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WOAH Reference Laboratory for Lumpy skin disease

Reference Centre World Organisation for Animal Health Founded as OIE

EU Reference Laboratory for Capripox viruses

Funded by the European Union

healthy all life long

REQUIREMENTS FOR VACCINE PRODUCTION

QUALITY CONTROL

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Laboratory Diagnostics and Vaccines seminar

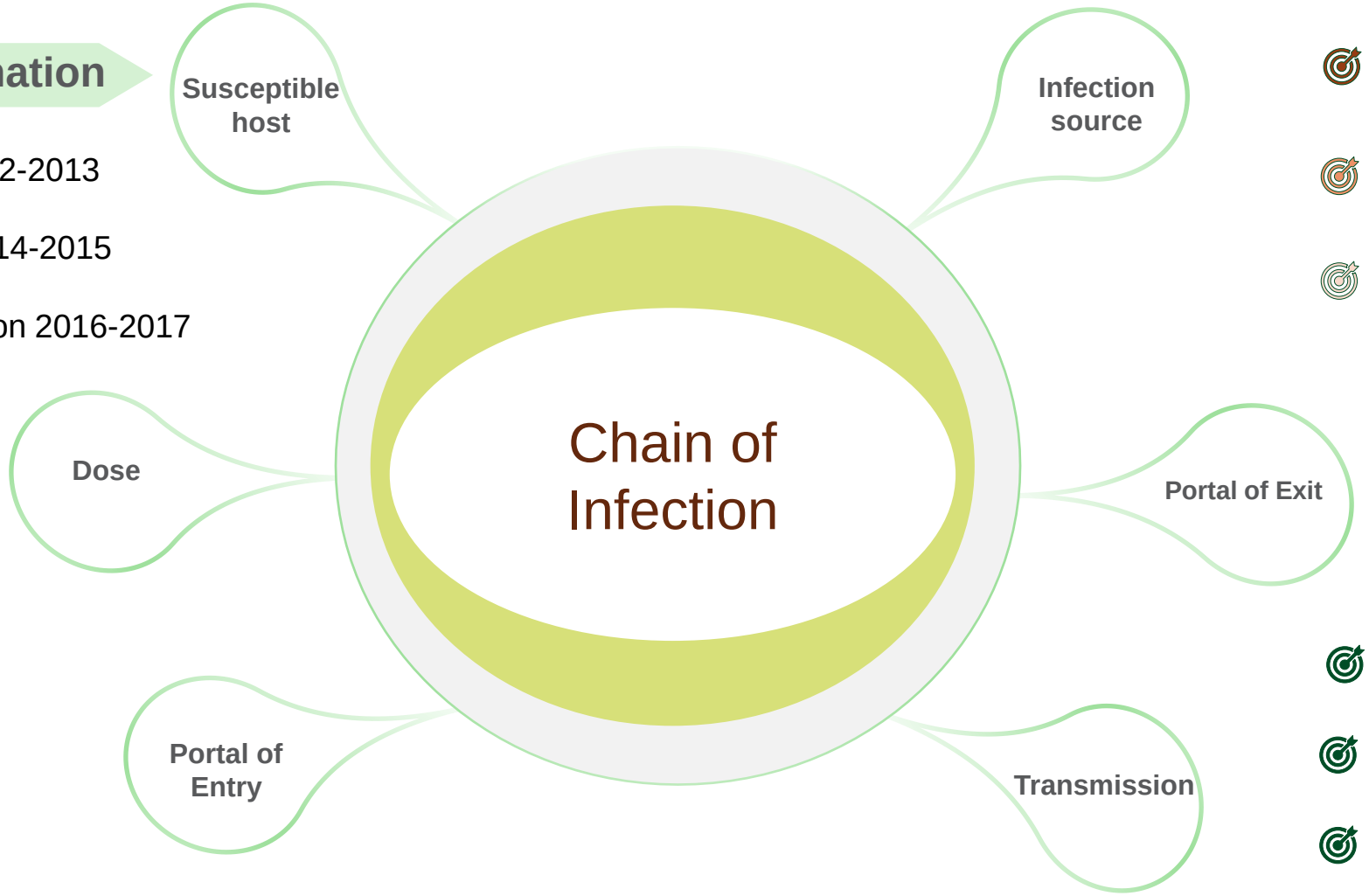
13 December 2023

.be

LSDV Control Measures

Vaccination

- Israël 2012-2013
- Cyprus 2014-2015
- Balkan region 2016-2017



- Early detection
- Stamping out
- Restriction zones
- Disinfection

- Animal movement control
- Quarantine
- Biosecurity measures
- Vector control

LSDV Vaccines

Live attenuated vaccines (LAV)

Homologous vaccines

LSDV-based vaccine (Neethling strain, KSGP strain)

Heterologous vaccines

SPPV (RM65, Romania, Bakirköy, … strain) based vaccines

GTPV (Kedong, Isiolo, Mysorc, Gorgan, Uttarkashi … strain) based vaccines

Inactivated vaccines (INAC)

Multivalent vaccines

Subunit and mRNA vaccines under development

Currently, there are no commercially available vaccines against LSDV with a DIVA component.

Manufacturer	Product Name and Virus Strain	Target Species	Titre, Dose, Administration	Presentation Doses/Vial
Onderstepoort Biological Products (OBP) South Africa Email: info@obpvaccines.co.za http://www.obpvaccines.co.za (accessed on 22 September 2021)	Lumpy Skin Disease Vaccine for Cattle (LSD Neethling strain)	Cattle	Not known 2 ml SC	25/50
Intervet (Pty) South Africa/MSD Animal Health http://www.msd-animal-health.co.za (accessed on 29 September 2021)	Lumpyvax™ (LSD SIS Neethling type strain)	Cattle	$10^{4.0}$TCID$_{50}$/dose 1 ml SC	20/100
MCI Santé Animale Morocco Email: contact@mci-santeanimale.com http://www.mci-santeanimale.com/en/ (accessed on 29 September 2021)	Bovivax-LSD™ (LSD Neethling strain)	Cattle	$10^{3.5}$TCID$_{50}$/dose 2 ml SC	25/50/100
Jordan Bio-Industries Center (JOVAC) Jordan Email: sales@jovaccenter.com http://www.jovaccenter.com (accessed on 29 September 2021)	LumpyShield-N™ (LSD Neethling strain)	Cattle	$10^{4.0}$TCID$_{50}$/dose 1 ml SC	5/10/25/50/100
Middle East for Vaccines (MEVAC) Egypt Email: marketing@me_vac.com https://www.me-vac.com/about (accessed on 29 September 2021)	MEVAC LSD (LSD Neethling strain)	Cattle	$10^{3.5}$TCID$_{50}$/dose 1 ml SC	10/25/50

https://www.mdpi.com/2076-393X/9/10/1136

Requirements for LSDV Vaccines

WOAH Terrestrial Manual

Chapter 1.1.8

- *Principles of veterinary vaccine production*

Chapter 2.3.3

- *Minimum requirements for the organisation and management of a vaccine manufacturing facility*

Chapter 2.3.4

- *Minimum requirements for the production and quality control of vaccine*

Chapter 3.4.12

Lumpy skin disease – part C: requirements for vaccines

https://www.woah.org/fileadmin/Home/eng/Health_standards/tahm/A_summry.htm
European pharmacopoeia
https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-requirements-production-control-immunological-veterinary-medicinal-products_en-0.pdf

Quality Requirements - Development and Manufacturing

Starting materials

Master seed virus

Original isolate, easy to grow in cell culture

Epidemiologically relevant, known geographical and host origin

Identified: species and strain identification using DNA sequencing

Pure: absence of bacteria, fungi, mycoplasma, and other viruses

Tested for safety and efficacy

Working Seed Virus

Cell Banks

Master cell stock identity

Genetic stability from the lowest to the highest passage used for production

Freedom from oncogenicity or tumorigenicity by using *in-vivo* studies using the highest cell passage that may be used for production

Purity of MCSs from extraneous bacteria, fungi, mycoplasma, and viruses

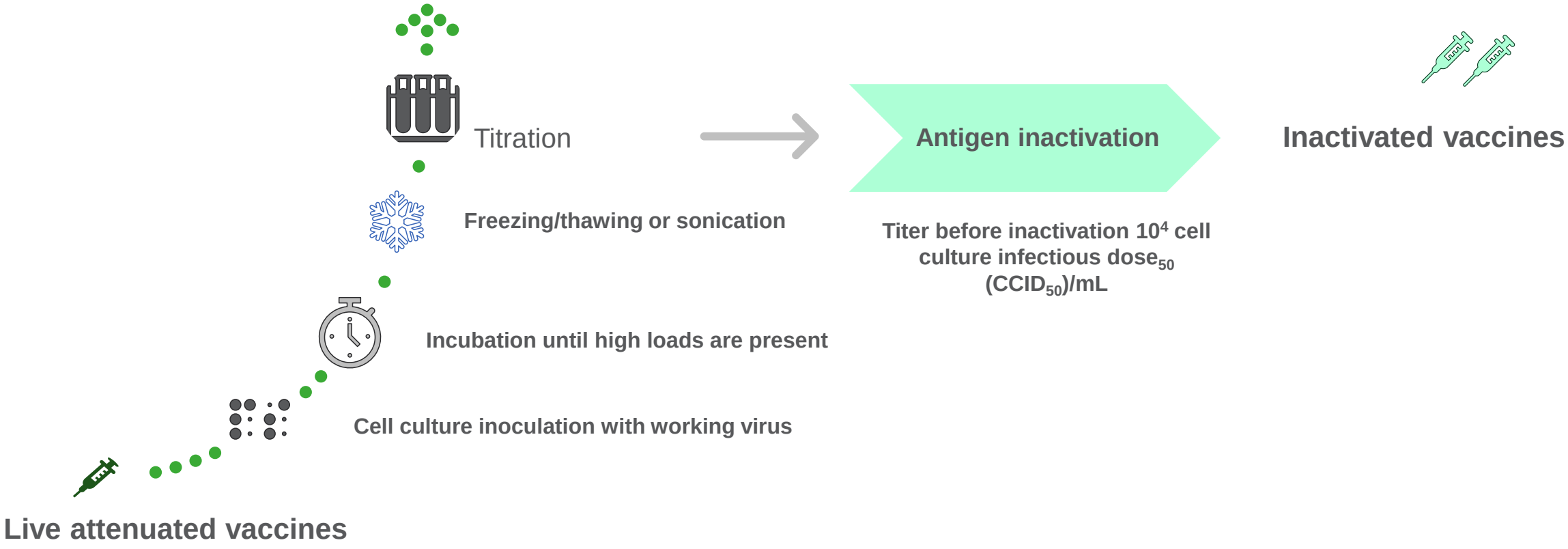
System of Limited Passages

Prevention of Unwanted Drift of Properties

Implemented measures to lower TSE contamination risk

Each master seed strain selected for production of live attenuated LSD vaccines must remain attenuated after further passage in animals, produce minimal clinical reaction, provide complete protection against challenge with virulent field strains, and is not transmissible

LSD Vaccine Batch Production



Vaccine Safety

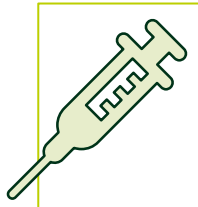
Guidelines for safety evaluation

- **European Medicine Agency (EMEA) – VICH GL44**
- **WOAH Chapter 1.1.8**.

Target animal batch safety test - TABST
Vaccine safety testing on representative animals - calves, heifers, bulls, cows

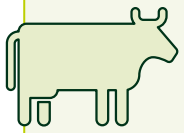
Essential parameters

- Local/ systemic reactions to vaccination
- Fever
- Effect on milk production
- ‘Neethling’ response



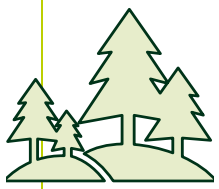
Overdose, One dose and repeat dose test

- The most sensitive breed, age and sex proposed on the label should be used
- Seronegative animals should be used



Reversion to virulence tests

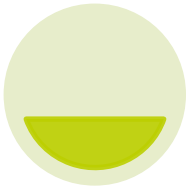
- MSV - 4 passage studies in animals – reisolation and characterisation



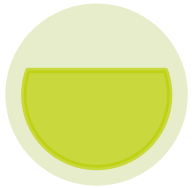
Environmental consideration

- Shedding
- Spreading
- Infection of contact target and non-target animals
- Persistence in the environment

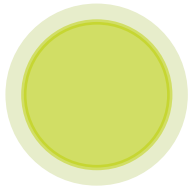
Vaccine Efficacy



Vaccine candidate at the highest passage level



Onset of protection



The duration of immunity

Efficacy (and safety) should be demonstrated in vaccination–challenge studies using representative (by species, age and category) seronegative healthy animals for which the vaccine is intended and which are tested negative for standard viral pathogens

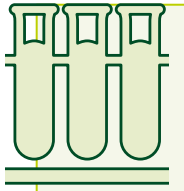
Batch Quality Control Before Distribution

Purity

- the absence of contaminants
- implemented measures to minimise the risk of TSE contamination

Identity

- the absence of other strains or members of the genus
- the absence of any other viral contaminant - PCRs, sanger sequencing, NGS)



Potency tests

- LAV - virus titration;
- IV - vaccination–challenge efficacy studies in animal hosts

Safety/efficacy

- Local/systemic reaction has to be in line with those described in dossier

Duration of immunity

- Challenge or serology
- Efficacy testing at the end of the claimed period of protection
- Effectivenes of booster regime – magnitude and kinetics of serological response

Post marketing studies

- Stability
- Post-marketing surveillance

LSDV Vaccine In Vitro Batch Control: Case Study 1

- In vitro quality control of LSDV and SPPV vaccines (manufacturer not specified)

ELSEVIER

Vaccine

Volume 34, Issue 28, 14 June 2016, Pages 3317-3323

Detection and isolation of Bluetongue virus from commercial vaccine batches

Velizar Bumbarov, Natalia Golender, Oran Erster, Yevgeny Khinich

Announcement | 5 March 2020

Complete Coding Sequence of a Novel Bluetongue Virus Isolated from a Commercial Sheeppox Vaccine

Authors: Paulina Rajko-Nenow, Natalia Golender, Velizar Bumbarov, Hannah Brown, Lorraine Frost, Karin Darpel, Chandana Tennakoon, John Flannery, Carrie Batten | AUTHORS INFO & AFFILIATIONS

Infectious BTV (-9 and -26) detected in commercial LSDV and SPPV vaccines

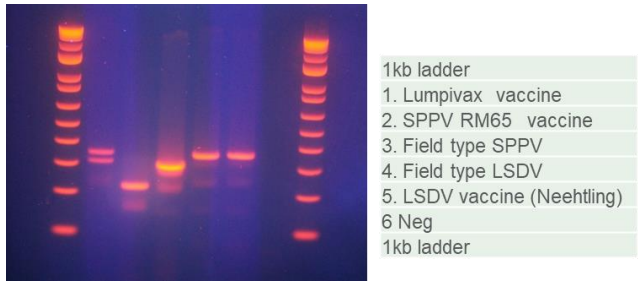
SPPV vaccine (Jovac) contained BTV-26 and BTV-28 strains

LSDV Vaccine In Vitro Batch Control: Case Study 2

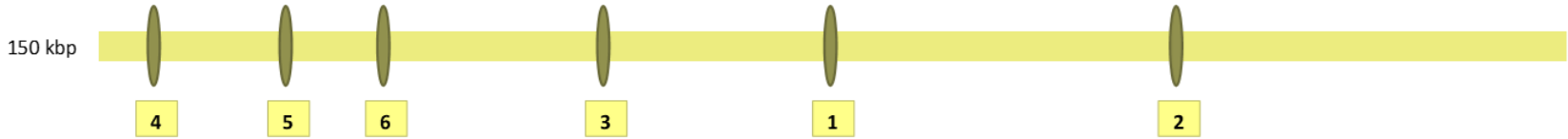
- Vaccine control of LSDV vaccine used in Kazakhstan before the emergence of recombinant strains

1. Confirmation of virus titer ✓
2. Absence of contaminants ✓
3. PCR control of strain purity

   - Pan capripox: ok
   - DIVA 1: Vac: Pos - Field type: Pos!!
   - DIVA 2: Vac: Pos - Field type: Pos!!
   - DIVA 3: LSDV - Field type SPPV/GTPV



4. Partial genome sequencing (6 regions)



5. Full length genome sequencing

LSDV Vaccine In Vitro Batch Control: Case Study 2

vaccines

MDPI

Article

The Importance of Quality Control of LSDV Live Attenuated Vaccines for Its Safe Application in the Field

Andy Haegeman [1,*], Ilse De Leeuw [1], Meruyert Saduakassova [2], Willem Van Campe [3], Laetitia Aerts [4], Wannes Philips [4], Akhmetzhan Sultanov [2], Laurent Mostin [3] and Kris De Clercq [1]

Open Access Article

Recombinant LSDV Strains in Asia: Vaccine Spillover or Natural Emergence?

by Frank Vandenbussche [1,†], Elisabeth Mathijs [1,†], Wannes Philips [1], Meruyert Saduakassova [2], Ilse De Leeuw [3], Akhmetzhan Sultanov [2], Andy Haegeman [3] and Kris De Clercq [3,*]

- Neethling like LSDV vaccine strain
- KSGP-like LSDV vaccine strain
- Sudan-like GTPV strain
- Multiple recombinant strains (almost) identical to recently described recombinant vaccine-like strains
- Most likely source of recombinant strains in the field

One specific badly produced and insufficiently controlled LSDV vaccine was responsible for the release of recombinant LSDV strains in the field

↳ Highlights that efforts need to be done to stimulate a thorough vaccine batch quality control

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