kenyan strains were originally isolated from sheep (Davies 1976; Davies and Atema 1978; Davies and Mbugwa 1985; Kitching et al. 1987), they were consequently named according to the host as SPPV. However, after molecular techniques became available, these isolates were shown to be in fact LSDV strains (Black et al. 1986; Tulman et al. 2001; Lamien et al. 2011; Tuppurainen et al. 2014).

The efficacy of the different SPPV vaccine strains against LSDV is known to vary and final selection of the vaccine should always be based only on demonstrated efficacy. SPPV-derived vaccines have been used against LSDV in countries where SPP is endemic. For example, the Yugoslavian RM65 SPPV, at a 10 times stronger dose than used for sheep, has been used for cattle against LSDV in Israel and Jordan (Abutarbush et al. 2015; Ben-Gera et al. 2015). Since 2006, Romanian SPPV vaccine has been used for cattle in Egypt and Oman (Davies 1991; Brenner et al. 2009; Somasundaram 2011). In Turkey and the northern Caucasus region, the Bakirköy SPPV vaccine has been used in cattle at both three and 10 times the dose used for sheep.

Several studies have shown the efficacy of GTPV vaccines for protecting cattle from challenge by LSDV. The Kedong and Isiolo strains were isolated from sheep in Kenya during the 1950s but were later shown to be actually GTPV (Tuppurainen et al. 2014). In studies by Coackley and Capstick (1961), both strains were shown to protect cattle from LSDV challenge. Recently, in a study conducted in Ethiopia, an attenuated Gorgan GTPV-containing vaccine was demonstrated to provide good protection for cattle against a highly virulent LSD field strain (Gari et al. 2015). Currently, there is one GTPV-based vaccine commercially available against LSDV in cattle, from a Jordanian manufacturer (Table 28.1).

The price of SPPV and GTPV vaccines is considerably lower than that of homologous LSDV vaccines, which makes them attractive alternatives in countries with a large cattle population and limited financial resources available for disease control.

28.2.2 Vaccines against Sheep Pox and Goat Pox

KSGPV O-240, O-180, and RM65 vaccines are used against SPPV in the Middle East and Africa and the Bakirköy SPPV vaccine is used in Turkey. The Gorgan and Mysore GTPV strains are used in vaccines against GTPV (Kitching 1986b). Several local attenuated SPPV and GTPV strains are used in the Indian subcontinent.

28.2.3 Inactivated Vaccines

Killed vaccines are currently being developed against SPPV (Boumart et al. 2016) and LSDV and the field trials are ongoing. The availability of a safe, nonreplicating but effective vaccine with fewer side effects would assist both endemic and nonendemic countries to protect themselves against incursion of CaPV. As an inactivated vaccine causes fewer severe

Table 28.1 List of lumpy skin disease (LSD), sheep pox (SPP), and goat pox (GTP) vaccine manufacturers.

Manufacturer	Contact information	Product(s)[a]
Abic Biological Laboratories Ltd. (Phibro)	Abic Veterinary, Veterinary Products, 3 Hamelacha Street, P.O.B. 489, Beit Shemesh 99100, Israel Phone: +972 2 9906916 Fax: +972 2 9906900	RM65 SPPV
Agrovet	23 Academic Skryabin Street, 109472 Moscow, Russia Phone: +7 495 377 69.97 Fax: +7 495 377 69 87 Email: info@agrovet.ru www.agrovet.ru/index.eng.htm	Sheep Pox™ (Live SPPV Nishi)
Biopharma	Avenue Hassan II, km 2 route de Casablanca, Rabat-Akkari, Morocco Phone: +212 6 74 90 67 17/ +212 6 74 90 66 19 Fax:+ 212 5 37 69 36 32 Email: biopharma_ma@yahoo.fr	Romanian SPPV
Deltamune (Pty) Ltd.	PO Box 14167, Lyttleton 0140, South Africa Phone: +27 12 664 5730 Fax: +27 12 664 5149	Herbivac LS™ (Modified Neethling type)
Dollvet	Organize Sanayi Bölgesi 8, No: 3 Cadde Merkez Sanliurfa, Turkey Phone: +90 414 3691133 Fax: +90 414 3691662 Email: dollvet@dollvet.com.tr www.dollvet.com.tr	Poxdoll™ (Live SPPV Bakirköy strain) LSD-NDOLL (Neethling)
Federal Center for Animal Health (FGBI)	600901, Vladimir, Tur'evets, FGBI ARRIAH, Russia Phone: +7 4922 26 06 14 Fax: +7 4922 26 38 77 Email: mail@arriah.ru www.arriah.ru	Sheep pox Cultyral Dry™
Hester Biosciences Ltd.	1st Floor, Pushpak, Panchvati Circle, Motilal Hirabhai Road, Ahmedabad-380006, Gujarat, India Phone: +91 79 2644 5106, +91 79 2644 5107 Fax: +91 79 2644 5105 Email: mail@hester.in www.hesterbiosciences.co.in	Goat Pox Vaccine™ (Uttarkashi strain)
Indian Immunologicals Ltd	Road 44, Jubilee Hills, Hyderabad 500033, A.P., Telangana, India Phone: +91 40 23544585 Fax: +91 40 23544007 Email: info@indimmune.com www.indimmune.com	Raksha SP™
Institut Pasteur d'Algérie	Route du Petit Staouéli, Dély-Brahim, Alger Phone: +213 21 372674/ 363588 Fax: +213 21361748 Email: contact@pasteur.dz www.pasteur.dz	Sheep and goat pox (RM65 SPPV)

(Continued)

Table 28.1 (Continued)

Manufacturer	Contact information	Product(s)[a]
Intervac Pvt Ltd.	113/3 Allama Iqbal Road, Ghari Shahu, Lahore 54141, Pakistan Phone: +92 42 36306957, +92 42 6364411 Fax: +92 42 6374378 Email: info@intervacpvtltd.com www.intervacpvtltd.com	Intervac sheep pox vaccine (RM65 SPPV)
Jordan Bio-Industries Center (JOVAC)	PO Box 43, Amman 11941, Jordan Phone: +962 6 523 2162 Fax: +962 6 523 2210 Email: sales@jovaccenter.com www.jovaccenter.com	Jovivac™ (SPPV RM65) Caprivac (GTPV Gorgan strain) Kenyavac™ (KSGP O-240) Lumpyshield™ (GTPV Gorgan strain)
Intervet (Pty) South Africa/MSD Animal Health	20 Spartan Road, Spartan Ext 20, Kempton Park, 1619 South Africa Phone: +27 11 923 9300 Fax: +27 11 974 9320 www.msd-animal-health.co.za	Lumpyvax™ (attenuated LSDV field strain)
National Veterinary Institute	PO Box 19, Debre Zeit, Ethiopia Phone: +251 114 33 84 11/16 or 33 21 18 Fax: +251 114 33 93 00 Email: nvi-rt@ethionet.et	Sheep and goat pox vaccine (KSGP O-180) Lumpy skin disease vaccine (Neethling strain)
MCI Santé Animale	Lot 157, Zone Industrielle Sud-Ouest (ERAC) B.P.: 278 Mohammedia 28810, Morocco Phone: +212 523 30 31 32 Email: contact@mci-santeanimale.com	Bovivax LSD™ Ovivax ™ (SPP Perego strain) Lyopox™ (SPP and PPR)
Onderstepoort Biological Products	100 Old Soutpan Road, Onderstepoort 0110, Private Bag X07, South Africa Phone: +27 12 522 1500 Fax: +27 12 522 1591 Email: renah@obpvaccines.co.za, info@obpvaccines.co.za www.obpvaccines.co.za	Lumpy skin disease vaccine for cattle (Neethling strain)
Pendik Veterinary Control Institute/ Ministry of Agriculture	Batı Mah., Ankara Cad. No:1, 34890 Istanbul, Turkey Tel: +90 216 390 12 80-156 Fax: +90 216 354 76 92	Penpox-M™ Live SPPV (Bakirköy SPPV strain)
Razi Vaccine & Serum Research Institute	PO Box 31975/148 Hessarak, Karaj, Alborz, Iran Phone: +98 26 34554658 Fax: +98 26 34552194 Email: int@rvsri.ac.ir, www.rvsri.ac.ir	Sheep pox vaccine (RM65 SPPV) Goat pox vaccine (Gorgan GTPV)
Vetal Company	Gölbasi Yolu Uzeri 7 km, Adiyaman, Turkey Phone: +90 416 223 20 30 or +90 531 272 32 68 Fax: +90 416 223 1456 Email: vetal@vetal.com.tr www.vetal.com.tr	Poxvac™ Lumpyvac™
Veterinary Research Institute	59, Jalan Sultan Azlan Shah, 31400 Ipoh, Perak, Malaysia Phone: +605 5457166 or 187 Fax: +605 5463368 Email: admin@jphvri.gov.my	Sheep and goat pox

Table 28.1 (Continued)

Manufacturer	Contact information	Product(s)[a]
Veterinary Serum and Vaccine Research Institute	131 02 El-Sekka El-Bida St, Abbassia, Cairo, PO Box 131, 11381, Egypt Phone: + 02 23421866 or +02 23421406 Fax: +02 2342821 Email: svri@idsc.gov.eg http://vsvri-eg.com	Tissue culture sheep pox vaccine (KSGP O-240 or O-180)
Kenya Veterinary Vaccines Production Institute (KEVEVAPI)	P.O. Box 53260 00200, Head Office, Embakasi off Enterprise Road, Road A, Nairobi, Kenya www.kevevapi.org	S&G Vax™ Lumpivax™
China Animal Husbandry Group	Building 18-19, Block 8, 188 West Road, South 4th Ring Road, Beijing, P. R. China 100070 Fax: +86-10-5226-0088	Live goat pox vaccine
Laboratoire Central Vétérinaire	Km 8, Route de Koulikoro, BP 2295, Bamako, Mali Phone: +223 224 33 44/224 23 04/224 23 05 Fax: +223 224 98 09	Dermapox™
Institut Sénégalais de Recherches Agricoles (ISRA)	Route des Hydrocarbures, Bel-Air, BP 3120 Dakar, Sénégal Tel: +221 33 859 17 25 Fax: +221 33 832 24 27 www.isra.sn	Clavesec™

[a] This list of vaccines does not represent any authentication of the quality or efficacy of the products.

Disclaimer: It was the authors' intention to list all vaccine producers and are not responsible for the safety, quality, and effectiveness of the vaccines listed in the table.

side effects in fully susceptible animals than a live one, they could be ideal for use in preventive vaccination campaigns, for example in buffer zones created between affected and nonaffected countries. Inactivated vaccines could also be used to protect fully susceptible animals prior to importation from disease-free to recently affected regions. On arrival, the protection provided by the killed vaccine could be strengthened by giving a live attenuated booster vaccine. In some cases, the use of inactivated vaccines could also be considered as a short-term solution in an emergency (Tuppurainen and Oura 2014). However, protection provided by inactivated vaccines is shorter than that provided by live vaccines and booster vaccinations given twice per year are usually recommended (Kitching 1986b). Meanwhile, there is no difference in the current OIE or European Union (EU) trade regulations for live animals and their products whether the vaccine used by the exporting country is a live or inactivated one.

To date, no marker vaccines are commercially available against CaPV, making development of a differentiation between infected and vaccinated animals (DIVA) vaccine a major goal for vaccine research in coming years.

It should be underlined that vaccination with any type of vaccine should always be combined with other control and eradication measures, such as strict movement restrictions, a robust database for animal identification and health records, as well as stamping out where feasible.

28.3 Immune Response and Duration of Immunity

As for all poxviruses, immunity against CaPVs is both cell mediated and humoral. After vaccination or natural infection, antibodies appear within 15 days and reach a peak 21–30 days postinfection. The protective role of antibodies against CaPV has been demonstrated in sheep by passive transfer of sera from infected to naïve sheep (Kitching 1986a). However, locally, in the skin, the virus may spread from cell to cell without release of virus particles into the extracellular space. Therefore, a humoral response may not be sufficient to eliminate the infection completely (Kitching 1986b; Carn 1993).

Animals recovered from a natural infection with one member of the genus are believed to be protected from infection by another (Coackley and Capstick 1961; Kitching et al. 1987; Kitching 2003). However, this protection is likely to vary between different CaPV strains. Field studies in Israel and elsewhere have clearly demonstrated the superiority of homologous vaccines against LSDV (Ben-Gera et al. 2015). Calves, lambs, and kids born to immunized or naturally infected mothers have passive immunity that persists for approximately 3–6 months (Weiss 1968). New data on the persistence of the maternal antibodies in calves born to vaccinated dams have been published

demonstrating that a significant number of calves were not protected by maternal antibodies after the age of 3 months and probably even after the age of 2 months (Agianniotaki et al. 2018).

Affected animals will clear the infection and no carrier stage is known to occur.

Duration of immunity provided by vaccination is likely to depend on the vaccine virus strain and host factors. It is estimated to vary between 12 and 23 months (Kitching 2003) and, therefore, an annual vaccination regimen is currently recommended by vaccine manufacturers. More studies are required to investigate the duration of antibody responses, using different serological methods. According to the validation report published by the manufacturer, the commercially available ELISA kit (ID Screen Capripox Double Antigen Multi-species) detected CaPV antibodies up to 7 months postvaccination.

28.4 Vaccine Quality Assurance and Control Testing

In commercially available CaPV vaccines, the origin of the vaccine virus should be clearly indicated. An even more essential part of vaccine quality control is to confirm the identity of the vaccine seed virus, using molecular methods, as there have been cases when molecular investigations revealed that the true identity of the vaccine virus was not what was believed. As an example, the KSGP O-240 strain vaccine was actually LSDV vaccine, being underattenuated and causing clinical signs for cattle but working well in sheep and goats (Tuppurainen et al. 2014). Failure to accurately identify the vaccine seed virus may lead to a situation where less effective or unsafe vaccines are used, or of accidentally using a vaccine containing a live CaPV otherwise absent in the country.

The titer of the virus in the CaPV vaccine product should exceed $10^{2.5}$–$10^{3.5}$ $TCID_{50}$, as recommended by the OIE *Manual of Diagnostic Tests and Vaccines* (OIE 2018b). As some vaccines against CaPV are propagated in primary lamb testis cell cultures, each vaccine batch should be tested for freedom from viruses that affect sheep, such as pestiviruses, different strains of bluetongue (BT), foot and mouth disease, and rabies viruses. In a recent study, LSD and SPP vaccines were shown to be contaminated by a BT serotype 26 virus (Bumbarov et al. 2016).

In addition, the product must be shown to be free of cross-contamination by other viruses handled in the same facilities, such as Aujeszky's disease (pseudorabies) virus. Freedom from *Mycoplasma* spp. and other adventitious bacterial and fungal organisms should be certified for each batch.

Animal species, breed, and numbers used for the safety and efficacy testing should be clearly indicated and potential adverse reactions described. A challenge model for LSD vaccine testing has been developed by researchers at Coda-Cerva, Belgium (Kris de Clercq, personal communication). The correct storage temperature and need for a cold chain during transport, as well as the shelf-life of the product, should be clearly indicated.

28.5 Vaccine Application for Disease Control

In general, live attenuated vaccines against CaPV provide good protection for cattle, sheep, and goats, so long as a homologous vaccine is used in combination with sufficient vaccination coverage. However, the available live vaccines may not provide each individual animal with complete protection against the disease. For a long time, it was believed that a single CaPV vaccine would protect against all members of the genus (Kitching et al. 1987) as more than 96% homology exists between the genomes of SPPV, GTPV, and LSDV (Black et al. 1986; Tulman et al. 2001; 2002; Balinski et al. 2007). However, recent experience obtained from the Middle East and the Horn of Africa indicates that the cross-protection provided by nonhomologue vaccines can be only partial (Khalafalla et al. 1993; Yeruham et al. 1994; Brenner et al. 2009; Somasundaram 2011; Ayelet et al. 2013; Tageldin et al. 2014). The experience obtained from LSDV outbreaks in Israel in 2012–2013 indicated the superiority of LSDV vaccines compared with SPPV vaccines for protecting cattle against LSDV (Ben-Gera et al. 2015). SPPV and GTPV containing vaccines can be used in countries where these CaPV diseases overlap.

Although a homologous vaccine is recommended against LSDV, the price of LSD vaccines is considerably higher than SPPV- and GTPV-containing vaccines. In countries with limited financial resources and a vast number of cattle, SPP or GTP vaccines may be a more affordable option. In these cases, selection of the vaccine should be based strictly on vaccine challenge trials to confirm that the vaccine is effective in cattle. Using heterologous vaccines, it is also possible to create sufficient herd immunity to stop the spread of the disease. In these cases, other supportive disease control and eradication measures, such as stamping out accompanied by an appropriate compensation policy, cattle movement controls, and a proper cattle ID, vaccination, and movement register should also be fully implemented. It should be underlined that in addition to full characterization of the vaccine seed virus, the safety and efficacy of any vaccine used for cattle against LSDV needs to be known prior to vaccine selection. For example,

because of its residual pathogenicity for cattle, the KSGP O-240 (LSDV vaccine) caused serious adverse reactions in dairy cattle (Yeruham et al. 1994).

If homologous vaccines are not available or affordable, attenuated GTPV vaccine seems to be a good alternative for those regions where both LSD and GTP occur. Interestingly, in a recent vaccine challenge study in Ethiopia, a commercially available Gorgan GTPV vaccine (Caprivac™, Jordan Bio-Industries Center, Amman, Jordan) provided good protection for cattle against a highly virulent LSDV field strain (Gari et al. 2015).

More data on the safety and efficacy of a Gorgan GTPV-containing vaccine against LSDV in cattle are expected to be published soon by other research groups. Wider field studies need to be carried out to evaluate the safety and efficacy of other GTP virus vaccines against LSD.

28.5.1 Vaccination Strategy

In response to an outbreak, large-scale vaccination should be started without delay. All susceptible animals within and around the infected zone should be immunized, creating more than 80% vaccination coverage. Regional vaccinations are currently preferred and recommended instead of ring vaccinations. However, if a ring vaccination policy is adopted, the radius of the ring should be at least 25–50 km, covering the flying distance of blood-feeding insects and estimated animal movements to pasture, slaughterhouses, or for trade. The herd immunity should be maintained by an annual vaccination program.

Vaccination is recommended also around temporary slaughter plants or slaughterhouses and animal market places, because it is highly likely that during an outbreak, despite the ban on animal movements, some already affected or subclinically infected animals will be sent to slaughter or markets. Also, naïve pregnant animals should be vaccinated. Calves, lambs, and kids from vaccinated mothers should be immunized at the age of 3–6 months and from nonvaccinated mothers as soon as possible. Animals that are not healthy should be vaccinated without delay once recovered.

Ideally, animals showing characteristic clinical signs of CaPV diseases should be culled, but unfortunately, this is not affordable or feasible in all endemic countries. In these cases, vaccination of animals showing fever, skin lesions, or other typical clinical signs of LSD, SPP, or GTP is not recommended, as vaccination is likely to worsen the clinical disease of infected animals and after recovery affected animals will be protected from reinfection without vaccination. However, in these animals, CaPV infection should be confirmed by laboratory testing, in order to avoid a situation in which clinical signs were actually caused by some other conditions and these animals are left without protection. If animals are moved to seasonal grazing, they need to be vaccinated 28 days before the start of the event.

Correct handling of the live attenuated CaPV vaccines requires maintenance of a cold chain. Live pox vaccine must be protected from direct sunlight and opened bottles must be used within 2–6 hours and then discarded. Needles should be changed between animals, particularly if there is any doubt that the herd could be already incubating the disease.

28.6 Vaccines Against CaPV and Other Diseases

In Africa, the Middle East, and Asia, the geographic distribution of LSD, SPP, and GTP overlaps with the distribution of other, highly infectious, economically important or zoonotic diseases, such as peste des petits ruminants (PPR), contagious caprine pleuropneumonia, foot and mouth disease, and Rift Valley fever (RVF) against which vaccines are available.

The major cost of a vaccination campaign is delivery of the vaccine which is nearly the same whether animals are inoculated with one or more compatible vaccines. A significant cost–benefit improvement could be achieved by vaccination concurrently against several ruminant diseases (www.fao.org/3/a-i4460e.pdf), such as PPR, SPP, and GTP (Hosamani et al. 2006; Chaudhary et al. 2009). Alternatively, vaccination costs can be cut by using a single recombinant multivalent vaccine with a CaPV genome backbone and taking advantage of the following characteristics of the CaPV:

- the relative thermotolerance of a freeze-dried CaPV
- the large size and packaging flexibility of the CaPV genome, which contains genes that can be deleted and replaced by foreign genes without affecting the replication and performance of the resultant virus
- the limited host range of CaPV
- the lack of persistence of the virus in the host and the lack of integration of the virus genome in the host genome, facilitating the acceptance of CaPV-based recombinant vaccines.

The following recombinant capripox vaccines have been developed: CaPV/PPR virus (Diallo et al. 2002; Berhe et al. 2003; Chen et al. 2010; Caufour et al. 2014), CaPV/rinderpest (Romero et al. 1993, 1994; Ngichabe et al. 1997), CaPV/BT (Wade-Evans et al. 1996; Perrin et al. 2007), CaPV/rabies (Aspden et al. 2002), and CaPV/RVF virus (Wallace et al. 2006).

28.7 Vaccine Effectiveness and Postvaccination Monitoring

Due to various factors originating from either the host's immune response or varying efficacy of different vaccine products, not all animals will develop full protective immunity against LSDV. Incomplete protection by CaPV vaccines has been reported, for example, in Egypt (2006) (Salib and Osman 2011), Israel (2006) (Brenner et al. 2009), and Ethiopia (Ayelet et al. 2013; Gelaye et al. 2015). These cases were linked to both incomplete protection by the vaccine against the local LSDV strain and the use of SPP vaccine in cattle at the same dose as used for sheep.

The most common factor contributing to real or apparent vaccine breakdown is vaccination of an already infected herd or flock. During hectic mass vaccination campaigns, some animals may be accidentally missed. Sometimes catching free-ranging beef cattle for vaccination can be technically challenging and time-consuming, leaving small pockets of unvaccinated animals within otherwise fully vaccinated regions. Earlier, using the same needle for many animals for vaccine administration was a common practice but nowadays, due to better awareness, it rarely occurs. In cattle which are not used to handling, a subcutaneous administration of a vaccine can easily fail, or animals may receive only part of the vaccine dosage. Inappropriate storage of vaccine or failure in the maintenance of the cold chain can happen during hot summer months. Vaccine may also be inactivated due to exposure to direct sunlight in the field. Maternally derived antibodies may cause interference with the development of active immunity in calves less than 3–6 months of age (Carn 1993; Kitching 2003).

Postvaccination monitoring is based on passive or active clinical surveillance in vaccinated herds. Retrospective serological surveys are complicated by the fact that some vaccinated animals and those individuals showing mild disease may develop only low levels of neutralizing antibodies although these animals would be fully protected (Weiss 1968; Kitching 1986b). Current availability of a sensitive CaPV ELISA suitable for large-scale testing allows better monitoring of seroconversion and duration of humoral responses in vaccinated herds.

28.8 Vaccine Adverse Reactions

Mild adverse reactions may occur when using live attenuated LSDV vaccines. Small local reactions at the vaccination site are acceptable, showing that the vaccine virus is replicating and producing a good immune response. It is expected that the live vaccine virus can be isolated in skin samples collected from the vaccination site. Temporary fever and drop in milk yield have been reported in vaccinated animals. In a study investigating the adverse reactions caused by LSDV-containing vaccines in a cattle herd in Greece, the decrease in milk yield lasted for 12 days (Katsoulos et al. 2017). More data on the side effects caused by LSD vaccines have been obtained from Croatia which was the first country practising preventive vaccination in 2016. In a small number of cattle, vaccination caused a short low-level viremia and the presence of vaccine viral DNA was detected in nasal and skin samples (Bedeković et al. 2017). It is also known that after vaccination, some animals may show mild generalized disease, the so-called "Neethling disease" (Ben-Gera et al. 2015; Abutarbush et al. 2016). However, the generalized skin lesions caused by an attenuated virus are smaller and clearly different from those caused by fully virulent field strains.

To date, there is no evidence of LSD vaccine viruses regaining their virulence. This may be the result of the laborious and lengthy attenuation process required to remove the virulence of LSDV viruses. For full attenuation, LSD prototype Neethling strain virus required 60 serial passages on lamb kidney cells, followed by 20 serial passages in the chorioallantoic membranes of 8-day-old embryonated chicken eggs (Weiss 1968). The whole attenuation process takes more than a year. During the preventive vaccination campaign in Croatia (2017), 421 720 cattle were vaccinated against LSD (with 85% vaccination coverage). Despite the large number of vaccinated cattle, no spread of the vaccine virus to fully susceptible animals, either within Croatia or in neighboring countries, has been reported. Understandably, farmers complained about the skin reactions and decrease in milk yield in vaccinated herds.

Adverse reactions due to residual pathogenicity have been reported in cattle in Israel (Yeruham et al. 1994) after use of the so-called KSGP O-240 strain for which the attenuation process was less than 20 passages (Tuppurainen et al. 2014). In many cases, generalized reactions were linked to utilization of the KS1 strain which is in fact an LSDV, as indicated earlier.

Sheep pox virus and GTPV vaccines rarely cause adverse reactions in cattle, although it has been reported (Aburtabush and Tuppurainen 2018). If cattle are vaccinated first with SPPV or GTP vaccine and then a booster vaccination is given using a LSDV vaccine, animals have shown fewer adverse reactions postvaccination with LSDV vaccine. Based on the field experience, adverse reactions are typically detected only after the first vaccination and

the number of side effects reduces dramatically after the second round of vaccination. Farmers should be informed in advance about potential adverse reactions caused by live vaccines. In addition, if vaccines are purchased from black markets, cattle owners should be advised that these vaccines may not be safe, nor provide robust protection. Effective inactivated vaccines would offer a safer alternative for use in those countries practicing preventive vaccination.

28.9 Availability and a List of Manufacturers

Table 28.1 lists manufacturers of vaccines for lumpy skin disease, sheep pox, and goat pox.

28.10 Summary

In countries where CaPVs are endemic, where animal movement restrictions cannot be effectively implemented, and where active vector populations are abundant, large-scale immunization using effective vaccines is the only way to successfully control CaPVs. In general, live homologous vaccines provide excellent protection for cattle, sheep, and goats, if the vaccination coverage exceeds 80% and herd/flock immunity is maintained using annual vaccination. Vaccination campaigns should always be combined with other control and eradication measures. A homologous vaccine is preferred. The most recent study indicates that GTPV vaccines could provide a promising alternative for vaccinating cattle against LSD. Also, SPPV vaccines can be used for cattle if the dosage is adjusted accordingly. Importantly, if a heterologous vaccine is used, the efficacy and safety of the vaccine need to be confirmed by a challenge experiment. Effective, inactivated CaPV vaccines are being developed and are likely to become commercially available soon. Killed vaccines could be used in those countries not able to authorize live CaPV vaccines.

None of the vaccines provides all individuals with complete protection although sufficient herd immunity prevents further spread of the virus. The efficacy of CaPV vaccines may vary due to the capacity of the vaccine virus to replicate in nonhomologous host species. The finding that some vaccine strains were actually not what they were supposed to be underlines the importance of the molecular characterization of all commercially available vaccines.

Future vaccine research needs to focus on development of safer and more effective marker vaccines. Affordability of a vaccine is of major importance because the CaPV diseases mainly affect countries with limited financial resources and an outbreak has the most devastating effect on the livelihood of poor small-scale farmers. In particular, the currently available homologous LSDV vaccines are expensive. For example, in Africa, vaccines are used only by large commercial cattle farms. During 2015–2018, highly successful large-scale LSD vaccination campaigns in south-east Europe were co-financed by local governments and the European Commission. SPP and GTP vaccines are considerably cheaper although the actual manufacturing process does not differ between the LSD and SPP/GTP vaccines. An ideal single CaPV vaccine should be able to replicate well in cattle, sheep, and goats and it should have lost many of its pathogenic genes.

Along with the growing amount of genome sequence data, novel information is being accumulated on the pathogenesis of poxviruses. Expression of pathogenic or virulence proteins by the virus will influence the severity of disease. Poxviruses have developed a variety of strategies to divert the host immune response, such as by encoding proteins capable of masking signals associated with the virus infection, mimicking the host cytokines and receptors, and by blocking the host innate defense cell death mechanism (Johnston and McFadden 2003; Stanford et al. 2007). The attenuated vaccinia virus, NYVAC vaccine strain, was developed by disruption or deletion of most of those genes (Tartaglia et al. 1992; Paoletti 1994). Similar genes have been identified in the CaPV genome (Tulman et al. 2001, 2002; Balinsky et al. 2007; Lamien and Diallo, unpublished data) and are potential targets for studies to improve CaPV vaccines, such as deletion of the virus immunomodulatory genes (Tartaglia et al. 1992; Perdiguero et al. 2013; Filali-Mouhim et al. 2015). In order to improve the replication of the virus, the viral genes enabling replication in different host species could be combined in a single CaPV genome, as described for NYVAC vaccine (Kibler et al. 2011; Quakkelaar et al. 2011).

Alternatively, selected cytokine genes could be inserted in the CaPV genome, leading to their expression by the vector in the host. The delivery of the IL-12 and IL-18 genes by recombinant vaccinia virus improved the clearance of infection in mice (Gherardi et al. 2003). However, before an ideal CaPV vaccine will be developed, it is fundamental for the successful control and eradication of capripox diseases that the safety and efficacy of the currently used vaccines against LSD, SPP, and GTP are thoroughly evaluated by challenge experiments, using sufficient numbers of fully susceptible animals under controlled conditions and in the field.

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