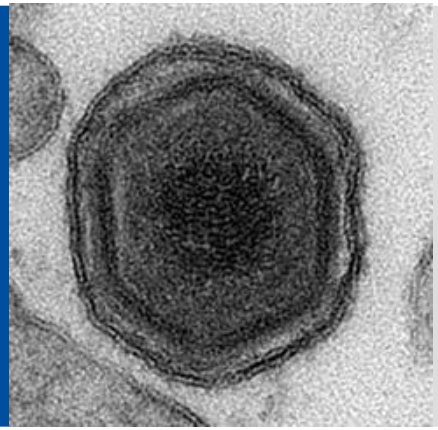
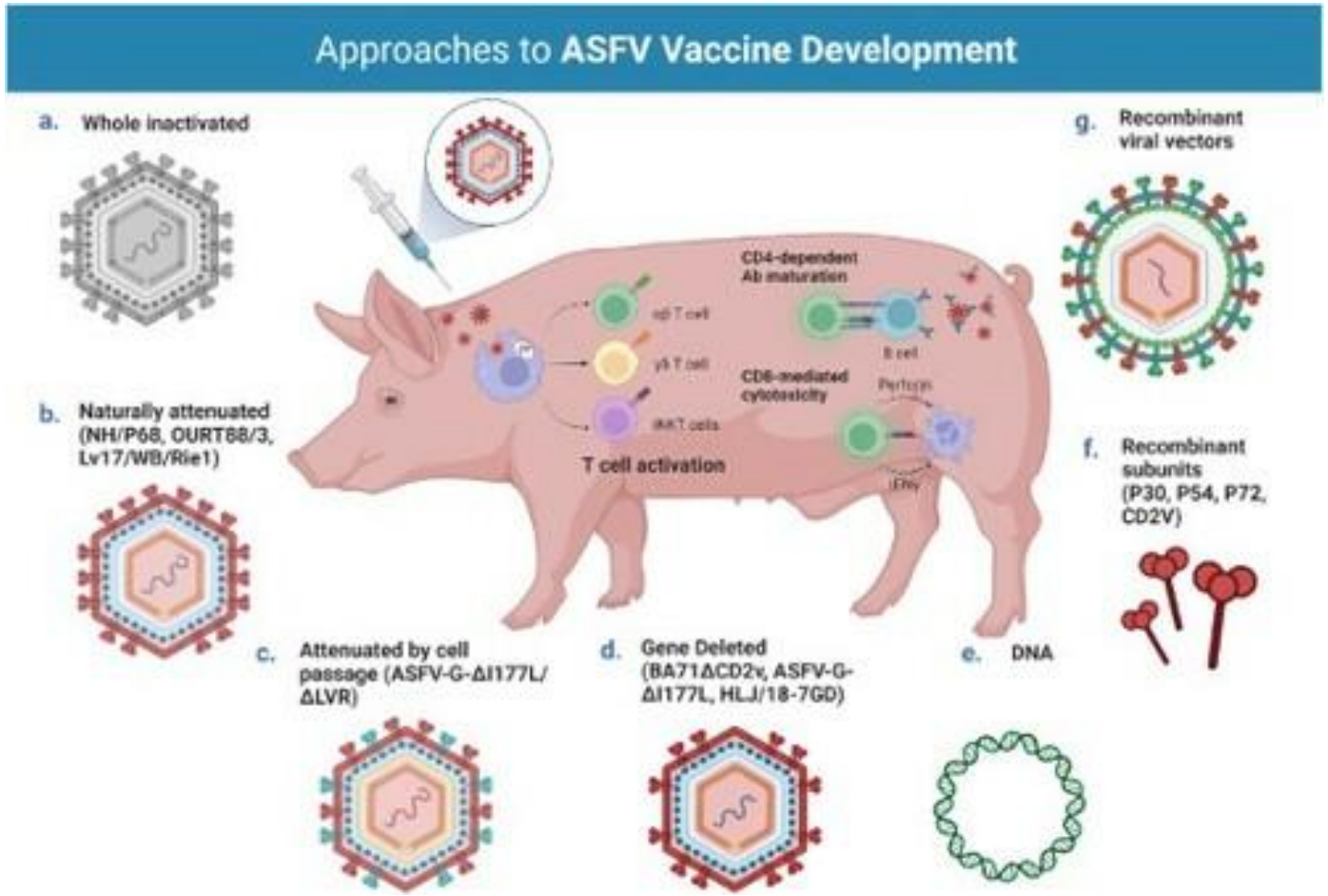
The search for the ASF vaccine – an endless story?



Vaccines against ASF



Inactivated vaccines

- good safety profile
- have never induced robust immunity

Naturally attenuated strains and live vaccines obtained by passage

- Induction of humoral and cellular responses
- Oral administration possible
- Partly negative side effects, chronic infections
- Different results with different candidates

Vector vaccines, subunit, DNA vaccines

- Easy to scale up, good safety profile
- Depending on the system, both humoral and cellular reactions, high DIVA potential
- So far only partial protection (if any)

Gene-deleted live vaccines

- Deletions targeting "virulence" genes
- Cellular and humoral responses, DIVA potential
- All advantages and disadvantages of live vaccines

→ Only live vaccines showed real promise so far

Urbano and Ferreira 2022, doi: 10.1080/22221751.2022.2108342

Only a few deletions led to viable vaccine candidates

viruses
MDPI

Review

Recombinant ASF Live Attenuated Virus Strains as Experimental Vaccine Candidates

Douglas P. Gladue * and Manuel V. Borca *

Plum Island Animal Disease Center, Agricultural Research Service, U.S. Department of Agriculture, Greenport, NY 11944, USA
* Correspondence: douglas.gladue@usda.gov (D.P.G.); manuel.borca@usda.gov (M.V.B.)

Table 3. Determinants of virulence that attenuate ASFV-Georgia-derived viruses.

Gene Deleted	Fully Attenuated	Homologous Protection	Reference
9GL	Low doses, higher doses lethal	Yes	[35]
9Gl, UK	Yes	Yes	[48]
A137	Yes, only low doses tested	Yes	[46]
CD2, UK	Yes	Yes	[49]
E184L	No	Surviving animals	[47]
I177L	Yes	Yes	[36–38]
I226R	Yes	Yes	[45]
I267L	No	-	[43,44]
L7L–L11L *	No	Surviving animals	[50]
MGF-110-9L	Partial at low doses	-	[40]
MGF360-9L	Partial at low doses	-	[42]
MGF-505-7R	Yes, only low doses tested	-	[41]
Multiple MGF #	Yes	Yes	[25,51]
QP509L/QP383R	Yes	No	[52]

* L7L-L11L consists of genes L7L, L8L, L9R, L10L, L11L; # multiple MGF consists of a deletion of 6 MGF genes.

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Wild boar in a Hungarian forest may be key to protecting Europe's pig herds

As African swine fever stalks the EU's biggest livestock population, researchers aim to deploy a vaccine to halt the disease's spread and shield millions of animals.

Gene Deleted	Dose Tested with Full Attenuation	Homologous Protection	Challenge Route and Dose	Reference
9GL	10^2, 10^3	Yes	IM 10^2	[35]
9GI, UK	10^2, 10^4, 10^6	Yes	IM 10^3	[48]
A137	10^4, 10^7	Yes	IM 10^2	[46]
CD2, UK	10^4	Yes	IM 10^2	[49]
DI 177L/DLVR *	10^2, 10^4, 10^6	Yes	IM 10^2	[39]
I177L	10^2, 10^4, 10^6	Yes	IM 10^2	[36,37,38]
I1226R	10^2	Yes	IM 10^4	[45]
Multiple MGF *	10^2, 10^4	Yes	IM 10^3	[25,51]

* multiple MGF consists of a deletion of 6 MGF genes.

Quelle: Gladue und Borca 2022, Recombinant ASF Live Attenuated Virus Strains as Experimental Vaccine Candidates

EU-Projekt (HORIZON): ASFaVIP

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European Commission | Funding & tender opportunities
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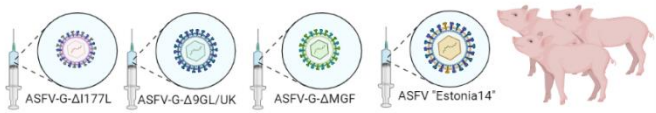
Advancing vaccine development for African swine fever

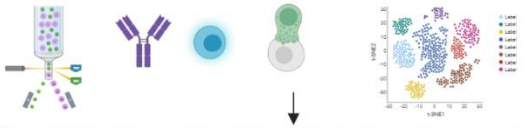
TOPIC ID: HORIZON-CL6-2023-FARM2FORK-01-5

Theme 1: Establish standards and define correlates and mechanisms of protection



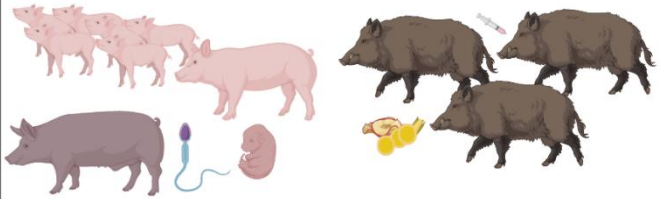
Multi-center studies using established vaccine candidates and comparators

Harmonizaition of immunization and challenge, laboratory procedures and read out



Investigate correlates and mechanism of protection and immunopathology

Theme 3: Move ASFV-G-ΔI177L towards central licensing at the European Medicines Agency

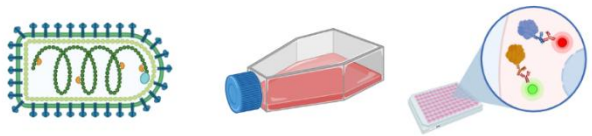


Safety and efficacy tests with oral and intramuscular vaccination

Bait uptake studies and proof of concept in European wild boar

Establish contactwith the European Medicines Agency and other regulators towards licensing

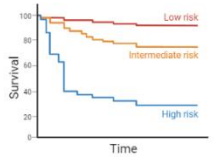
Theme 2: Explore possibilities to generate innovative next generation vaccine approaches



Use knowledge generated in Theme 1 to express new antigens in established systems

Further development of effective candidates - strengthening of the DIVA potential

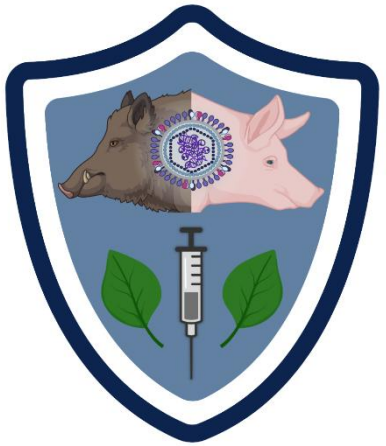
Theme 4: Designing and validating vaccination concepts for domestic pigs and wild boar



Modelling vaccination using safety and efficacy data generated in the project

Optimize oral vaccination of wild boar taking into account wild boar ecology

Involve regulators, hunters, farmers, veterinary authorities and other stakeholders



Start: 01.01.2024
6 Mio Euro
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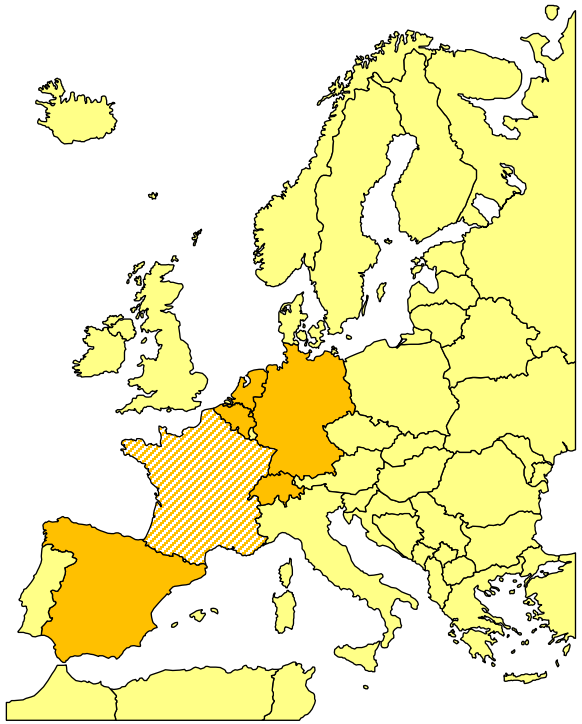

Understanding performance characteristics of live attenuated vaccines for the prevention and control of African swine fever in wild boar and domestic pigs

ASF vaccines – Turning dream into reality?

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	Safety Studies	Efficacy Studies	Oral or ON studies	Field experience
ASFV-G-ΔI177L	✓ IM	✓ IM	✓	✓ IM
ASFV-G-ΔMGF	✓ IM	✓ IM	✓	(✓) IM
ASFV-G-Δ9GL/UK	✓ IM	✓ IM	×	×

Urbano and Ferreira 2022, doi: 10.1080/22221751.2022.2108342

Why’s it gotta be so complicated?

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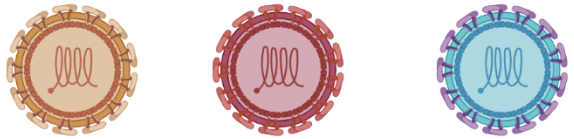
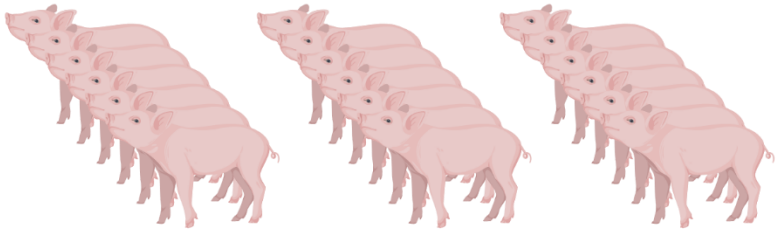
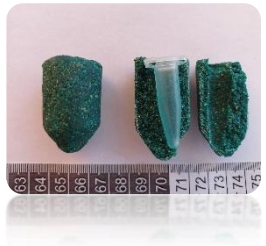
CSF



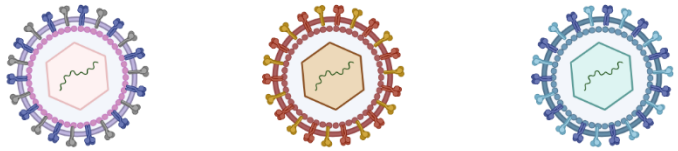


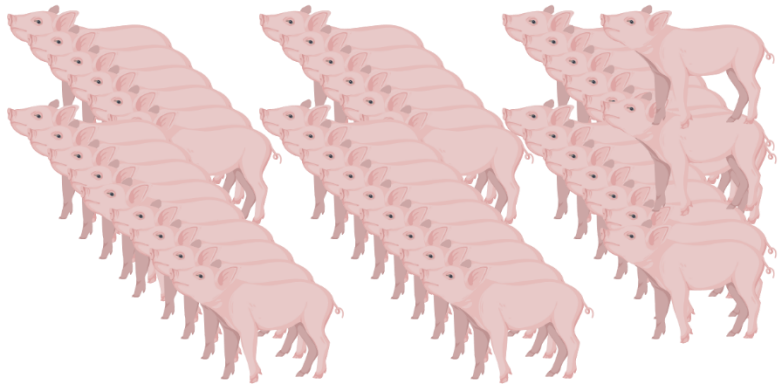


Response rate:
CP7_E2alf: 100%
flc 11: 100%
C-Strain: 100%

Challenge - efficacy in responders
CP7_E2alf: 100%
flc 11: 100%
C-Strain: 100%

ASF





Response rate:
ASFV-G-ΔI177L: 20%
ASFV-G-Δ9GL/UK: 0%
ASFV-G-ΔMGF: 0%

Challenge - efficacy in responders
ASFV-G-ΔI177L: 100%
ASFV-G-Δ9GL/UK: no responders, no protection
ASFV-G-ΔMGF: no responders, no protection

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Optimization of oral bait vaccination

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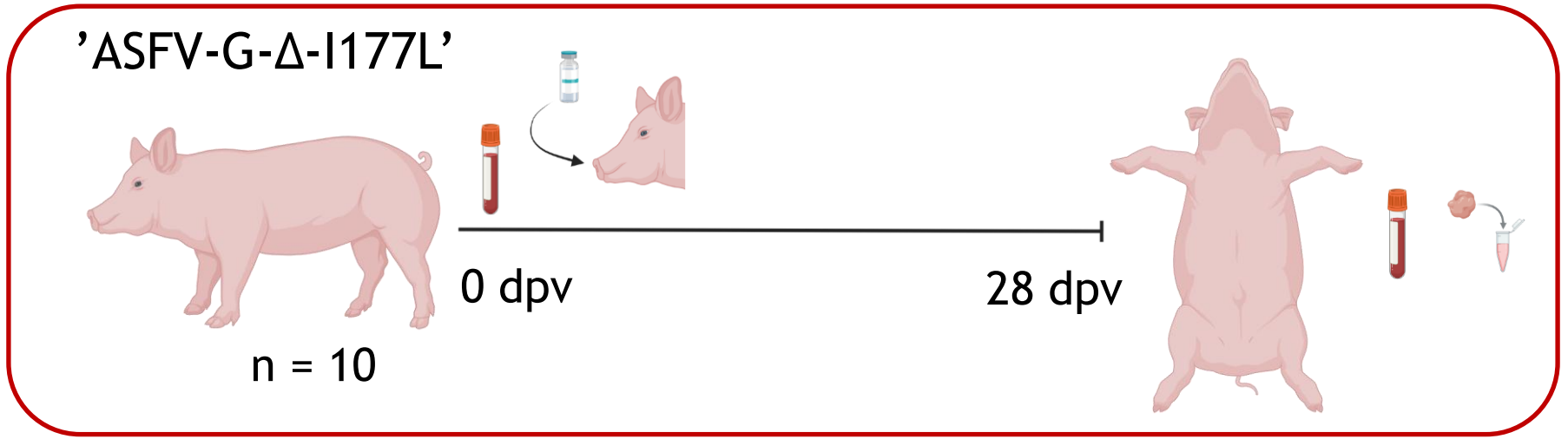

1. Without bait and increased titer
2. Montanide GR
3. Inactivated Mycobacteria
4. Walnut shreds
5. 5 x bait
6. Montanide Gel

Optimization - Results

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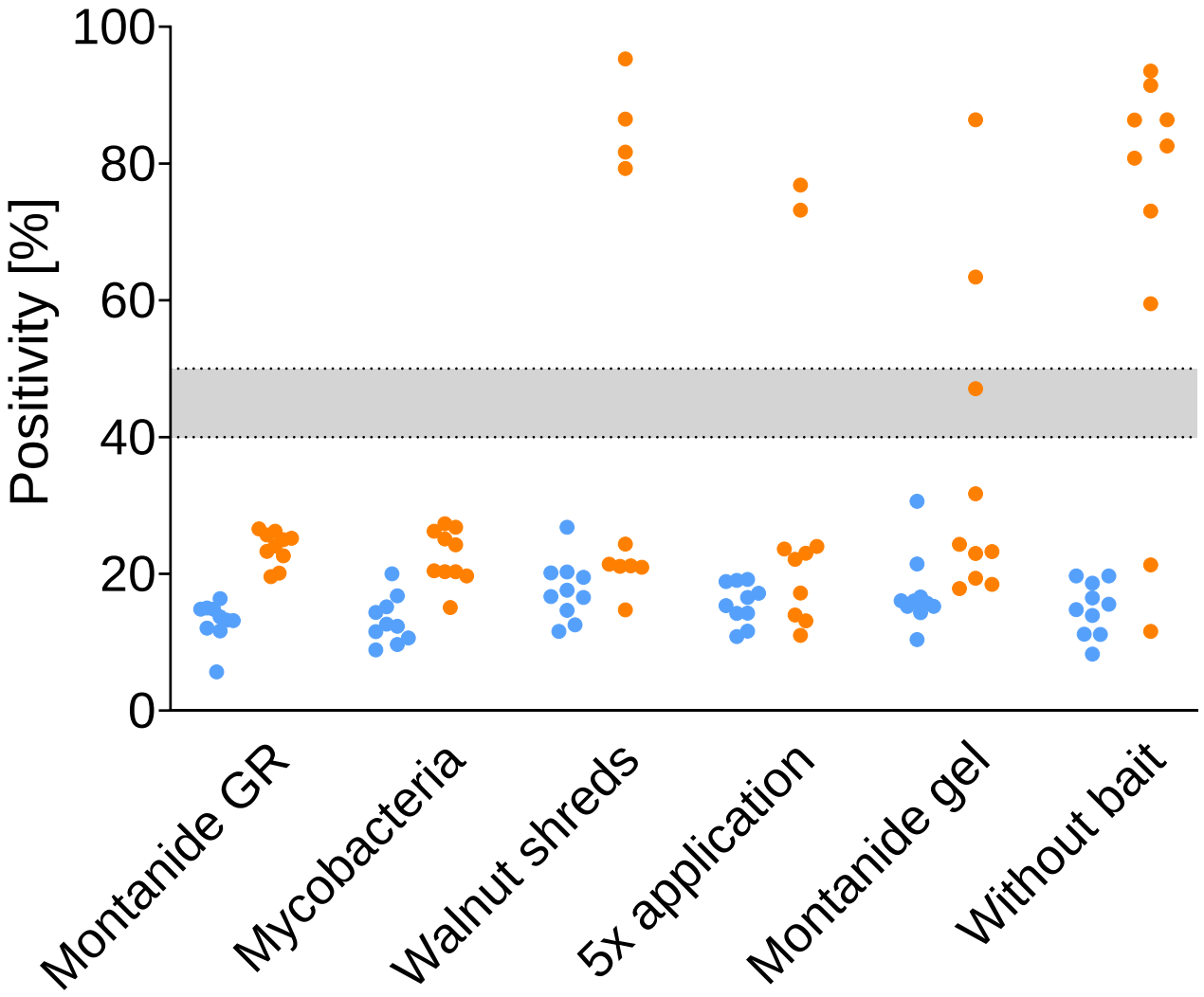

Serokonversion:

- Without bait, high dose: 80 %
- Walnut shreds: 40 %
- Montanide Gel: 20 - 30 %

Safety in adult breeding boars

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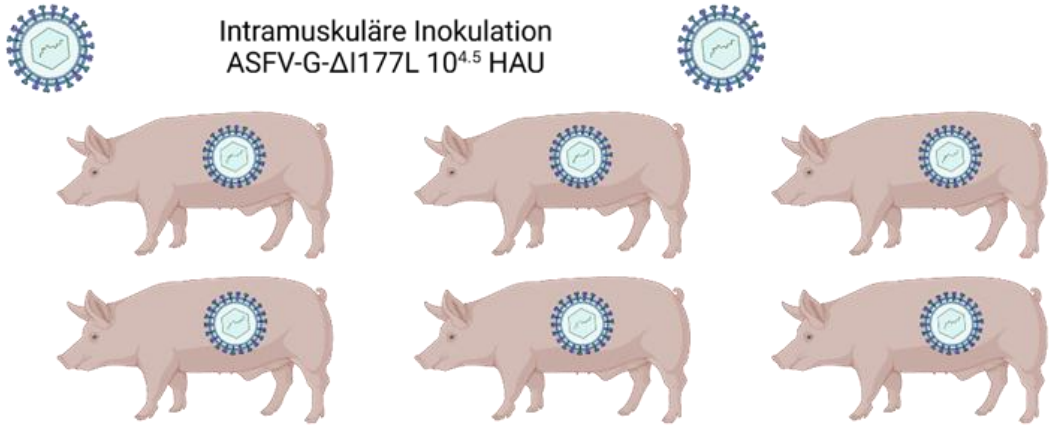
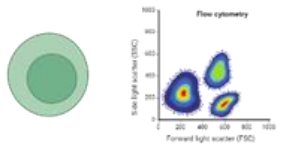


Probennahme: Sperma, Nativblut und EDTA-Blut an den Tagen -4, 0, 4, 7, 10, 14, 21 und 28 nach der Inokulation.
Nicht-invasive Kaustrickbeprobung in den Stalleinheiten.
Pathologisch-anatomische und histopathologische Untersuchung

Durchflusszytometrie und Restimulierung



qPCR aller Proben; ggf. Virusisolierung für positive Matrizes, Serologie (ELISA und IIPT)

In a nutshell: the vaccine is NOT safe for adult boars…

- high fever (even over 41 °C) in almost all boars
- High viral (genomic) loads in blood and organs
- Detection of viral genome and virus in semen
- 4 out of 8 boars reached the moderate humane endpoint

Abbildung mit biorender

Ongoing and future studies

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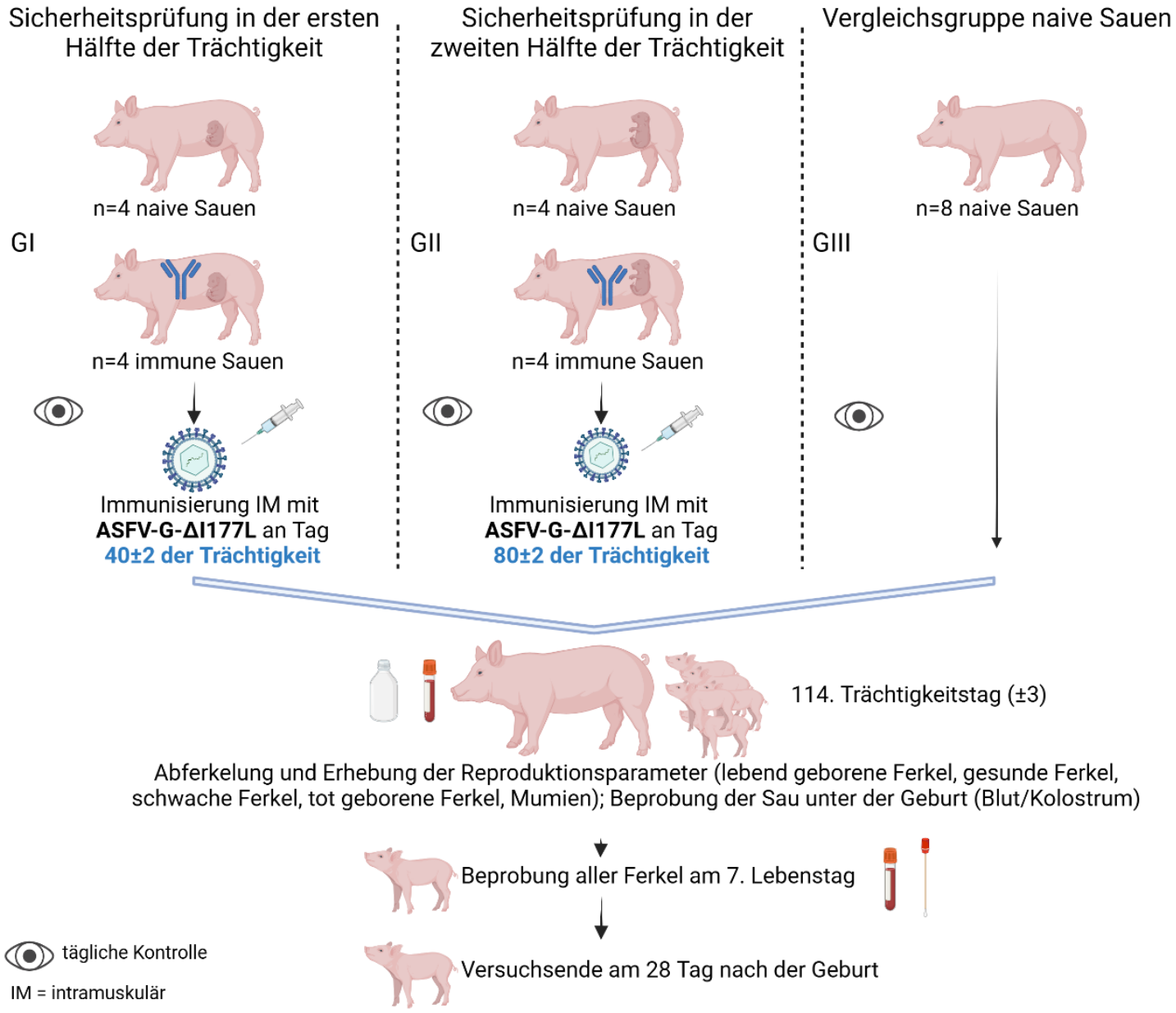

Safety aspects – showcased to impressive effect

npj | vaccines
Article
Published in partnership with the Sealy Institute for Vaccine Sciences
https://doi.org/10.1038/s41541-025-01099-9

African swine fever virus vaccine strain Asfv-G-ΔI177l reverts to virulence and negatively affects reproductive performance

Check for updates

Erwin van den Born[1], Ferenc Olasz[2,3], István Mészáros[2], Eszter Göltl[2,3], Barbara Oláh[2], Jui Joshi[1], Emma van Kilsdonk[1], Ruud Segers[1] & Zoltán Zádori[2,3]

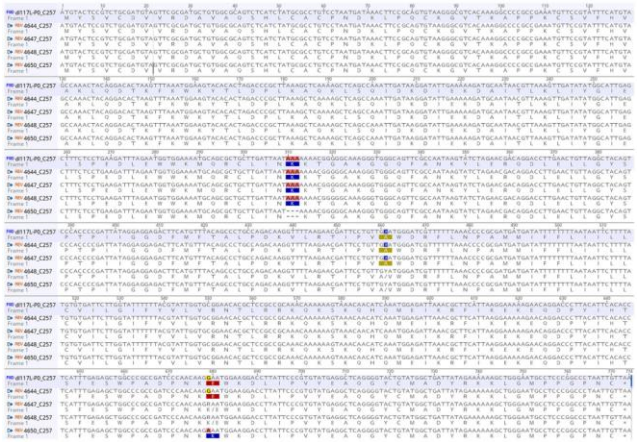

Table 1 | Reproductive performance of the ASFV-G-ΔI177L-inoculated and control sows

	ASFV-G-ΔI177L-inoculated sows		Control sows	
	1	2	1	2
Total piglets born	23	17	27	19
Normal piglets	8	6	21	15
Weak piglets	9	0	2	0
Dead piglets	6	10	4	4
Mummified piglets	0	1	0	0
Alive at end of experiment	4	0	23	15

Reversion to virulence study:

- Two 7–9-week-old pigs were used for passages 1–4
- The virus regained virulence in passages 3 and 4 (mutations did not occur in the original deletion site)
- Severe ASF signs and increased viremia were observed
- Mutations in the C257L gene were identified as a possible cause of enhanced replication and virulence

Reproductive safety

- Two pregnant sows in the last third of gestation were vaccinated with ASFV-G-ΔI177L
- One sow developed moderate ASF signs
- 43% of the piglets were stillborn
- The live-born piglets showed clinical signs of ASF and became viremic
- Only 17% of the live-born piglets survived until the end of the study

Between the devil and the deep blue sea

www.nature.com/scientificreports

scientific reports

Check for updates

OPEN

An African swine fever vaccine-like variant with multiple gene deletions caused reproductive failure in a Vietnamese breeding herd

Thanh Che Nguyen[1,2,4,11], Nga To Thi Bui[3,11], Lua Thi Nguyen[3], Tram Ngoc Thi Ngo[4], Cuong Van Nguyen[4], Luan Minh Nguyen[4], Janin Nouhin[5], Erik Karlsson[5], Pawin Padungtod[6], Nakarin Pamornchainavakul[7], Sawang Kesdangsakonwut[2,8,9], Roongroje Thanawongnuwech[2,10]✉ & Duy Tien Do[4]✉

- Introduction of a vaccine like ASFV variant into a breeding farm without prior outbreak or vaccination history
- Farm with 2.400 Sauen (Land race/Yorkshire); very high replacement rate from external sources
- Poor biosecurity, active ASF circulation in the surrounding area
- No clinical signs in gilts, but reproductive disorders in pregnant animals
- Ulcerative lesions on the udders of lactating sows, necrotizing vasculitis, suspected immune complex involvement
- Virus with characteristics of ASFV-G-ΔMGF, but also additional mutations (including EP402R)

Like that wasn't enough…

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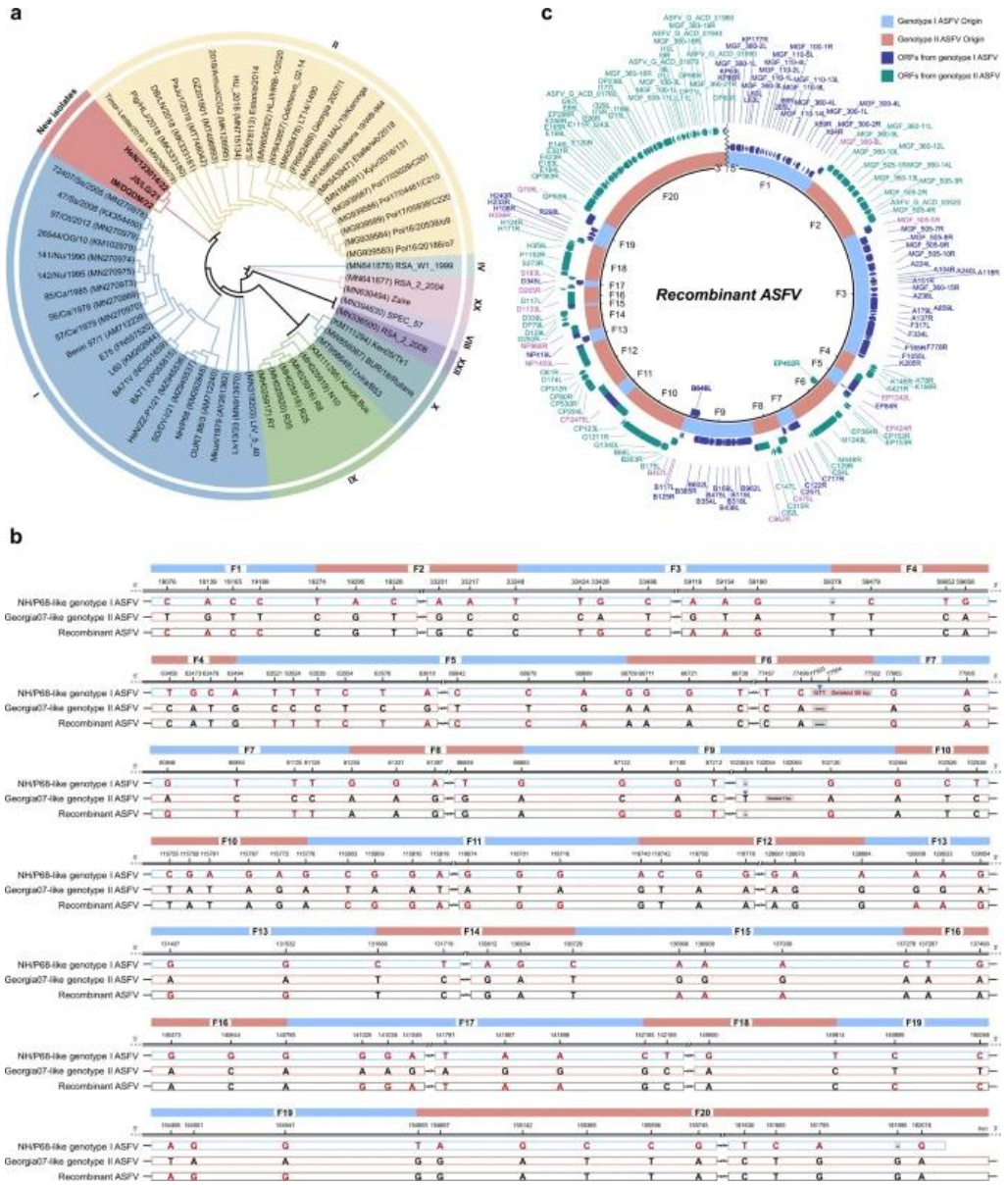
Article | Open access | Published: 29 May 2023

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 ✉

Nature Communications **14**, Article number: 3096 (2023) | Cite this article



- Recombinant of genotypes I and II
- Our vaccines would NOT protect against this chimera
- Reported in China, Vietnam and the Russian Federation
- New vaccine deletion mutants are under development…

Time to Pull the Plug on the Vaccines?

- ASFV-G-ΔI177L showed genetic changes and increased virulence after forced animal passages.
- Only live vaccines have been effective against ASF so far – the risks are generally known.
- There are successful examples of attenuated vaccines despite documented risks (also against CSF → GPE-).
- Reversion studies simulate artificial extreme conditions – they are informative but not solely decisive.
- Live vaccines against ASF pose significant risks in pregnant animals and breeding boars.
- Vaccination of breeding animals, especially pregnant sows, should be avoided or done prior to insemination; no vaccination of breeding boars.
- Planned transmission experiments aim to clarify whether altered viruses transmit more efficiently (in naïve and vaccinated populations).
- Recombination can occur; the impact depends on the scenario.
- There are also successful vaccines that undergo recombination (e.g., BHV-1).

My recommendation:

👉 **No rushed decisions** –

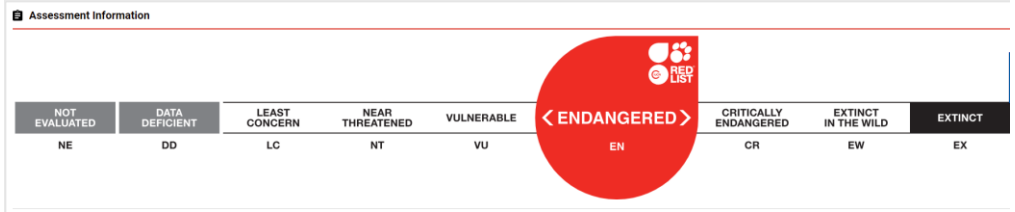
a fact-based, context-specific benefit - risk assessment is crucial!

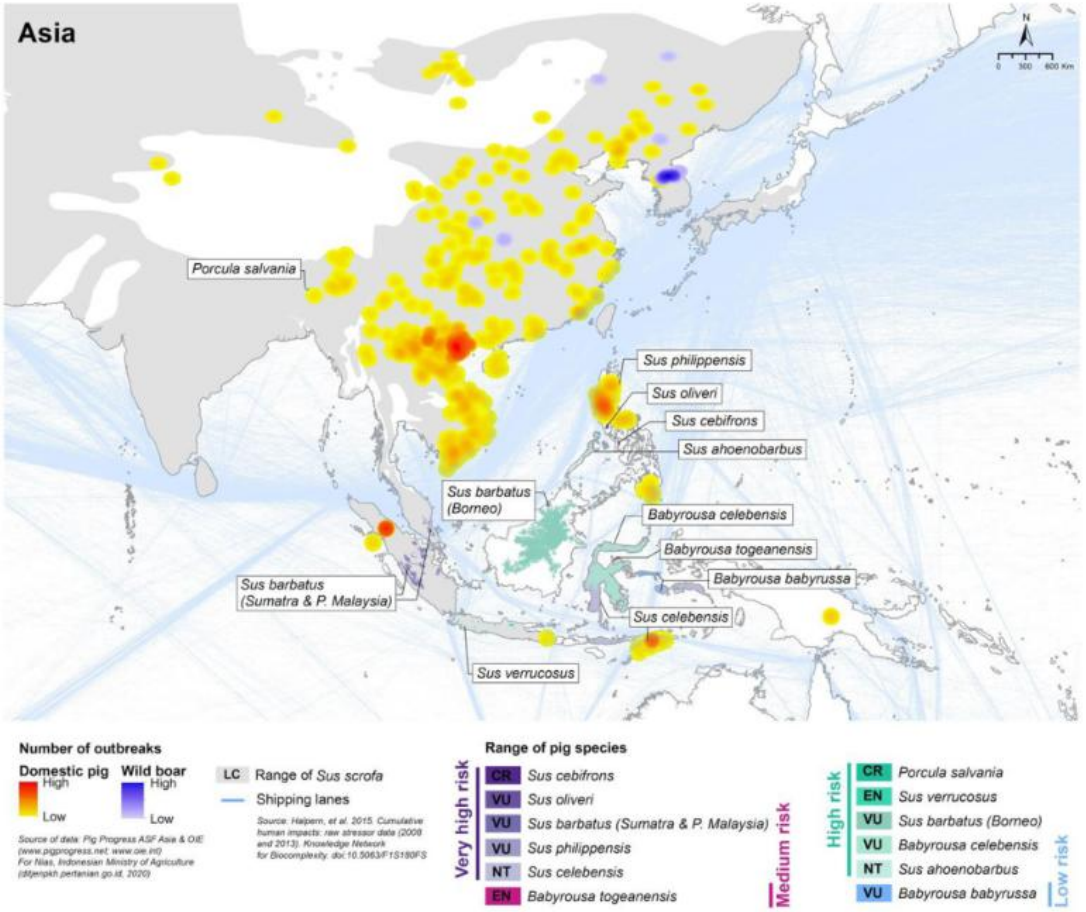
Not all suids are numerous…

FAO, IUCN SSC and OIE warn of African swine fever impact on wildlife conservation

Mon, 23 Aug 2021

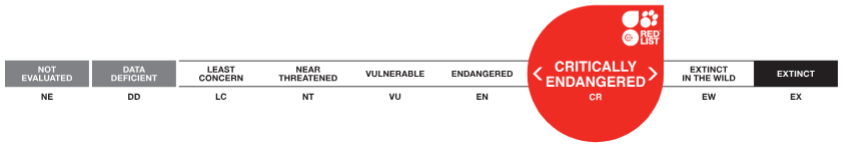
The increasing rate of infection of African swine fever (ASF) among domestic and wild pigs in the Asia-Pacific region has prompted the Food and Agriculture Organization of the United Nations (FAO), the International Union for Conservation of Nature's Species Survival Commission (IUCN SSC), and the World Organisation for Animal Health (OIE) to issue a joint call for countries in the region to develop stronger policies and implement strategies to mitigate the impacts of ASF on wildlife, livestock health, and rural livelihoods.





Quelle: Luskin, Matthew Scott, et al. "African swine fever threatens Southeast Asia's 11 endemic wild pig species." Conservation Letters 14.3 (2021): e12784.

▸ Meijaard, E., Oliver, W.R.T. & Leus, K. 2017. *Sus cebifrons. The IUCN Red List of Threatened Species* 2017: e.T21175A44…



EAZA and its Members contribute to vital research on African Swine Fever (ASF)

September 2023

At the request of the IUCN Species Survival Commission's Wild Pig Specialist Group, EAZA and its Members are contributing to an international research project on the African Swine Fever (ASF). This fast-spreading virus is threatening pig species in the wild and in human care, due to the lack of a vaccine or an effective treatment.

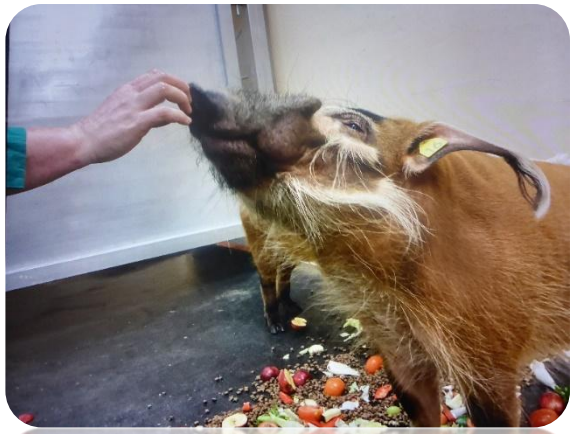
The disease

ASF is currently posing the greatest risk to pig conservation, both *in situ* and *ex situ*[i]. It is caused by a DNA virus that is lethal for many pig species but is harmless to people and other animals. When infected, some pig species show no apparent signs, while others develop a viral hemorrhagic illness with almost 100% case fatality.

Human activity brought ASF out of Africa in 2007 (to Georgia), and the virus has since been spreading in Europe and Asia. It threatens many wild pig species as well as domestic pigs, with further knock-on effects for their ecosystems as well as for human livelihoods.

In May 2023, ASF reached Negros Island in the Philippines, home to the Critically Endangered Visayan warty pig. This also reminded the world how acutely vulnerable the 12 Southeast Asian endemic pig species are when facing the virus. All of them have small populations and small ranges[ii].

ASF has already killed all Visayan warty pigs kept in human care in a breeding station in the Philippines as well as babirusa housed in an Asian zoo. In zoos across EAZA, the virus is a threat to all pig species in EAZA Ex-situ Programmes (EEPs): Visayan warty pig, babirusa, red river hog, and warthog.



icrad
International coordination of research on infectious animal disease

GARA
Global African Swine Fever Research Alliance

Thanks for your attention!