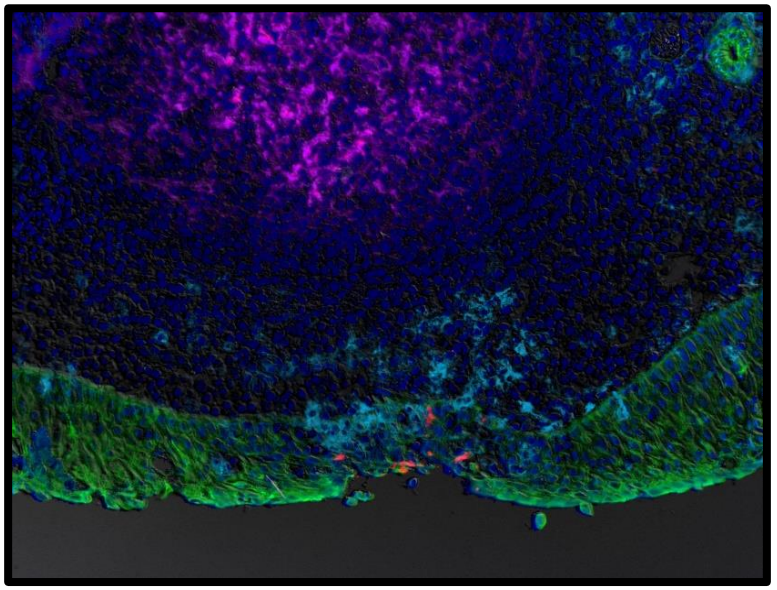
THE INTERDEPENDENCE OF FMDV PATHOGENESIS, CHALLENGE SYSTEM, AND OUTCOME OF VACCINE STUDIES



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Agricultural Research Service

University of Minnesota
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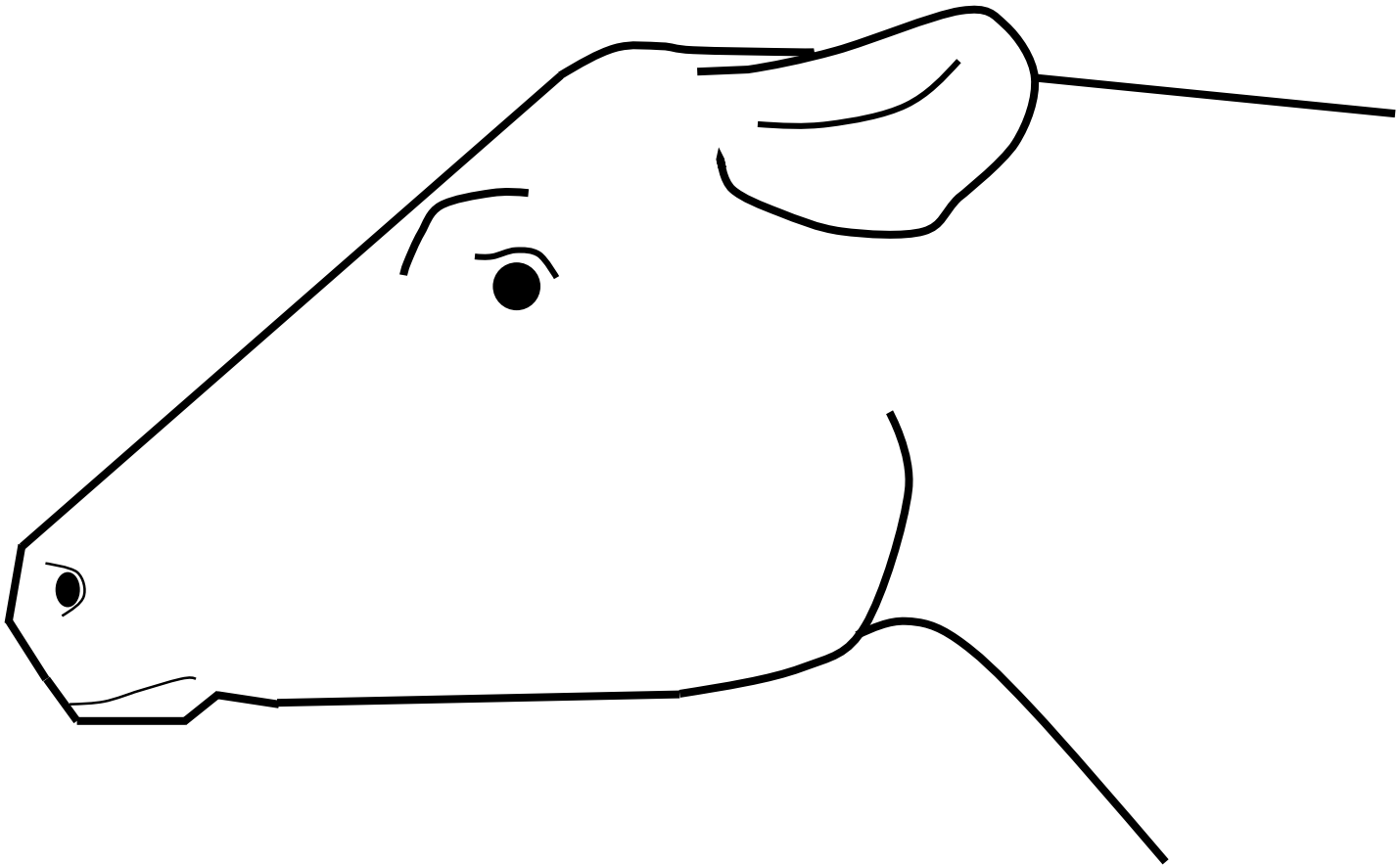
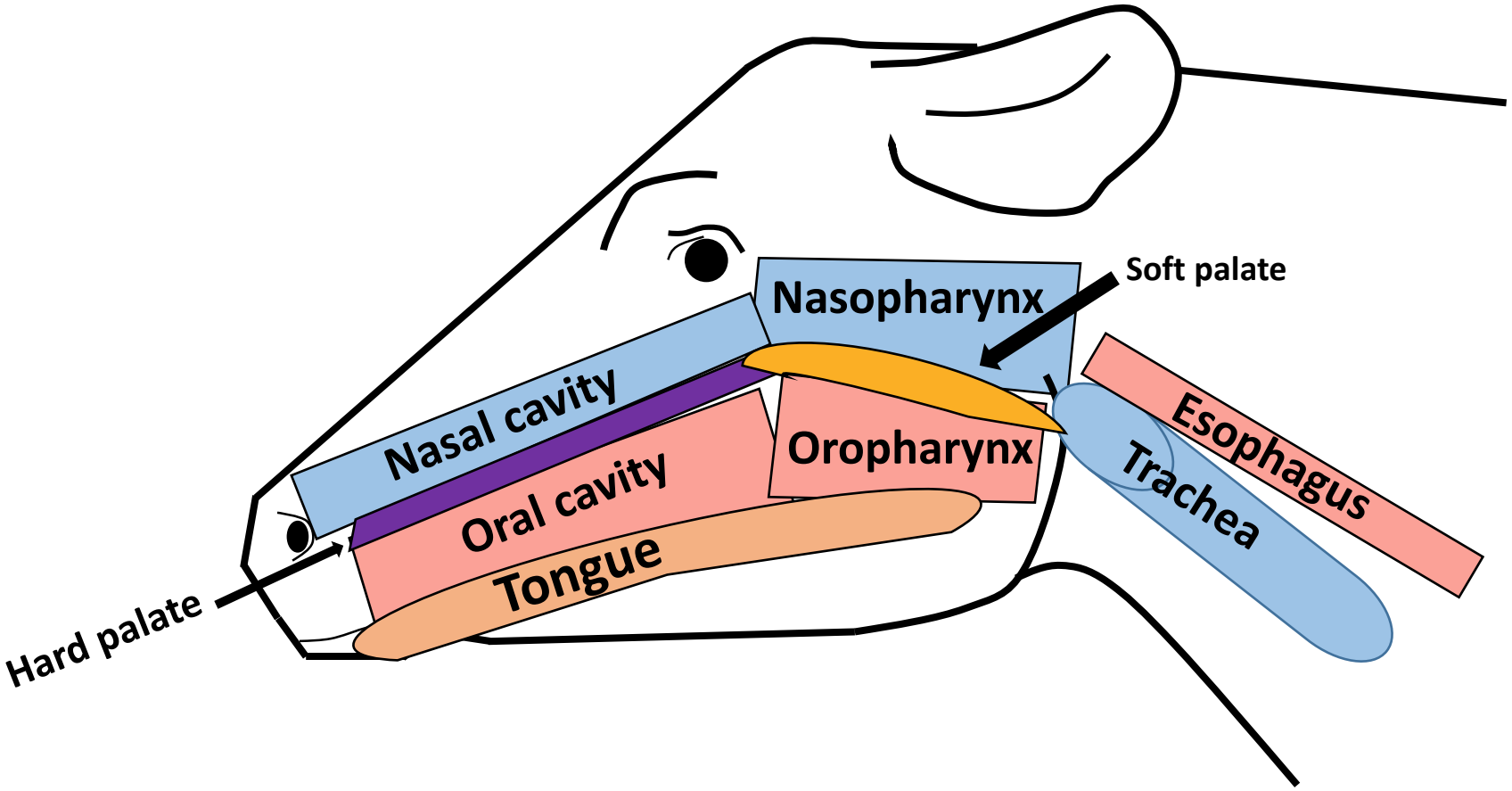
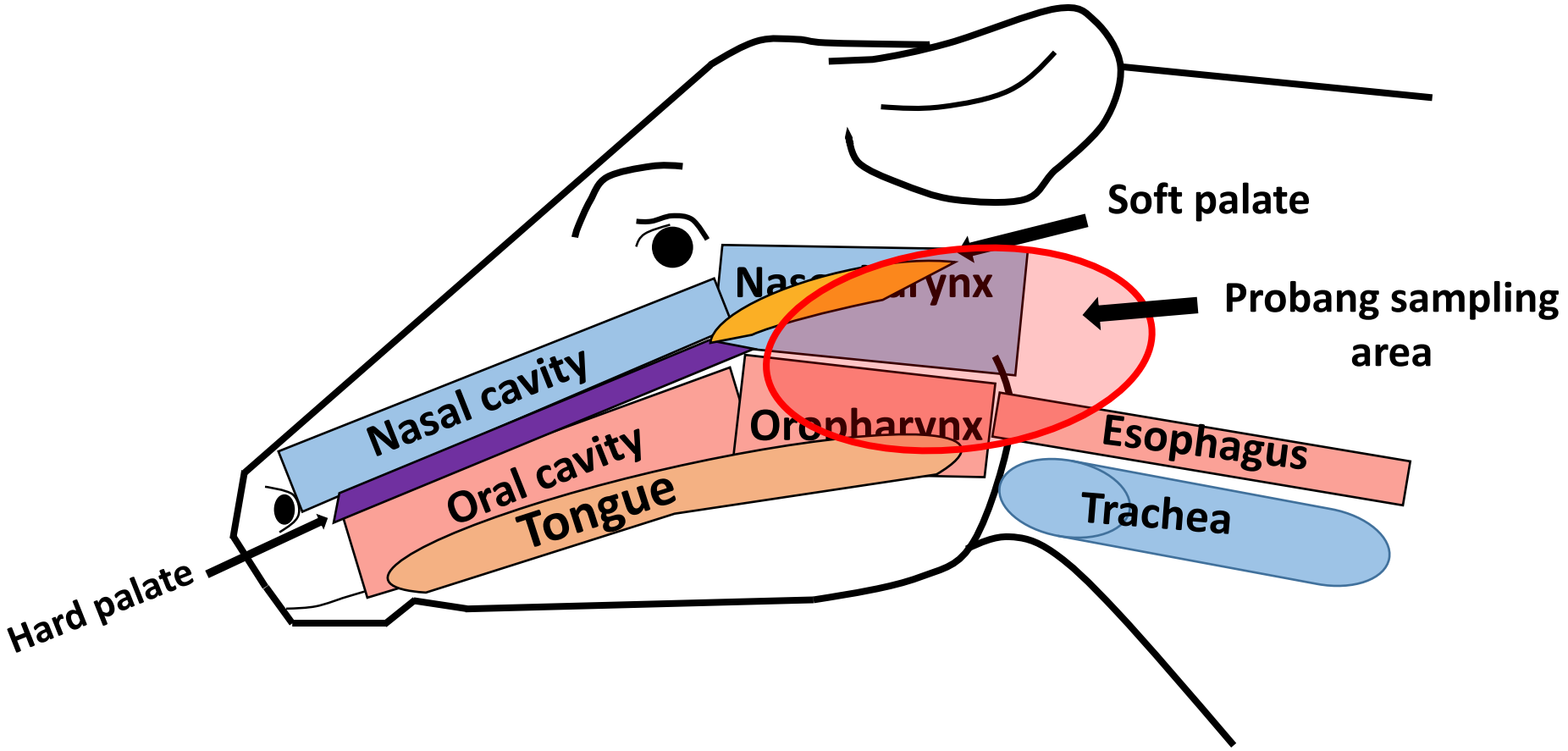
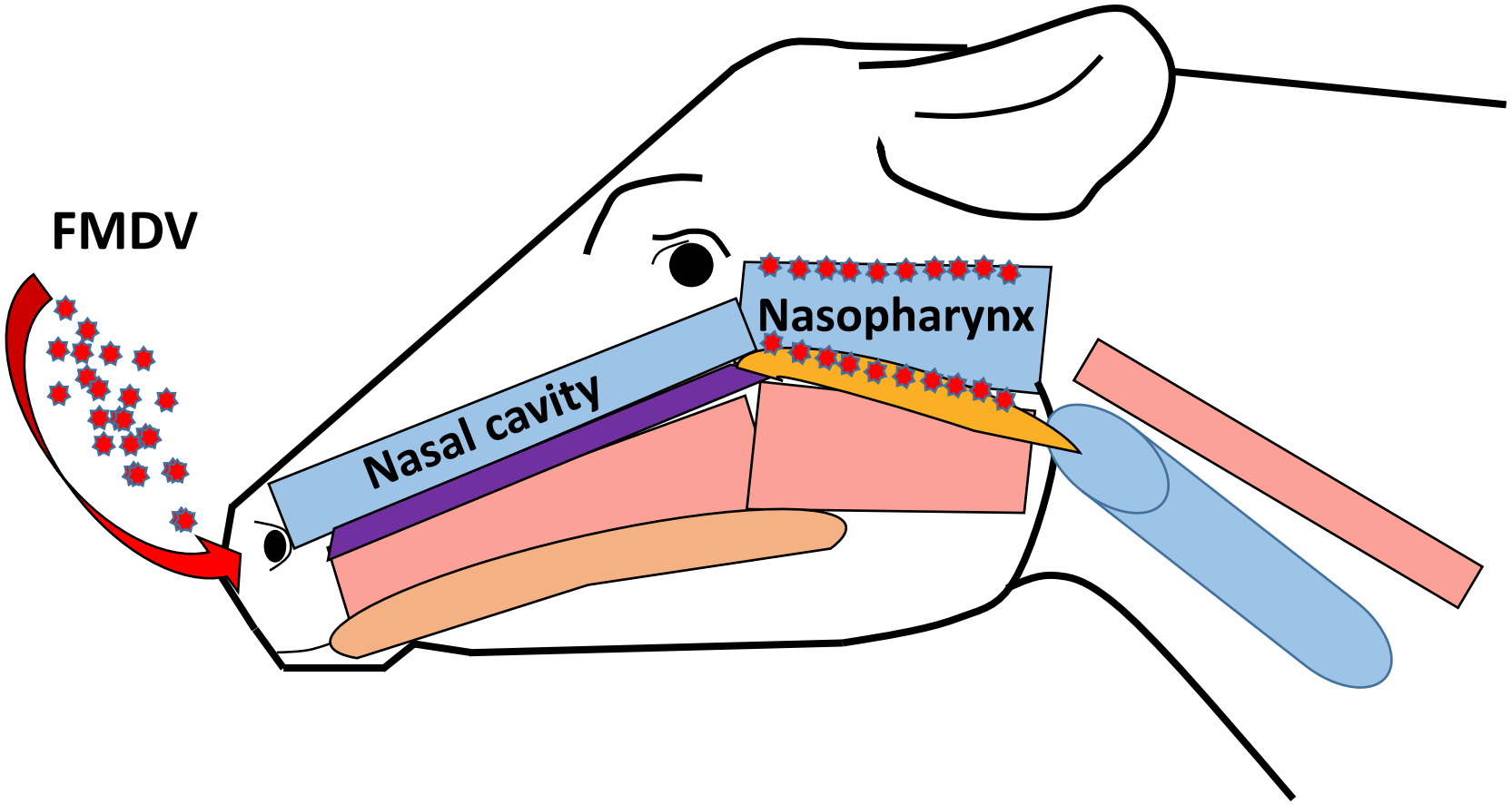
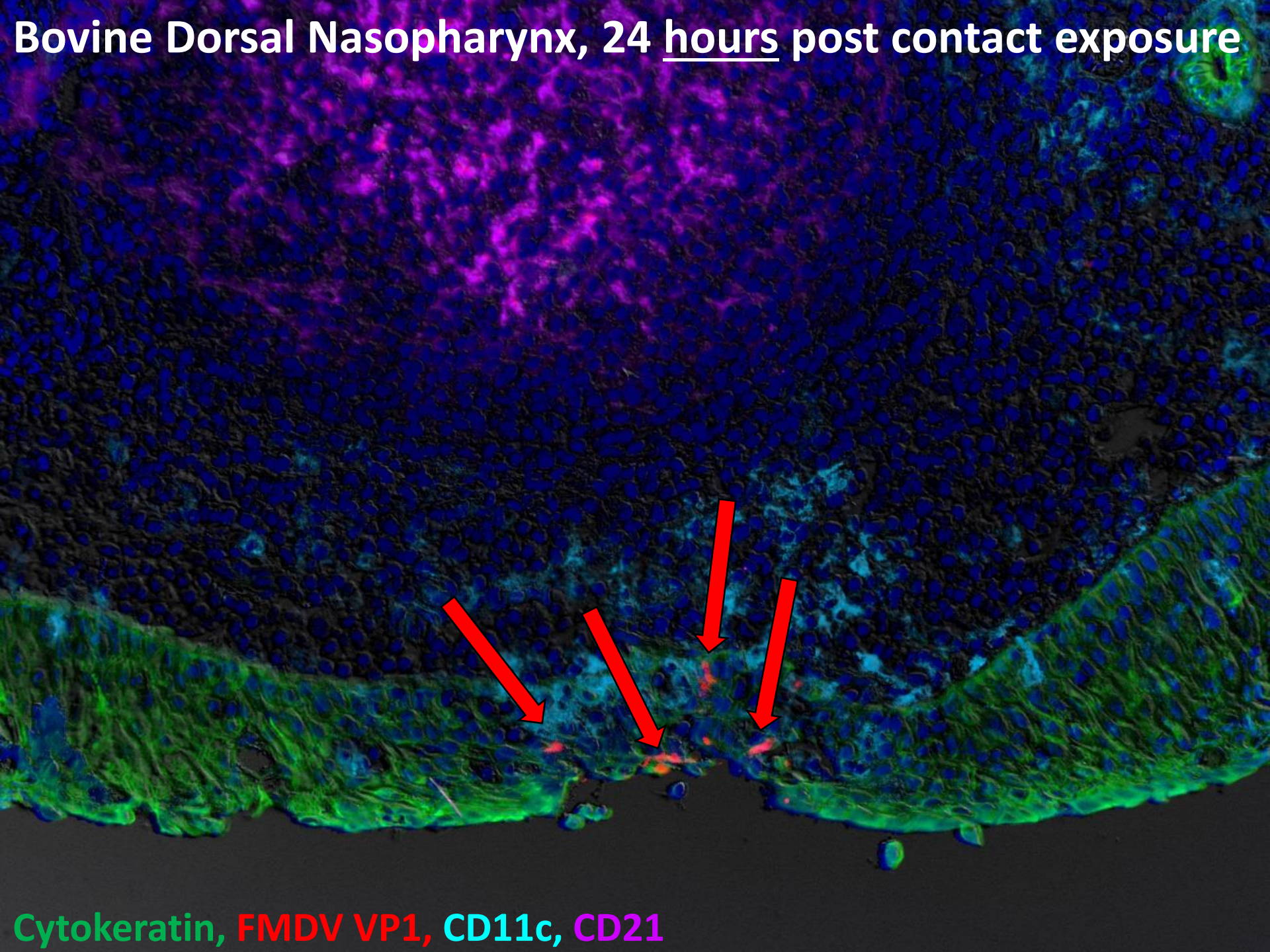



Nasopharynx
Soft palate
Nasal cavity
Oral cavity
Oropharynx
Tongue
Esophagus
Trachea
Hard palate


Soft palate
Probang sampling area
Nasal cavity
Oral cavity
Tongue
Oropharynx
Esophagus
Trachea
Hard palate

Primary FMDV infection of the nasopharyngeal mucosa




Bovine Dorsal Nasopharynx, 24 hours post contact exposure
Cytokeratin, FMDV VP1, CD11c, CD21

FMDV pathogenesis following natural exposure

(NAIVE CATTLE)

Primary infection

Nasopharynx/upper respiratory tract

↓

Systemic Generalization

Viremia + Vesicular lesions

↓

Systemic Clearance

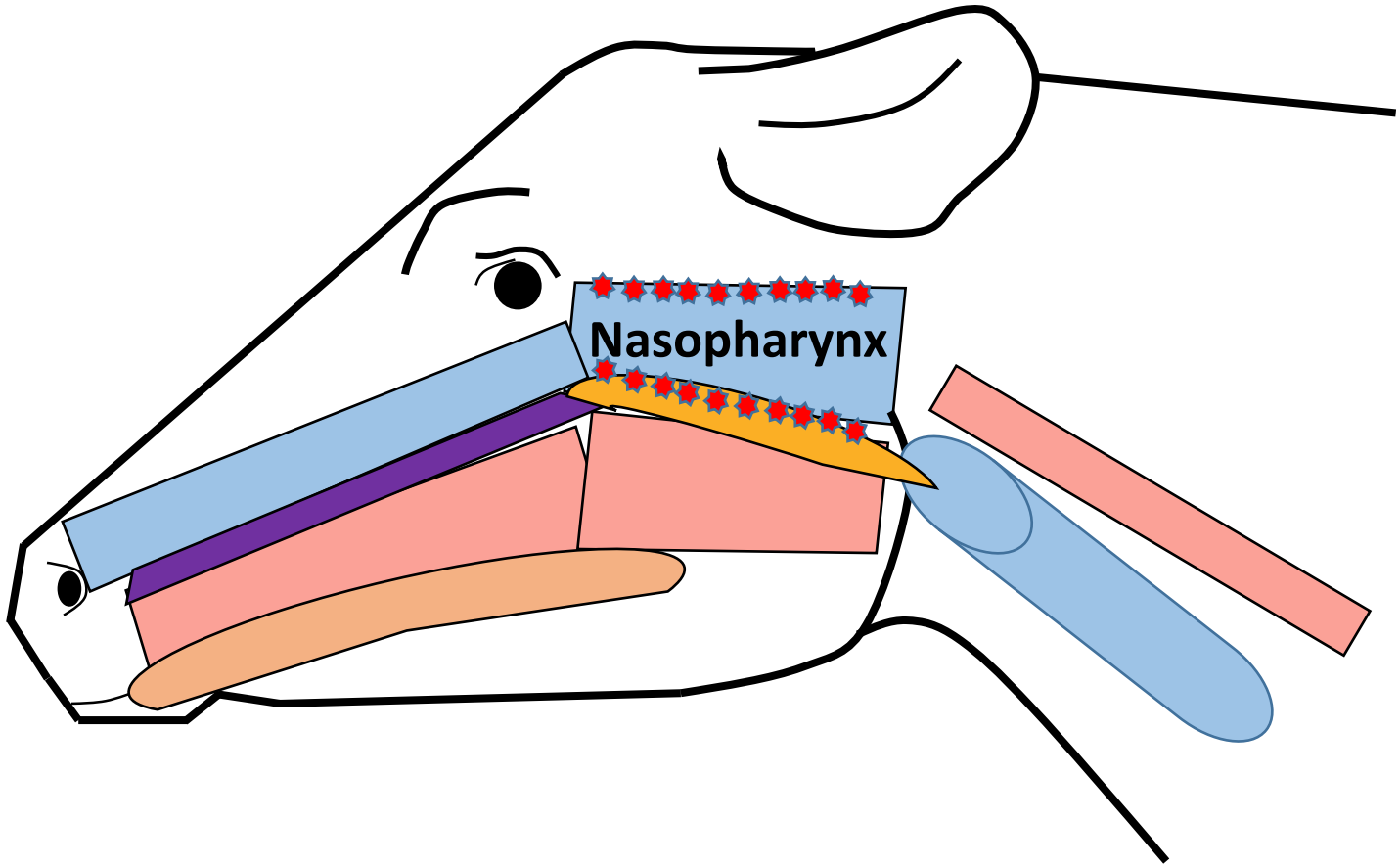
Antibody response

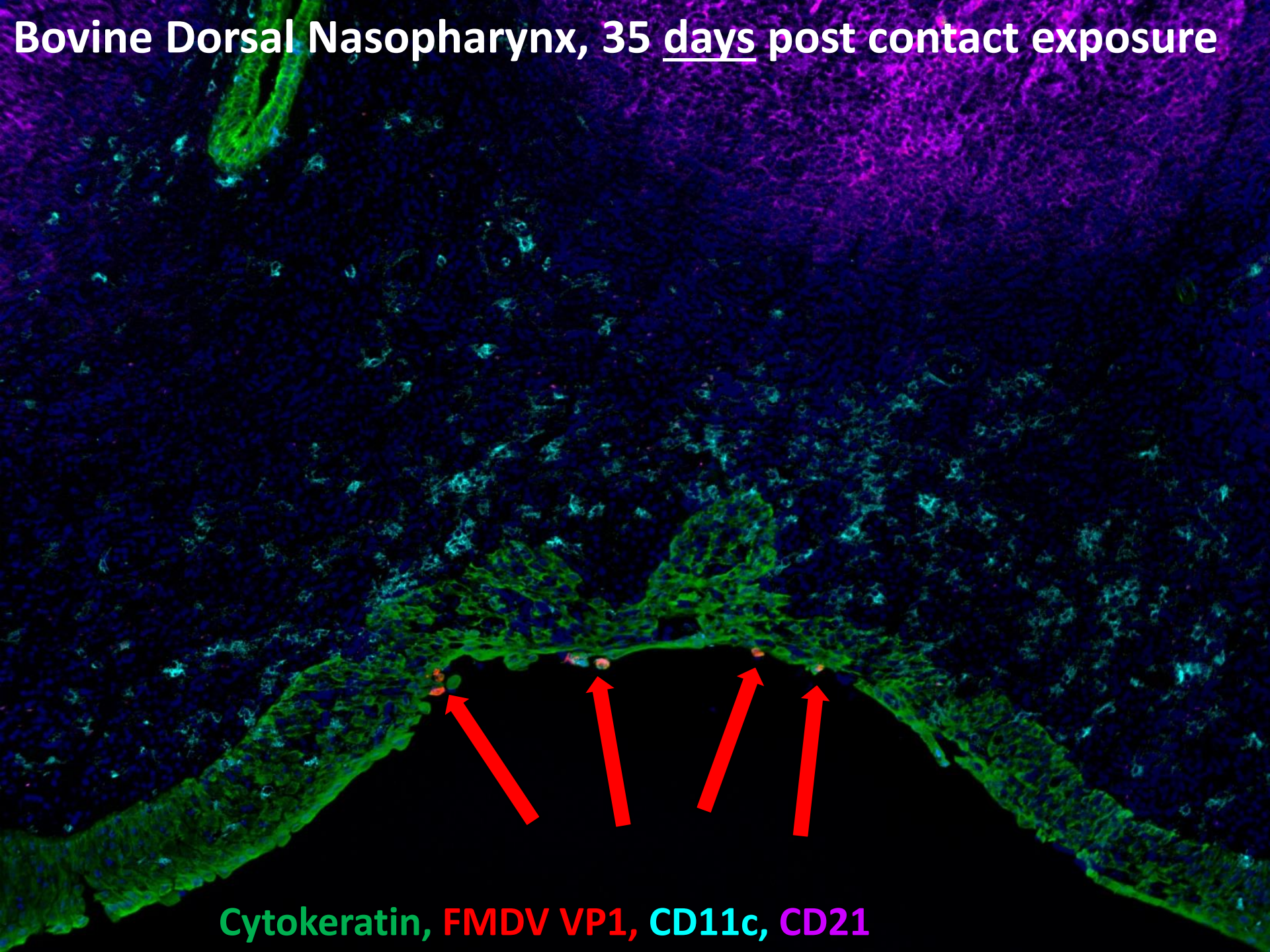
↓

FMDV persistence

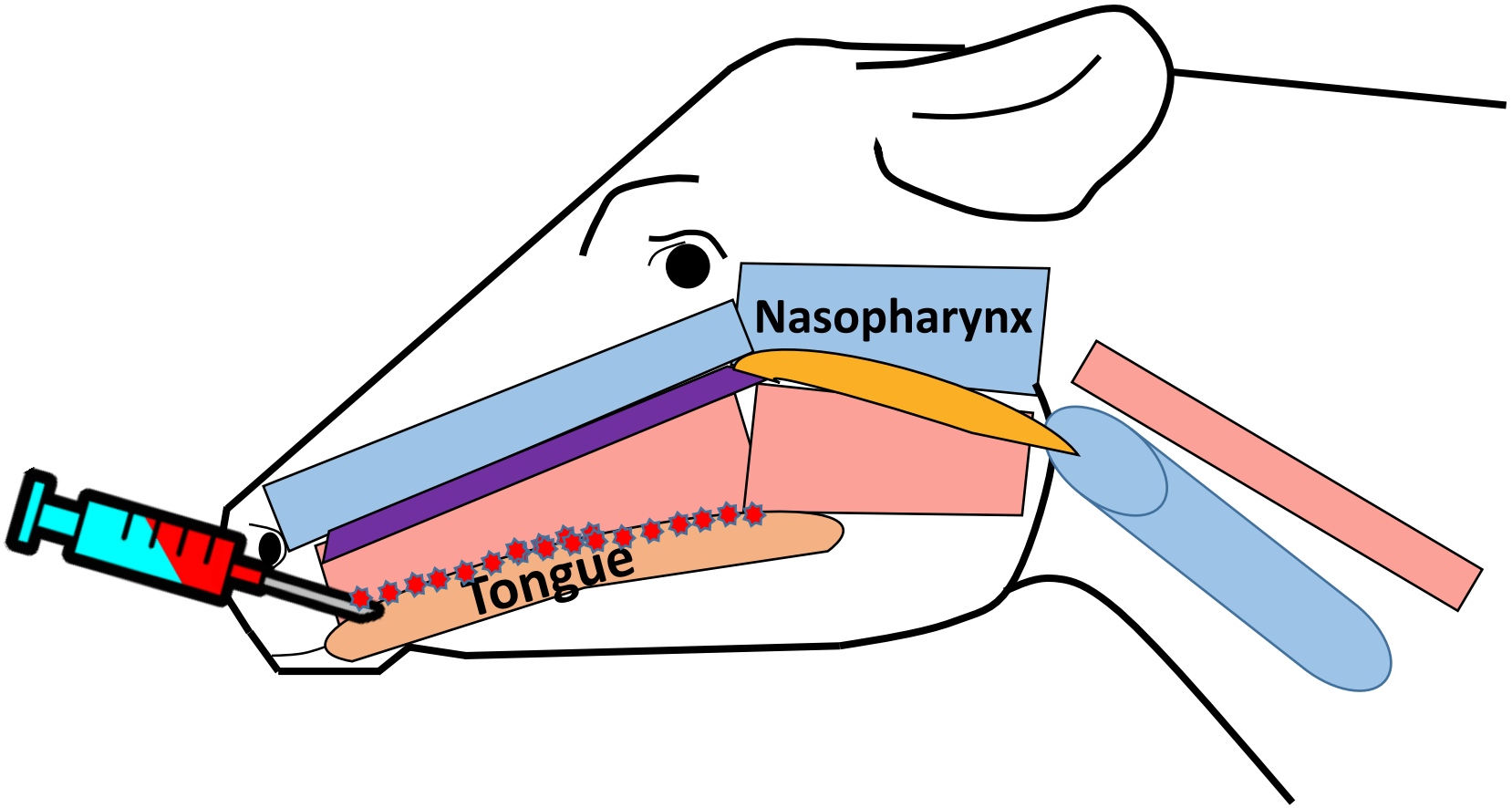
Nasopharynx/upper respiratory tract

Persistent FMDV infection:
Continued presence of infectious FMDV in bovine nasopharynx




Bovine Dorsal Nasopharynx, 35 days post contact exposure
Cytokeratin, FMDV VP1, CD11c, CD21

FMDV tongue inoculation



FMDV pathogenesis following Tongue inoculation

(NAÏVE CATTLE)

Primary infection

TONGUE EPITHELIUM

Systemic Generalization

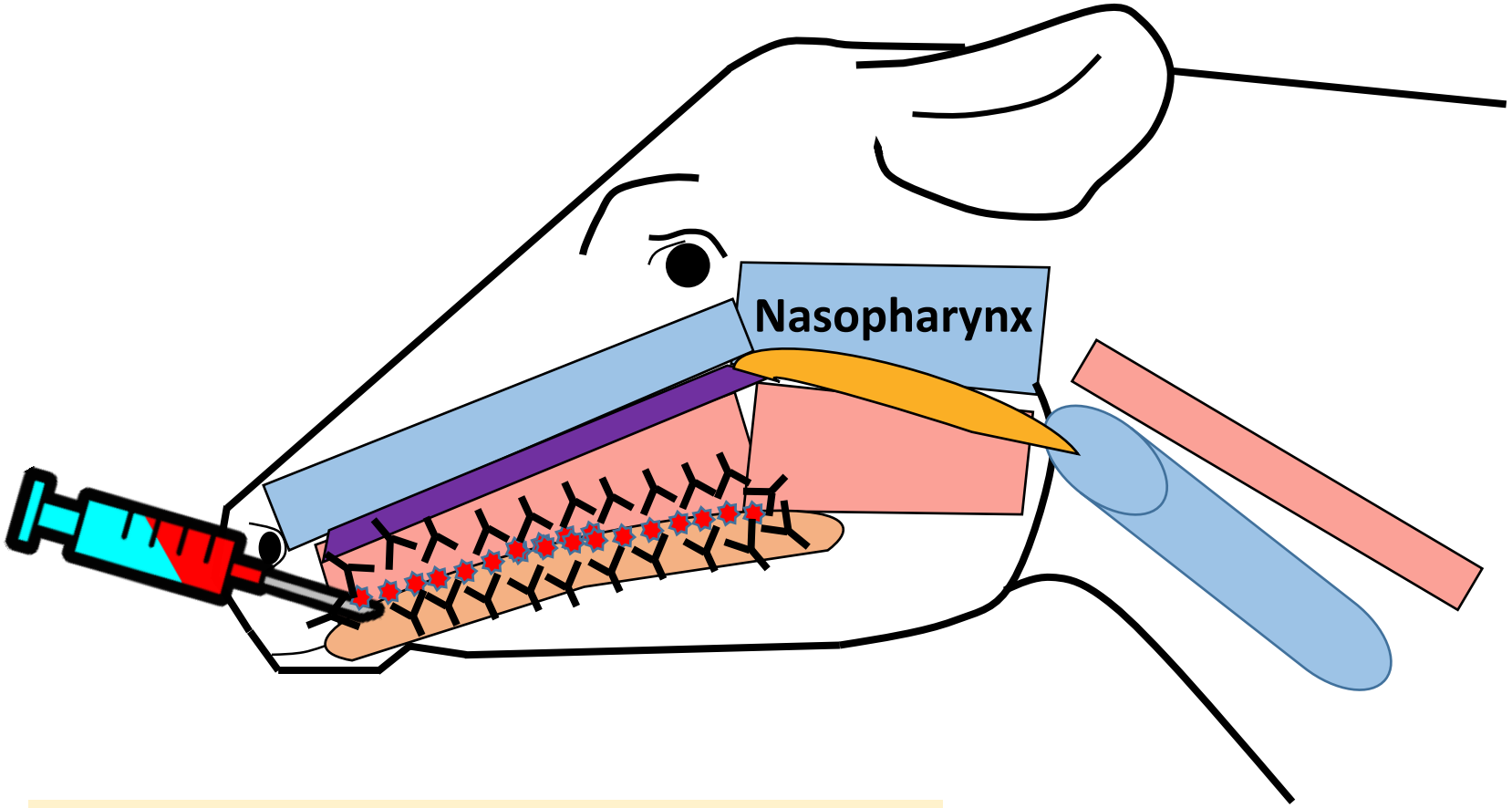
Viremia + Vesicular lesions

Systemic Clearance

FMDV persistence

Nasopharynx/upper respiratory tract

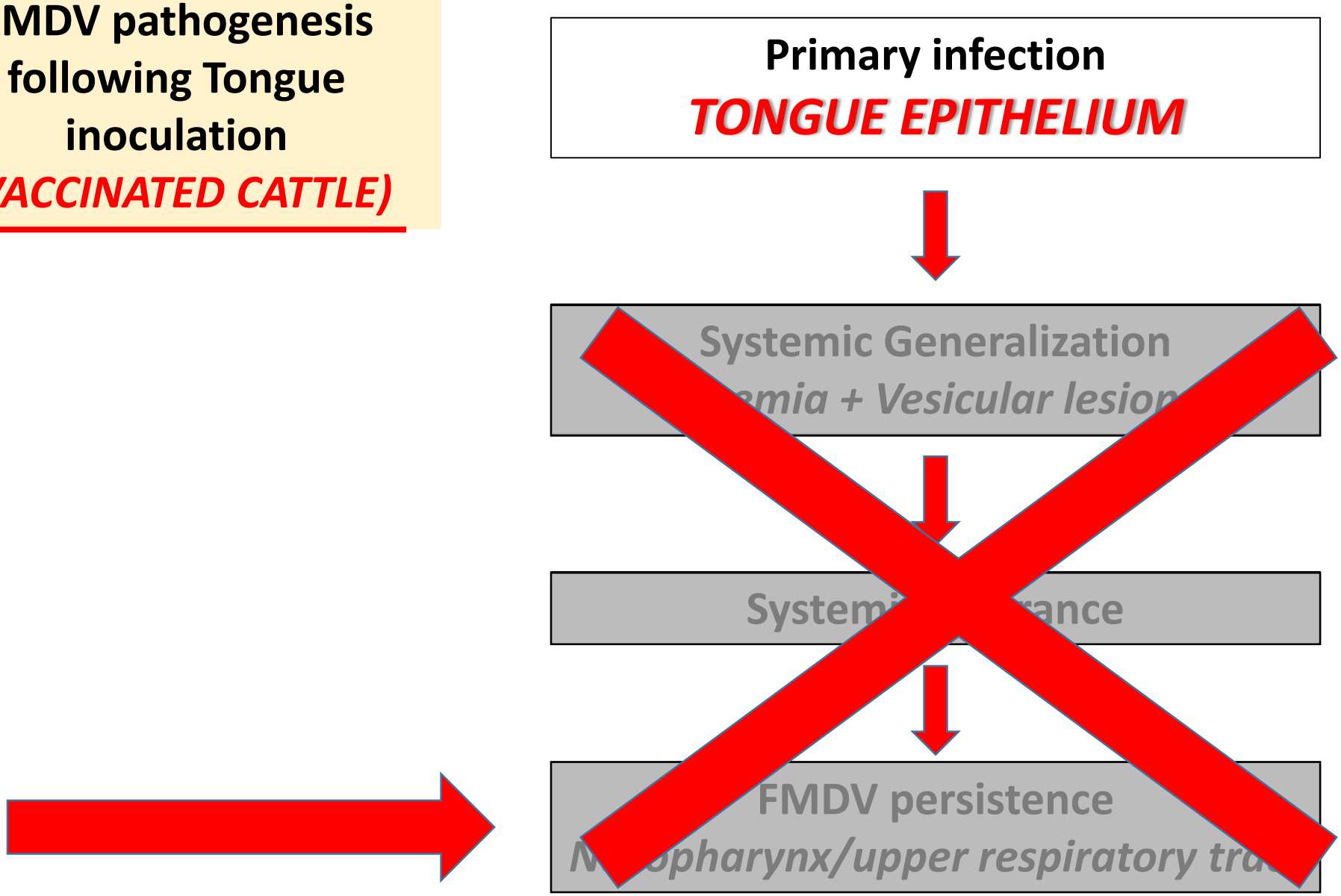
FMDV vaccine challenge:



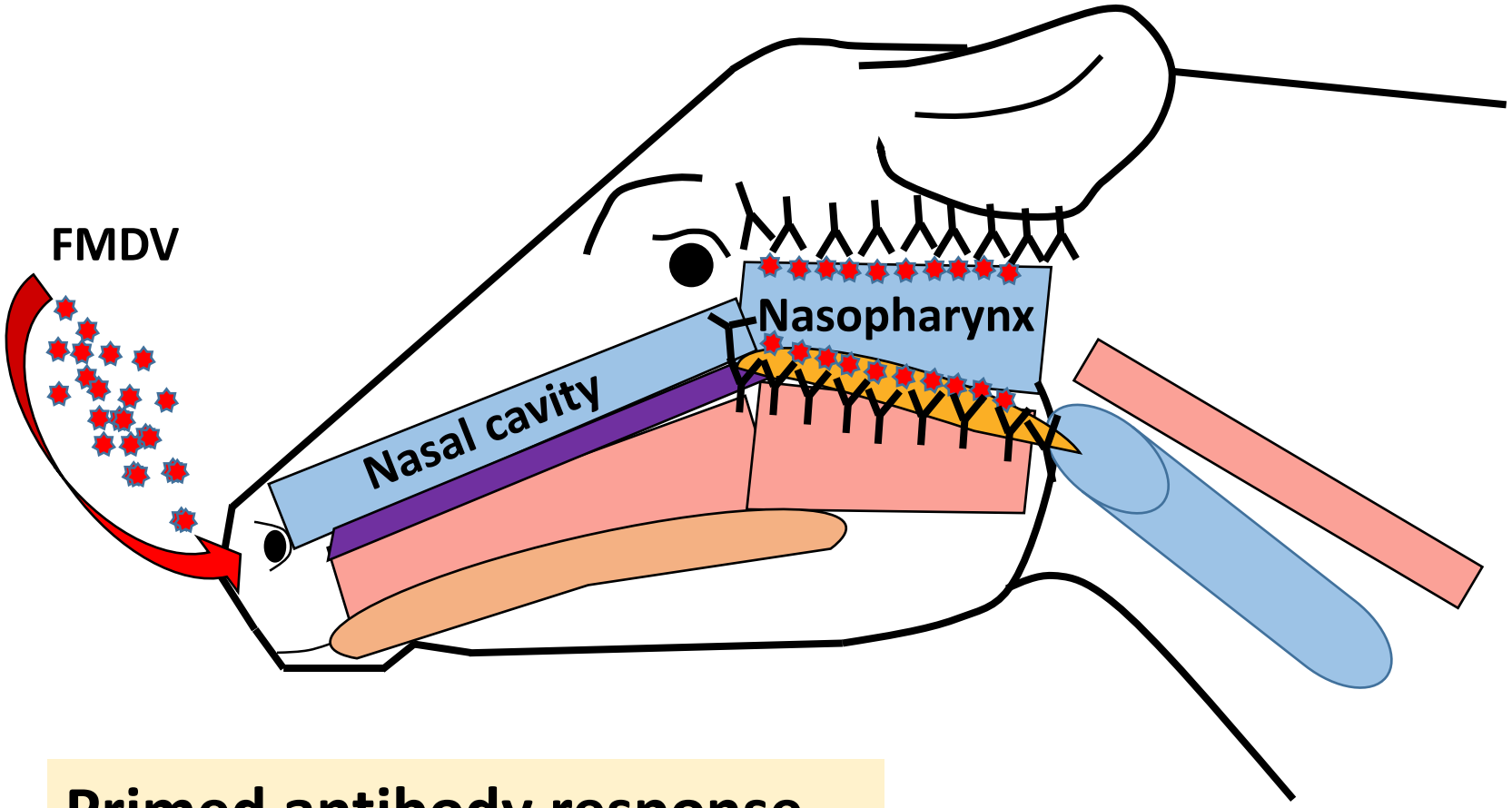
Primed antibody response

FMDV pathogenesis following Tongue inoculation

(VACCINATED CATTLE)

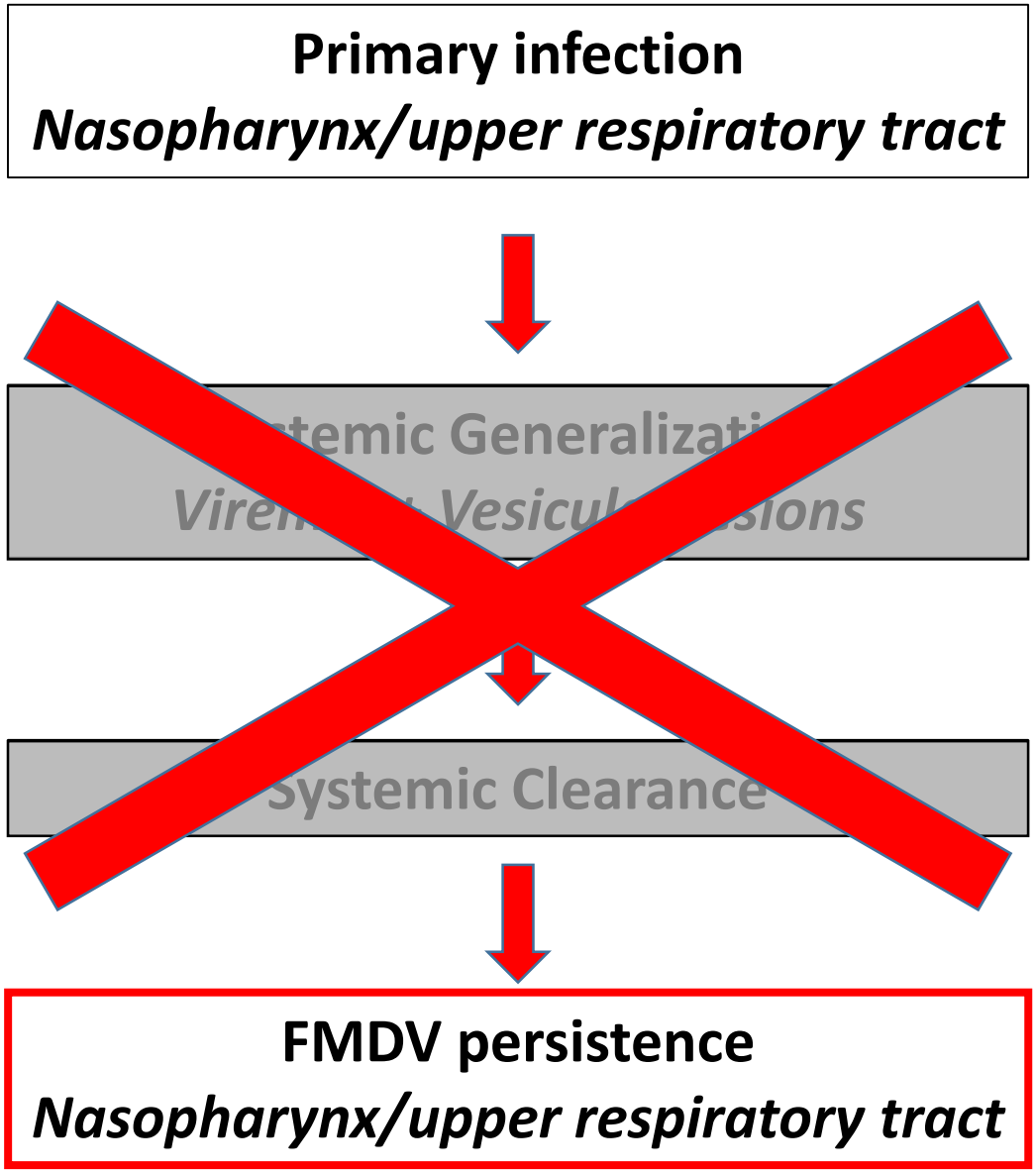


Natural FMDV exposure
VACCINATED CATTLE



Primed antibody response

FMDV pathogenesis following Tongue inoculation
(VACCINATED CATTLE)



Real-life example

Two separate studies: same vaccine and challenge virus

Scenario 1

Tongue inoculation

- 8 vaccinated cattle
- FMDV challenge at 21 dpv
- 100% clinical protection
- 0/8 (0%) FMDV carriers

Scenario 2

Simulated-natural challenge

- 10 vaccinated cattle
- FMDV challenge at 21 dpv
- 100% clinical protection
- 9/10 (90%) FMDV carriers

Other sources of variability

- **Time from vaccination to challenge**
- **Exposure system**

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Vaccine

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Foot and mouth disease virus transmission among vaccinated pigs after exposure to virus shedding pigs

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Other sources of variability

- **Antigen payload**
  - **Vaccine-dependent?**

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The Foot-and-Mouth Disease Carrier State Divergence in Cattle

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ABSTRACT

The pathogenesis of persistent foot-and-mouth disease virus (FMDV) infection was investigated in 46 cattle that were either naive or had been vaccinated using a recombinant, adenovirus-vectored vaccine 2 weeks before challenge. The prevalence of FMDV persistence was similar in both groups (62% in vaccinated cattle, 67% in nonvaccinated cattle), despite vaccinated cattle having been protected from clinical disease. Analysis of antemortem infection dynamics demonstrated that the subclinical divergence between FMDV carriers and animals that cleared the infection had occurred by 10 days postinfection (dpi) in vaccinated cattle and by 21 dpi in nonvaccinated animals. The anatomic distribution of virus in subclinically infected, vaccinated cattle was restricted to the pharynx throughout both the early and the persistent phases of infection. In nonvaccinated cattle, systemically disseminated virus was cleared from peripheral sites by 10 dpi, while virus selectively persisted within the nasopharynx of a subset of animals. The quantities of viral RNA shed in oropharyngeal fluid during FMDV persistence were similar in vaccinated and nonvaccinated cattle. FMDV structural and nonstructural proteins were localized to follicle-associated epithelium of the dorsal soft palate and dorsal nasopharynx in persistently infected cattle. Host transcriptome analysis of tissue samples processed by laser capture microdissection indicated suppression of antiviral host factors (interferon regulatory factor 7, CXCL10 [gamma interferon-inducible protein 10], gamma interferon, and lambda interferon) in association with persistent FMDV. In contrast, during the transitional phase of infection, the level of expression of IFN-λ mRNA was higher in follicle-associated epithelium of animals that had cleared the infection. This work provides novel insights into the intricate mechanisms of FMDV persistence and contributes to further understanding of this critical aspect of FMDV pathogenesis.

Conclusions

- The study design determines what conclusions can be made
- Be careful if extrapolating information from a study that was not designed to answer your specific question(s)
- Vaccine performance depends on an interplay of multiple factors
- Standardized models are important… But, be careful to not over-standardize your model

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