

Vaccines and vaccination against exotic animal diseases 2018

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$$P_{RG} = \frac{AP+Sp-1}{Se+Sp-1} \int_a^b \varepsilon \Theta^{\sqrt{17}} + \Omega \int \delta e^{i\pi} = \{2.7182818284\}$$

Δ ∞ χ^2 Σ $!$ \gg \gg

Content

- Control policies and use of vaccines
- Vaccines against FMD/CSF/LSD/ASF:
 - Presence of the disease
 - Availability of vaccines
 - Characteristics of available vaccines
 - Vaccine banks
 - Future perspective for vaccines

Epidemic disease control policies

- Enhanced biosecurity
- Stamping out and pre-emptive culling
- Movement restrictions
- Monitoring and surveillance
- **Emergency vaccination**



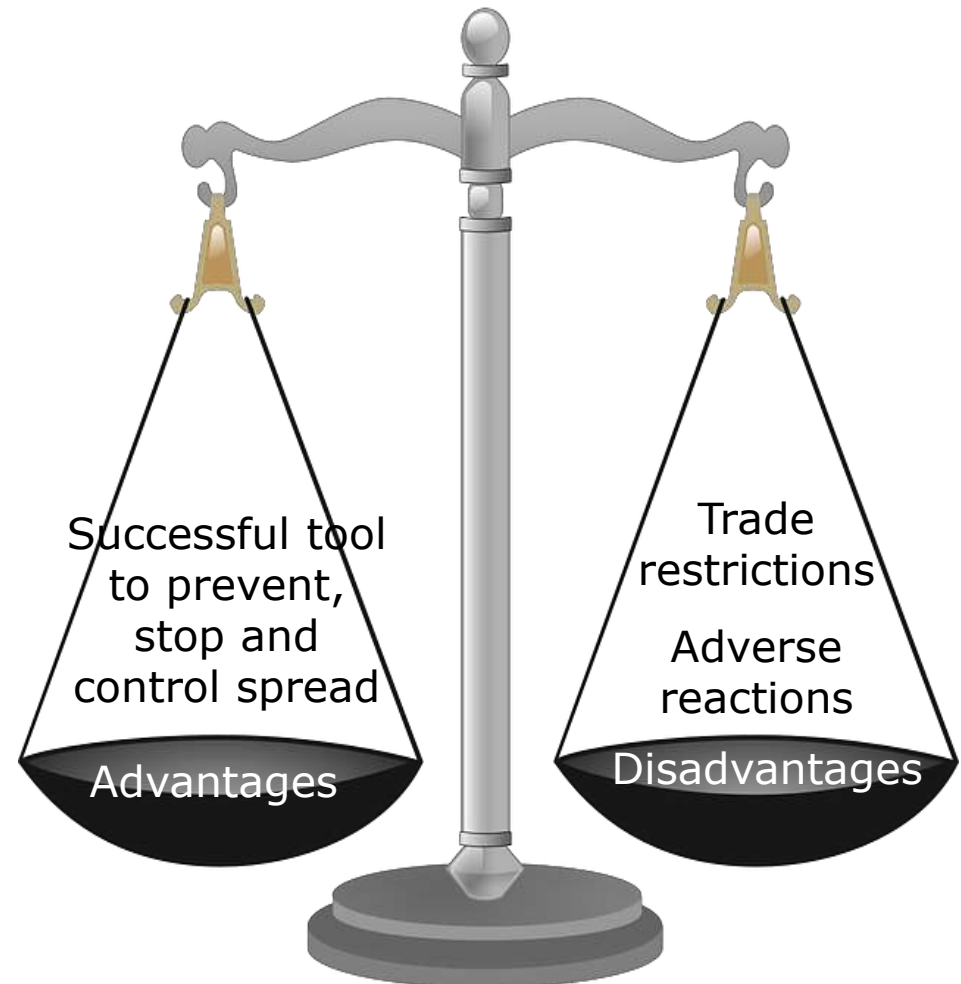
There is a clear need to implement prevention and control strategies based on a **combination of measures** that may include the use of **vaccination**

Vaccination – tool for disease control

Vaccination

Type:

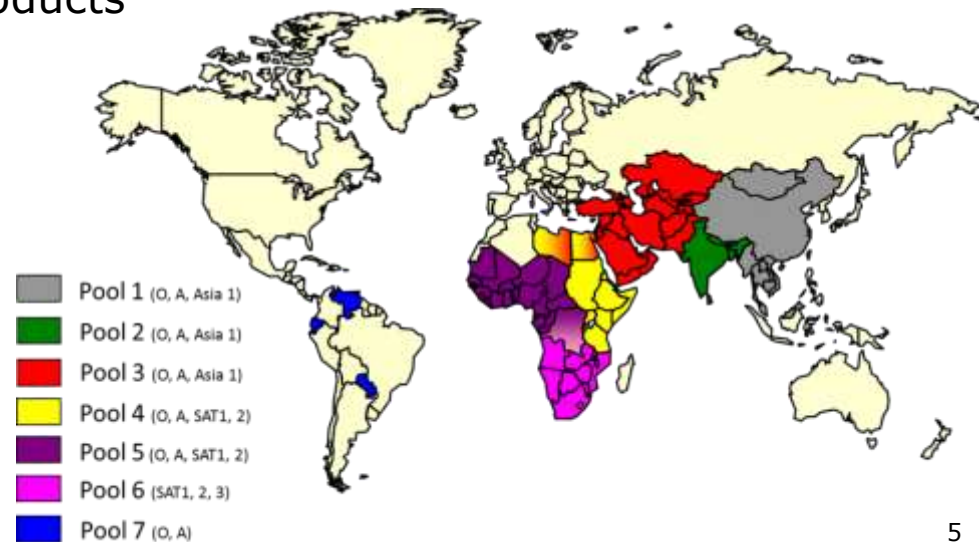
- **Prophylactic**
- **Emergency:**
 - Vaccination-to-live (protective)
 - with post-vaccination monitoring
 - Vaccination-to-kill (suppressive)



The importance of Foot-and-Mouth Disease

- Economically most important infectious disease of farm animals
 - estimated global cost, > US\$ 10,000,000,000 per year
- Outbreak in UK in 2001, cost ca. US \$ 10.000.000.000
- >100 countries affected globally – mainly Africa and Asia
- Huge barrier to trade in animals/products

Last outbreak in EU
Bulgaria 2010/2011

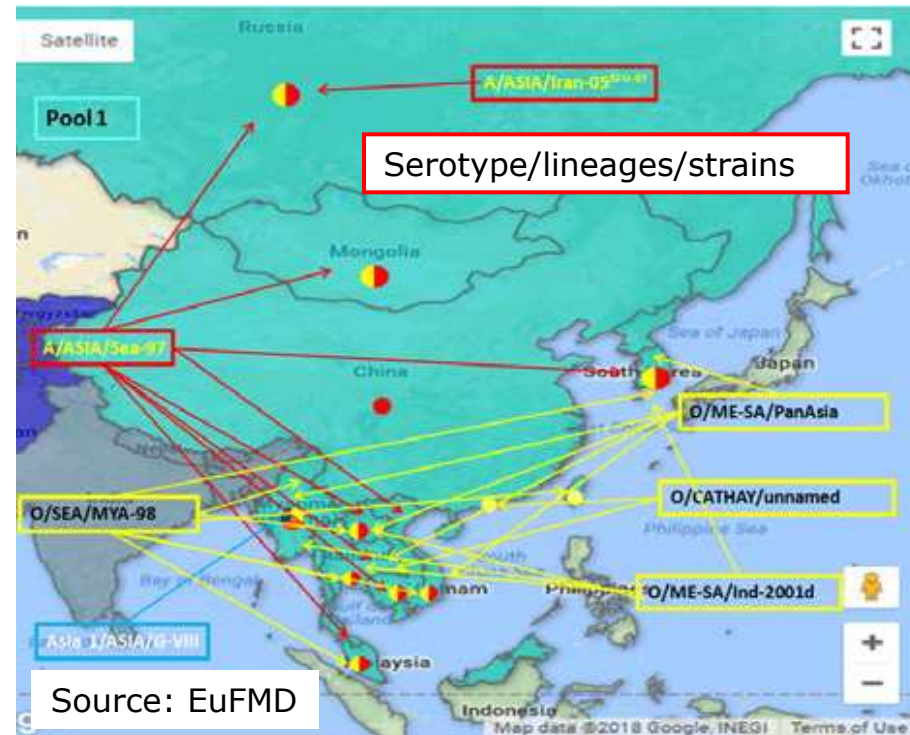


Complexity of FMD virus

- FMDV exists in 7 serotypes:
 - O, A, Asia1 and C
 - SAT1, SAT2, SAT3

- Distinct **lineages** within a serotype

- Distinct **strains** within a lineage



Control of FMD

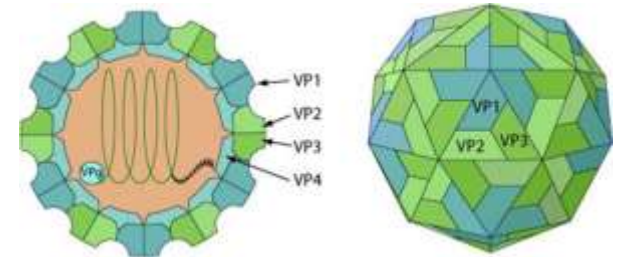
- Incursion in the EU:
 - **Infected herds:** culling, cleaning, disinfection
 - **Zoning:** movement restrictions and increased surveillance
 - **Preventive culling** and/or **emergency vaccination** of in-contact herds or herds at risk



FMD virus and DIVA

FMD virus

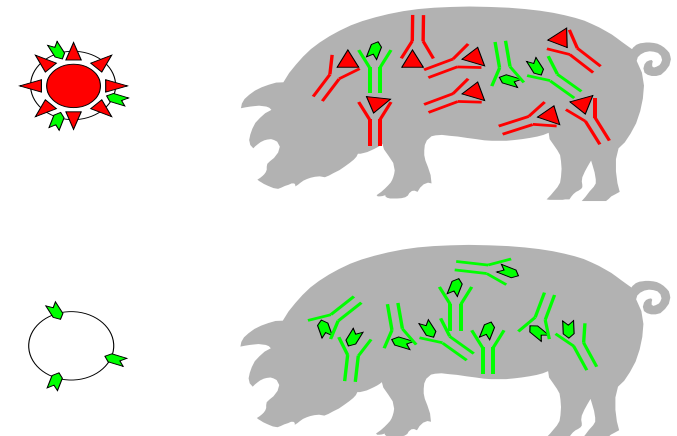
- Virions consist of structural proteins (SP) and RNA
- Non-structural proteins (NSP) expressed in the host cell during viral replication
- NSP not present in the virion



DIVA vaccines

Differentiating Infected from Vaccinated Animals

- Infected animals: antibodies against SP and NSP
- Vaccinated animals: only antibodies against SP
- Commercial ELISAs available for detection of antibodies against NSP to demonstrate freedom from infection



FMDV vaccines

- Chemically inactivated virus (grown in cell culture)
- Vaccine needs to be matched to outbreak virus (not only serotype)
- Duration of protective immunity is very limited (revaccination every 6 months in endemic areas)
- Immunity is dependent on serum antibodies
- DIVA - Use of purified vaccines (lacking non-structural proteins)
- Vaccines induce protection against disease in about 1 week



Persistence of FMD virus

- Clinical signs of disease normally resolve within about 14 days
- However, about 50% of cattle (but not pigs) become long term “carriers” of the virus in the oropharynx
- Carriers defined as having detectable virus more than 28 days post-infection
- Transmission of virus from carrier animals to susceptible hosts is difficult but not impossible (buffalo to cattle in field and by direct transfer of OPF from cattle to cattle)
- **Persistence can occur following virus exposure of vaccinated animals (infected without any clinical signs)**



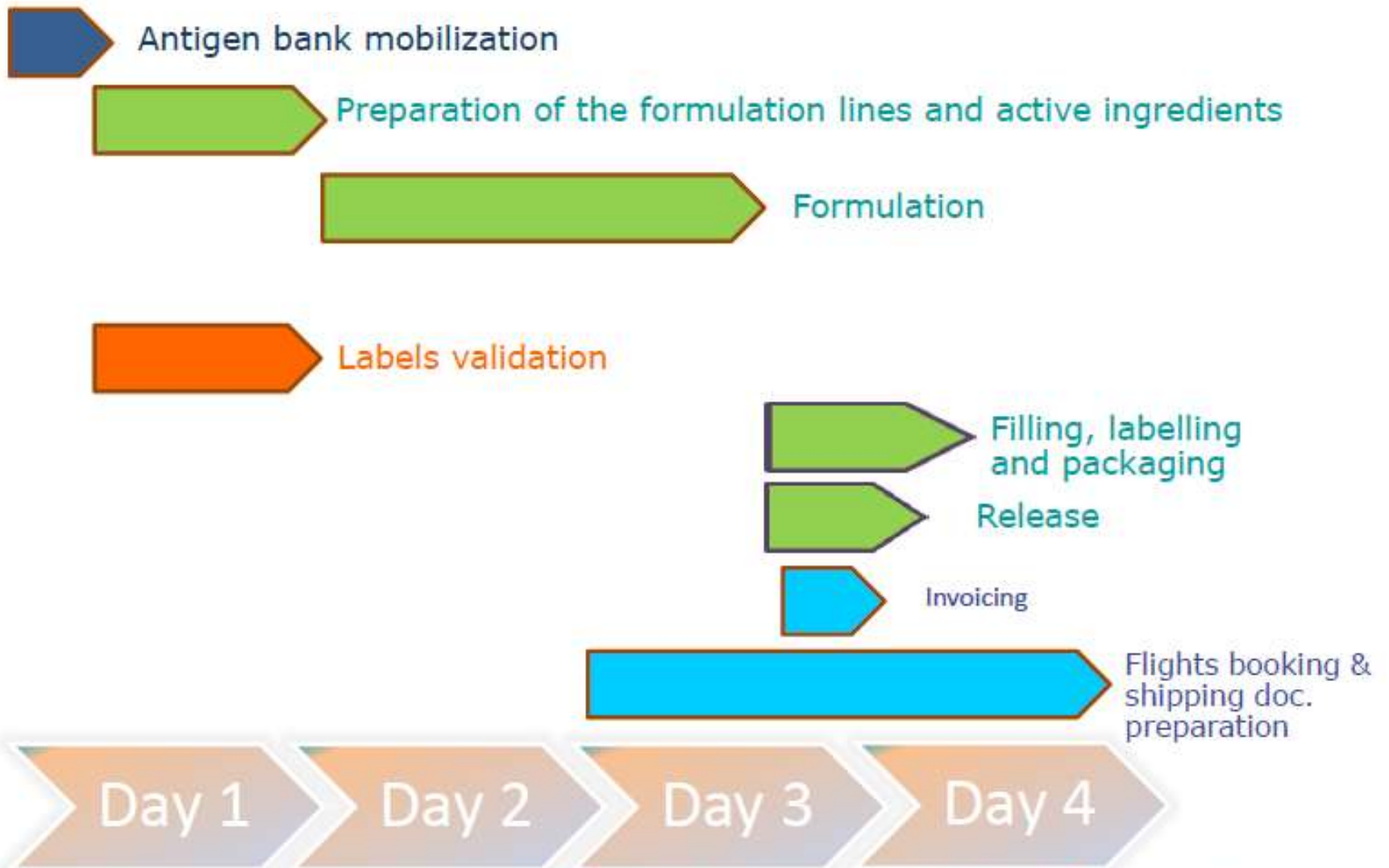
FMD vaccine banks

- 4 EU member states and 1 EEA country have national stocks of frozen FMD antigens including 33 million doses, comprising 16 different strains and covering 5 out of 7 serotypes
- The EU has 36 million doses, comprising 16 strains and covering all 7 serotypes
- Management of vaccine stocks is coordinated by EuFMD for all 37 EuFMD members



- **Antigen banks** for Disease Free Countries

ANTIGEN BANK MOBILIZATION PROCESS



Emergency vaccines for FMD in the EU

- Available for all **7** serotypes and certain subtypes
- Directly available from **antigen banks** in the EU (4 working days):
 - Contracts with commercial manufacturers
 - Formulation of emergency vaccines from frozen, concentrated antigens
 - EU antigen bank managed by DG-SANTE
 - National antigen banks managed by national authorities

Selection of FMDV emergency vaccine strain

- Circulating FMDV strains (serotype/lineage/strain) are characterized by
 - World Reference Laboratory for FMD (UK)
 - EU-RL for FMD (from 1/1/2019 – France and Belgium)
 - Global Network of OIE and FAO Reference Laboratories for FMD
 - Other national reference laboratories for FMD
 - International vaccine manufacturers

- In case of an incursion into the EU, fast characterization of the FMDV field strain (NRL, EU-RL) in combination with prior knowledge gives a good indication of the best suited vaccine strain

- Confirmation of the suitability of a vaccine strain mostly performed by seroneutralisation test (NRL, EU-RL)

Drawbacks of current FMD vaccines

- Large scale growth of highly infectious FMDV under high-containment
 - Potential for virus escape
- Chemical inactivation
 - Use of highly toxic agents
- Vaccine requires maintenance in cold
- Short term duration of immunity (revaccination 2-3 times per year)
- Sub-clinical infection in vaccinated animals
 - apparently healthy vaccinated animals can spread disease
 - low immune response against the non-structural proteins (DIVA challenge)



Testing to declare freedom after vaccination

- **In a population of vaccinated animals**, FMD virus may circulate sub-clinically
- Serological surveillance for antibodies against NSP to detect circulation of FMD virus in a vaccinated herd (NSP not perfect)
- **NSP** antibody-positive herds are considered as “cases” and destruction of these herds applies to regain the status free of FMD

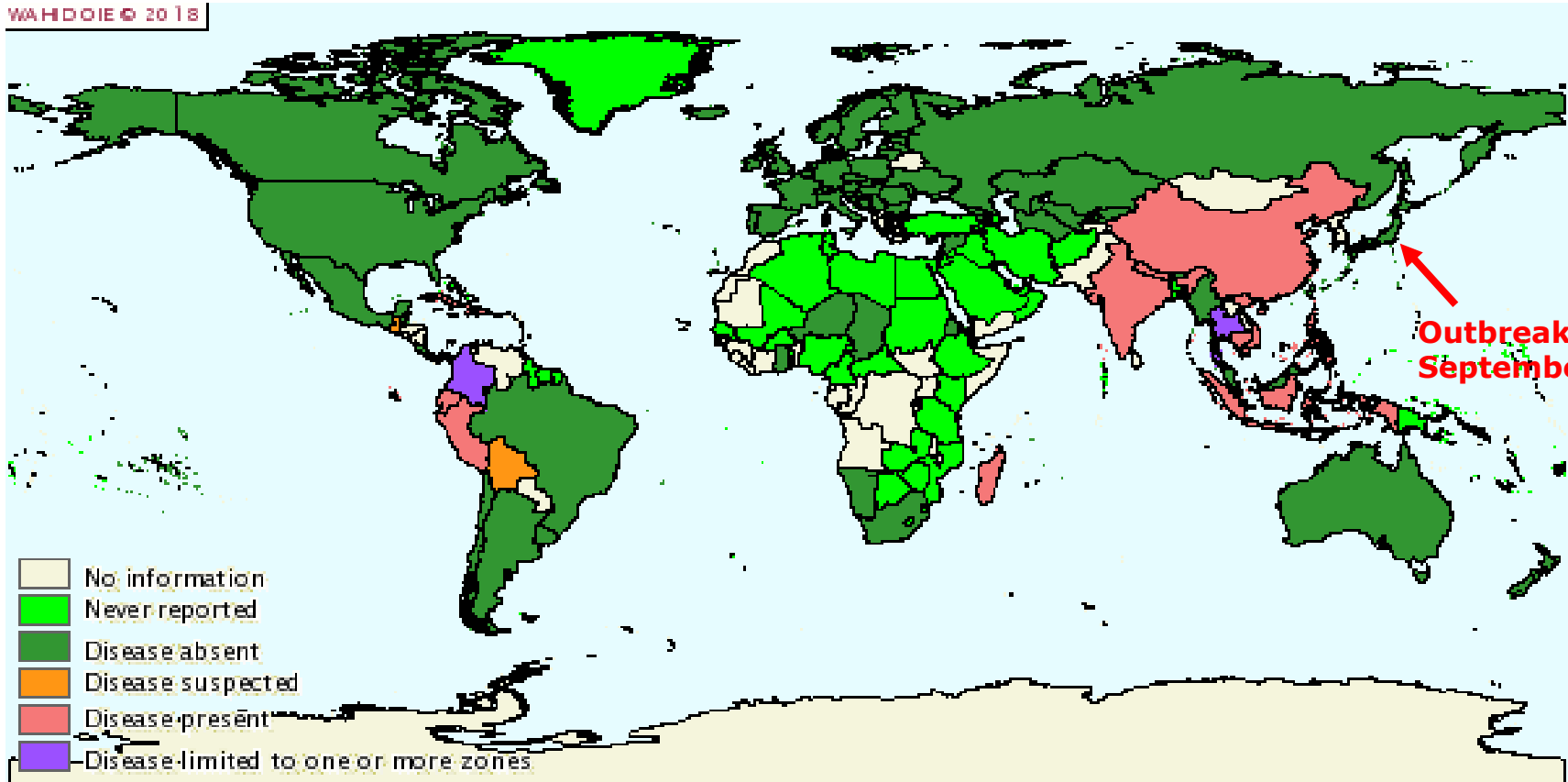
Novel FMDV vaccine technologies

- Subunit vaccines
- Empty capsids
- DNA vaccines
- Viral vector vaccines

So far no next generation vaccines licensed for FMD

Classical swine fever 2018

WAHDOIE © 2018



CSF in EU 2012-15

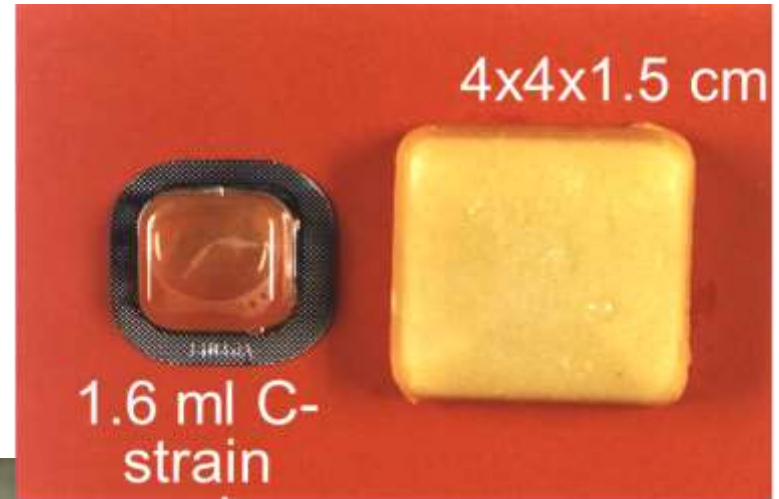


**No outbreaks
reported in EU
since 2015**

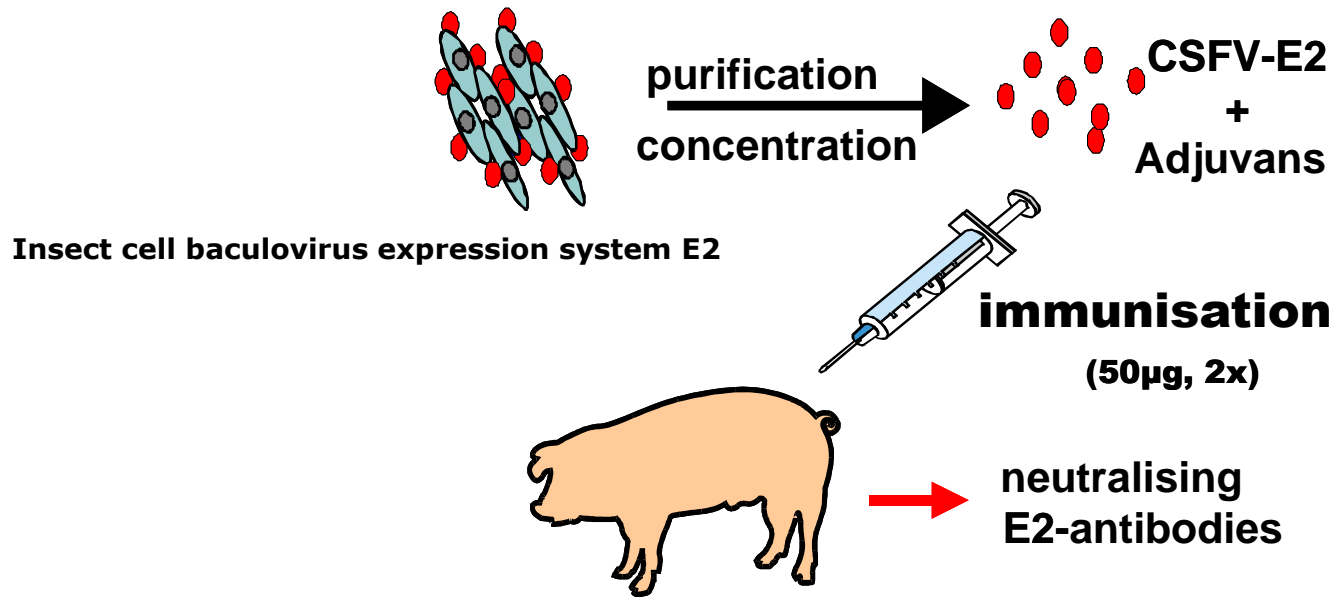
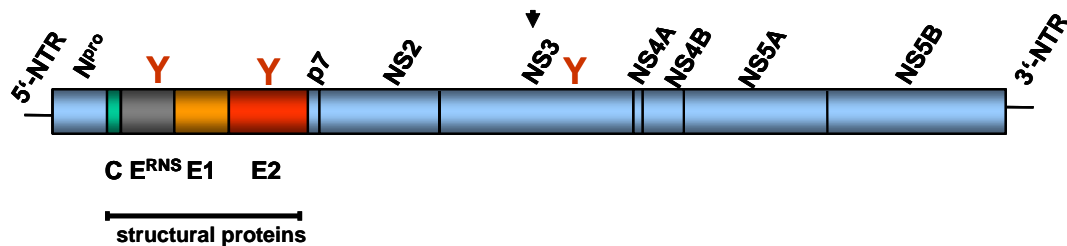
CSF vaccine (C-strain)

- Attenuated live CSFV vaccine, Chinese strain=C-strain
 - 1 x vaccination
 - immunity after 1-7 days
 - oral vaccination possible
 - used for wild boars (all ages)

- No DIVA

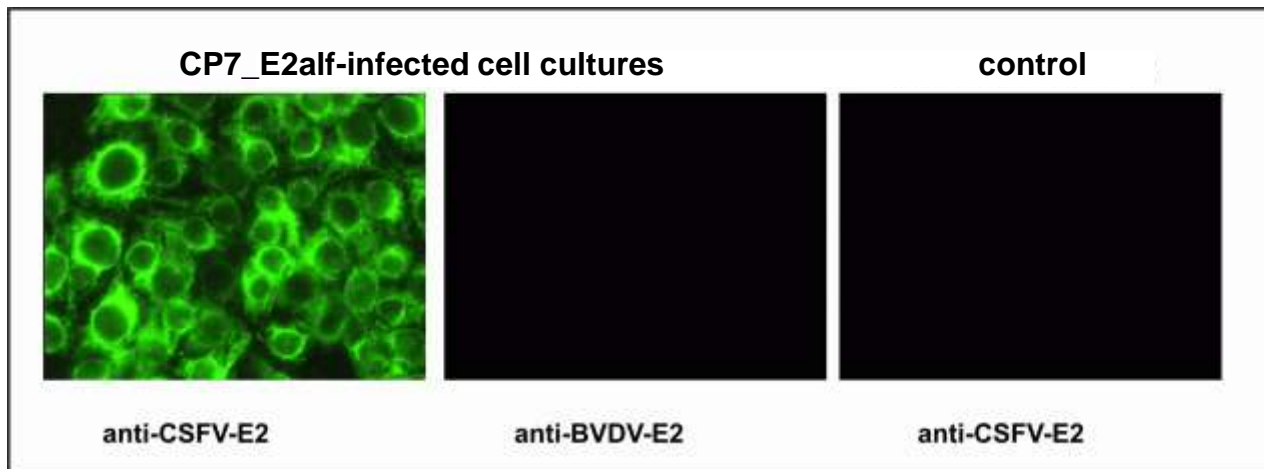
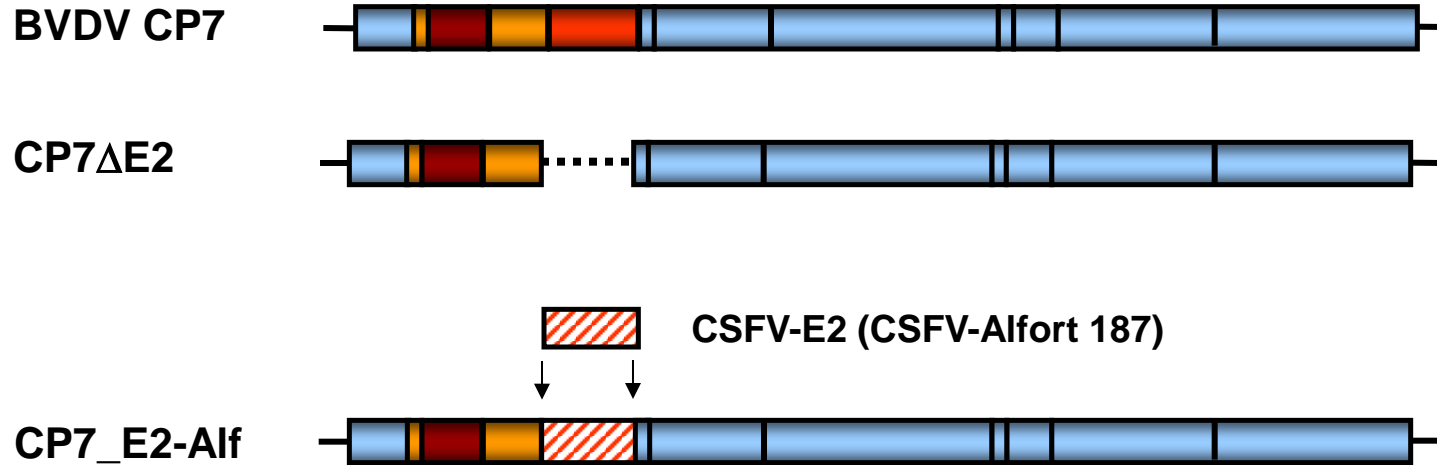


CSFV E2-subunit vaccine

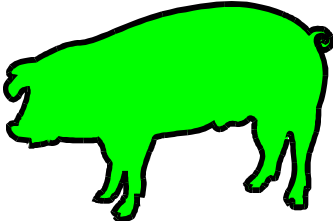
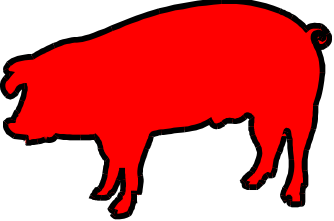
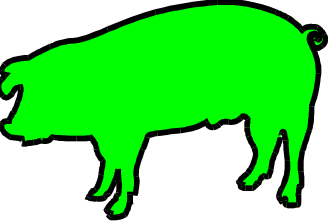
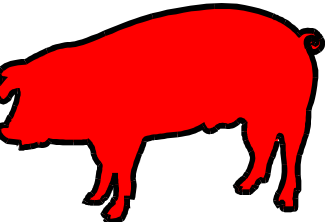


- DIVA (detection of CSFV-specific Erns antibodies)
- 2 vaccinations needed
- Slower development of immunity, → 10-14 days until full protection
- Oral immunisation not possible (wild boar)

Chimeric pestivirus CP7_E2alf



Cp7_E2alf allows DIVA

<u>Vaccine/Infection</u>		<u>CSFV-ELISA/ marker test (E^{RNS} ELISA)</u>
naive		anti-E2: negative anti-E ^{RNS} : negative
CSFV	→ 	anti-E2: positive anti-E ^{RNS} : positive
CP7_E2alf	→ 	anti-E2: positive anti-E ^{RNS} : negative
Cp7_E2alf + CSFV	→ 	anti-E2: positive anti-E ^{RNS} : positive

Chimeric pestivirus CP7_E2alf vaccine

- Safe and efficacious as conventional live attenuated vaccines
- 1 x vaccination
- Immunity within 1 week
- Oral vaccination is possible
 - licensing of "CP7_E2alf" for use in wild boar is still pending
- DIVA
 - Based on the detection of CSFV-specific Erns antibodies
 - BVDV backbone of CP7_E2alf enables genetic differentiation from wild type by PCR



Modified live marker vaccine candidate CP7_E2alf provides early onset of protection against lethal challenge infection with classical swine fever virus after both intramuscular and oral immunization

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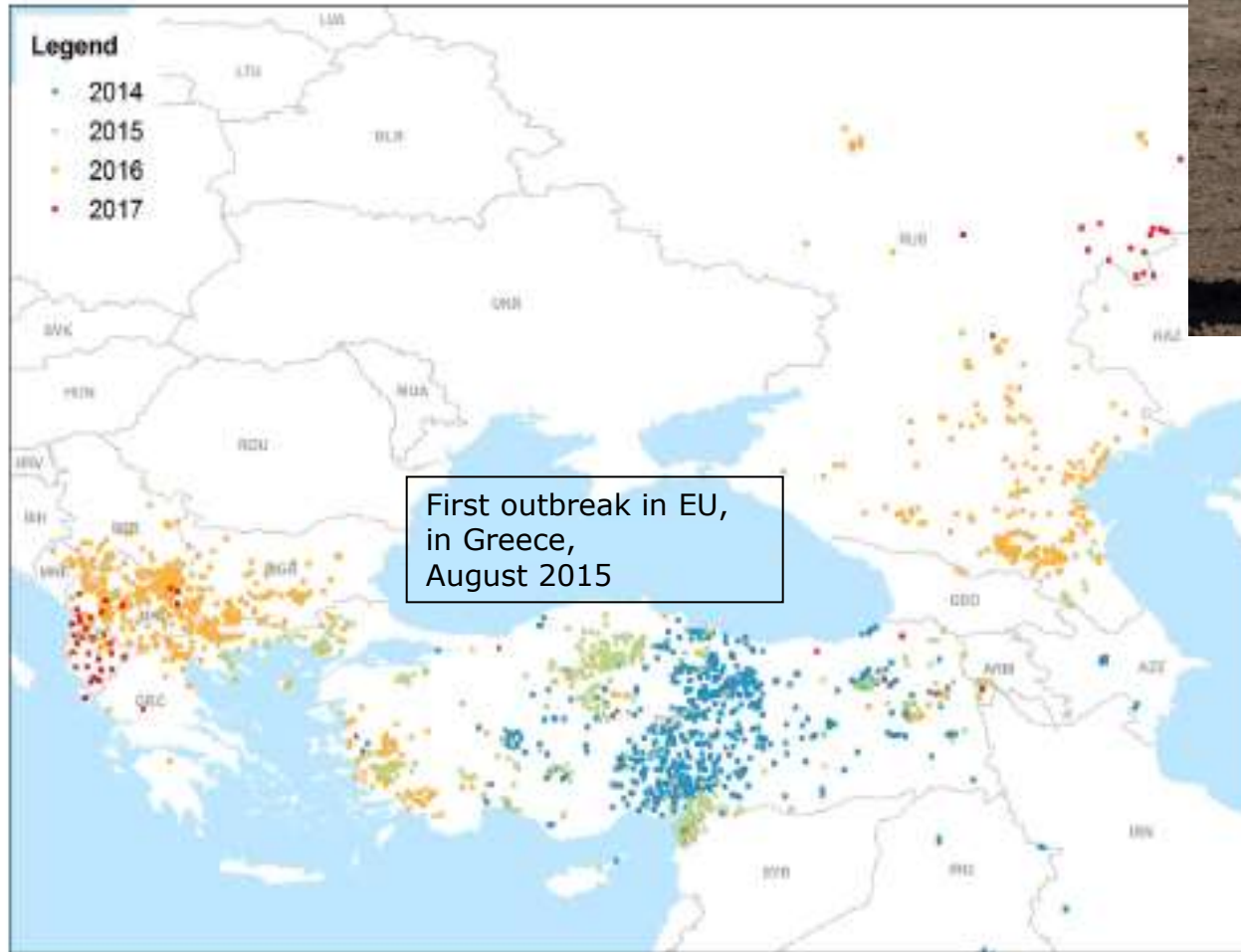
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Protection at **7 days** post i.m. vaccination and
14 days after oral application

Lumpy skin disease (LSD)

Outbreaks in Europe and Middle East 2014-2017

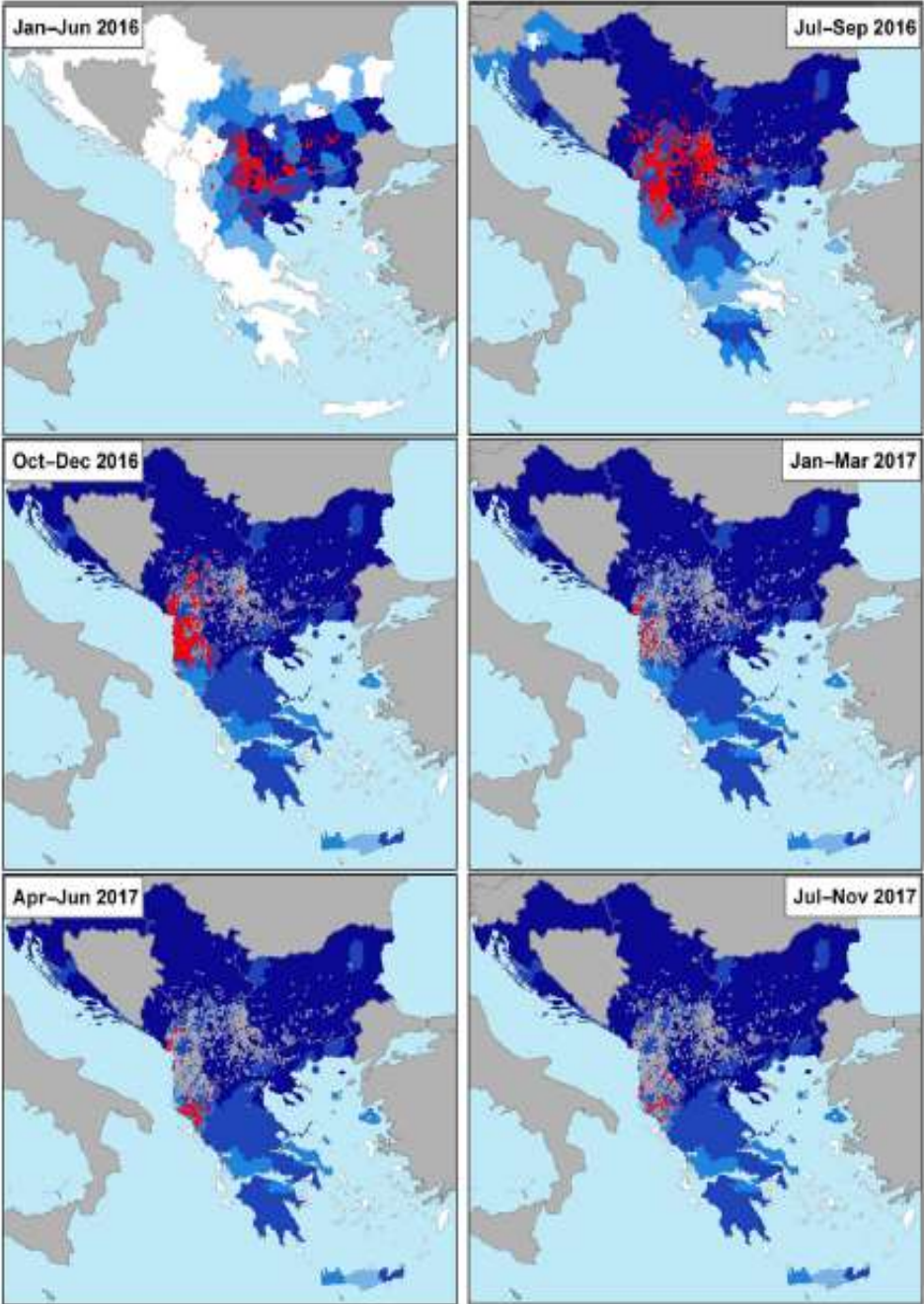


LSD vaccination Jan 2016-Nov 2017



- New LSD outbreaks
- Previous LSD outbreaks

2016: 7,483 outbreaks
2017: 385 outbreaks



The LSD virus

- Lumpy skin disease virus belong to the *Capripoxvirus*-genus within the *Poxviridae* family
- Other members of the genus are sheeppox virus (SPPV) and goatpox virus (GTPV)
- Serological cross-reaction within the *Capripoxvirus*-genus



General knowledge regarding LSD

- Natural resistance to LSD is known to occur in cattle
- Typically sub-clinical infection has been demonstrated in one third of infected animals
- Also sub-clinical infected animals become viraemic and may transmit the virus via blood feeding insects
- Main mode of transmission seems to be via these mechanical vectors
- LSD is extremely difficult to control using only stamping-out and other control measures without vaccination
- None of the currently infected countries has been able to limit the spread or eradicate the disease without vaccination

New EFSA Opinion (July 2016)



- 'No vaccination' is the least effective option in reducing LSDV spread.
- Vaccination is recommended in regions at risk of LSDV introduction
- To increase the likelihood of extinction of outbreaks, high within- and between-farm vaccination coverage should be achieved.
- The implementation of vaccination could be accompanied with partial stamping out instead of total stamping out



Vaccines against LSD



- Only live attenuated LSDV vaccines are currently available
- Three commercially available vaccines from South Africa are derived from the LSDV vaccine strain, Neethling strain (used in EU)
- None of these authorised for use within the European Union; none produced under GMP conditions
- Live attenuated LSDV vaccines provide good protection in cattle and is superior to sheeppox virus (SPPV) vaccines
- Live attenuated vaccines generate more broad protective immunity than inactivated vaccines
 - Immunity against LSDV is mainly cell-mediated
- Live attenuated vaccines provide good protection in case a homologous vaccine is used in combination with sufficient vaccination coverage (>80%)
- No DIVA vaccine available

Heterologous vaccines for LSD

- Where distribution of SPPV and GTPV overlaps with LSDV
 - SPPV vaccines may be used for cattle against LSDV if sufficient vaccination coverage and other appropriate control measures are in place
 - GTPV containing vaccines are not yet used against LSD but have been demonstrated to provide good protection against LSDV



Adverse reaction to MLV LSD vaccines

- Live vaccines may cause adverse reactions in some animals
 - Generally skin reaction at injection site and slight reduction in milk production observed for 4-5 days in 2-10% of the animals
 - Two of the South African MLV are reported to cause < 1% side effects in the field
 - Some vaccines reported to cause up to 30% adverse reactions



Surveillance after vaccination

- No DIVA vaccines
- Active and passive clinical surveillance in vaccinated herds
 - Hampered by adverse reactions resembling disease symptoms
- DIVA-PCR testing (genetic differentiating) of suspected cases
 - “Duplex-PCR” detects and differentiate wild type and vaccine LSDV strains
 - Can be used to confirm cases of adverse reactions/field virus infections



Inactivated vaccines

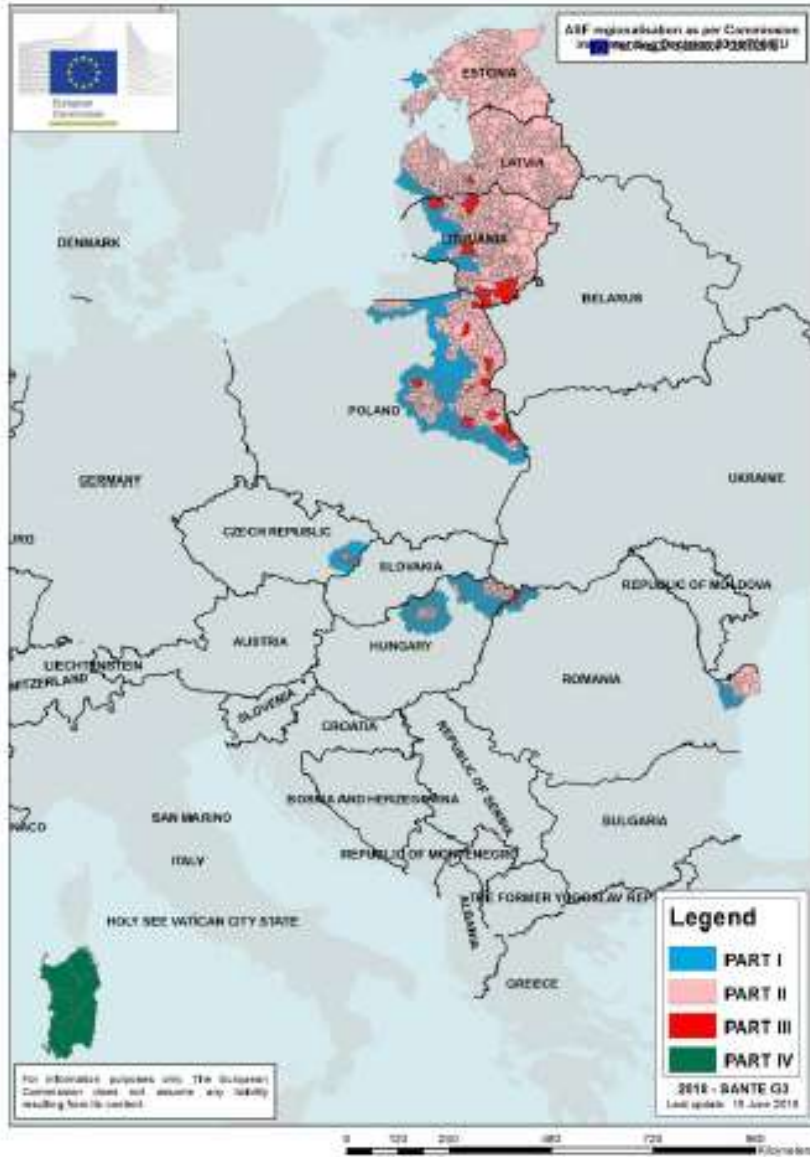
- Safe to use in non-endemic country
- A recent study on SPPV has shown that also inactivated vaccines can confer a protective immunity in sheep, comparable to that provided by a live attenuated SPPV vaccine
- Usually raise higher antibody levels than live vaccines but no cell-mediated response
- Booster vaccination needed
- No published studies on the duration of the protection
- Efficacy of inactivated vaccines is under re-evaluation

African swine fever

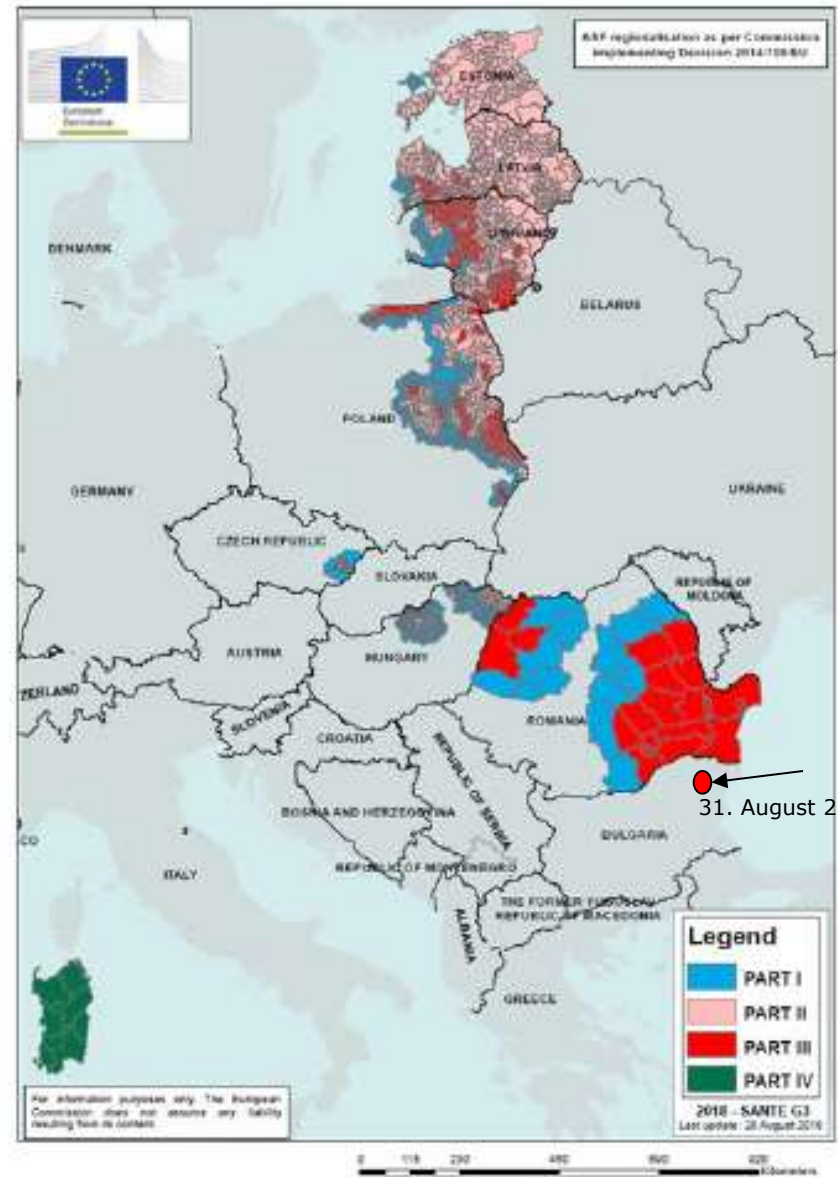
- A (new) threat

Infected areas





June 2018



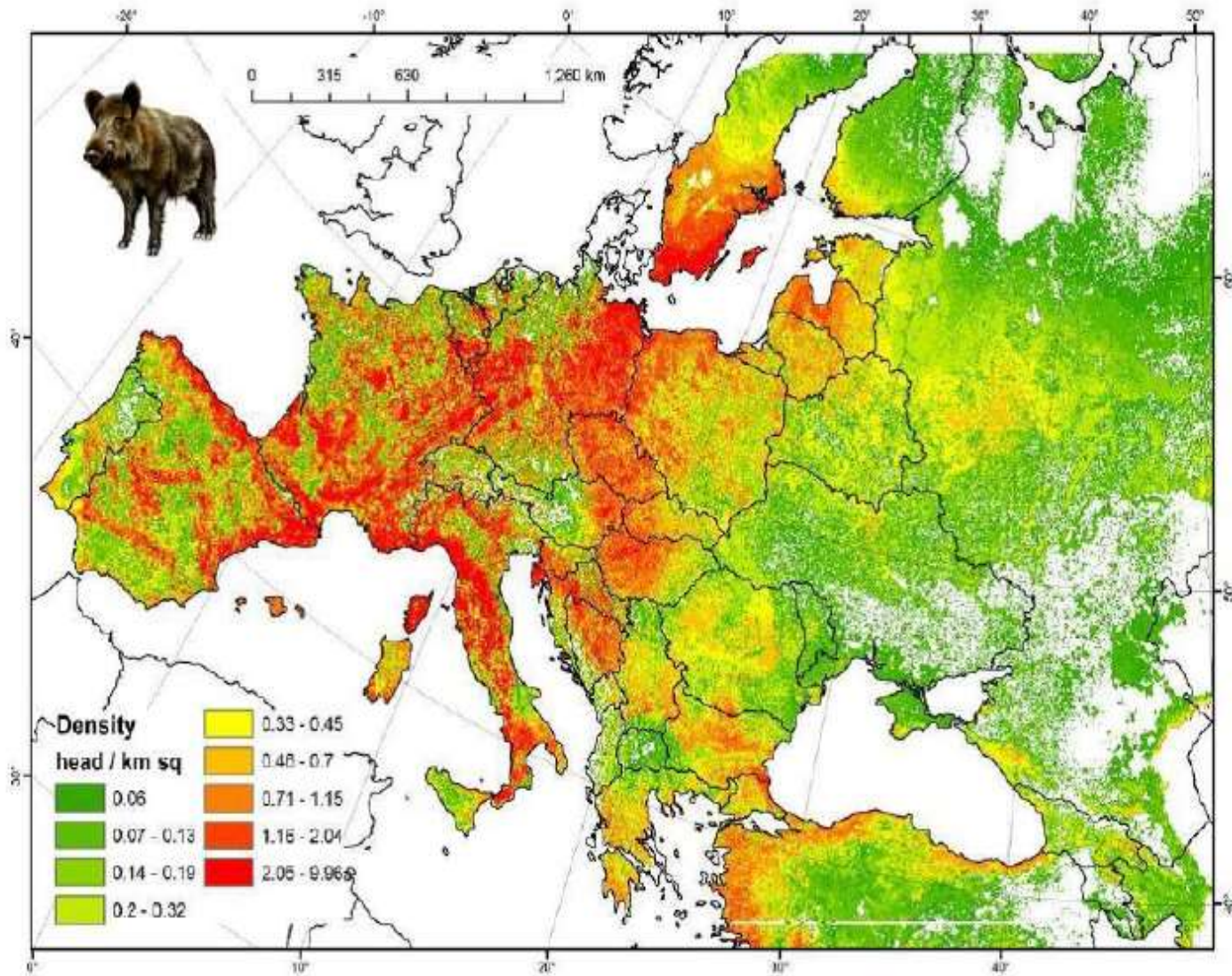
August 2018

Belgium, 2 wild boar

September 13, 2018



Wild boar density



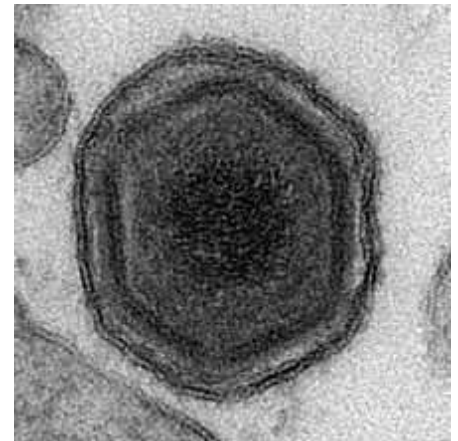
Present ASF in Europe

- ASFV present in Europe causes high mortality
- Uncontrolled spread of disease with wild boar
- High density of wild boar in many areas
- No vaccines available



ASF virus

- A large complex DNA virus
- dsDNA ca. 170.000 - 193.000 bp
- Virion contains more than 50 proteins
- Large DNA encodes more than 160 proteins



ASFV infection and the immune system

- ASFV interferes with various cellular signaling pathways resulting in inhibition of the host's immune system
- Molecular mechanisms used by ASFV to modulate host immune response are not clear
- Humoral and cellular arm of protective immunity is not clear

Challenges for making an efficacious ASF vaccine

- Inactivated preparations of ASFV do not confer protection
- DNA/"subunit" vaccines only confer partial protection
- MLV vaccines are most promising– conferring some level of protection but
 - Little information about ASFV antigen(s) inducing a protective immunity
 - No good heterologous protection
 - Side effects
 - Safety issues (reversion to virulence)
- Protection against reinfection with homologous strain demonstrated
 - So vaccination should be a possible way to obtain protection
- More trial-and-error than rational designed approach at present

Vaccine information 2018

Diseases and Vaccines	Classical swine fever	Foot-and-mouth disease	Lumpy skin disease	African swine fever
TYPE				
Live Inactivated DIVA	Live DIVA	Inactivated DIVA	Live	None
AVAILABILITY				
EU Bank	No	Yes	Yes	No
National banks	No	Yes (some)	Yes (some)	No
From industry	Yes	Yes	Yes	No
Produced in EU	Yes	Yes	No	No
Last use in EU SINCE 2000				
Year	2017	2001	2015, 2016, 2017	-
Country (Example)	Latvia (wild boar)	The Netherlands	e.g. Greece, Bulgaria, Croatia	-

Thank you for your attention!

