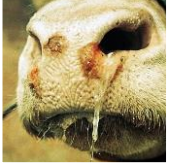




# FMD-LL3B3D Vaccine Platform

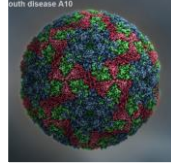
2019 Global Foot and Mouth Research Alliance  
John Hardham, Ph.D.  
October 29- 31, 2019  
Bangkok, Thailand

# FOOT AND MOUTH DISEASE - VERY COMPLEX AND COSTLY DISEASE



## Disease

- Caused by FMDV
  - Picornavirus
  - Genus Aphthovirus
- Vesicular disease of cloven hoofed animals
- Seven global FMDV pools
  - Multiple serotypes within a pool
  - Multiple strains within serotype
- Each pool requires a tailored, multivalent vaccine



## Global Impact

- Highly politicized disease
- Vaccination programs often under Government control
- Largest impact on trade of any animal disease
- Animal welfare issues
- Impact on farmers and producers
- Significant economic burden
- Severe impact of incursion for “FMD-Free” Countries



## Existing Vaccines

- Regional production
- Produced from virulent, wild-type strains
  - Risk of release from manufacturing sites
- Do not protect across serotypes, limited cross-protection within a serotype
- NSP-depletion to accommodate “DIVA” compatibility
  - Not 100% due to residual NSP's present in vaccines
- Protect from clinical signs
- Do not fully prevent fever, viremia, shedding, or persistence



## Unmet Needs

- Safe vaccine platform
- Prevention of fever, viremia, shedding, and persistence
- Rapid onset of immunity
- Long duration of immunity
- Full DIVA compatibility
- Ability to rapidly address new strains

# DISRUPTIVE FMD VACCINE - LL3B3D PLATFORM

- **Rapid Response Capability**

- Allows rapid insertion of capsid coding regions from emerging strains

- **Improved Safety**

- FMD-LL3B3D A24 Cruzeiro platform backbone lacks L<sup>pro</sup> region
- Attenuated in cattle and pig
- Non-transmissible (cattle & swine)
- Uses the same production systems as current inactivated FMDV vaccines

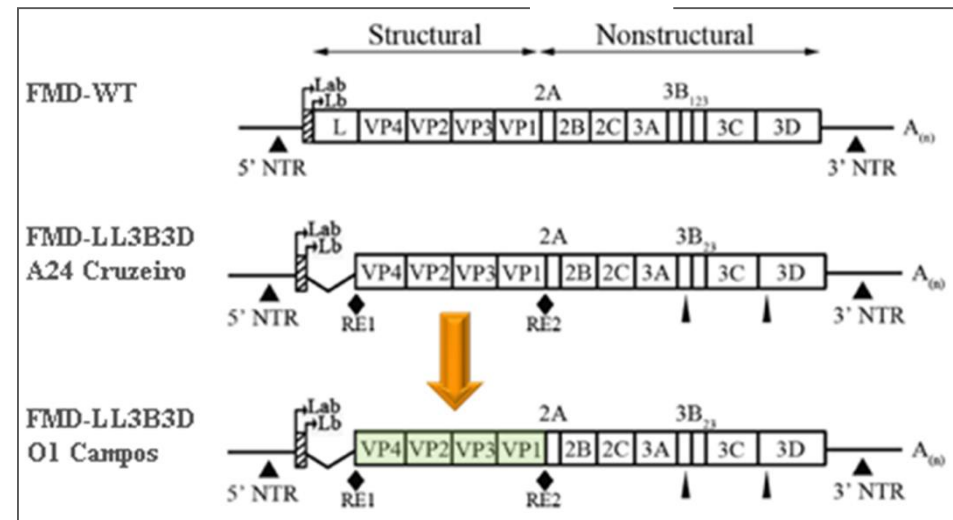
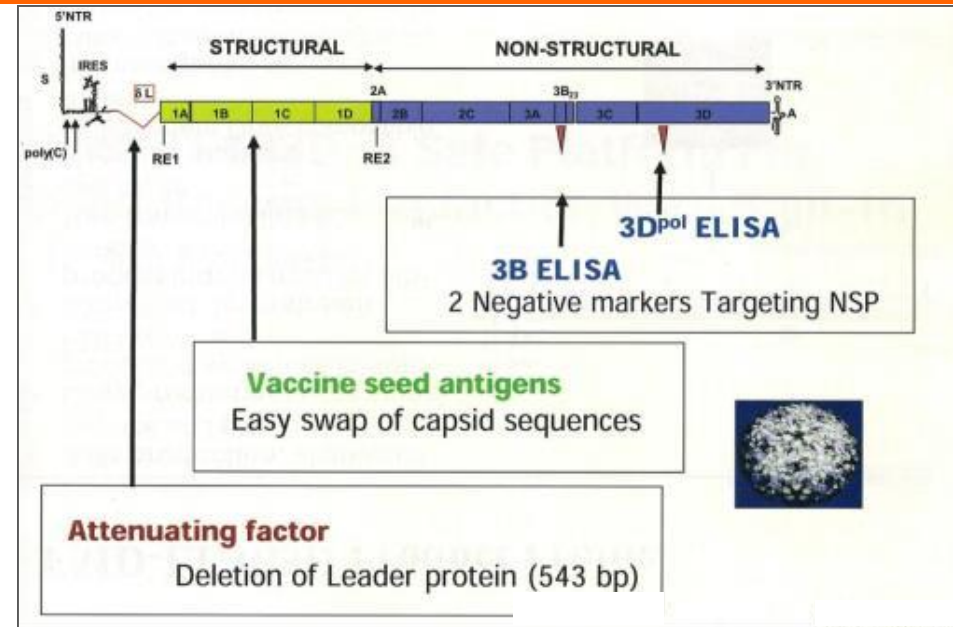
- **High Potency**

- Double BEI inactivated and formulated with a proprietary oil-based adjuvant
- Potent immune responses to inserted capsid proteins of target strain
- Proprietary adjuvant increases antibody and cellular immune responses

- **Fully DIVA Compatible**

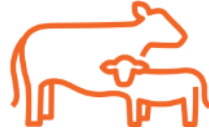
- Two independent and stable negative markers
- Genetically altered key epitopes in 3B and 3D NSPs

Collaborative effort between the USDA-ARS and Zoetis



# SAFETY OF THE LIVE FMD LL3B3D VACCINE STRAINS – CATTLE AND SWINE

FMD-LL3B3D platform viruses are incapable of replicating to detectable levels in cattle or swine



Most susceptible species

Construct	Inoculation Route	# Animals
FMD-LL3B3D-A24 Cruzeiro	Intralingual (7x10 <sup>6</sup> )	2
FMD-LL3B3D-A24 Cruzeiro	Aerosol (1x10 <sup>6</sup> to 3x10 <sup>6</sup> )	3
FMD-LL3B3D-A24 Cruzeiro	Aerosol and Contact / (1x10 <sup>6</sup> )	9

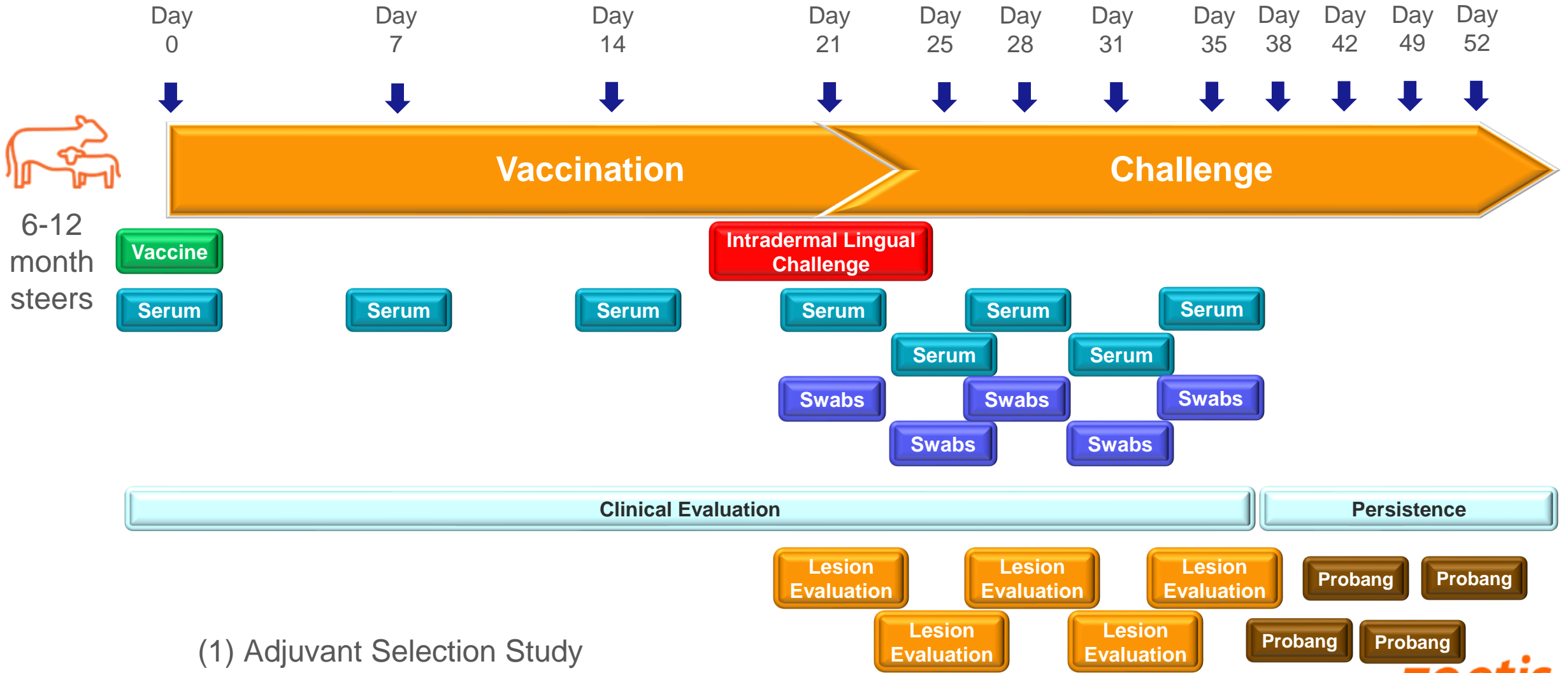
Construct	Inoculation Route	# Animals
FMD-LL3B3D-A24 Cruzeiro	Heelbulb and Contact (1x10 <sup>5</sup> )	4
FMD-LL3B3D-Asia1 Shamir	Heelbulb and Contact (1x10 <sup>6</sup> )	5
FMD-LL3B3D-A Turkey 06	Heelbulb and Contact (1x10 <sup>6</sup> )	5
FMD-LL3B3D-O1 Campos	Heelbulb and Contact (1x10 <sup>6</sup> )	4
FMD-LL3B3D-A Argentina 2001	Heelbulb and Contact (2x10 <sup>6</sup> )	4
FMD-LL3B3D-C3 Indaial	Heelbulb and Contact (2.8x10 <sup>6</sup> )	4

## ➤ Results

- ✓ No clinical disease
- ✓ No viral shedding
- ✓ No fever spike
- ✓ No contact transmission
- ✓ Very limited if any immune response

- Safety study results supported the US Select Agent Exclusion

# SUMMARY OF FMD-LL3B3D A24 CRUZEIRO CATTLE EFFICACY STUDY DESIGNS

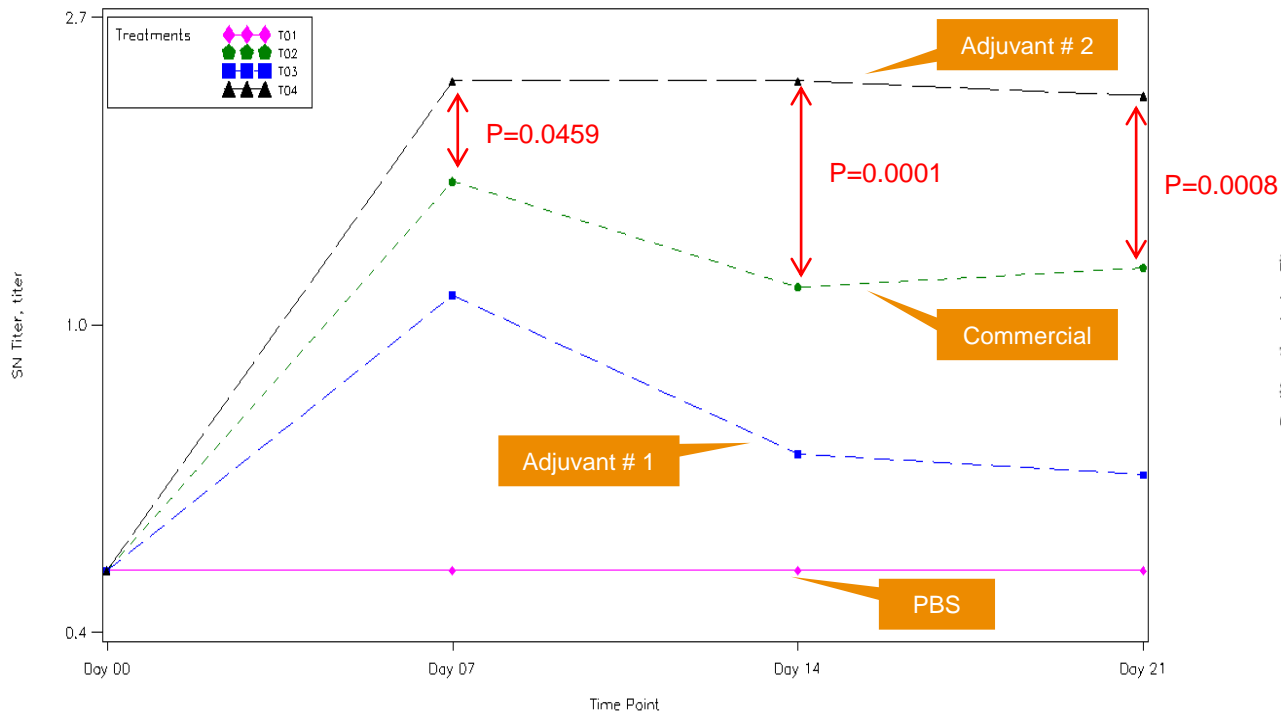


(1) Adjuvant Selection Study  
 (2) PD50 Study

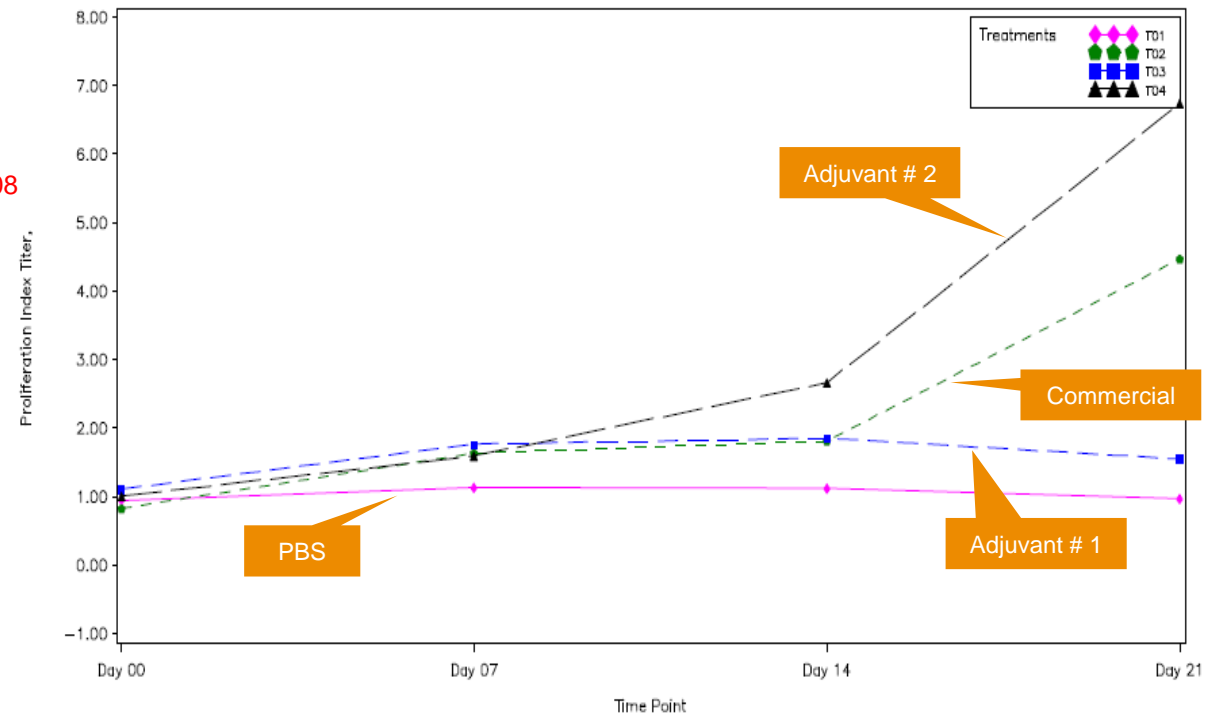
# (1) FMD-LL3B3D A24 CRUZEIRO ADJUVANT SELECTION STUDY – CATTLE SEROLOGY/CMI

## Robust antibody and cellular responses with Adjuvant # 2

A: Serologic Responses



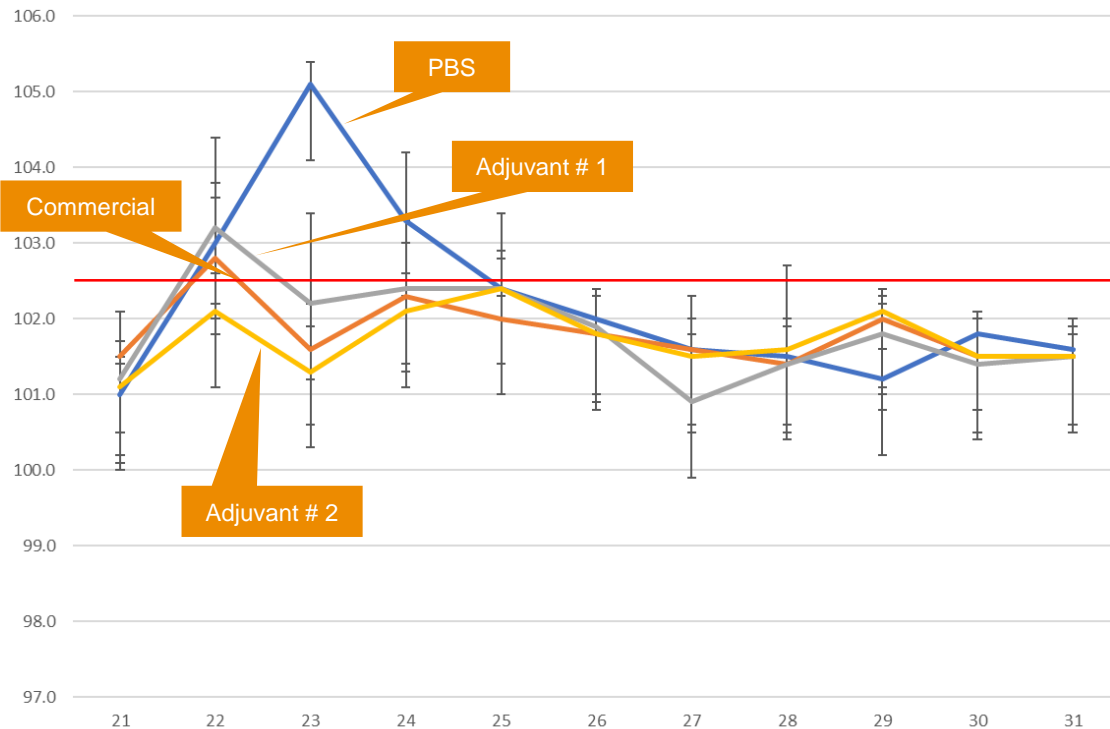
B: Cellular Responses



# (1) FMD-LL3B3D A24 CRUZEIRO ADJUVANT SELECTION STUDY CATTLE CLINICAL

## Prevention of clinical signs of FMD with Adjuvant # 2 upon challenge

**A: Temperature**



**B: Clinical Signs**

Cattle Number	DPI	T01				T02				T03				T04					
		D0	D3	D7	D10	D0	D3	D7	D10	D0	D3	D7	D10	D0	D3	D7	D10		
Adjuvant		(PBS)				Commercial				Adjuvant # 1				Adjuvant # 2					
28		0	0	0	0	0	0	0	0	0	4	4	4	32	0	0	0	0	
30		0	0	0	0	0	0	0	0	0	3	4	4	34	0	0	0	0	
33		0	0	0	0	0	0	0	0	0	1	2	3	36	0	0	0	0	
25		0	4	4	4	38	0	0	0	35	0	0	3	3	39	0	0	0	0
41		0	4	4	4	42	0	0	0	40	0	0	3	3	44	0	0	0	0
48		0	4	4	4	45	0	0	0	27	0	0	0	0	46	0	0	0	0
31		0	0	2	4	47	0	0	0	37	0	0	0	0	49	0	0	0	0

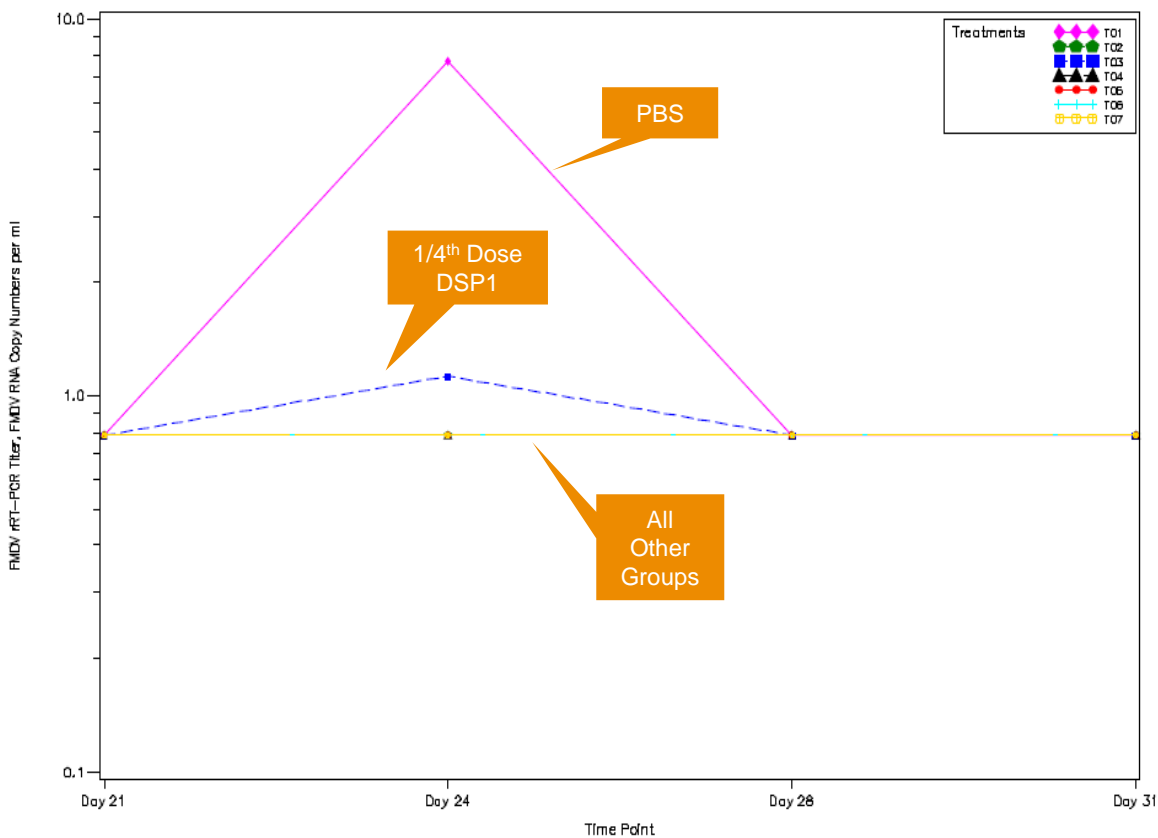
Clinical Score Code



# (2) FMD-LL3B3D A24 CRUZEIRO VACCINE IN ADJUVANT # 2 – PRELIMINARY CATTLE PD50 STUDY

High potency: \* >16 PD50 per dose  
 \* Full dose prevented viremia, clinical signs, & persistent infection

## A: Viremia



## B: Clinical Signs and Persistence

Group	Animal	Clinical Signs				Log10 RNA Copies (Probang)				Virus Isolation (Probang)			
		Day of Study								38	42	49	52
		20	23	27	30	38	42	49	52				
PBS	R14-84	0	2	4	4	4.29	4.72	0	3.83	Positive	Positive	Positive	Positive
	R14-85	0	4	4	4	4.26	6.01	5.14	4.7	Positive	Positive	Positive	Positive
	R14-86	0	1	4	4	0	3.62	0	0	Negative	Negative	Negative	Negative
	R14-87	0	4	4	4	0	0	0	0	Negative	Negative	Negative	Negative
Full Dose DSP1	R14-72	0	No	No	No	0	0	0	0	Negative	Negative	Negative	Negative
	R14-73	0	No	No	No	0	0	0	0	Negative	Negative	Negative	Negative
	R14-74	0	No	No	No	0	0	0	0	Negative	Negative	Negative	Negative
	R14-75	0	No	No	No	0	0	0	0	Negative	Negative	Negative	Negative
1/4th Dose DSP1	R14-76	0	No	No	No	4.98	4.68	0	0	Positive	Positive	Negative	Positive
	R14-77	0	1	1	1	5.52	3.43	0	0	Positive	Positive	Negative	Negative
	R14-78	0	No	No	No	0	4.35	0	5.3	Positive	Positive	Positive	Positive
	R14-79	0	No	No	No	0	0	0	0	Negative	Negative	Negative	Negative
1/16th Dose DSP1	R14-80	0	No	No	No	0	0	4.88	4.59	Positive	Negative	Positive	Positive
	R14-81	0	No	No	No	5.08	4.01	3.98	4.65	Positive	Positive	Positive	Positive
	R14-82	0	No	No	No	0	4.47	6.12	4.32	Positive	Positive	Positive	Positive
	R14-83	0	No	No	No	0	0	0	0	Positive	Positive	Positive	Positive
Full Dose DSP2	R14-60	0	No	No	No	0	0	0	0	Negative	Negative	Negative	Negative
	R14-61	0	No	No	No	0	0	0	0	Negative	Negative	Negative	Negative
	R14-62	0	No	No	No	4.75	0	0	0	Negative	Negative	Negative	Negative
	R14-63	0	No	No	No	0	0	0	0	Negative	Negative	Negative	Negative
1/4th Dose DSP2	R14-64	0	No	No	No	0	0	0	0	Negative	Negative	Negative	Negative
	R14-65	0	No	No	No	4.1	4.11	0	3.39	Positive	Positive	Positive	Positive
	R14-66	0	No	No	No	0	0	0	0	Negative	Negative	Negative	Negative
	R14-67	0	No	No	No	4.14	5.08	5.18	4.82	Positive	Positive	Positive	Positive
1/16th Dose DSP2	R14-68	0	No	No	No	0	0	0	0	Negative	Negative	Negative	Negative
	R14-69	0	No	No	No	0	0	0	0	Negative	Negative	Negative	Negative
	R14-70	0	No	No	No	0	0	0	0	Negative	Negative	Negative	Negative
	R14-71	0	No	No	No	5.34	5.46	4.49	3.7	Positive	Positive	Positive	Positive

Total abnormal vesicle score code





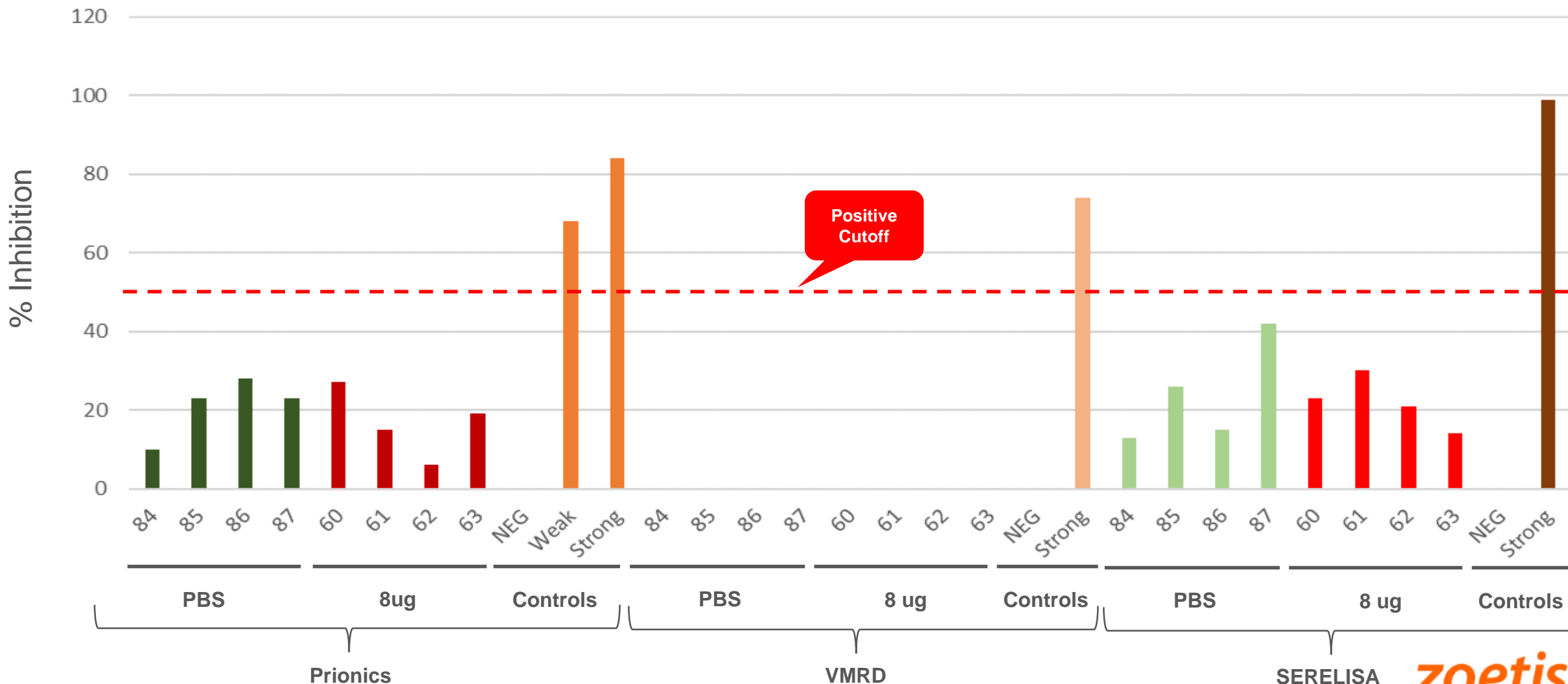
# EFFICACY OF THE FMD-LL3B3D A24 CRUZEIRO IN CATTLE

## FMD-LL3B3D A24 Cruzeiro vaccine prevented FMD lesions at 1/16<sup>th</sup> dose

- Vaccines formulated with inactivated FMD-LL3B3D A24 Cruzeiro and a proprietary Zoetis oil-based adjuvant
- Clinical outcomes
  - Significantly higher serum antibody titers compared to conventional vaccine
  - Significantly more robust CMI response compared to conventional vaccine
  - Complete prevention of FMD lesions
    - Even with 1/16 dose (0.5 µg antigen)
  - Full dose (8 µg) vaccine prevented persistent infection (DSP # 1 and # 2)
  - Prevention of fever
  - Prevention of viremia (DSP # 2)
  - Significant reduction in shedding (data not shown)

# DIVA COMPATIBILITY WITH CURRENT COMMERCIAL ASSAYS - (PrioCHECK, VMRD, AND SERELISA)

## Complete DIVA compatibility due to absence of target epitope



# TRANSBOUNDARY AND EMERGING DISEASE VACCINE DEVELOPMENT FACILITY

- Zoetis facility for Transboundary and Emerging Disease vaccine development activities
- Located in the Westinghouse Building; College Station, TX
- G-CON Modular Clean Rooms
- Development programs to be conducted as part of a Master Service Agreement with Texas A&M University System



<https://www.gconbio.com/>



<https://oldhamgoodwin.com/>

<https://news.zoetis.com/press-release/partnerships/zoetis-establishes-research-facility-Texas-am-university-develop-vaccines>

# LL3B3D PLATFORM VACCINE - CONCLUSIONS

Inactivated FMD-LL3B3D platform vaccine offers protection of livestock from the threat of natural or intended FMD outbreaks with full DIVA compatibility

- ✓ Prevents FMD lesions and fever even after 1 vaccination in cattle
- ✓ Prevents FMD persistent infection
- ✓ Allows differentiation of infected from vaccinated animals (DIVA)
- ✓ Safe *in vitro* and *in vivo*: produced without the need for virulent FMDV
- ✓ No need for adaptation of field strains to cell culture
- ✓ Provides rapid-response capability to address new FMD serotypes

# ACKNOWLEDGEMENTS

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PREDICT



PREVENT



DETECT



TREAT



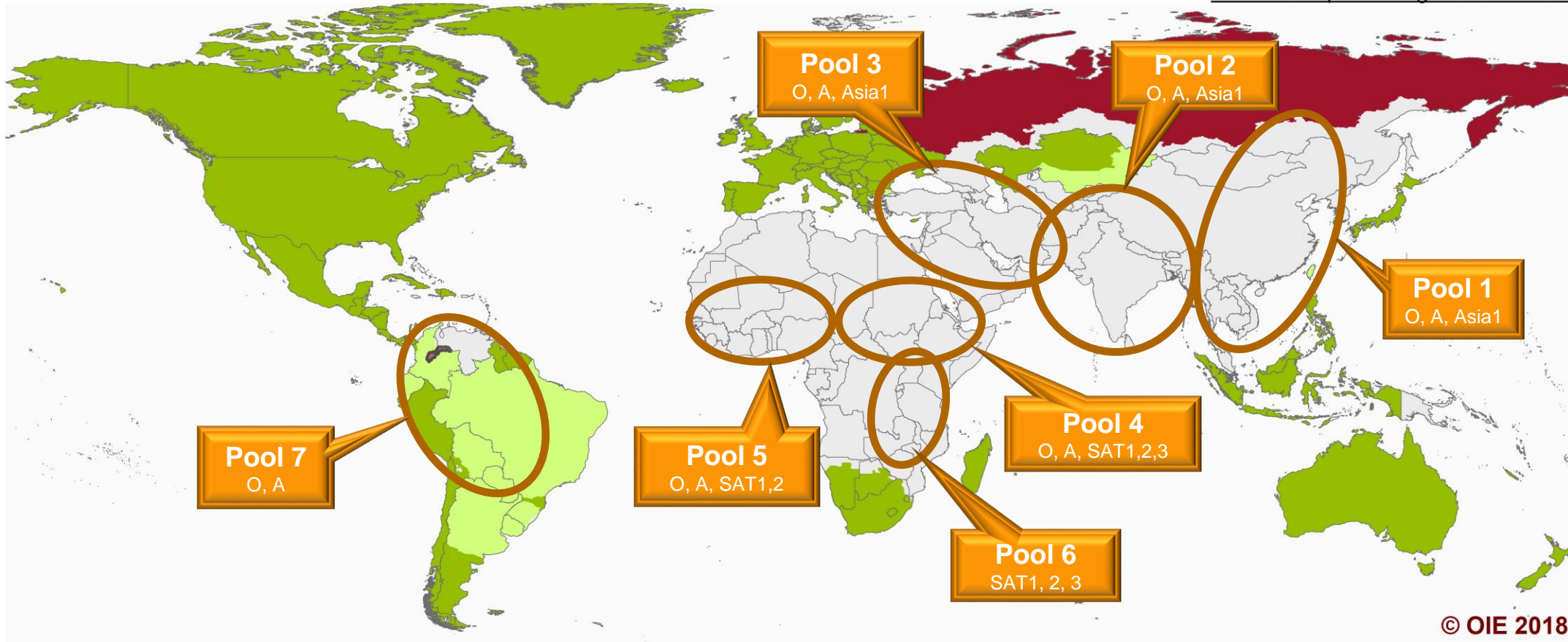
*zoetis*

# WORLD-WIDE DISTRIBUTION OF FMD

## OIE Members' official FMD status map

Last update July 2018

[Click on a specific region to zoom in](#)



- Members and zones recognised as free from FMD without vaccination
- Members and zones recognised as free from FMD with vaccination

- Containment zone within a FMD free zone
- Suspension of FMD free status

Countries and zones without an OIE official status for FMD