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The WOAH standard adopted at the GS-92 (2025) on ASF vaccine manufacturing, safety and efficacy testing for authorisation

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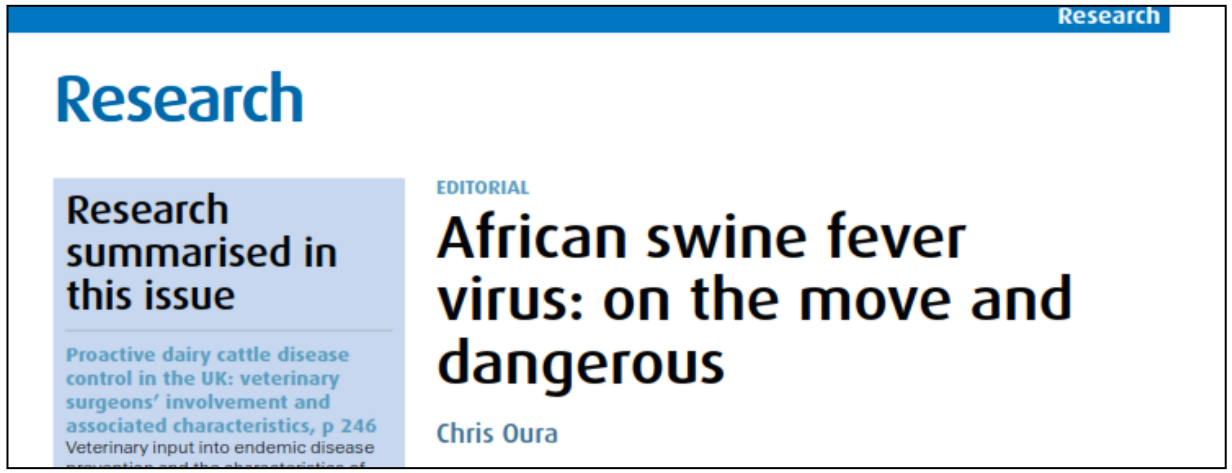
WOAH - BSC

Outline

- Some background on ASF vaccines
- Why vaccine standards now?
- What are the main challenges?
- How are we doing it?
- What have we done?
- The path forward from here…..

There is an urgency to develop and agree on ASF Modified Live Attenuated Vaccine (LAV) standards now



Why has it proved so difficult to find a safe and effective ASF vaccine?

- Large complex virus with many genes and proteins
- Genome size : 170-194 kb, linear and double-stranded DNA molecule
- 24 genotypes
- Inactivated virus does not protect
- Live virus vaccines (attenuated by cell passages) have caused disease
- Neutralising antibody only partially effective
- Historically - few research groups involved in ASFV research and vaccine discovery

Vietnam approves commercial use of first African swine fever vaccines

Reuters

July 24, 2023 11:53 AM GMT-4 · Updated 4 months ago

Open Access Article

Recombinant African Swine Fever Virus Arm/07/CBM/c2 Lacking CD2v and A238L Is Attenuated and Protects Pigs against Virulent Korean Paju Strain

J Virol. 2021 Oct 13;95(21):e0113921. doi: 10.1128/JVI.01139-21. Epub 2021 Aug 18.

Deletion of the A137R Gene from the Pandemic Strain of African Swine Fever Virus Attenuates the Strain and Offers Protection against the Virulent Pandemic Virus

Viruses. 2022 Dec; 14(12): 2777. PMCID: PMC9784117
Published online 2022 Dec 13. doi: 10.3390/v14122777 PMID: 36560781

Oronasal or Intramuscular Immunization with a Thermo-Attenuated ASFV Strain Provides Full Clinical Protection against Georgia 2007/1 Challenge

ORIGINAL RESEARCH article
Front. Vet. Sci., 26 April 2019
Sec. Veterinary Epidemiology and Economics
Volume 6 - 2019 | https://doi.org/10.3389/fvets.2019.00137

First Oral Vaccination of Eurasian Wild Boar Against African Swine Fever Virus Genotype II

Many promising ASF MLV vaccine candidates targeting the p72 genotype II pandemic strain under development, including:

- A naturally attenuated field strain (Lv17/WB/Rei1) (Barasona et al., 2019) being developed as an oral bait vaccine.
- A laboratory thermo-attenuated field strain (ASFV-989) (Bourry et al., 2022).
- Single gene-deleted, recombinant viruses (Gladue et al., 2021; Zhang et al., 2021).
- Double gene-deleted, recombinant viruses (O'Donnell et al., 2016; Pérez-Núñez et al., 2022; Teklue et al., 2020).
- Multiple gene-deleted, recombinant viruses ((Borca et al., 2021; Chen et al., 2020; Liu et al., 2023, Monteagudo et al., 2017; O'Donnell et al., 2015).

Clandestine Pig Vaccines Create 'Chaos' in China, Caixin Reports

Mar 01, 2021 08:24 PM CHINA

African Swine Fever Mutation Spreads in China, Sparking New Control Fears

By Du Caicai, Sun Xiaoxue and Lin Ting

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Article | Open access | Published: 29 May 2023

Highly lethal genotype I and II recombinant African swine fever viruses detected in pigs

Dongming Zhao, Encheng Sun, Lianyu Huang, Leilei Ding, Yuanmao Zhu, Jiwen Zhang, Dongdong Shen, Xianfeng Zhang, Zhenjiang Zhang, Tao Ren, Wan Wang, Fang Li, Xijun He & Zhigao Bu

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EID Journal > Volume 30 > Number 5—May 2024 > Main Article

Volume 30, Number 5—May 2024

Dispatch

Detection of Recombinant African Swine Fever Virus Strains of p72 Genotypes I and II in Domestic Pigs, Vietnam, 2023

ABSTRACT:

African swine fever virus (ASFV) genotype II is endemic to Vietnam. We detected recombinant ASFV genotypes I and II (rASFV I/II) strains in domestic pigs from 6 northern provinces in Vietnam. The introduction of rASFV I/II strains could complicate ongoing ASFV control measures in the region.

Modified live vaccines are often not perfect!

- Often some level of shedding of vaccine virus
- Often some level of transmission to contact pigs and the environment
- Often not completely protective against the field strain

- BUT
- Effective at protecting animals from clinical signs and death
- Often protect for long periods of time

Vaccines for disease scenarios

Different vaccine use scenarios may require different vaccine safety / efficacy profiles

- In epidemic situations, vaccination may offer a tool to lower the impact of the disease and reduce the spread or be used as a first step in a control and eradication programme.
- During newly confirmed outbreaks in previously free areas, emergency vaccination can be an additional tool to control and eradicate the disease.
- Vaccination in at-risk but ASF-free countries……

Any future use of the vaccine candidate should be based on a thorough risk - benefit assessment considering all safety and efficacy features as well as the potential vaccination scenario.

Developing ASF Vaccine minimum standards - challenges

- Limited cross-protection between genotypes – focus on the circulating genotype
- Availability of stable cell lines for manufacturing vaccines.
- Genome stability and maintenance of immunogenicity after continuous passages.

Development of post-vaccination complications – chronic clinical signs

- Vaccine virus shedding into the environment – consequences?
- Horizontal transmission and onward spread – consequences?
- Reversion to virulence - Genetic recombination / rearrangement
- Virulence in pregnant animals?
- Risks from vertical transmission?

Development Process of ASF Vaccine Standards

- Source information from international guidelines (WOAH Terrestrial Manual, VICH etc) and peer-reviewed publications on ASF MLV lead vaccine candidates.
- Surveys and 4 technical workshops with ASF experts and leaders from regulatory sector.
- Draft set of Guidelines came to the Biological Standards Commission in Sept 2023
- Revised text sent out to WOAH Member countries for feedback by Jan 2024
- Input from WOAH ASF experts, further consideration from BSC (Feb 2024) and revised text standards sent to WOAH Member countries for feedback by April 2024.

Development Process of ASF Vaccine Standards (cont'd)

- Many comments. Decision made to **not seek** endorsement of chapter at WOAH GS
- Input from WOAH ASF experts, further consideration by BSC (Sept 2024) and revised text standards sent to WOAH Member countries for feedback by Nov 2025.
- Input from WOAH ASF experts, further consideration from BSC (Feb 2025) and revised text standards sent to WOAH Member countries for feedback by April 2025.

- **Chapter unanimously approved at May 2025 WOAH General Session.**

An optimal ASF MLV first generation vaccine for the target host should have the following general characteristics (minimum standards):

Safe: demonstrate absence of persistent fever and clinical signs of acute or chronic ASF in vaccinated and in-contact animals, have no detected impact on the reproductive safety of pregnant sows, minimal and ideally no vaccine virus horizontal transmission, genetic stability and absence of an increase in virulence (phenotypic stability).

Efficacious: protects against mortality, reduces acute and other forms of disease (fever accompanied by the appearance of clinical signs caused by ASF) and reduces levels of challenge virus viraemia and shedding.

Quality - Purity: free from wild-type ASFV and extraneous microorganisms that could adversely affect the safety, potency or efficacy of the product.

An optimal ASF MLV first generation vaccine for the target host should have the following general characteristics (minimum standards)[cont'd]

Quality – Stability: – the virus titre is maintained at or above the minimum immunising (protective) dose throughout the vaccine shelf life, ensuring efficacy.

Vaccine Matched - based on the capacity to protect against the genotype II pandemic strain or other genotypes of recognised epidemiologic importance.

What is included in the Standards?

2. Outline of production and minimum requirements for vaccines
   - 2.1. Characteristics of the seed
   - 2.2. Method of manufacture
   - 2.3. Requirements for authorisation/registration/licensing
     - 2.3.1. Manufacturing process
     - 2.3.2. Safety requirements
     - 2.3.3. Efficacy requirements
     - 2.3.4. Duration of immunity
     - 2.3.5. Stability

SECTION 3.9.

SUIDAE

CHAPTER 3.9.1.

AFRICAN SWINE FEVER (INFECTION WITH AFRICAN SWINE FEVER VIRUS)

Presented the newly drafted section after four rounds of comment

Manual of Diagnostic Tests and Vaccines for Terrestrial Animals, twelfth edition 2023

MLV Vaccine safety testing :

- Vaccine safety testing in young pigs
- Vaccine Safety testing in pregnant sows
- Horizontal transmission of vaccine virus
- Vaccine virus shed and spread (MLV blood, tissue, excretions) study
- **Reversion to virulence of vaccine virus**

Safety testing - Young Pigs: The vaccine is compliant if:

- No piglet shows abnormal (local or systemic) reactions or notable signs of disease, or reaches the pre-determined humane endpoint defined in the clinical scoring system or dies from causes attributable to the vaccine; minor local reactions may be acceptable if they are transient and not indicative of a serious adverse event.
- No individual pig should show a rise in temperature above baseline greater than 1.5°C for a period exceeding 2 consecutive days that is attributable to ASFV infection. In cases where pigs exceed the temperature standard but show no behavioural changes or other clinical signs, regulators may determine vaccine safety through a risk–benefit balance assessment without solely relying on temperature for non-compliance.
- No vaccinated pigs show notable signs of disease by gross pathology

Safety testing – Pregnant Sows.
The vaccine is compliant if:

- No pregnant sows show abnormalities in their gestation or in their piglets compared with the control group (i.e. abortion, the birth of mummified foetuses and reduced numbers of piglets born alive).
- No pregnant sows show notable signs of disease or dies from causes attributable to the vaccine;
- No vaccine virus or antibodies against ASFV are present in blood samples from newborn piglets.

Safety testing - Horizontal transmission: The vaccine is compliant if:

- No vaccinated or naïve contact piglet shows abnormal (local or systemic) reactions, or notable signs of disease, reaches the predetermined humane endpoint defined in the clinical scoring system or dies from causes attributable to the vaccine;
- No individual naïve contact pig show a rise in temperature above baseline greater than 1.5°C for a period exceeding 2 consecutive days that is attributable to ASFV infection. In cases where pigs exceed the temperature standard but show no behavioural changes or other clinical signs, regulators may determine vaccine safety through a risk–benefit balance assessment without solely relying on temperature for non-compliance;
- No naive, contact piglet shows notable signs of disease by gross pathology
- A low percentage of or ideally no naïve contact piglets test positive to the vaccine virus and/or to antibodies against the vaccine virus.

Safety testing - Vaccine shed and spread (MLV blood and tissue dissemination) study:

One study should be performed to determine the post-vaccination kinetics of virus replication in the blood (viremia), tissues and viral shedding.

- Clinical disease (acute and chronic)
- Viraemia (multiple time points)
- Vaccine virus in tissues and excretions (oral, nasal and faecal swabs) (multiple time points)

Determine which tissues and timepoint(s) should be used in the design of the reversion to virulence study

Safety testing - Reversion to virulence: The vaccine virus complies with the test if:

- No piglet shows abnormal local or systemic reaction, reaches the pre-determined humane endpoint defined in the clinical scoring system or dies from causes attributable to the vaccine; and
- There is no indication of increasing virulence (as monitored by daily body temperature accompanied by clinical sign observations) of the maximally passaged virus compared with the master seed virus.

The test should be carried out consistent with VICH GL41 (Examination of live veterinary vaccines in target animals for absence of reversion to virulence, 2008).

Annex 32: Chapter 3.9.1. 'African swine fever (infection with African swine fever virus)' (vaccine section only) (2021)

- **Thoroughly updated Section C** '*Requirements for vaccines*' of the African swine fever (ASF) chapter, covering the manufacture of pure, potent, safe, and efficacious vaccines for ASF, including key vaccine performance and quality criteria

- **Acknowledged that live modified vaccines** are already in use in some Members highlighting the Commission's decision to establish a minimum standard in the WOAH *Terrestrial Manual*, with a commitment to reviewing it regularly as new scientific evidence becomes available

- **Introduced mock-vaccinated control groups** in the piglet and sow safety studies

- **Clarified the reversion-to-virulence experiment**, specifying that: The same quantity and viral titre of the master seed vaccine virus used in the first passage (P1) must be used

- An equal quantity and viral titre (diluted if necessary) of the positive material used for the final passage (P5) should be used to inoculate the two groups of pigs

- **Supported the clarification with expert input**, ensuring that the final experiment measures the true reversion to virulence, avoiding dose-dependent changes in virulence that could occur if virus titres in P1 and P5 were different

At a minimum, a safe MLV vaccine shall demonstrate ALL the following features (minimal standards):

- Absence of fever. No individual pig should show a rise in temperature above baseline greater than 1.5°C for a period exceeding 2 days that is attributable to ASFV infection. In cases where pigs exceed the temperature standard but show no behavioural changes or other clinical signs, regulators may determine vaccine safety without solely relying on temperature for non-compliance;
- Absence of chronic and acute clinical signs and gross pathology over the entire test period.
- Absence of abnormal (local or systemic) reactions;

At a minimum, a safe MLV vaccine shall demonstrate ALL the following features (minimal standards) (ctd)

- A low percentage or ideally no naïve, contact pigs test positive to the vaccine virus and/or to antibodies against the vaccine virus;
- Absence of an increase in virulence (as monitored by daily body temperature increases above the baseline accompanied by clinical signs) of the maximally passaged virus compared with the master seed virus (complies with the reversion to virulence test).
- No pregnant sows show abnormalities in their gestation or in their piglets compared to the control group.

MLV Vaccine efficacy testing:

At a minimum, an efficacious MLV vaccine shall demonstrate ALL the following features:

- No vaccinated challenged piglet dies or reaches the humane endpoint from causes attributable to ASF. It might also be acceptable that a low percentage of vaccinated challenged piglets die or reach the humane endpoint from causes attributable to ASF, depending on the purpose of vaccination, for instance, in cases where the aim is to control the disease rather than eradicate it;
- The vaccinated challenged piglets display a reduction in typical acute clinical signs (including fever, acute and chronic clinical signs) and gross pathology, and a reduction or absence of challenge virus levels in blood (viraemia), swabs and tissues (viral shedding).

Advancing ASF Vaccine Standards: **Next Steps**

- Acknowledge the dynamic nature of Standards and commit to continuous improvement as more data appears.
- Semi-annual reviews and comprehensive literature reviews.
- Collaborative effort – input from ASF and vaccine experts essential

We need to ensure standards are practical, adequate and reflect the latest science

Thank you
Merci
Gracias

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