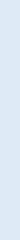
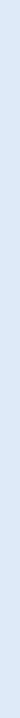
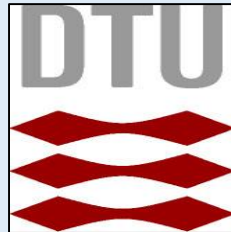


Transmission of foot-and-mouth disease from persistently infected carrier cattle to naive cattle via transfer of oropharyngeal fluid

Jonathan Arzt, Graham Belsham, Louise Lohse, Anette Bøtner, Luis Rodriguez, Carolina Stenfeldt



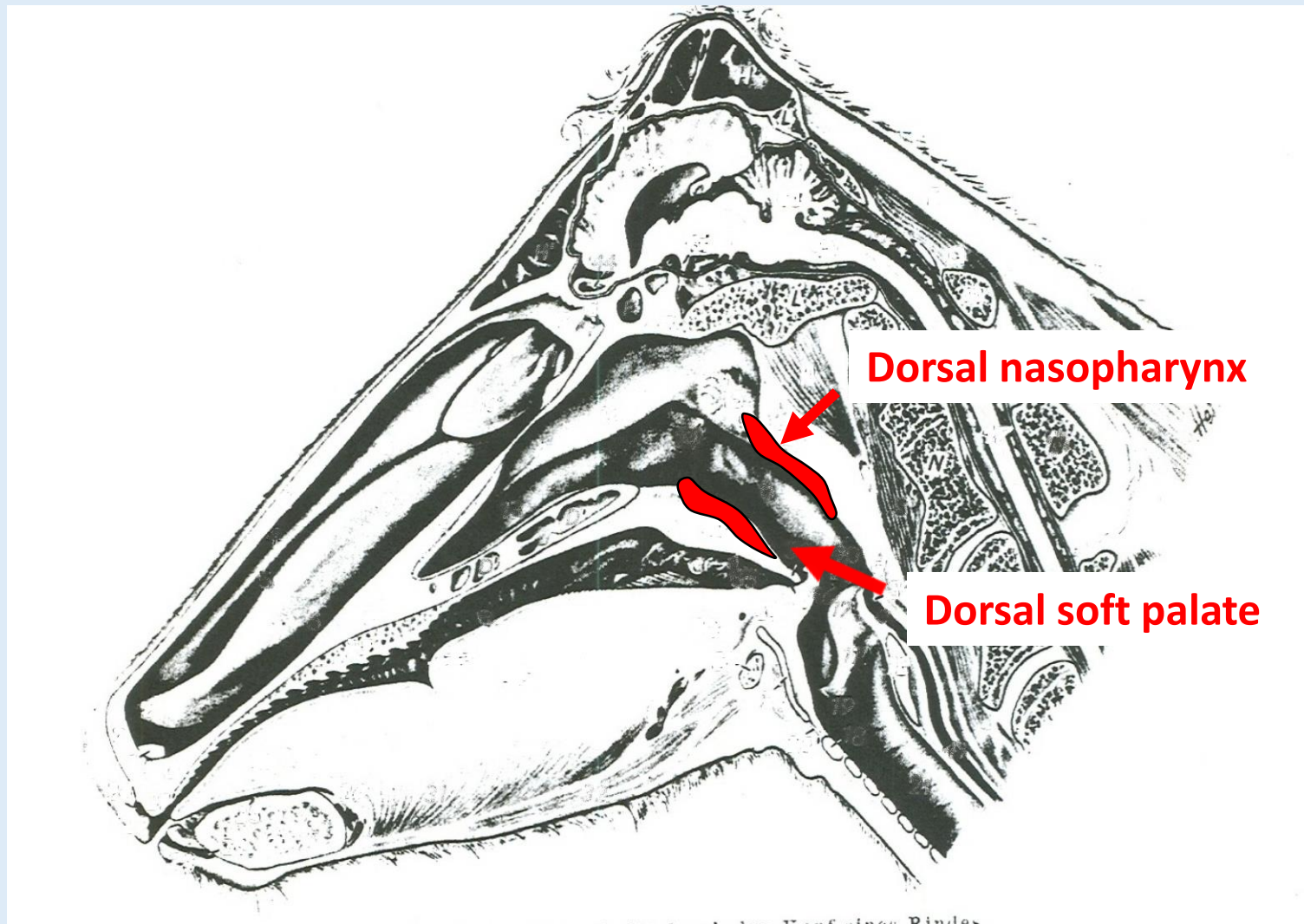
Jonathan Arzt
ARS, USDA
Plum Island Animal Disease Center
EUFMD-OS-2018



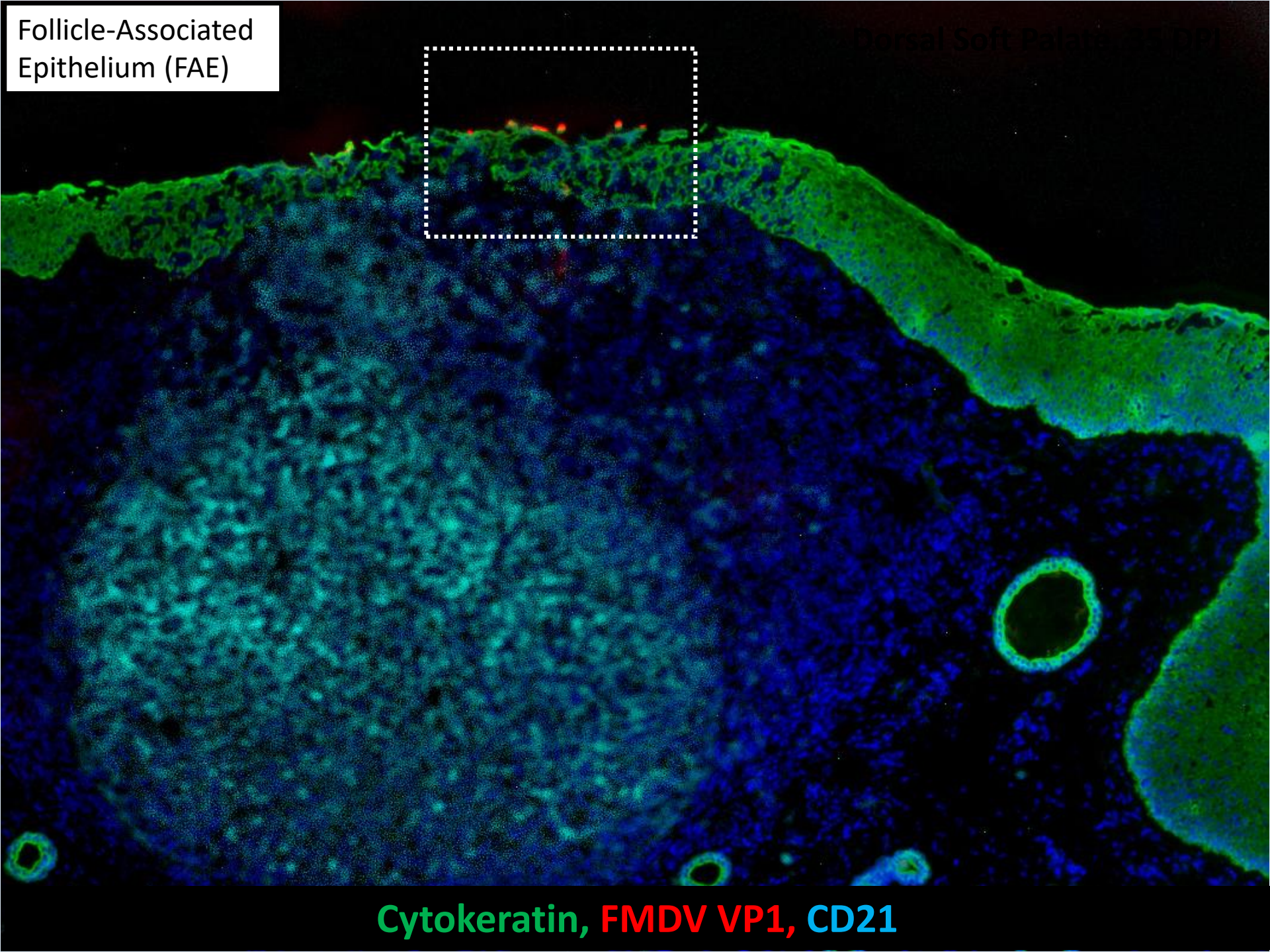
The FMDV Carrier State; landmark papers

- ***Van Bekkum et al., 1959***
 - Recovery of infectious FMDV in OPF (saliva) up to 8 months after recovery from clinical FMD
 - Similar subclinical persistence found in vaccinated cattle
 - Reports that FMDV carriers do not transmit infection further
- ***Sutmoller and Gaggero, 1965***
 - Standardization of probang sampling technique
 - Although, similar approach as used by van Bekkum
- ***Burrows 1966***
 - Isolation of infectious FMDV from nasopharyngeal tissues of persistently infected cattle
- ***Sutmoller et al 1968***
 - Definition of carriers at 28dpi
- ***Stenfeldt et al 2016***
 - Definition of the transitional phase and early determination of divergence

Anatomic localization of persistent FMDV: **Nasopharynx**



NOT OROPHARYNX



Follicle-Associated Epithelium (FAE)

Dorsal Soft Palate (DSP)

Cytokeratin, FMDV VP1, CD21

Can carrier cattle transmit FMD?

Do carriers matter?

Transmission from FMDV carriers; experimental studies

Table II. List of Experiments Used for the Estimation of Transmission Rate Parameter β

Ref. No. ^a	Number of			N ^b	Contact Days	Species
	Cases	Carriers	Susceptibles			
(7)	0	6	4	10	35	Cattle to cattle
(30)	0	14	8	22	43	Cattle to cattle
(28)	0	17	1	18	549	Cattle to cattle
(31)	0	1	1	2	61	Cattle to cattle
(31)	0	2	2	4	274	Cattle to cattle
(31)	0	2	2	4	274	Cattle to cattle
(31)	0	2	1	3	274	Cattle to cattle
(11)	0	1	2	3	42	Cattle to cattle
(11)	0	1	2	3	42	Cattle to cattle
(11)	0	1	2	3	42	Cattle to cattle
(11)	0	1	2	3	28	Cattle to cattle
(11)	0	1	2	3	28	Cattle to cattle
(11)	0	1	2	3	28	Cattle to cattle
(31)	0	2	1	3	84	Sheep to cattle
(9)	0	5	6	11	548	Buffalo ^c to cattle
(32)	0	1	2	3	175	Buffalo to cattle
(32)	0	1	2	3	152	Buffalo to cattle
(33)	0	6	6	12	456	Buffalo to cattle
(34)	1	3	4	7	168	Buffalo to cattle
(35)	0	6	3	9	731	Buffalo to cattle
(36)	2 ^d	3	2	5	312	Buffalo to cattle
(37)	0	1	7	8	122	Buffalo to buffalo
(36)	1	3	1	4	198	Buffalo to buffalo
(38)	0	4	6	10	30	Cattle to pigs
(38)	0	4	6	10	30	Cattle to pigs
(38)	0	4	6	10	30	Cattle to pigs
(38)	0	4	6	10	30	Cattle to pigs
(38)	0	4	6	10	30	Cattle to pigs
(39)	2	3	6	9	75	Cattle to pigs
(39)	0	2	6	8	86	Cattle to pigs
(39)	0	3	4	7	44	Cattle to pigs
(39)	0	1	4	5	34	Cattle to pigs
(39)	0	1	4	5	35	Cattle to pigs
(39)	0	2	4	6	29	Cattle to pigs
(31)	0	2	4	6	91	Cattle to pigs

^aNumber of reference (in list). In one paper, more than one experiment or experimental unit could be included.

^bN = Total number of animals (carriers + susceptible).

^cAfrican buffalo (*Syncerus caffer*).

^dIt was assumed that only one susceptible became infected due to contact with the carrier, and the second was infected by the first contact-infected animal.

Meta-analysis of transmission from persistently infected cattle and buffalo

$\beta = 0.0256$ infections per carrier per month

Tenzin et al., 2008

Parthiban-Parida'15 (recent addition)

SM'76

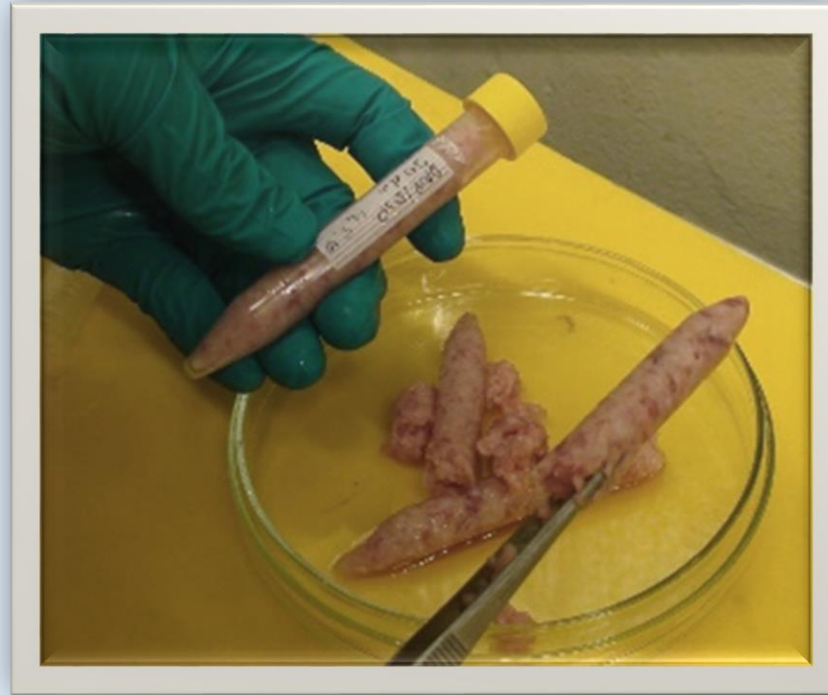
Carrier transmission trial under natural conditions in Vietnam



No transmission

Force of infection = 0.0 /month

Challenging the conventional wisdom of “dead-end carriers”.



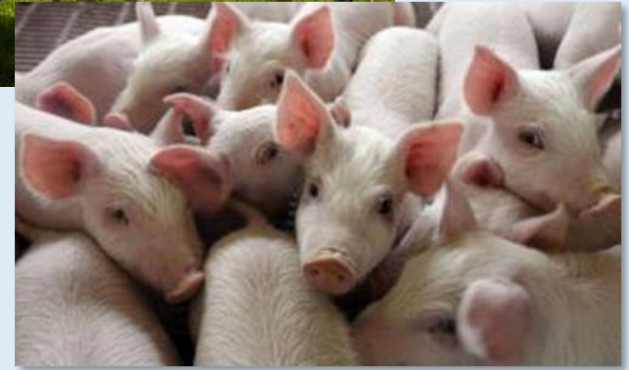
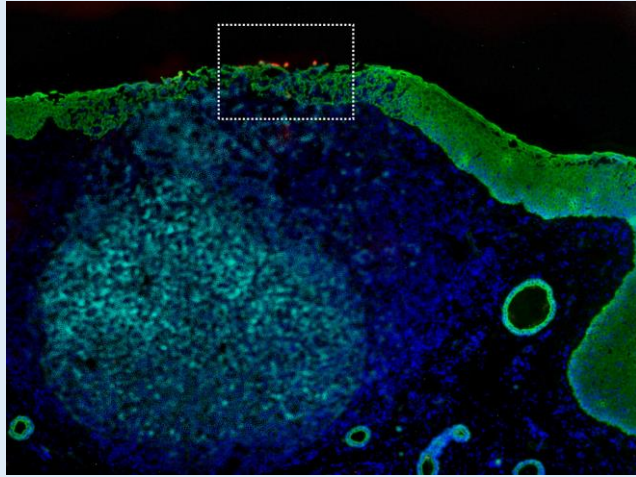
AMERICAN
SOCIETY FOR
MICROBIOLOGY



RESEARCH ARTICLE
Clinical Science and Epidemiology

Transmission of Foot-and-Mouth Disease from Persistently Infected Carrier Cattle to Naive Cattle via Transfer of Oropharyngeal Fluid

Jonathan Arzt,^a Graham J. Belsham,^b Louise Lohse,^b Anette Bötner,^b Carolina Stenfeldt^{a,c}

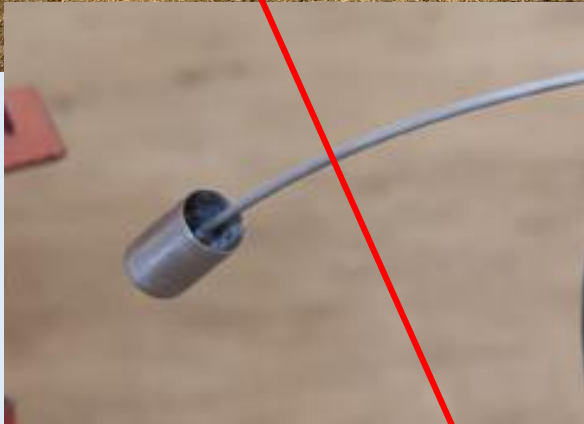


Simulated
Natural
Exposure

? Infection ↓ FMD?

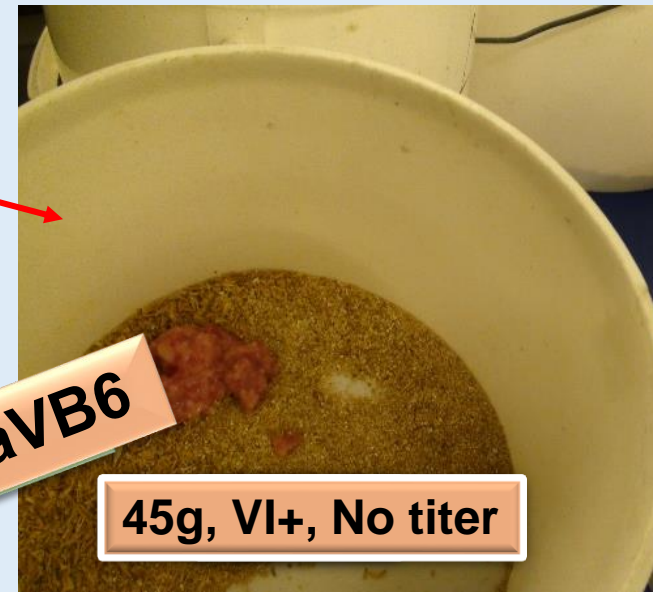


7 Confirmed Carriers
FMDV A24
(30 dpi)

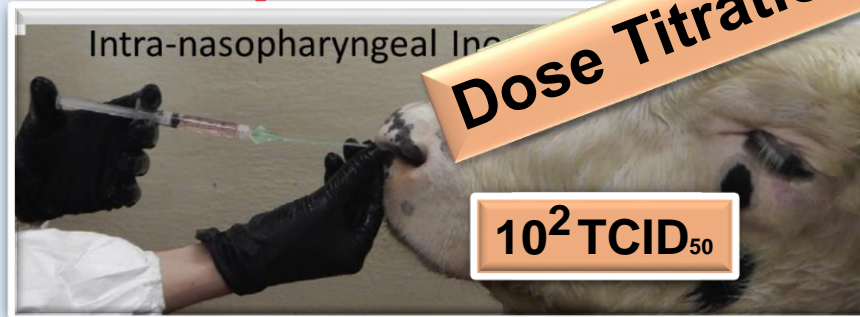


7 Confirmed Carriers

FMDV A24

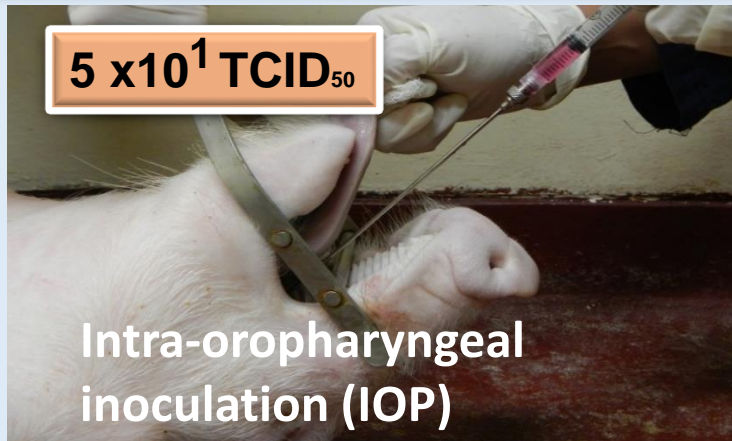


45g, VI+, No titer



Dose Titrations on LFBK-aVB6

10^2 TCID₅₀



5×10^1 TCID₅₀

Intra-oropharyngeal
inoculation (IOP)



Experimental Outcomes



→ No infection



→ No Infection

-nasopharyngeal Inoculation (INP)

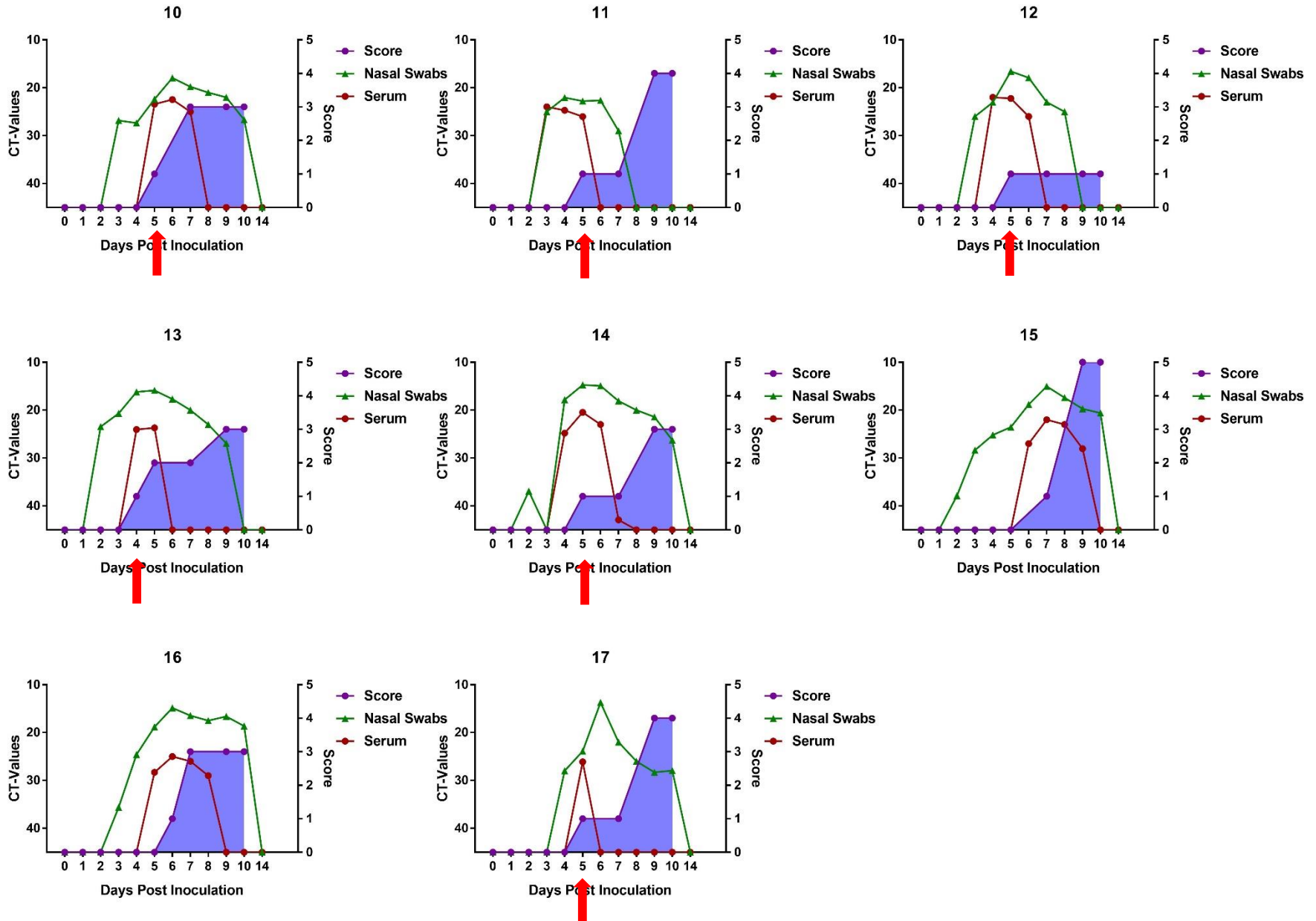


→

OPF



Infection dynamics, "Recipients"



VP1-GH loop Consensus (7 cattle)

CPN10 (calf 10, dpi 6) (post carrier)

N G T S K Y A V G G S G R R G D T G

CPN72 (calf 12, dpi 5)

N G M S K Y A V G G S G R R G D M G

CPN73 (calf 13, dpi 4)

N G T S K Y A V G G S G R R G D T G

CPN74 (calf 14, dpi 5)

N G M S K Y A V G G S G R R G D M G

CPN75 (calf 15, dpi 7)

N G M S K Y A V G G S G R R G D M G

CPN76 (calf 16, dpi 6)

N G M S K Y A V G G S G R R G D M G

CPN77 (calf 17, dpi 6)

N G M S K Y A V G G S G R R G D M G

Experimental Conclusions

- OPF (Probang) from carrier cattle **WAS** infectious to naïve cattle
- OPF (Probang) from carrier cattle **WAS NOT** infectious to naïve pigs
- Nasopharyngeal tissue from carrier cattle **WAS NOT** infectious to naïve pigs by ingestion

Can carrier cattle transmit FMD?



Endemic setting: Unlikely, but.....

$0.0256 \times (\text{__ Million Carriers}) = \text{__ Transmission events}$

250 million cases/year (KS)

Non-zero risk

Do carriers matter?

Outbreak Cessation



Stamping Out



Fear of Persistence

Article 8.8.7

Recovery of free status (see Figures 1 and 2)

- 1) When a FMD case occurs in a FMD free country or zone where vaccination is not practised, one of the following waiting periods is required to regain this free status:
 - a) three months after the disposal of the last animal killed where a *stamping-out policy*, without emergency vaccination, and *surveillance* are applied in accordance with Articles 8.8.40. to 8.8.42.; or
 - b) three months after the disposal of the last animal killed or the *slaughter* of all vaccinated animals, whichever occurred last, where a *stamping-out policy*, emergency vaccination and *surveillance* in accordance with Articles 8.8.40. to 8.8.42. are applied; or
 - c) six months after the disposal of the last animal killed or the last vaccination whichever occurred last, where a *stamping-out policy*, emergency vaccination not followed by the slaughtering of all vaccinated animals, and *surveillance* in accordance with Articles 8.8.40. to 8.8.42. are applied. However, this requires a serological survey based on the detection of antibodies to nonstructural proteins of FMDV to demonstrate no evidence of *infection* in the remaining vaccinated population.
- 3) When a case of FMD occurs in a FMD free country or zone where vaccination is practised, one of the following waiting periods is required to regain this free status:
 - a) six months after the disposal of the last animal killed where a *stamping-out policy*, with emergency vaccination, and *surveillance* in accordance with Articles 8.8.40. to 8.8.42. are applied, provided that serological *surveillance* based on the detection of antibodies to nonstructural proteins of FMDV demonstrates no evidence of virus transmission; or
 - b) 12 months after the detection of the last case where a *stamping-out policy* is not applied, but where emergency vaccination and *surveillance* in accordance with Articles 8.8.40. to 8.8.42. are applied, provided that serological *surveillance* based on the detection of antibodies to nonstructural proteins of FMDV demonstrates no evidence of virus transmission.



Neoteric subclinical infection (Vaccination)

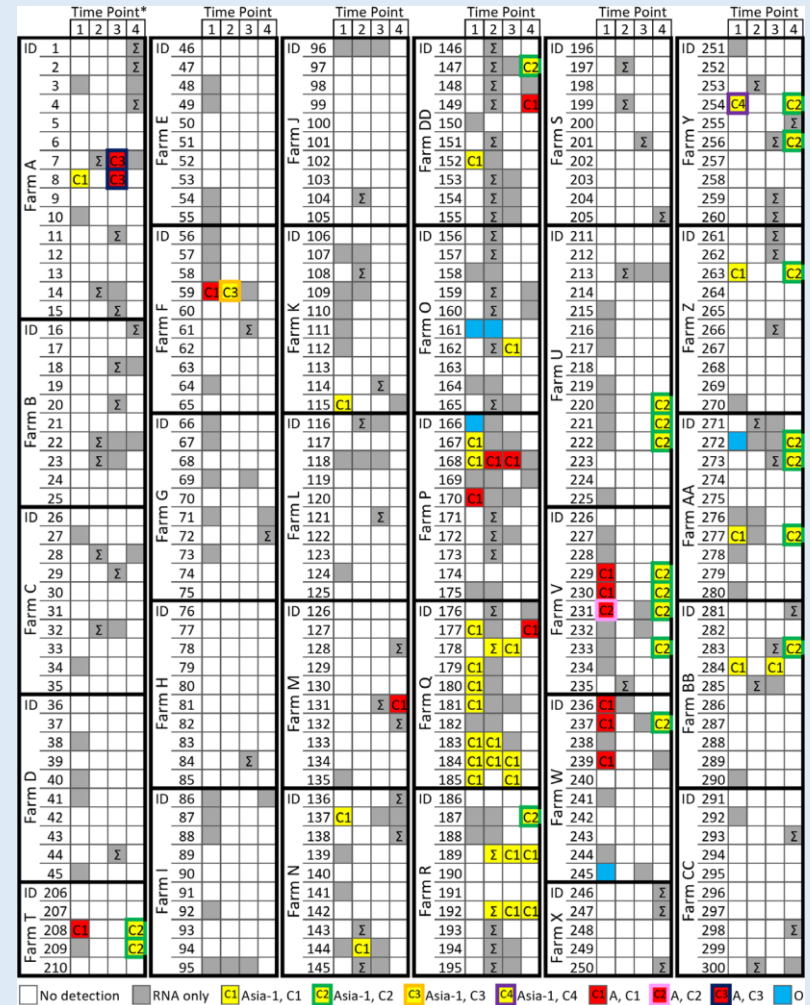


ORIGINAL ARTICLE

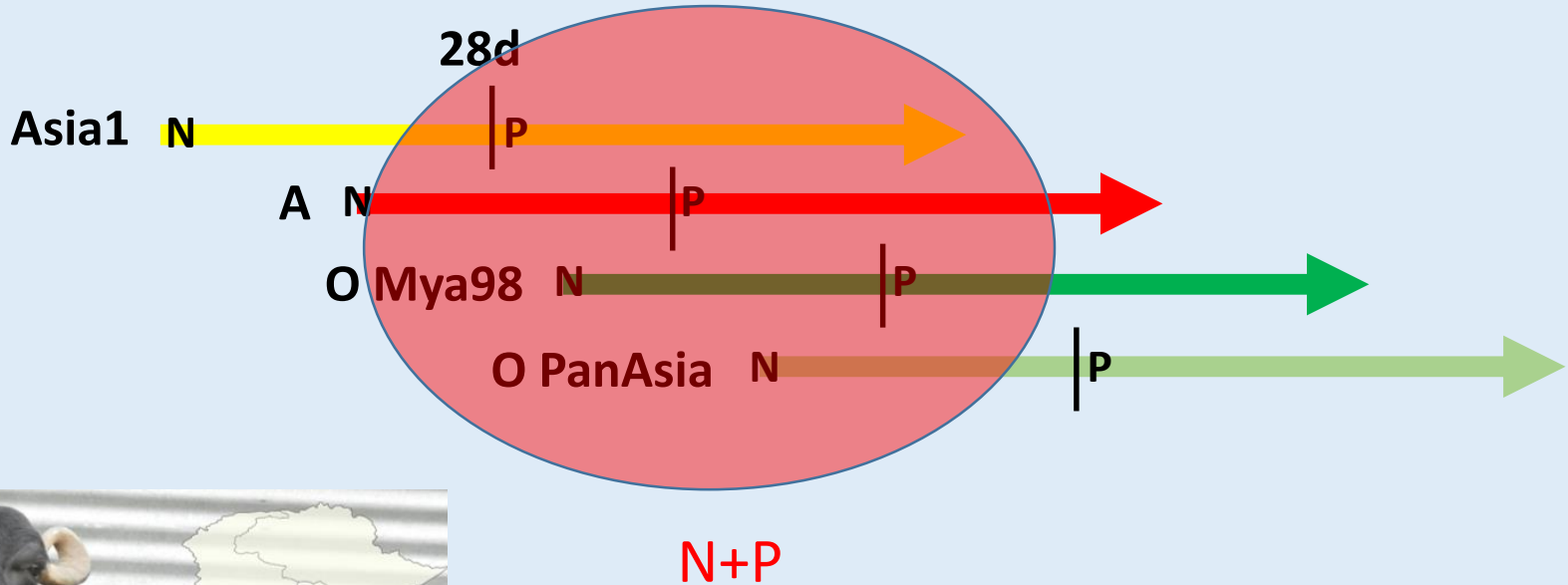
WILEY

Characterization of naturally occurring, new and persistent subclinical foot-and-mouth disease virus infection in vaccinated Asian buffalo in Islamabad Capital Territory, Pakistan

Umer Farooq¹ | Zaheer Ahmed^{2,3} | Khalid Naeem¹ | Miranda Bertram^{2,3} |
Barbara Brito^{2,3} | Carolina Stenfeldt^{2,4} | Steven J. Pauszek² | Michael LaRocco² |
Luis Rodriguez² | Jonathan Arzt²



Neoteric (new) subclinical FMD → Persistent subclinical FMD



ORIGINAL ARTICLE WILEY

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Neoteric subclinical infection (Indigenous breeds)



N+P

Image: N. Lyons

Overarching Conclusions

- Progressive path to global FMD eradication should include active surveillance for subclinical infection
 - Neoteric subclinical
 - Persistent subclinical
- Current vaccines do not prevent primary/persistent infection
- Continue laboratory-based research to develop products to prevent persistent and primary infection to strive towards global eradication of FMD

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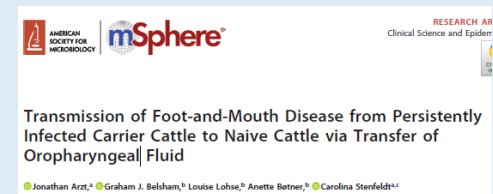
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